Official Protocol Title:	Protocol/Amendment No.: 004-02 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:	NCT05494736
Document Date:	19-JUL-2023

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: 004-02

Compound Number: MK-8527

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

Legal Registered Address:

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P.O. Box 2000
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Regulatory Agency Identifying Number(s):

NCT	Not Applicable
EU CT	2023-503682-39-00
EudraCT	Not Applicable
JAPIC-CT	Not Applicable
WHO	Not Applicable
UTN	Not Applicable
IND	Not Applicable

Approval Date: 19 July 2023

Sponsor Signatory

Typed Name:	Date
Title:	

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

Investigator Signatory

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

Typed Name:	Date
Title:	

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	19-JUL-2023	An additional panel was added to allow for the evaluation of a lower dose of MK-8527; a statement of compliance with European Union Clinical Trials Regulations (EU CTR) No 536/2014 was also added.
Amendment 01	09-FEB-2023	Modifications were made to expand clinical site locations, including the European Union.
Original Protocol	27-MAY-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 004-02

Overall Rationale for the Amendment:

To add additional panels that would include lower doses of MK-8527 and to add compliance language for European Union Clinical Trial Regulations. (EU CTR)

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
4.1 Overall Design	Updated the study design to make Panel C a serial panel following Panel B and to add Panel D. The dose for Panels C and D is 0.25 mg of MK-8527.	The addition of a fourth panel will allow for the continued evaluation of safety, tolerability, and antiviral efficacy of MK-8527, in Panels C and D. Both panels will explore a dose of 0.25 mg of MK-8527.This amendment provides an update that Panel C will run following Panel B, and clarifies that Panel D will run following Panel C.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Throughout Document	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To improve upon the clarity of the protocol.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	The Intervention table was updated to show the actual dose of 0.5 mg was given to Panel B, and to add the 0.25 mg dose of MK-8527 for Panel C and the newly-added Panel D.	This update allows for the investigation of doses of 0.25 mg in Panels C and D.
1.1 Synopsis	Updated the total number of intervention groups and arms from 3 to 4.	This change reflects the addition of Panel D to the study design.
1.2 Schema	Updated the Overall Study Diagram and Study Schema to make Panel C a serial panel following Panel B and to add Panel D.	Refer to Section 4.1 rationale
2.2.2 Preclinical and Clinical Studies	Added data from the 6- and 9-month chronic toxicology studies and oral Embryo-Fetal Developmental Toxicity and Toxicokinetic studies. Added preclinical data related to lymphocyte toxicity and MK-8527-TP levels.	The update supports continued clinical evaluation of MK-8527.
2.2.3 Ongoing Clinical Studies	Added clinical data from Panels A and B from this study.	The update supports continued evaluation of additional doses of MK-8527.
4.2 Scientific Rationale for Study Design	Updated to include viral load data from Panels A and B in this study.	The update supports continued evaluation of additional doses of MK-8527.
4.3.1 Starting Dose for This Study	Preclinical data updated and new exposure multiple was added.	The update supports continued clinical evaluation of MK-8527.
4.3.3 Rationale for Dose Interval and Study Design	Updated based on new study design.	Refer to Section 4.1 rationale
4.4.1 Clinical Criteria for Early Study Termination	Updated based on new study design.	Refer to Section 4.1 rationale
6.1 Study Intervention(s) Administered	Updated to show the actual dose of 0.5 mg given to Panel B, and to add the 0.25 mg dose of MK-8527 for Panel C and the newly-added Panel D.	This update allows for the investigation of doses of 0.25 mg in Panels C and D.
6.3.1 Intervention Assignment	Updated based on new study design.	Refer to Section 4.1 rationale
6.5 Concomitant Therapy	ART start was changed from before Day 10 to before postdose Day 11.	This change is to correct a typographical error.
6.6 Dose Modification (Escalation/Titration/Other)	Updated based on new study design.	Refer to Section 4.1 rationale
8.11.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters	Removed the statement that Panels B and C may be run concurrently or sequentially.	This change reflects an update to the study design to run all study panels sequentially.
10.1.1 Code of Conduct for Interventional Clinical Trials	Added compliance language for European Union Clinical Trial Regulations. (EU CTR).	This is for the addition of a site in Romania.
10.8 Appendix 8: Blood Volume	Added a table for the blood volumes that will be collected in Romania	This shows the difference in blood volumes collected in Romania compared to South Aftica

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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: N/A

Hypotheses, Objectives, and Endpoints:

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

Study Population: Treatment naïve HIV-1 infected participants

Primary Objective	**Primary Endpoint**
- To evaluate the antiretroviral activity of MK-8527 in HIV-1 infected participants. - Hypothesis: At a dose that is safe and generally well tolerated, MK-8527 has antiretroviral activity, as measured by change from predose 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 predose after MK-8527 is at least 1.0 log10 copies/mL.	- Plasma HIV-RNA (log10 copies/mL) reduction from predose
- To evaluate the safety and tolerability of MK-8527 in HIV-1 infected participants.	- Adverse events
Secondary Objectives	**Secondary Endpoints**
- To evaluate the intracellular PK of MK-8527-TP in PBMC after administration of single oral doses of MK-8527 to HIV-1 infected participants. - Estimation: The GM C168h MK-8527-TP will be estimated	- MK-8527-TP AUC0-168, AUC0-last, AUC0-inf, T_{max}, C_{max}, 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-last, AUC0-inf, T_{max}, C_{max}, Clast, and apparent terminal t1/2
- To evaluate the PK- pharmacodynamic association of intracellular MK-8527-TP with viral load reduction.	- PK (MK-8527-TP in PBMC) / pharmacodynamic (plasma HIV-1 RNA) correlation.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	HIV infection
Population	HIV-1 Infected Participants
Study Type	Interventional
Intervention Model	Sequential This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 11 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 26 participants will be allocated in this study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Panel A	MK-8527	1 mg	1.0 mg	Oral	Single Dose	Test Product
Panel B	MK-8527	0.5 mg	0.5	Oral	Single Dose	Test Product
Panel C	MK-8527	0.25 mg	0.25 mg	Oral	Single Dose	Test Product
Panel D	MK-8527	0.25 mg	0.25 mg	Oral	Single Dose	Test Product

Total Number of Intervention Groups/Arms	4
Duration of Participation	Each participant will participate in the study for approximately 8 weeks from the time the participant signs the 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:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.

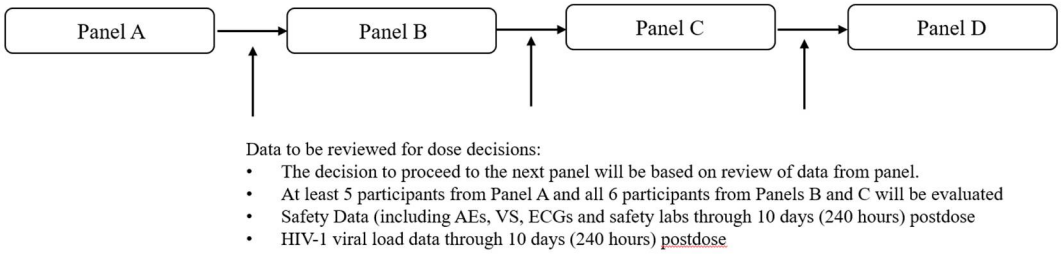
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1 and Table 1.

Figure 1 Overall Study Diagram



AE=adverse event; ECG=echocardiogram; VS=vital signs.

Table 1 Study Schema

Panel[a]	Dose of MK-8527			
A	1.0 mg			
B[b]		0.5 mg		
C[b]			0.25 mg	
D[b]				0.25 mg

VL=viral load.
[a] Panel A will have 8 participants and Panels B, C and D will have 6 participants. All participants will receive a single oral 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 11 (ie,240 hours postdose) from the preceding panel.

1.3 Schedule of Activities

All Panels											
Study Period	**Screening**	**Intervention**								**Poststudy[b]**	**Notes**
Scheduled Hour	**Screening[a]**	**Predose**	**0**	**1**	**4**	**24**	**48 to 144**	**168**	**192 to 504**	**672**	
Administrative Procedures											
Informed Consent	X										Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X										Sec. 5.1, 8.1.1.2
Participant ID Card	X										Sec. 8.1.3
Inclusion/Exclusion Criteria	X	X	X								Sec. 5.1, 5.2, 8.1.2
Medical History (includes substance usage)	X										Includes collection of drug, alcohol, tobacco, and caffeine use. Sec. 8.1.4
Prior/Concomitant Medication Review	X----------X										Sec. 5.2, 6.5, 8.1.5
Assignment of Screening Number	X										Sec. 8.1.6
Assignment of Treatment Number			X								Sec. 8.1.7
MK-8527 Administration			X								Fast for at least 8 hours prior to administration. Sec. 8.1.8, 8.1.8.1, 5.3.1

All Panels											
Study Period	**Screening**	**Intervention**								**Poststudy[b]**	**Notes**
Scheduled Hour	**Screening[a]**	**Predose**	**0**	**1**	**4**	**24**	**48 to 144**	**168**	**192 to 504**	**672**	
Domiciling		X----------X									Report to the CRU the evening of Day 1 Sec. 8.1.11
Standard Meals					X---X[c]						Sec. 5.3.1
Safety Procedures											
Full physical examination	X	X				X		X		X	Sec. 8.3.1, 8.11.5
Height	X										Sec. 8.3.1
Weight	X									X	Sec. 8.3.1
Vital Signs (HR, BP)	X	X		X[d]		X		X		X	Duplicate Predose HR and BP, Sec. 8.3.2
Vital Signs (RR, BT)	X	X		X		X		X		X	Sec. 8.3.2
Orthostatic Vital Signs (HR, BP)	X	X		X		X		X		X	Sec. 8.3.2
12-lead ECG	X	X		X[d]		X		X		X	Triplicate Predose ECG, Sec. 8.3.3
Urine/Serum β-hCG; WOCBP only	X	X								X	Sec. 8.3.5, Appendix 2
Serum FSH, WONCBP only)	X										Sec .5.1, Appendix 2
HIV, hepatitis B and C screen (per site SOP)	X										Sec. 5.1, 8.3.4 Appendix 2

All Panels											
Study Period	**Screening**	**Intervention**								**Poststudy[b]**	**Notes**
Scheduled Hour	**Screening[a]**	**Predose**	**0**	**1**	**4**	**24**	**48 to 144**	**168**	**192 to 504**	**672**	
UDS (per site SOP)	X	X									Sec 8.3.4, Appendix 2 Screening UDS is mandatory, any additional UDS/ are conducted per site SOP
Hematology, Urinalysis, Chemistry	X	X				X		X		X	Sec 8.3.4, Appendix 2 Collect after fasting for at least 8 hours. Sec. 8.3.4, 8.11.5, Appendix 2
AE/SAE review	X----------X										Sec. 8.4
Pharmacokinetics											
Blood for Plasma MK-8527 Assay		X----------X									Collect: Predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours postdose Sec 8.6.1, 8.11.5, Appendix 8
Blood for MK-8527 PBMC-TP Assay[e]		X			X----------X						Collect: Predose, 4, 12, 24, 96, 120, 144, 168, 192, 240, 336, 504, 672 hours postdose Sec 8.6.1, 8.11.5, Appendix 8

All Panels											
Study Period	**Screening**	**Intervention**								**Poststudy[b]**	**Notes**
Scheduled Hour	**Screening[a]**	**Predose**	**0**	**1**	**4**	**24**	**48 to 144**	**168**	**192 to 504**	**672**	
Pharmacodynamics											
Blood for HIV RNA[f]	X	X			X----------X[g]						Collect: Screening, predose, 4, 12, 24, 96, 120, 144, 168, 192, 240, 336, 504, 672 hours postdose Sec 8.7, 8.11.5, Appendix 8
Blood for HIV viral resistance	X	X			X----------X[g]						Collect: Screening, predose, 4, 12, 24, 96, 120, 144, 168, 192, 240, 336, 504, 672 hours postdose Sec 8.7, 8.11.5, Appendix 8
CD-4 Cell Count	X							X		X	Sec. 5.1, Appendix 2
Biomarkers											
Blood for Genetic Analysis[h]		X									Sec. 8.8.1, Appendix 8 Collect predose from enrolled participants only.

All Panels											
Study Period	**Screening**	**Intervention**								**Poststudy[b]**	**Notes**
Scheduled Hour	**Screening[a]**	**Predose**	**0**	**1**	**4**	**24**	**48 to 144**	**168**	**192 to 504**	**672**	

AE=adverse event; ART=antiretroviral therapy; BDS=blood drug screen; BP=blood pressure; BT=body temperature; CRU=clinical research unit; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IEC=Independent Ethics Committee; IRB=Institutional Review Board; NGS=next generation sequencing; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetics; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; TP=triphosphate; UDS=urine drug screen; VS=vital signs; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

[a] Participants will be screened within approximately 4 weeks prior to administration of study drug.

[b] 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. The 672-hour sample may be collected at the post-trial visit.

[c] Standard meals will be provided as follows on the full PK sampling Day 1: lunch at approximately 4-hours postdose, dinner at approximately 10-hours postdose, and snacks at approximately 7-hours and 13-hours postdose. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in terms of caloric content, composition and timing.

[d] Predose VS (HR and BP) will be collected in duplicate and Predose ECGs will be collected in triplicate within 3 hours prior to dosing MK-8527.

[e] For all panels, PBMC samples may be collected up to the post-trial visit regardless of initiation of ART.

[f] Analysis of viral resistance is done using NGS or Sanger technique depending on local lab.

[g] 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. HIV-1 RNA samples will not be collected if participants have initiated ART at 336, 504, 672 hours postdose.

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

2 INTRODUCTION

2.1 Study Rationale

The purpose of this study is to assess the activity of single doses of MK-8527 in ART-naïve HIV-1 infected participants for a planned once weekly dosing regimen. A previous single dose trial of MK-8527 in HIV infected participants (MK-8527-002) established robust efficacy of 3 mg and 10 mg doses. However, while a single 1 mg dose was highly efficacious in three of five participants, two participants did not achieve the efficacy target, possibly due to confounding factors. This study is being performed to more definitively establish the lowest efficacious dose of MK-8527 as monotherapy, therefore guiding dose selection for future studies.

2.2 Background

Refer to the IB for detailed background information on MK-8527.

2.2.1 Pharmaceutical and Therapeutic Background

As treatment for HIV-1 has improved, HIV-1 infection has become a chronic, manageable disease, provided patients remain adherent. There is clear medical need for antiretroviral agents that are highly effective, more tolerable, and more convenient to administer, both for treatment and prophylaxis, with improved tolerability compared to existing treatments. A highly potent 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 either a 3-agent regimen consisting of 2 NRTIs in combination with either an integrase strand transfer inhibitor, a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor or a two-drug regimen that includes one agent with a high resistance barrier [Panel on Antiretroviral Guidelines for Adults and Adolescents 2021]. Currently marketed NRTIs in common use include tenofovir disoproxil fumarate, tenofovir alafenamide fumarate, lamivudine, emtricitabine, and abacavir. While the currently approved NRTIs represent a cornerstone of modern ART, there are significant toxicities, including loss of bone mineral density, worsening renal function, dyslipidemia, and serious hypersensitivity reactions.

MK-8527 is a novel potent deoxyadenosine analog being developed for the treatment and prevention of HIV-1 infection. The mechanism of action of MK-8527 is similar to that of islatravir [Michailidis, E., et al 2014], leading to a high potency and a high barrier to resistance.

The parent drug MK-8527 is converted intracellularly to MK-8527 TP, the active moiety, which is a potent and specific inhibitor of HIV-1 RT activity in vitro with CCI [redacted] significantly more potent than marketed nucleosides. CCI [redacted]

Based on preclinical and clinical data, the pharmacokinetic properties of MK-8527 support extended duration dosing of once weekly or longer. CCI [redacted]

2.2.2 Preclinical and Clinical Studies

Preclinical studies to date

MK-8527 was well tolerated in repeat dose studies in rats and monkeys up to 6 and 9 months in duration respectively, and no adverse changes were noted up to the highest doses evaluated. CCI [redacted]

There was no MK-8527-related maternal or developmental toxicity in the oral EFD study in pregnant rats when dosed CCI [redacted]

Overall, nonclinical safety studies support continued clinical development of MK-8527.

Clinical trials to date

Three Phase 1 studies of MK-8527 have been completed. MK-8527-001 was a randomized, placebo controlled, alternating panel, double-blind trial evaluating the safety, tolerability, and PK of single oral doses of MK-8527 in healthy adult participants. CCI [redacted]

As detailed in the IB, PK of plasma MK-8527 in P001 was dose proportional over the entire single dose range. CCI [redacted]
There was no clinically meaningful effect of a high-fat meal on MK-8527 PK.

MK-8527-003 was a randomized, placebo-controlled, serial panel, multiple rising dose double-blinded study evaluating safety, tolerability and PK of multiple doses of MK-8527 in healthy participants. CCI [redacted]

MK-8527-002 was an open-label, single dose, multiple panel study to evaluate the safety, tolerability, antiretroviral activity, and PK of MK-8527 monotherapy in treatment naïve HIV 1 infected participants. Participants received a single oral dose of 1 mg, 3 mg, or 10 mg of MK-8527. All doses were generally well-tolerated, with no SAEs, ECIs, or discontinuations due to an AE. Only 2 participants reported a total of 3 AEs (pharyngitis, dizziness, insomnia), and the AEs were considered unrelated to study intervention. There were no abnormalities in laboratory values, vital signs, or ECGs. PK of both parent and MK-8527-TP was generally similar between HIV+-positive participants in P002 and in non-HIV-infected study participants in P001.

Single doses of 3 mg and 10 mg were shown to achieve target intracellular MK-8527-TP C168hr of 0.2 pmol/10^6 cells. Single 1 mg doses led to robust declines in viral load in 3 of the 5 participants but failed to achieve target reduction in 2 of the 5 participants, 1 of whom had no response. Across all 3 Phase 1 studies, MK-8527 was rapidly absorbed with a median T_{max} of 0.5 to 1 hour. Plasma concentrations decreased in a biphasic manner with an apparent terminal half-life of ~ 36 to 81 hours and exposures appeared to increase in an approximately dose-proportional manner. The active MK-8527-TP moiety reached intracellular C_{max} at a median T_{max} of 10 to 48 hours and the concentrations in PBMC declined with an apparent terminal half-life of ~ 94 to 291 hours across doses.

Refer to the IB for additional information on these Phase 1 studies.

CCI [redacted]

CCI [redacted]

CCI [redacted]

As noted in the IB, the profile of MK-8527 includes structural differences with islatravir and differences in intracellular anabolites and PK. CCI [redacted]

CCI

[redacted]

2.2.3 Ongoing Clinical Studies

This study, MK-8527-004, is a repeat PoC study being conducted to definitively establish the lowest efficacious dose of MK-8527 as monotherapy.

As of 29-JUN-2023, 8 participants in Panel A received 1-mg doses of MK-8527 and 6 participants in Panel B received 0.5-mg doses of MK-8527. In both panels, the true mean reduction in the plasma HIV-1 RNA from predose at 1 week after MK-8527 administration was greater than 1.0 log10 copies/mL.

Safety analysis is preliminary and ongoing. CCI

[redacted]

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Study Population: Treatment naïve HIV-1 infected participants

Primary Objective	**Primary Endpoint**
- To evaluate the antiretroviral activity of MK-8527 in HIV-1 infected participants. - Hypothesis: At a dose that is safe and generally well tolerated, MK-8527 has antiretroviral activity, as measured by change from predose 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 predose after MK-8527 is at least 1.0 log10 copies/mL.	- Plasma HIV-RNA (log10 copies/mL) reduction from predose
- To evaluate the safety and tolerability of MK-8527 in HIV-1 infected participants.	- Adverse events
Secondary Objectives	**Secondary Endpoints**
- To evaluate the intracellular PK of MK-8527-TP in PBMC after administration of single oral doses of MK-8527 to HIV-1 infected participants. - Estimation: The GM C168h MK-8527-TP will be estimated	- MK-8527-TP AUC0-168, AUC0-last, AUC0-inf, T_{max}, C_{max}, 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-last, AUC0-inf, T_{max}, C_{max}, Clast, and apparent terminal t1/2
- To evaluate the PK- pharmacodynamic association of intracellular MK-8527-TP with viral load reduction.	- PK (MK-8527-TP in PBMC) / pharmacodynamic (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 explore the relationship between genetic variation at response to the treatment administration and mechanisms of disease. Variation across the human genome may be analyzed for association with the clinical data collected in this study.	- Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, single-dose, multiple panel trial of MK-8527 in participants with HIV-1 infection. This study will be conducted in conformance with GCP.

A total of up to 4 panels (Panels A to D) will be enrolled. Panel A will consist of up to 8 participants, and Panels B, C and D will consist of up to 6 participants in each panel. In each panel, participants will receive a single oral dose of MK-8527 as outlined in [Table 1] and will undergo safety assessments and blood sampling for PK and VL analysis.

In Panel A, 8 participants were administered single 1.0 mg doses of MK-8527. In Panel B, 6 participants were administered single 0.5 mg doses of MK-8527. Panel C dose selection 0.25 mg MK-8527) follow the review of safety, tolerability, PK, and viral load data from Panels A and B through at least 10-days (240 hours) postdose.. Based on analysis of safety and antiviral efficacy in Panel C, a repeat of the 0.25 mg dose of MK-8527 may be evaluated in Panel D.

All doses of study drug intervention will be administered following at least an 8-hour fast.

Participants will be strongly encouraged to initiate an appropriate ART regimen within ~30 days of dosing MK-8527. The exact timing and regimen will be decided by the participant in consultation with the PI or their physician, but ART initiation should not occur before 10 days (240 hours) postdose in order to determine efficacy up to this time point.

All participants will be followed for safety monitoring for approximately 28 days after dosing of MK-8527. If participants start ART as planned, after the completion of the 240 hour procedures, the final blood draw for 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 VL changes and viral resistance for up to ~28 days postdose. 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. Blood for MK8527-TP PBMCs will be collected throughout the study regardless of ART initiation.

If the physician and/or Investigator believe that there is a strong indication to start ART before 10 days (240 hours) postdose this should be discussed with the Sponsor prior to starting. The initiation of follow-on ART is not a requirement for participation in the study and is ultimately a decision of the participant and the primary investigator or the participant's physician; the Sponsor will not source the ART.

Because this is a Phase 1 assessment of MK-8527 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

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

4.2 Scientific Rationale for Study Design

This protocol is designed with up to 4 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. This design provides the advantages of progressing through multiple dose levels expeditiously while allowing sufficient time intervals to assess durability of effect in each panel. 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 findings in the previous MK-8527 002 study, where 3 mg and 10 mg doses were highly efficacious, but 1 mg doses failed to achieve target reductions in viral load in 2 of the 5 participants. Preliminary results from Panels A and B of this study demonstrated antiviral efficacy at both the1.0 mg and 0.5 mg doses of MK-8527. This study will evaluate the efficacy and kinetics by which MK-8527 reduces HIV-1 RNA VL over time and establish the lowest efficacious monotherapy dose in suppressing viral replication.

The study is specifically designed with an emphasis on collecting single dose viral dynamic data. This is consistent with HIV study guidelines where the mean change in VL from baseline is a primary efficacy measure in dose finding monotherapy studies [European Medicines Agency 2016]. Although ARV 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. Therefore, only treatment naïve participants will be enrolled in this study in keeping with regulatory guidelines [European Medicines Agency 2016]. Since only a single dose will be administered and the half-life of the active MK-8527-TP anabolite is ~4-12 days, 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 (eg, M184V or M184I) will be excluded from the study.

Blood samples will be collected predose 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.

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 Protocols P001, P002, and P003. Standard laboratory assessments include measurement of total lymphocyte counts; CD4+ T cell counts will also be assessed.

4.2.1.2 Pharmacokinetic Endpoints

One objective of this study is to further characterize the plasma MK-8527 and intracellular MK-8527-TP PK profile in HIV-1 infected males and females. CCI

[redacted]

For the PK assessment, plasma concentrations of MK-8527 will be determined for the first 24 hours following single dose administration. Active MK-8527-TP in PBMCs will be determined up to 28 days postdose. These data will enable estimation of a predicted target associated with significant viral load reduction in a weekly dosing regimen.

4.2.1.3 Pharmacodynamic Endpoints

A pharmacodynamic endpoint of a >1.0 log10 suppression of HIV-1 RNA from baseline on Day 7, relative to predose baseline, will be used. A 70% posterior probability of achieving the target VL 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 to ensure that the dose(s) that can achieve the pharmacodynamic target is (are) taken into subsequent studies in the patient population. This target is consistent with historical NRTI compounds that utilized VL reduction targets of 0.5 log10, and more recent NRTIs that have demonstrated VL lowering greater than 1.0 log10. In addition, these thresholds, and limiting NRTI monotherapy studies to 7-10 days in duration, are consistent with regulatory guidance [Committee for Medicinal Products for Human Use (CHMP) 2016]. A decrease of at least 1.0 log10 after 7 to 10 days supports assessment in a larger trial, as part of 2-drug regimen for treatment, or as monotherapy for prophylaxis.

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 following a single dose of MK-8527. Periodic blood samples will be collected to assess MK 8527 associated changes in absolute VL over time and will be compared relative to predose

baseline. In addition, samples will be collected to detect the emergence of HIV resistance mutations.

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. Additionally, based on both PK and pharmacodynamic endpoints, the kinetics of VL reduction vs. dose and C168 will 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 ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

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

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

4.2.1.5 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

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

4.3 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 and active triphosphate anabolite are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

This study will not include a placebo arm. 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.

4.3.1 Starting Dose for This Study

CCI [redacted]

4.3.2 Maximum Dose Exposure for This Study

In P001, the plasma MK-8527 AUC0-168 at the 10 mg dose CCI [redacted]

4.3.3 Rationale for Dose Interval and Study Design

MK-8527is 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 Medicines Agency 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, findings in non-clinical safety studies, and clinical findings in healthy volunteers and treatment naïve HIV positive participants (P001, P002, and P003). Furthermore, it acts via a well-established mechanism (inhibition of HIV-1 viral replication), for which multiple marketed agents act similarly (tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, emtricitabine, and abacavir). Safety assessment toxicity studies, ancillary pharmacology studies, and findings in clinical studies of MK-8527 provide no contraindications to further clinical investigation.

This study (Protocol 004) proposes to study up to 4 Panels. In Panel A, 8 participants (all 8 active treatment) were administered a single 1 mg dose of MK-8527 on Day 1 in spaced time intervals according to Phase 1 clinical research standards for compounds not considered to be of high risk. In Panel B, 6 participants were administered a single 0.5 mg dose of MK-8527. Based on review of the safety, tolerability, and anti-viral efficacy data from Panel B, it is currently planned to evaluate a lower dose of MK-8527 in Panel C and/or D; a lower strength formulation (0.25 mg capsule) will be provided to support such an evaluation. After careful review of the safety, tolerability, and anti-viral efficacy data from Panel C, a Panel D may be enrolled. There will be frequent, careful assessments of 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 (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor

decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

A primary objective of this Phase 1 study is to identify the lowest dose of MK-8527 that is well tolerated, has acceptable PK, pharmacodynamic, and achieves target viral load reduction. Therefore, it is possible that Panel D may not be enrolled if this objective is achieved after review of data from Panels A through C. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(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.

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Other than HIV-1 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 (eg, Western Blot).
3. Has a screening plasma HIV-1 RNA ≥ 5,000 copies/mL within 30 days prior to the treatment phase of this study.
4. Has a screening plasma CD4+ T-cell count of >200/mm3.
5. Is ART-naïve, which is defined as not having received any marketed antiretroviral agent for the treatment of HIV-1 infection. Previous use of an antiretroviral agent for PrEP or as an investigational treatment is permitted if the most recent administration of the previous agent was at least 30 days prior to study drug administration.
6. Is willing to receive no other ART for the monitoring period of this study.
7. Has no evidence at screening for mutations conferring resistance to NRTIs (including but not limited to M184V, M184I) as previously defined.
8. 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

9. Is male or female, from 18 years to 60 years of age inclusive, at the time of providing informed consent

Male Participants

10. If male, agrees to the following during the intervention period and for at least 8 weeks after the last dose of study intervention:

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

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

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

- Not a WOCBP

  OR

- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 8 weeks after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
  - Has a negative highly sensitive pregnancy test (Urine or serum as required by local regulations) within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

- Abstains from breastfeeding during the study intervention period and for at least 56 days after study intervention MK-8527
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

12. Has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a history of clinically significant endocrine, GI, 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, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.
3. Has a history of cancer (malignancy).

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

4. Has an estimated eGFR ≤80 mL/min/1.73 m2], based on the 2021 CKD-EPI Creatinine Equation [Delgado, C., et al 2021].

   2021 CKD-EPI Creatinine (CKD-EPIcr_R) Equation:

   eGFR = 142 X min (Scr/k,1) α X max (Scr/k,1)-1.200 X 0.994age X 1.012 [if female]

   Where Scr is serum creatinine, k is 0.7 for females and 0.9 males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

   eGFR values indexed to BSA 1.73 will be de-indexed by dividing the value obtained from either formula by 1.73 and then multiplying by participant BSA.

   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 eGFR.

   Participants who have an eGFR or measured CrCl of up to 10% below of either 80 mL/min (for CrCl) or 80 mL/min/1.73m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

5. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.
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. Has had a major surgery and/or 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 intervention, throughout the study, until the poststudy visit. There may be certain medications that are permitted if the investigator and Sponsor agree (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 the following laboratory values at screening: direct bilirubin > 1.0 mg/dL, AST (SGOT) or ALT (SGPT) > 2 x upper limit of normal.
12. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females).

Other Exclusions

13. Is under the age of legal consent.
14. Is an excessive smoker (ie, more than 10 cigarettes/day) and is unwilling to restrict smoking to ≤10 cigarettes per day. Does not agree to follow the smoking restrictions as defined by the CRU.
15. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.
16. 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.
17. Has a positive urine drug screen (except for cannabis or benzodiazepines, for which there is a current prescription from a licensed medical provider) at screening and/or predose; rechecks are allowed.
18. There is any concern by the investigator regarding safe participation in the study, or for any other reason the participant is considered inappropriate for participation in the study by the investigator.
19. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

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

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

Meals and snack(s) will be provided by the investigator at time points indicated in the study flowchart. Participants will fast from all food and drinks, except water, between meals and snacks. The caloric content and composition of meals will be the same in each 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 study intervention administration. Water will be restricted 1 hour before and 1 hour after study intervention 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 before administration of the initial dose of study intervention, throughout the study and until the poststudy visit.

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

5.3.2.3 Tobacco Restrictions

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 (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study and until the poststudy visit.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Panel A	Experimental	MK-8527	Drug	Capsule	1 mg	1.0 mg	Oral	Single Dose	Test Product	IMP	Sponsor
Panel B	Experimental	MK-8527	Drug	Capsule	0.5 mg	0.5	Oral	Single Dose	Test Product	IMP	Sponsor
Panel C	Experimental	MK-8527	Drug	Capsule	0.25 mg	0.25 mg	Oral	Single Dose	Test Product	IMP	Sponsor
Panel D	Experimental	MK-8527	Drug	Capsule	0.25 mg	0.25 mg	Oral	Single Dose	Test Product	IMP	Sponosor

IMP=investigational medicinal product; NIMP/AxIMP=noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in [Table 2] will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment. A sample allocation schedule is shown in [Table 3].

Table 3 Sample Allocation Schedule

Panel	n	Dose of MK-8527[a]			
A	8	1.0 mg			
B	6		0.5 mg		
C	6			0.25 mg	
D	6				0.25 mg

a. The decision to proceed to the next panel will be made following review of safety and viral load data out to at least Day 11 (ie., 240 hours postdose) from the proceeding panel.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

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

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

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.

6.5 Concomitant Therapy

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

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

Paracetamol/acetaminophen (up to 2 grams/day) or non-prescription doses of nonsteroidal anti-inflammatory drugs may be used for minor ailments without prior consultation with the Sponsor.

All participants will be encouraged to initiate ART within one month after their dose of MK 8527 but not before 10 days (240 hours) postdose. 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 PoC trials, in which low-dose anti-retroviral monotherapy has been administered for as long as 28 days and with EMA guidance [European Medicines Agency 2016]. The exact timing of ART initiation and regimen will be decided by the participant in consultation with PI/his/her physician, If the physician and/or Investigator believe there is a strong indication to start ART before Day 11, this should be discussed with the Sponsor prior to starting, as with other concomitant medications (see above).

COVID-19 vaccine may be administered until 72 hours prior to the initial dose of study drug and/or starting from 48 hours after the last dose of study drug.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

Prior to each intervention, the clinical and laboratory safety data, and VL 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.

Dose selection for Panel B were made jointly by the investigator and the Sponsor. Dose escalation decision occurred after VL data from at least 5 evaluable participants were available from Panel A. The dose for Panels C and D were based on the review of all safety and VL data from participants in Panels A and B.

The decision to conduct Panel D will be made jointly by the investigator and the Sponsor, and will occur after VL data from Panel C is available.

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 240 hours. 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 evaluate that particular dose level;
- receive a lower dose of the study intervention;
- receive the same or lower dose as a divided dose;
- receive the same or lower dose with or without food.
- dosing may be stopped.

Participant discontinuation criteria are outlined in Section 7.

6.6.1 Stopping Rules

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

1. One participant reports a SAE 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.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Not Applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

7.2 Participant Withdrawal From the Study

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

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in Appendix 8.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides documented informed consent. At the time of intervention, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before first dose of study intervention.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Study Operations Manual and/or Dose Preparation Memo. Administration of study intervention will be witnessed by the investigator and/or study staff.

Refer to Section 5.3.1 regarding administration instructions regarding food and water intake.

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 single doses of MK-8527.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.11.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

Participants will report to the CRU the evening before the scheduled day of study intervention administration for each treatment period and remain in the unit until 24 hours postdose.

Participants who will be spending the night near the CRU can decrease domiciling at the CRU to 12 hours if there are no participant safety issues. Study staff will be with the participant overnight and the primary investigator/sub investigator will be on call.

At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

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

8.2 Efficacy/Immunogenicity Assessments

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

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Appendix 8.

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

8.3.1 Physical Examinations

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

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

8.3.2 Vital Signs

- BP and HR Measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- VS measurement should be taken before blood collection for laboratory tests.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

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

The predose (baseline) HR and BP will be a duplicate measurements, obtained at least 1 to 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). Postdose VS measurements will be single measurements.

Body Temperature

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

8.3.2.2 Orthostatic Vital Signs

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

8.3.3 Electrocardiograms

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

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

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

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

The correction formula to be used for QTc is Fridericia.

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

Predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before 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).

During each treatment period, 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.

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

If the QRS duration from any postdose ECG is 20% greater than the mean baseline QRS duration and is >120 msec (and change is not considered rate related or pacing induced) or there appears to be new onset intermittent bundle branch block, then the ECG will be immediately repeated twice within 5 minutes. The mean value of the QRS interval from the 3 ECGs will represent the value at that time point. If the mean QRS interval increase from baseline for any postdose time point is >20%, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QRS is within 20% of baseline. If a >20% prolongation of the QRS interval persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

If at any time the QRS duration is prolonged ≥200 msec (and change is not considered rate related or pacing induced), then the Sponsor should be notified. The ECGs should be

reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

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

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

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

8.3.4 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 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.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing urine or serum (as required by local regulations) prior to dosing.
  - Pregnancy testing urine or serum (as required by local regulations) should be conducted at the end of relevant systemic exposure.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3.6 Photograph of Rash

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

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

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

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator under any of the following circumstances:

- if the participant is receiving placebo run-in or other run-in treatment,
- if the event causes the participant to be excluded from the study,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention randomization through 28 days after cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

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

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

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

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

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

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

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) that occurs during the study are reportable to the Sponsor.

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

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

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

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

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

Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are not applicable to this study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

8.5 Treatment of Overdose

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

Sponsor does not recommend specific treatment for an overdose.

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable

drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-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 in the operations/laboratory manual.

8.8 Biomarkers

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

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

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

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

8.11.2 Treatment Period Visit

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

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

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

8.11.4 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.

8.11.5 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 pharmacodynamic collection (viral load) as outlined in [Table 5].

Table 5 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
0 to <1 h	5 min
1 to <2 h	10 min
2 to <24 h	15 min
24 to <48 h	1 h
48 to <96 h	2 h
96 to 168 h	4 h
>168 to <672 h	24 h
672 h	48 h

- Predose standard safety evaluations: VS and ECG up to 3 hours; laboratory safety tests and physical exam up to 24 hours
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam
  - <24 hours postdose may be obtained within 15 min of the theoretical sampling time
  - 24 hours to <48 hours postdose may be obtained within 1 hour of the theoretical sampling time
  - 48 hours to <96 hours postdose may be obtained within 2 hours of the theoretical sampling time
  - 96 hours to 168 hours postdose may be obtained within 4 hours of the theoretical sampling time
  - >168 hours to <672 hours postdose may be obtained within 24 hours of the theoretical sampling time
  - 672-hours postdose may be obtained within 48 hours of the theoretical sampling time

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

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

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

- Entire panel(s) may be omitted
- Adjustment of the dosing interval (eg, 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 processing and shipping details based on newly available data

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

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

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

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

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (Sections 9.2-9.9).

Statistical Methods

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 (predose, 168 hours postdose) 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. Using the posterior distributions for each dose level the posterior distribution of the true mean will be generated, and the posterior probability that the true mean in the log10 plasma HIV-1 RNA reduction from baseline of MK-8527 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.

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.

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 Medicine Department of the Sponsor.

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

9.3 Hypothesis/Estimation

Primary

At a dose that is safe and generally well tolerated, MK-8527 has antiretroviral activity, as measured by change from predose 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 predose between MK-8527 is at least 1.0 log10 copies/mL.

Secondary

The GM C168h MK-8527-TP will be estimated.

9.4 Analysis Endpoints

Primary Pharmacodynamic Endpoint

The primary pharmacodynamic variables in this study include plasma HIV -1 RNA reduction from predose at 4, 24, 96, 120, 144, 168, 240, 336, 504 and 672 hours postdose. The change in VL from predose to 168 hours is of primary interest.

Primary Safety Endpoint

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, T_{max}, C_{max}, C168hr, AUC0-last, AUC0-inf, apparent terminal t1/2 for MK-8527-TP in PBMC and AUC0-last, AUC0-inf, T_{max}, C_{max}, Clast, and apparent terminal t1/2 for plasma MK-8527 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 (APaT) – 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 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 pharmacodynamic, secondary PK and exploratory PK and pharmacodynamic analyses.

9.6 Statistical Methods

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 (predose, 168 hours postdose) 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.

Using the posterior distributions for each dose level the posterior distribution of the true mean will be generated, and the posterior probability that the true mean in the log10 plasma HIV-1 RNA reduction from baseline of MK-8527 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. 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.

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 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.

Secondary (Pharmacokinetic)

Values of MK-8527 plasma and intracellular MK-8527-TP in PBMC pharmacokinetic parameters AUC0-168, AUC0-last, AUC0-inf, C_{max}, and C168hr from participants in all panels will be analyzed. 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. Data will be examined for departures from the assumptions of the statistical model(s) as appropriate; eg, 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 (AUC0-168, AUC0-last, AUC0-inf, T_{max}, C_{max}, C168hr, 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-pharmacodynamic and dose-pharmacodynamic 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 (eg, C168hr, C336hr, C672hr, AUC0-168hr, AUC0-last, AUC0-inf, and C_{max}) and dose may 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 (eg, 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 the primary hypothesis will be assessed using posterior probabilities, 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, or 0.43, for this study, there is ~80% power to yield at least 70% posterior probability if the true mean log10 reduction is at least 1.25 or 1.3log10 with N=6 participants in a panel. The assumed SDs are from the CSR of MK-8527-002.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

This section is not applicable as there are no study governance committees.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Because the glucose assessment is part of the standard chemistry laboratory tests and requires fasting (approximately 8 hours), participants should fast prior to all instances of chemistry laboratory collection.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN or Urea	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)			

Laboratory Assessments	Parameters
Other Screening Tests	• FSH (as needed in WONCBP only) • Serum or urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) will be used at screening. The predose drug screen can be performed with a urine dipstick that may not include all of the above tests. • Virology (HIV including HIV-1 RNA and at least resistance mutations to NNRTIs, HBsAg, and hepatitis C virus antibody) • CD4+ T-cell count (absolute and %)
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; INR=International Normalized Ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; NNRTI=non-nucleoside reverse transcriptase inhibitors; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential	

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

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

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

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

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

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

Assessment of causality

- Did the Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
  - **Exposure**: Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course**: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause**: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge**: Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

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

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
- No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
- Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

Not Applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • IUSc,e • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [If hormonal contraception efficacy for a female participant is potentially decreased due to interaction(s) with study intervention(s), add the following footnote. If hormonal contraception is prohibited, or if hormonal contraception efficacy is NOT decreased due to interaction with study intervention(s), delete the following footnote:] [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

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

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

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

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

This appendix is not applicable to this study.

10.8 Appendix 8: Blood Volume Table

Blood collection volumes for sites in South Africa

All Panels	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests[b]	1	3	1	5	13	65
Serum β-hCG (if applicable)	1	1	1	3	5	15
FSH (if applicable)	1	0	0	1	5	5
HIV and Hepatitis Screen	1	0	0	1	5	5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
Blood for PBMC-TP Assay	0	12	1	13	16	208
Blood for MK-8527 Assay	0	11	0	11	3	33
Blood for HIV RNA, viral resistance[c]	1	12	1	14	13	182
Total Blood Volume per Participant[a]						
					Males	**501.5 mL**
					Females	**516.5 mL**
					Females Postmenopausal	**506.5 mL**

FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; PBMC=peripheral blood mononuclear cells; RNA=ribonucleic acid;

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

[b] Blood for CD4 cell count is included in the laboratory safety blood draw volume.

[c] Blood for HIV-1Viral RNA and Viral Resistance may be collected up to the post trial visit if participant do not start ART therapy. An additional 4 mL of blood may be drawn at 168 hours post dose if ultra deep sequencing is needed.

Blood collection volumes for sites in Romania

All Panels	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests[b]	1	3	1	5	10.5	52.5
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
Blood for PBMC-TP Assay	0	12	1	13	16	208
Blood for MK-8527 Assay	0	11	0	11	3	33
Blood for HIV RNA, viral resistance[c]	1	12	1	14	13	182
Blood for Hep C testing	1	0	0	1	5	5
Blood for CD4 cell Count	1	1	1	3	3	9
Total Blood Volume per Participant[a]						
					Males	**498 mL**
					Females	**498 mL**
					Females Postmenopausal	**498 mL**

FSH=follicle stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; PBMC=peripheral blood mononuclear cells; RNA=ribonucleic acid;

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

[b] Blood for Serum β-hCG (if applicable), FSH (if applicable), and HIV Screen are included in the laboratory safety blood draw volume.

[c] Blood for HIV-1Viral RNA and Viral Resistance may be collected up to the post trial visit if participant do not start ART therapy. An additional 4 mL of blood may be drawn at 168 hours post dose if ultra deep sequencing is needed.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

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

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

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

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

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

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

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

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

a. The participant may be excluded from the study;

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

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

OR

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

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

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

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-168hr	area under the curve for 0 to 168 hours
BDS	blood drug screen
BP	blood pressure
BT	body temperature
C168hr	concentration at 168 hours
CCU	Cardiac care unit
C_{max}	maximum plasma concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
Ctrough	trough concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU CTR	European Union Clinical Trial Regulations
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
GI	gastrointestinal
GM	Geometric mean
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVD	in vitro diagnostic
LAM	lactational amenorrhea method
MAD	multiple ascending dose study
NA	not applicable
NCS	not clinically significant
NHP	non-human primate
NOAEL	no observed adverse effect level
NRTI	Nucleoside reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cells
PCL	Protocol Clarification Letter
PK	pharmacokinetic
PN	protocol number
PP	per-protocol
PR	pulse rate
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcome
qd	once daily
QTc	QT interval corrected for heart rate
RNA	ribonucleic acid
RR	respiratory rate
RT	reverse transcriptase
SAD	single ascending dose
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SHIV	Simian-Human Immunodeficiency Virus
SGPT	Serum glutamic pyruvic transaminase
SLAB	Supplemental laboratory test(s)

Abbreviation	Expanded Term
SoA	schedule of activities
SOP	Standard Operating Procedures
t1/2	half life
tid	three times daily
T_{max}	time to maximum plasma concentration
TP	trisphosphate
UDS	urine drug screen
ULN	upper limit of normal
VL	Viral load
VS	vital signs
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

11 REFERENCES

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