Official Protocol Title:	A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8527 Once Monthly in Participants at Low-Risk for HIV-1 Infection
NCT Number:	NCT06045507
Document Date:	03-Oct-2024

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8527 Once Monthly in Participants at Low-Risk for HIV-1 Infection

Protocol Number: 007-02

Compound Number: MK-8527

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

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT06045507
EU CT	Not applicable
EudraCT	Not applicable
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	165532

Approval Date: 03 October 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	03-OCT-2024	The protocol is being amended to unblind all Sponsor personnel except for a blinded medical monitoring team after the last expected Follow-up Week 4 visit, to enable earlier program strategic decision-making by the Sponsor.
Amendment 1	13-FEB-2024	The protocol is being amended to update contraception requirements for participants of childbearing potential and to remove contraception requirements for male participants with partners of childbearing potential.
Original Protocol	28-JUL-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

The protocol is being amended to unblind all Sponsor personnel except for a blinded medical monitoring team after the last expected Follow-up Week 4 visit, to enable earlier program strategic decision-making by the Sponsor.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 6.3.3 Blinding	Revised text to indicate that all Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit, to enable earlier program strategic decision-making by the Sponsor.	The protocol currently permits select Sponsor personnel to be unblinded during the study. This amendment is being made due to a change in strategy. All Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit, to enable earlier program strategic decision making by the Sponsor. All participants and study-site personnel directly associated with study conduct will continue to remain blinded to study intervention assignment through Follow-up Week 8.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.2 Schema	Added text to footnote “b” to indicate the changes in blinding strategy for the Sponsor.	See rationale for Section 6.3.3
Section 1.3.1 Schedule of Activities (Main)	Added footnote “f” to indicate the changes in blinding strategy for the Sponsor.	See rationale for Section 6.3.3
Section 4.1 Overall Design	Updated to align with the changes in blinding strategy for the Sponsor.	See rationale for Section 6.3.3
Section 9.1 Responsibility for Analyses/In-house Blinding	Changed the word “unblinded” to “locked” in the third sentence of the second paragraph.	For alignment of timing with the changes in blinding strategy for the Sponsor.
Section 9.1 Responsibility for Analyses/In-house Blinding	Revised text to indicate that in addition to the unblinded Sponsor team that has been unblinded since the trial started, all other Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit.	See rationale for Section 6.3.3
Throughout	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8527 Once Monthly in Participants at Low-Risk for HIV-1 Infection

Short Title: Safety and Pharmacokinetic Study of Oral MK-8527 QM in Participants at Low-Risk for HIV-1 Infection

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There are no hypotheses to be tested in this study.

The following objectives will be evaluated in adults at low-risk of human immunodeficiency virus type 1 (HIV-1) infection.

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of MK-8527 once monthly (3 mg, 6 mg, and 12 mg) during treatment and through the last follow-up visit.	Adverse events Adverse events leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
To characterize the plasma pharmacokinetic profile of MK-8527 once monthly (3 mg, 6 mg, and 12 mg).	MK-8527 $AUC_{0\text{-last}}$ and C_{max}

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	HIV infection
Population	Adults at low-risk for HIV-1 infection
Study Type	Interventional
Intervention Model	<<Intervention Model>> This is a multi site study.
Type of Control	Placebo

Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Sponsor Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 58 weeks 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 350 participants will be randomized in a 2:2:2:1 ratio to 1 of 4 intervention groups: Group 1: MK-8527 (3 mg), N=~100; Group 2: MK-8527 (6 mg), N=~100; Group 3: MK-8527 (12 mg), N=~100; Group 4: placebo, N=~50.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Group 1	MK-8527	3 mg	3 mg QM	Oral	Day 1 to Week 20	Test Product
Group 1	Placebo	0 mg	0 mg QM	Oral	Day 1 to Week 20	Placebo
Group 2	MK-8527	3 mg	6 mg QM	Oral	Day 1 to Week 20	Test Product
Group 2	Placebo	0 mg	0 mg QM	Oral	Day 1 to Week 20	Placebo
Group 3	MK-8527	3 mg	12 mg QM	Oral	Day 1 to Week 20	Test Product
Group 4	Placebo	0 mg	0 mg QM	Oral	Day 1 to Week 20	Placebo

QM=once monthly.

Total Number of Intervention Groups/Arms	4 intervention groups (3 active, 1 placebo)
Duration of Participation	Participants will be in the study for approximately 34 weeks from the time the participant provides documented informed consent (for the main study) through the final contact. After a screening phase of up to 45 days (6 weeks), each participant will receive 6 once monthly doses of assigned intervention with the final dose administered at Week 20. All participants will complete an 8-week blinded follow-up period after the last dose.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes (Internal)
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

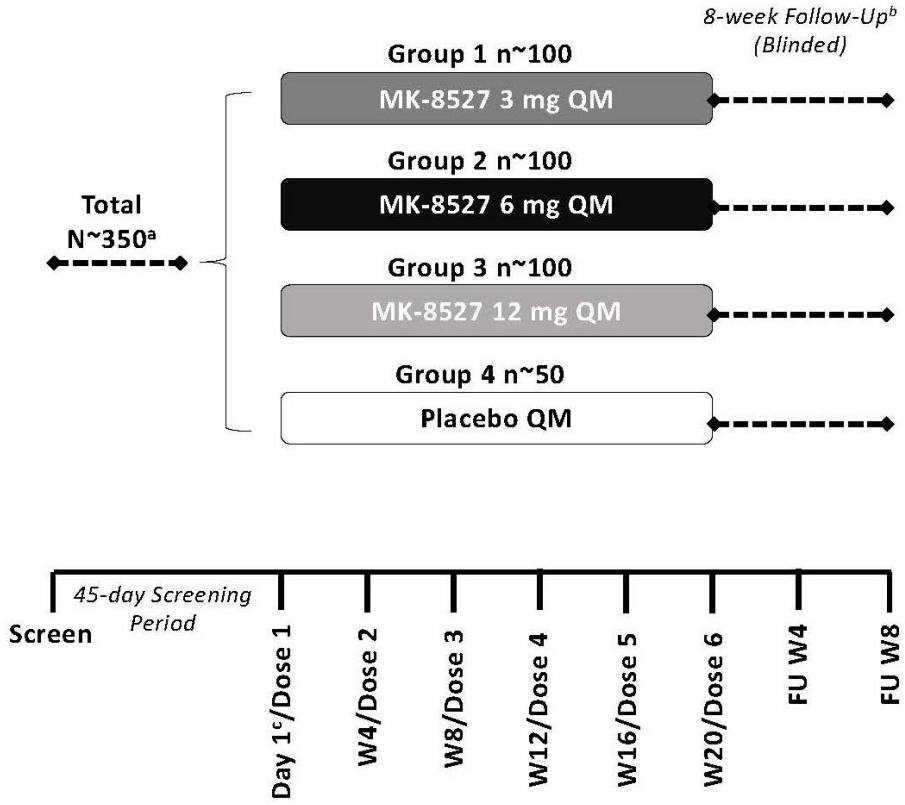
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



FU W=follow-up week; N=total number of participants in the study; n=number of participants in each treatment group; PBMC=peripheral blood mononuclear cells; QM=once monthly.

[a] A subset of ~20 participants per study intervention group will be included in the PBMC Subset; these participants will have additional in-clinic visits as specified in the SoA (Section 1.3.1).

[b] Participants who discontinue study intervention early will be asked to complete the blinded follow-up visits. As per amendment 02, all Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit.

[c] Randomization to study intervention will occur at Day 1 and will be stratified by sex (female, male) and region (Africa, non-Africa).

1.3 Schedule of Activities

1.3.1 Schedule of Activities (Main)

Study Period	**Screening**	**Study Intervention (Blinded)**										**Follow-up (Blinded)[f]**				**Notes** **All Day 1 procedures are predose unless otherwise noted.** **Day 2 PK samples must be collected 24 hours (±6 hours) after the Day 1 dose.** **Follow-up Day 1 PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20/ EOT[b]	Follow-up Day 1[c]	Follow-up Week 4[c] (Week 24)	Follow-up Week 6[a,c] (Week 26)	Follow-up Week 8[c] (Week 28)	
Window	≤45 days	N/A	N/A	±2 days				±7 days				N/A	±7 days	±2 days	±7 days	
Administrative Procedures																
Informed consent	X															Informed consent marks the start of the screening window.
Informed consent for FBR	X															
Inclusion/exclusion criteria	X	X														Participants may be rescreened 1 time; see Section 8.11.1.2.
Participant identification card	X	X														Add randomization number on Day 1.
Register study visit in IRT	X	X					X	X	X	X	X					
Randomization		X														
Dispense study intervention using IRT and administer study intervention		X					X	X	X	X	X					Directly observed dosing. Add randomization number and visit number to the bottles at time of dispensing.
Offer condoms and lubricant		X					X	X	X	X	X		X			For sexually active participants. Document in participant chart.
Safety Procedures																
Medical history	X	X														

Study Period	**Screening**	**Study Intervention (Blinded)**										**Follow-up (Blinded)[f]**				**Notes** **All Day 1 procedures are predose unless otherwise noted.** **Day 2 PK samples must be collected 24 hours (±6 hours) after the Day 1 dose.** **Follow-up Day 1 PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20/ EOT[b]	Follow-up Day 1[c]	Follow-up Week 4[c] (Week 24)	Follow-up Week 6[a,c] (Week 26)	Follow-up Week 8[c] (Week 28)	
Window	≤45 days	N/A	N/A	±2 days				±7 days				N/A	±7 days	±2 days	±7 days	
HIV infection risk evaluation	X	X					X	X	X	X	X		X		X	Document in participant chart. Assess as per Inclusion Criterion #2 at Screening and Day 1 (prior to dose). After Day 1, assess changes in risk status and PrEP eligibility using Appendix 8.
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contraceptive use confirmation (POCBP only)	X	X					X	X	X	X	X		X		X	Document in participant chart.
Complete physical exam	X															
Symptom-directed physical exam		X	X				X	X	X	X	X		X		X	
Vital signs	X	X	X				X	X	X	X	X		X		X	Includes body temperature, pulse, respiratory rate, and systolic and diastolic blood pressure.
Height	X															
Weight	X	X					X	X	X	X	X		X		X	
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Assess before and after dose on Day 1.
AE assessment phone call (participants not in PBMC Subset)					X											Participants not in the PBMC Subset will have this AE assessment phone call (no in-clinic visit is required).

Study Period	Screening	Study Intervention (Blinded)										Follow-up (Blinded)[f]				**Notes** **All Day 1 procedures are predose unless otherwise noted.** **Day 2 PK samples must be collected 24 hours (±6 hours) after the Day 1 dose.** **Follow-up Day 1 PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20/ EOT[b]	Follow-up Day 1[c]	Follow-up Week 4[c] (Week 24)	Follow-up Week 6[a,c] (Week 26)	Follow-up Week 8[c] (Week 28)	
Window	≤45 days	N/A	N/A	±2 days				±7 days				N/A	±7 days	±2 days	±7 days	
12-lead ECG	X										X					Perform postdose at Week 20. Perform at EOT if participant discontinues study intervention early.
Laboratory Evaluations/Procedures																
HIV-1 and HIV-2 screen	X	X					X	X	X	X	X		X		X	Participants with a positive HIV-1/2 screen test will require additional testing. See Section 8.3.4.1.
HBV and HCV testing	X															
Syphilis serologic testing	X															
Urine GC/CT & trichomoniasis testing (females only)	X															
Urine GC/CT testing (males only)	X															
PT/INR	X															
Serum pregnancy test (β-hCG) (POCBP only)	X															Performed by central laboratory per local regulations. If results are inconclusive, additional testing and/or verification of medical history will be required to confirm eligibility.

Study Period	Screening	Study Intervention (Blinded)										Follow-up (Blinded)[f]				**Notes** **All Day 1 procedures are predose unless otherwise noted.** **Day 2 PK samples must be collected 24 hours (±6 hours) after the Day 1 dose.** **Follow-up Day 1 PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20/ EOT[b]	Follow-up Day 1[c]	Follow-up Week 4[c] (Week 24)	Follow-up Week 6[a,c] (Week 26)	Follow-up Week 8[c] (Week 28)	
Window	≤45 days	N/A	N/A	±2 days				±7 days				N/A	±7 days	±2 days	±7 days	
Urine pregnancy test (POCBP only)		X					X	X	X	X	X		X		X	Mandatory and performed locally as per local regulations and prior to administering/dispensing study intervention. Do NOT dispense study intervention if urine pregnancy test is positive. Confirm with serum test if urine test is positive.
Hematology[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TBNK Panel/CD4+ T-cell count[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X		X	X	X	X	X	X	X	X		X	X	X	
Creatinine clearance calculation (CG)	X	X		X	X	X	X	X	X	X	X		X	X	X	
Cystatin-C	X	X		X	X	X	X	X	X	X	X		X	X	X	
Pharmacokinetics (All Participants)																
Plasma PK sample collection(s)		X	X								X	X				Some visits require more than 1 sample collection. See Section 8.6 for additional details.
Pharmacokinetics (Participants NOT in the PBMC Subset)																
Venous microsampling (eg, Mitra®/VAMS)							X	X	X	X	X					See Section 8.6 for additional details.

Study Period	Screening	Study Intervention (Blinded)										Follow-up (Blinded)[f]				**Notes** **All Day 1 procedures are predose unless otherwise noted.** **Day 2 PK samples must be collected 24 hours (±6 hours) after the Day 1 dose.** **Follow-up Day 1 PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20/ EOT[b]	Follow-up Day 1[c]	Follow-up Week 4[c] (Week 24)	Follow-up Week 6[a,c] (Week 26)	Follow-up Week 8[c] (Week 28)	
Window	≤45 days	N/A	N/A	±2 days				±7 days				N/A	±7 days	±2 days	±7 days	
Pharmacokinetics (PBMC Subset)																Participation in the PBMC Subset will be optional. Participants are from preselected sites. Refer to operation/laboratory manual for sample handling requirements.
Informed consent for PBMC Subset sample collection	X															
PBMC collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Some visits require more than 1 sample collection. See Section 8.6 for additional details.
Venous microsampling (eg, Mitra®/VAMS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.6 for additional details

Study Period	Screening	Study Intervention (Blinded)										Follow-up (Blinded)[f]				**Notes** **All Day 1 procedures are predose unless otherwise noted.** **Day 2 PK samples must be collected 24 hours (±6 hours) after the Day 1 dose.** **Follow-up Day 1 PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20/ EOT[b]	Follow-up Day 1[c]	Follow-up Week 4[c] (Week 24)	Follow-up Week 6[a,c] (Week 26)	Follow-up Week 8[c] (Week 28)	
Window	≤45 days	N/A	N/A	±2 days				±7 days				N/A	±7 days	±2 days	±7 days	
Biomarkers																
Blood for genetic analysis[e]		X														Collect predose from enrolled participants only

AE=adverse event; β-hCG=beta human chorionic gonadotropin; CG=Cockcroft-Gault; CT=chlamydia trachomatis; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=End of Treatment; FBR=future biomedical research; GC=Neisseria gonorrhoeae; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; INR=International Normalized Ratio; IRB=Institutional Review Board; IRT=Interactive Response Technology; N/A=not applicable; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; POCBP=participants of childbearing potential; PrEP=pre-exposure prophylaxis; PT=prothrombin time; TBNK=T- and B-lymphocyte natural killer cell; VAMS=volumetric absorptive microsampling.

a. Week 1, 2, and 3, and Follow-up Week 6 are in-clinic visits only for participants in the PBMC Subset. At Week 2, participants not in the PBMC Subset will have an AE assessment phone call only (no in-clinic visit is required).
b. If Visit 11 is performed as an EOT visit prior to Week 20, all procedures listed should be performed but with the following procedure modifications: 1) no study intervention should be dispensed via the IRT or administered to the participant, 2) only 1 plasma PK sample should be collected at any time during the visit, and if in the PBMC Subset: only 1 PBMC sample and 1 VAMS venous sample should be collected at any time during the visit.
c. All participants will attend visits at Follow-up Day 1, Follow-up Week 4 and Follow-up Week 8; the PBMC Subset will also have a visit at Follow-up Week 6. Follow-up visits represent different study weeks for a participant that completes the final Week 20 dose versus a participant that discontinues study intervention prior to Week 20. See Section 8.11.6 for additional details.
d. Participants with confirmed decreases in total lymphocyte counts or CD4+ T-cell counts as outlined in Section 7.1, will be followed in the study until they no longer meet the criteria as outlined in Section 8.11.3.1.
e. 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.
f. As per amendment 02, all Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit.

1.3.2 Schedule of Activities (HIV Infection Confirmation or Early Withdrawal From Study)

Study Period	**HIV Infection Confirmation[a]**	**Early Withdrawal From Study[b]**	**Notes**
Visit Number	**Unscheduled**		
Scheduled Day/Week	**HIV Infection Confirmation**	**Early Withdrawal From Study**	
Visit Window	Within 14 days of HIV-positive test	NA	
Administrative Procedures			
Offer condoms and lubricant	X		For sexually active participants. Document in participant chart.
Register study visit in IRT		X	
Safety Procedures			
HIV infection risk evaluation	X	X	Document in participant chart. Assess any changes in risk status and PrEP eligibility (Appendix 8).
Concomitant medication review	X	X	
Contraceptive use confirmation (POCBP only)	X	X	Document in participant chart.
Symptom-directed physical exam		X	
Vital signs		X	Includes body temperature, pulse, respiratory rate, and systolic and diastolic blood pressure
Weight		X	
AE assessment	X	X	
12-lead ECG		X	Only perform at the Early Withdrawal visit if the participant discontinues prior to the Week 20 ECG collection.
Laboratory Evaluations/Procedures			
HIV-1 and HIV-2 screen		X	
HIV-1 RNA PCR	X		
HIV-1 drug resistance testing	X		
Urine pregnancy test (POCBP only)		X	Conduct per local regulations. Positive results to be confirmed with serum pregnancy test.
Hematology	X	X	
TBNK Panel/CD4+ T-cell count	X	X	
Chemistry		X	
Creatinine clearance calculation (CG)		X	
Cystatin-C		X	
Pharmacokinetics (All participants)			
Plasma PK sample collection	X	X	Not required if participant is beyond Follow-up Day 1.

Study Period	**HIV Infection Confirmation[a]**	**Early Withdrawal From Study[b]**	**Notes**
Visit Number	**Unscheduled**		
Scheduled Day/Week	**HIV Infection Confirmation**	**Early Withdrawal From Study**	
Visit Window	Within 14 days of HIV-positive test	NA	
Pharmacokinetics (PBMC Subset)			Participants are from preselected sites. Refer to laboratory/study operation manual for special collection and processing requirements.
PBMC collection	X	X	
Venous microsampling (eg, Mitra®/VAMS)	X	X	

AE=adverse event; CG=Cockcroft-Gault; ECG=electrocardiogram; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; PBMC=peripheral blood mononuclear cells; PCR=polymerase chain reaction; PK=pharmacokinetic; POCBP=participants of childbearing potential; PrEP=pre-exposure prophylaxis; RNA=ribonucleic acid; TBNK=T- and B-lymphocyte natural killer cell; VAMS=volumetric absorptive microsampling.

a. For any participant who has a positive HIV-1 or HIV-2 screen test, this visit should be conducted within 14 days of the positive result per Section 8.11.4.
b. If a participant receives the final Week 20 dose of study intervention and then withdraws from the study, an "Early Withdrawal from Study" visit should be performed as the final study visit. See Section 8.11.5 for additional details.

2 INTRODUCTION

MK-8527 is a novel deoxyadenosine analog with potent antiviral activity being developed for the prevention of HIV-1 infection.

2.1 Study Rationale

HIV-1 infection remains a worldwide epidemic with an estimated 38.4 million individuals infected globally at the end of 2021 [World Health Organization 2022]. Additional strategies to prevent HIV acquisition could help reduce the global burden. One proven biomedical intervention for the prevention of HIV-1 infection is PrEP. Although FTC/TDF and FTC/TAF have been approved in some countries for PrEP, approximately 1.5 million new HIV-1 infections occurred worldwide in 2021 [World Health Organization 2022]. Approximately 26 million individuals living with HIV at the end of 2021 were in the WHO African Region [World Health Organization 2022]. In this region, South Africa has a population of 32 million aged 15 to 49 years, of which ~18% were living with HIV in 2022 [Joint United Nations Programme on HIV/AIDS 2023]. HIV is a chronic infection requiring life-long treatment and is associated with risks for multiple complications. The ongoing epidemic, fueled by more than 1 million new cases annually, results in a growing collective care burden. The efficacy of FTC/TDF for PrEP is strongly correlated with adherence to daily therapy [O Murchu, E., et al 2022]. However, adherence to daily therapy is suboptimal in many people at risk of HIV-1 infection [Hojilla, J. C., et al 2021].

MK-8527 is characterized by high potency and a long half-life. Because of the long intracellular half-life (~94 to 291 hours across doses in Phase 1 studies) of the active form of MK-8527 (MK-8527-TP), a QM dosing regimen is being investigated. A QM dosing schedule is anticipated to facilitate adherence, improve discretion, and be highly effective in preventing HIV-1 acquisition.

This Phase 2a study will evaluate the safety, tolerability, and PK of oral MK-8527 QM compared with placebo in adults at low-risk of HIV-1 infection. Results from this study, along with data from completed Phase 1 studies, will be used to select a QM dose of oral MK-8527 to be evaluated as PrEP in efficacy studies.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

MK-8527 is a novel deoxyadenosine analog with antiretroviral activity that is being developed for the prevention of HIV-1 infection. The parent drug MK-8527 is converted intracellularly to its active triphosphate form, MK-8527-TP, which is a specific inhibitor of HIV-1 RT. In contrast to other approved NRTIs (AZT, TDF, FTC, and 3TC) with IC_{50} values >2.5 nM, MK-8527 is more potent with an in vitro IC_{50} of 0.21 nM. MK-8527 was comparable to TFV, ZDV, ABC, FTC, and 3TC in antiviral activity against isolates from 11 commonly occurring HIV subtypes (based on the Phenosense® assay in HEK293 cells).

However, MK-8527 had an 11-fold decrease in potency against HIV subtypes with the M184V/I mutation.

CCI [redacted]

The plasma half-life of MK-8527 was approximately 36 to 62 hours after single doses of 10, 25, 50, 100, 150, and 200 mg (MK-8527 P001) and approximately 44 to 81 hours after multiple doses of 10, 20, and 40 mg (MK-8527 P003). The half-life of MK-8527-TP in PBMCs was approximately 94 to 266 hours in MK-8527 P001 and approximately 216 to 291 hours in MK-8527 P003.

The antiretroviral activity of MK-8527 was evaluated in a Phase 1 open-label proof-of concept study in treatment-naïve participants with HIV-1 (MK-8527 P002). Antiretroviral activity following a single dose of MK-8527 (1 mg, 3 mg, or 10 mg) was assessed based on a mean HIV-1 viral load reduction of ≥1.0 log10 copies/mL at 7 days postdose. Participants receiving either a 3 mg or 10 mg dose of MK-8527 achieved a mean viral load reduction of 1.63 log10 copies/mL and 1.36 log10 copies/mL, respectively, at 7 days postdose. Additionally, 11/12 participants receiving either 3 mg or 10 mg of MK-8527 achieved a viral load reduction of >1.0 log10 copies/mL at 7 days postdose. A single 1 mg dose of MK-8527 led to a mean viral load reduction of 0.92 log10 copies/mL. Of the 5 participants who received the 1 mg dose, 2 did not achieve the >1.0 log10 copies/mL due to unknown reasons; the lack of response in these 2 participants was not due to appearance of mutant strains. Because of the inconsistent results at the 1 mg dose, a second proof-of-concept study (P004) was conducted. In MK-8527 P004 in treatment-naïve participants with HIV-1, single doses of MK-8527 (1 mg or 0.5 mg) achieved a mean HIV-1 viral load reduction of ≥1.0 log10 copies/mL at 7 days postdose (see additional details in Section 4.3).

Overall, the PK properties of MK-8527, along with nonclinical and clinical data for MK-8527, support QM dosing. CCI [redacted] MK-8527 has a low potential to be a perpetrator of drug-drug interactions mediated by these transporters.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. For this study, MK-8527 is being developed for

the prevention of HIV-1 infection; direct individual benefit to participants is minimal as participants in this study are neither HIV-1-infected nor at high risk of infection.

There remains significant unmet medical need for highly effective and well tolerated ART for PrEP that does not require daily dosing. High potency against wild-type HIV-1 and a long half-life make MK-8527 a suitable candidate for further development as a long-acting PrEP agent. Comprehensive nonclinical safety evaluation of MK-8527, including hematological and developmental toxicity studies, have not revealed toxicities of concern at the dose levels being evaluated in this study. MK-8527 demonstrated antiretroviral activity in the Phase 1 study MK-8527 P002, with single 3 mg and 10 mg doses achieving the target reduction in viral load of ≥1.0 log10 copies/mL at 7 days postdose in treatment-naïve HIV-1 positive participants. MK-8527 has also demonstrated antiretroviral activity in an ongoing Phase 1 study MK-8527 P004, with single 1 mg and 0.5 mg doses achieving the target reduction in viral load of ≥1.0 log10 copies/mL at 7 days postdose in treatment-naïve HIV-1 positive participants.

MK-8527 has been evaluated in 3 completed Phase 1 studies (P001, P002, P003) in 56 healthy adult participants and 17 treatment-naïve adult participants with HIV-1. An additional 14 treatment-naïve adult participants have received MK-8527 in the ongoing Phase 1 study MK-8527 P004. Single doses of up to 200 mg and multiple doses up to 40 mg of MK-8527 have been generally well tolerated in the 3 completed studies. All drug-related AEs were mild to moderate in severity and resolved by the end of each study. No SAEs, deaths, or events of clinical interest were observed. Three participants discontinued study intervention due to an AE, none of which were considered related to MK-8527. No dose-related changes in ECGs, vital signs, and laboratory test values were observed. The most frequently reported AEs were headache and nasopharyngitis.

MK-8527 is in the same antiretroviral class as ISL (MK-8591), an NRTI currently in development for the treatment of HIV-1 infection. Exposure/dose-dependent decreases in total lymphocyte and lymphocyte subset counts were observed in clinical studies with ISL. The risk of lymphocyte decreases for MK-8527 at the proposed doses is considered low based on available nonclinical and clinical data. In 3 completed Phase 1 studies, no AEs associated with lymphocyte reductions were observed, and mean lymphocyte counts were unchanged in both the single- and multiple-ascending dose studies. In the present study, hematology (including lymphocyte subsets) will be closely monitored; participants who meet predefined discontinuation criteria for total lymphocyte and CD4+ T-cell counts will be discontinued from study intervention.

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

There are no hypotheses to be tested in this study.

The following objectives will be evaluated in adults at low-risk of human immunodeficiency virus type 1 (HIV-1) infection.

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of MK-8527 once monthly (3 mg, 6 mg, and 12 mg) during treatment and through the last follow-up visit.	Adverse events Adverse events leading to discontinuation of study intervention
Secondary Objective	**Secondary Endpoint**
To characterize the plasma pharmacokinetic profile of MK-8527 once monthly (3 mg, 6 mg, and 12 mg).	MK-8527 $AUC_{0\text{-last}}$ and C_{max}
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To explore a relationship between intracellular MK-8527-MP, MK-8527-DP, and MK-8527-TP levels	PBMC MK-8527-MP, MK-8527-DP, and MK-8527-TP: $AUC_{0\text{-last}}$, C_{max}, C_{trough}, concentrations at common time points
To characterize the intracellular pharmacokinetic profile of MK-8527-TP in peripheral blood mononuclear cells up to 8 weeks after the last dose of MK-8527 once monthly (3 mg, 6 mg, and 12 mg).	MK-8527-TP $AUC_{0\text{-last}}$, C_{trough}, C_{max}, and $t_{1/2}$
To explore the relationship between genetic variation and response to study intervention, and mechanisms of disease. Variation across the human genome may be analyzed for association with the pharmacokinetic and safety 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 a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of oral MK-8527 administered QM in adults who are at low-risk of HIV-1 infection.

Approximately 350 participants will be randomized in a 2:2:2:1 ratio to 1 of 4 intervention groups: Group 1: MK-8527 (3 mg); Group 2: MK-8527 (6 mg); Group 3: MK-8527 (12 mg); and Group 4: Placebo. The screening window is 45 days and participants are allowed to rescreen 1 time (Section 8.11.1.2). The study population composition targets are: ≥30% women, ≥30% men, ≥80% aged ≤35 years, and ≥30% enrolled in Africa. Randomization will be stratified by sex (female, male) and region (Africa, non-Africa).

Participants will receive a total of 6 oral doses of the assigned blinded study intervention, 1 dose every 4 weeks, starting on Day 1. The final dose will be administered at the Week 20 visit. After the last dose, all participants will complete an 8-week blinded follow-up period.

The primary safety assessment will include all accumulated safety data during the intervention and follow-up period. AEs leading to discontinuation from study intervention will be assessed until Week 20 (last dose received). The Sponsor will perform an ongoing comprehensive review of safety parameters to assess for overall trends and outliers in reported AEs and event toxicities per standard monitoring procedures.

All participants will be evaluated for plasma MK-8527 PK drug levels, and a subset (approximately N=20 participants per intervention group) will be evaluated for MK-8527-TP in PBMC (PBMC Subset).

All participants and the investigators/clinical site personnel directly associated with study conduct will remain blinded to study intervention assignment through the 8-week follow-up period. The siDMC (internal) will be responsible for an interim safety review once 50% of the planned enrollment has reached Week 12 or discontinued from study intervention. Additional meetings of the siDMC may be triggered based on criteria outlined in the SAP/siDMC charter. An unblinded Sponsor team will review PK and safety data on an ongoing basis for the duration of the study. As per amendment 02, all Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit, to enable earlier program strategic decision-making by the Sponsor.

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

4.2 Scientific Rationale for Study Design

The main objectives of this study are to characterize the safety, tolerability, and PK of MK-8527 in a larger and more diverse population than studied to date. The study will enroll participants who are not infected with HIV-1 and are at low-risk of HIV-1 infection. According to CDC and WHO guidelines [Centers for Disease Control and Prevention 2018]

[World Health Organization 2015], persons who are at substantial risk of HIV-1 infection should be referred for local HIV prevention services that may include PrEP, for which there are approved products (FTC/TDF, FTC/TAF, or cabotegravir IM).

Population PK predictions based on clinical data to date indicate that MK-8527 6 mg to 8 mg QM will achieve threshold levels against wild-type virus for HIV-1 prevention that would last at least 4 weeks. Participants will be followed for 8 weeks after the last dose of MK-8527 to allow for full characterization of the MK-8527-TP PK profile.

The number of participants (N=~350), the inclusion of a placebo group, and the 6 QM doses allow for characterization of the safety profile of MK-8527 before the initiation of Phase 3 prevention efficacy studies. To ensure a study population that is representative of individuals most at risk for HIV-1 infection and corresponding to the demographics for the target population of the Phase 3 efficacy studies, the study population will comprise ≥30% women, ≥30% men, ≥80% of participants aged ≤35 years, and ≥30% enrolled in Africa.

4.2.1 Rationale for Endpoints

Efficacy is not being evaluated in this study.

4.2.1.1 Safety Endpoints

The primary safety endpoints are the number of participants experiencing AEs and the number of participants discontinuing study intervention due to AEs. Safety evaluations will include physical examinations (including vital signs) and laboratory tests performed per the SoA (Section 1.3). AEs will be evaluated at each visit and assessed according to the guidelines in Section 8.4. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

Dose-dependent decreases in total lymphocyte and lymphocyte subset counts were observed in clinical studies with ISL, another investigational NRTI agent. The risk of lymphocyte decreases for MK-8527 at the proposed doses is considered low based on available nonclinical and clinical data. To further assess the risk, hematology with lymphocyte subset counts will be monitored, in conjunction with MK-8527 in plasma and MK-8527-TP in PBMC measurements to allow correlation with any dose-related effects.

In this study, criteria for discontinuation of study intervention for confirmed on-treatment decreases of total lymphocyte count <1000 cells/mm^3 or CD4+ T-cell count <500 cells/mm^3 are based on literature that identifies an increased frequency of infections or increased risk of infections when cell counts drop below these levels, whether caused by disease (eg, HIV infection, systemic lupus erythematosus, rheumatoid arthritis) or by disease-modifying drugs [Giovannoni, G., et al 2018] [Spiezia, A. L., et al 2022] [Merayo-Chalico, J., et al 2013] [Subesinghe, S., et al 2020] [Warny, M., et al 2018], and DAIDS criteria (Version 2.1, July 2017) [National Institute of Allergy and Infectious Diseases 2017]. In addition, discontinuation requires a confirmed ≥30% decrease from baseline in either total lymphocytes or CD4+ T-cell counts (Table 3) so that participants whose baseline total lymphocyte counts or CD4+ T-cell counts are just above the discontinuation thresholds are

not discontinued for laboratory findings that are within the natural variability of these tests. A ≥30% decrease was chosen based on published literature demonstrating that lymphocyte counts vary as much as 25% in healthy adults when measured as frequently as day-to-day and over longer periods of time (every 6 months for many years) [Aziz, N., et al 2019] [Aziz, N., et al 2019a] [Statland, B. E., et al 1978].

Studies have shown that impaired kidney function (usually mild or moderate) may occur in a small proportion of people on FTC/TDF for PrEP, especially if they have other risk factors such as older age, diabetes mellitus, preexisting chronic kidney disease, and acute or chronic liver disease [Tetteh, R. A., et al 2017] [Wyatt, C. M., et al 2006] [Nadkarni, G. N., et al 2015]. This study provides the opportunity to evaluate the impact of MK-8527 on renal function as measured by serum analytes and calculations (eg, creatinine, cystatin-C, CrCl).

4.2.1.2 Pharmacokinetic Endpoints

Plasma samples (sparse) will be collected from all participants during the study. PK data will be used for building a population PK model for MK-8527 and MK-8527-TP.

4.2.1.2.1 PBMC Subset

The PBMC data collected from participants in the PBMC Subset will be used to build a population PK model for MK-8527 and MK-8527-TP. Sparse PBMC data from this study will be pooled with sparse PBMC data from Phase 1 studies to build a population PK model. The Mitra®/VAMS venous PK samples will not be used to evaluate doses of MK-8527, but to establish a correlation between this sampling method with more standard in-clinic PK sample collection methods (venipuncture) for potential use in future studies.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 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.

In addition to studying variation across the human genome, variation across the human genome may be analyzed for association with the PK and safety data collected in this study.

4.2.1.4 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Placebo

The primary objective of the study is to evaluate the safety and tolerability of oral MK-8527 in a population with low-risk of HIV-1-infection. A placebo-control is being used to allow for a robust, unbiased evaluation of the safety and tolerability profile of MK-8527.

4.2.3 Rationale for Collecting Race and Ethnicity

The differential effect on efficacy and safety based on any demographic parameter, including race or ethnicity, cannot be predicted when evaluating a new investigational drug. Therefore, it is important to collect race and ethnicity data to ensure that there is not a differential effect based on these parameters and to gain assurance the results observed in the clinical study will be representative of the drug's use in a broader population. As an example, non-Caucasian patients were found to have higher plasma concentrations of EFV (an NNRTI) than their Caucasian counterparts, indicating an increased risk of EFV-induced toxicity in non-Caucasian people [Burger, D., et al 2005]. As another example, among people living with HIV in the United States, those of African heritage have been found to be less likely to maintain virologic suppression compared with other groups, and the factors contributing to this remain to be elucidated [Weintrob, A. C., et al 2009] [Ribaudo, H. J., et al 2013].

4.2.4 Rationale for Collecting Gender Identity Data

Transgender people, defined as those whose gender identities and/or expressions differ from the sex assigned to them at birth, have a high prevalence and incidence of HIV infection globally [Poteat, T., et al 2016]. When considering HIV treatment, the WHO considers transgender people to be a separate key population because of their specific health needs and high vulnerability [Department of HIV/AIDS 2015]. Data will be collected in this study to assess clinical safety and toxicity in the transgender population.

4.3 Justification for Dose

In MK-8527 P002, a Phase 1 proof-of-concept study in treatment-naïve participants with HIV-1, antiretroviral activity following a single dose of MK-8527 (1 mg, 3 mg, or 10 mg) was assessed based on a mean HIV-1 viral load reduction of ≥1.0 log10 copies/mL at 7 days postdose. Participants receiving either a 3 mg or 10 mg dose of MK-8527 achieved a mean viral load reduction of 1.63 log10 copies/mL and 1.36 log10 copies/mL, respectively, at 7 days postdose. Additionally, 11/12 participants receiving either 3 mg or 10 mg of MK-8527 achieved a viral load reduction of >1.0 log10 copies/mL at 7 days postdose. A single 1 mg dose of MK-8527 led to a mean viral load reduction of 0.92 log10 copies/mL. Of the 5 participants who received the 1 mg dose, 2 did not achieve the >1.0 log10 copies/mL due to unknown reasons; the lack of response in these 2 participants was not due to appearance of mutant strains.

A single 1 mg dose of MK-8527 is being re-evaluated in a second Phase 1 proof-of-concept study (MK-8527 P004) in treatment-naïve participants with HIV-1 and preliminary results are available from this study for the single dose of 1 mg and 0.5 mg. Seven of 8 participants receiving a single 1 mg dose of MK-8527 achieved a viral load reduction of >1 log10 copies/mL at 7 days postdose, with the eighth participant achieving a reduction of 0.98 log10 copies/mL. The mean viral load decline at 7 days postdose for the 1 mg dose was 1.38 log10. Based on these results, the 0.5 mg dose was evaluated with all 6 participants who received the dose achieving a viral load reduction of ≥1.0 log10 copies/mL at 7 days postdose. The mean viral load decline at 7 days postdose was 1.39 log10. The results for both doses suggest similar efficacy was achieved for both the 1 mg and 0.5 mg doses.

The viral load data from P002 and P004, along with PK (MK-8527-TP C_{168}) data for doses studied in P002 (1 mg, 3 mg, and 10 mg) and P004 (1 mg and 0.5 mg) were used to construct an exposure-response model. From the analysis, the threshold of MK-8527-TP 0.03 pmol/10^6 cells is predicted to achieve efficacy against wild-type HIV-1 virus. At the threshold of MK-8527-TP 0.03 pmol/10^6 cells, a >1.0 log drop in viral load is projected in a treatment naive population. This threshold represents an IQ (inhibitory quotient), defined as the ratio of C_{trough} and the in vitro IC_{50}, of ~3.

Although the selected threshold of 0.03 pmol/10^6 cells is predicted to achieve efficacy against the wild-type HIV-1 virus, the threshold is not anticipated to maintain efficacy against the M184V/I variant. Transmission rates are low for NRTI mutants, likely because of reduced replicative fitness. Surveillance data of transmitted drug resistance have been collected for several years. While the prevalence of various mutations varies over time and by geography, these surveys consistently show that transmission of NRTI mutants is low [Chimukangara, B., et al 2019] [Rhee, S. Y., et al 2020]. For M184V/I, globally these rates are <1% [McClung, R. P., et al 2022].

CCI [redacted]

CCI [redacted]

A preliminary Phase 1 population PK model was developed to determine the doses that would achieve the efficacy threshold defined above. Based on this model, a ≥6 mg QM dose of MK-8527 should provide efficacy in >90% of the population based on the threshold of 0.03 pmol/10^6 cells. The 3 mg dose, despite being projected to be a suboptimal dose based on current data, would help characterize PK at a lower dose, allowing for any future refinements of the current projected efficacious dose based on subsequent lower dose panels of MK-8527 being studied in P004 and further refinement of the population PK model. The third dose evaluated in this study (12 mg QM) is 2-fold higher than the projected efficacious dose and will help provide safety and tolerability data in the Phase 2 study. In addition, the 12 mg dose will provide PK data at a dose >6 mg to help refine a potential Phase 3 dose and will potentially help to cover effects due to intrinsic and extrinsic factors. The dose of MK-8527 for Phase 3 may be interpolated from the 3 doses evaluated in this study.

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.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

Participants between the ages of 18 and 65 years (inclusive) will be enrolled in this study.

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. Is confirmed HIV-uninfected based on negative HIV-1/HIV-2 test result before randomization (completed by the central laboratory).

   Note: Additional testing to confirm suspected HIV infection during screening will be performed in accordance with local guidelines. If HIV infection is confirmed, the participant is not eligible for the study and will be referred for appropriate care, as necessary.

2. Has low-risk of HIV infection, defined as all of the following within 12 months prior to the screening visit or the rescreening visit (if applicable) (based on self-report by participant or medical history [if available]):
   - No anal or vaginal intercourse with someone known to be HIV-infected or of unknown HIV infection status who is at increased risk of HIV infection (see Appendix 8);
   - No stimulant use (cocaine [including crack], methamphetamine, or non-physician prescribed pharmaceutical-grade stimulants) or inhaled nitrate;
   - No illicit injection drug use of any kind;
   - No new diagnosis of an STI such as GC, CT, incident syphilis, or trichomoniasis;
   - Not greater than 3 different sexual partners for receptive or insertive vaginal or anal sex; and,
   - No history of antiretrovirals for HIV-1 PrEP or PEP.

   Note: Individuals who have participated in studies of an antiretroviral, such as Phase 1 studies (excluding MK-8527 and MK-8591), may be eligible after consultation with the Sponsor.

Demographics

3. Is an individual of any sex/gender, from 18 years to 65 years of age inclusive, at the time of providing the informed consent.

Male Participants

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

Female Participants

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

- Is not a POCBP
  OR
- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal 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 POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) 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.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

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

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.
2. Has an active diagnosis of hepatitis due to any cause, including active HBV infection (defined as HbsAg-positive) or HCV infection (defined as detectable HCV RNA).

   Note: Past HBV infection or previous HBV vaccination (defined as HbsAg-negative and positive for antibody against HbsAg), or prior/inactive HCV infection (defined as undetectable HCV RNA) are not exclusionary.

3. Has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
4. Has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance (including drug or alcohol use or dependence) that might, in the opinion of the investigator, confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate.

Prior/Concomitant Therapy

5. Is taking or is anticipated to require systemic immunosuppressive therapy, immune modulators, or any prohibited therapies outlined in Section 6.5 from 60 days prior to Day 1 through the duration of the study.

   Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) and topical agents are allowed.

Prior/Concurrent Clinical Study Experience

6. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 30 days prior to Day 1 (60 days if the investigational compound falls into the category outlined above in criterion #5) through the duration of the study.

   Note: Concurrent participation in observational or noninterventional studies may be permitted and should be discussed with the Sponsor before enrollment and through study duration.

7. Has previously received MK-8527 or MK-8591.

Diagnostic Assessments

8. Has QTc intervals (using Fridericia correction) >450 msec (for males) or >460 msec (for females) or an ECG finding deemed clinically abnormal by the investigator.
9. Has exclusionary laboratory values within 45 days prior to Day 1 as listed in Table 1.

   Note: Chemistry, hematology, and CD4+ T-cell count parameters that meet the exclusion criteria may be repeated once during the screening period.

Table 1 Laboratory Exclusion Criteria

Laboratory Assessment	Exclusionary Values
Hemoglobin	<10.5 g/dL for females and <11 g/dL for males
Lymphocyte	<1000 cells/mm^3
CD4+ T-cell Count	<500 cells/mm^3
Absolute neutrophil count	<1000 cells/mm^3
Platelet count	<125,000/mm^3
Calculated creatinine clearance	<90 mL/minute using the Cockcroft-Gault equation (Appendix 9)
Albumin	≤3.5 g/dL
INR	≥1.7
ALT	≥1.25 × ULN
AST	≥1.25 × ULN
Total bilirubin	>ULN unless history of Gilbert's disease (If Gilbert's disease is the proposed etiology, this must be documented in the participant's chart)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=International Normalized Ratio; ULN=upper limit of normal.

Other Exclusions

10. 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

Participants who are sexually active should be counseled on safer sex practices to prevent acquisition of HIV or other STIs.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Administration of study intervention will be witnessed by the investigator and/or study staff.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

At each monthly dosing visit, 4 bottles of blinded study intervention will be dispensed per participant, each containing 1 capsule (MK-8527 or placebo). All participants will take a total of 4 capsules for the assigned dose as follows:

- Group 1 (MK-8527 3 mg): Participants will receive 1 capsule of MK-8527 (3 mg) and 3 capsules of matching placebo.
- Group 2 (MK-8527 6 mg): Participants will receive 2 capsules of MK-8527 (3 mg) and 2 capsules of matching placebo.
- Group 3 (MK-8527 12 mg): Participants will receive 4 capsules of MK-8527 (3 mg).
- Group 4 (Placebo): Participants will receive 4 capsules of matching placebo.

All 4 capsules should be swallowed within ~5 minutes. The exact time of dosing, for each bottle, must be documented and reported on the study medication eCRF.

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	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Experimental	MK-8527	Drug	Capsule	3 mg	3 mg QM	Oral	Day 1 to Week 20	Test Product	IMP	Central
Group 1	Experimental	Placebo	Drug	Capsule	0 mg	0 mg QM	Oral	Day 1 to Week 20	Placebo	IMP	Central
Group 2	Experimental	MK-8527	Drug	Capsule	3 mg	6 mg QM	Oral	Day 1 to Week 20	Test Product	IMP	Central
Group 2	Experimental	Placebo	Drug	Capsule	0 mg	0 mg QM	Oral	Day 1 to Week 20	Placebo	IMP	Central
Group 3	Experimental	MK-8527	Drug	Capsule	3 mg	12 mg QM	Oral	Day 1 to Week 20	Test Product	IMP	Central
Group 4	Placebo Comparator	Placebo	Drug	Capsule	0 mg	0 mg QM	Oral	Day 1 to Week 20	Placebo	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QM=once monthly.
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 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.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 4 study intervention arms. Participants will be assigned randomly in a 2:2:2:1 ratio to MK-8527 (3 mg), MK-8527 (6 mg), MK-8527 (12 mg), or placebo, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Sex (female, male) (as assigned at birth)
2. Region (Africa, non-Africa)

The effects of study interventions may differ between these subgroups of sex and region. Therefore, sex and region are selected as the stratification factors to ensure that intervention groups will be well-balanced, and the effects of study interventions will not be confounded by those demographic characteristics.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments. MK-8527 and matching placebo will be packaged identically so that blinding is maintained.

All participants and study-site personnel directly associated with study conduct will remain blinded to study intervention assignment through Follow-up Week 8.

Two in-house teams of Sponsor personnel will be unblinded and will have access to treatment group assignments throughout the study duration:

- The unblinded clinical review team consisting of roles including but not limited to a clinical director, clinical scientist, statistician, and statistical programmer. This team will be responsible for an ongoing review of safety data, such as reported AEs, and laboratory data.
- The PK personnel responsible for population PK modeling.

The Sponsor's internal processes and procedures will be followed for documentation and handling of unblinded data by the unblinded Sponsor personnel. As per amendment 02, all Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit, to enable earlier program strategic decision-making by the Sponsor.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted. Refer to the study binder for more details on the unblinding procedure.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment ≥1 monthly dose 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.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study or during time periods specified by this protocol for that medication. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

The following are specific restrictions for prior and concomitant therapies not permitted for all participants:

- Investigational agents (including devices, but not including compounds covered below), except for study intervention(s), from 30 days before receiving study intervention through the study duration.

  Note: Participants are not permitted to enroll in a study of an investigational compound or investigational device during the entire study duration. Participants that discontinue study intervention early should refrain from enrolling in a study of an investigational compound or investigational device until at least 8 weeks from the last dose of study intervention in this study.

- Immune therapy agents, immune modulators, or other immunosuppressive therapies (ie, compounds that may affect lymphocyte counts), from 60 days before receiving study intervention through the study duration.

  Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) and topical agents are allowed.

  Note: Compounds with long half-lives (ie, ≥14 days) should be discussed with the Sponsor prior to participant enrollment.

Any agents (eg, vaccine or therapy for COVID-19) approved locally for Emergency Authorized Use, or equivalent, that do not have a known or anticipated DDI with study intervention, are permitted.

There are no restrictions identified for MK-8527 at this time.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

A participant's dose will not be modified during the study.

Decisions to temporarily withhold study intervention dosing because of an AE will be reviewed on a case by-case basis by the investigator. Interruptions from the protocol-specified dosing plan require consultation between the site and the Sponsor, and written documentation of the collaborative decision on participant management.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study; no poststudy ART will be provided.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period (last dose at Week 20) will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment is unblinded before Week 20.

  Note: The need for the participant to be discontinued from study intervention due to unblinding will be determined collaboratively between the investigator and the Sponsor's Clinical Director.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

  Note: If a participant has a change in HIV-1-associated risk behavior (Appendix 8), he/she may become eligible to receive a medication approved PrEP (eg, FTC/TDF, FTC/TAF, or cabotegravir IM), and discontinuation from study intervention may be indicated. The investigator should discuss any changes in HIV-1-associated risk behavior with the Sponsor's Clinical Director. The decision to continue the participant on study intervention or discontinue the participant with referral to locally available HIV prevention services, including services for approved PrEP, will be determined by agreement between the investigator and the Sponsor.

  Note: If a participant requires PEP for potential occupational or non-occupational HIV exposure, the decision to continue the participant on study intervention or discontinue the participant will be determined by agreement between the investigator and the Sponsor.
- The participant has a confirmed positive serum pregnancy test.
- The participant develops a malignancy after randomization.

- The participant has confirmed HIV-1 or HIV-2 infection.

  Note: Participants who become infected with HIV-1 or HIV-2 prior to Follow-up Week 8 may have their treatment unblinded.

  Note: Participants who become infected with HIV-1 or HIV-2 during the study will stop receiving study intervention and will be referred to local medical providers for HIV care and treatment. No poststudy ART will be provided by the study.
- The participant has an SAE or Grade 4 laboratory AE assessed by the investigator to be related to study intervention AND that is life-threatening or results in prolonged hospitalization.
- A participant must be discontinued from study intervention and managed per Section 8.11.3.1 if any of the criteria in Table 3 are confirmed. Participants should interrupt QM blinded dosing pending confirmatory testing.

  Note: If the investigator believes there is an alternative explanation for the result (eg, COVID-19), consultation between the investigator and Sponsor is required when evaluating the participant for discontinuation from study intervention.

Table 3 Discontinuation Criteria for Specified Decreases in Total Lymphocyte Counts or CD4+ T-cell Counts

Laboratory Test	**Criterion[a]**	**Confirmation[b,c]**
Total lymphocyte count	A confirmed on-treatment value <1000 cells/mm^3 with a ≥30% decline from baseline	Repeat measurement 1 to 4 weeks later or at the next scheduled study visit, whichever is sooner
CD4+ T-cell count	A confirmed on-treatment value <500 cells/mm^3 with a ≥30% decline from baseline	Repeat measurement 1 to 4 weeks later or at the next scheduled study visit, whichever is sooner

[a] Baseline is defined as the Day 1 value. If a Day 1 value is not available, then the most recent screening value prior to Day 1 should be considered a participant's baseline value.

[b] If a measurement meets the specified discontinuation criteria, a consecutive, confirmatory measurement within the specified time frame is required. Confirmatory laboratory measurements can be conducted at the next clinic visit if the next scheduled visit occurs within the interval required for repeat testing.

[c] The time frame for confirmation of decreases in total lymphocyte count or CD4+ T-cell count may be extended in the setting of intercurrent illness, immunization, or study intervention dosing interruptions (due to missed study visits). Allow approximately 4 weeks following resolution of illness, immunization, or study intervention dosing interruptions before collecting the confirmation sample to allow for evaluation of a potential other causal effect.

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

Participants who are discontinued from study intervention prior to the final dose at Week 20, should continue to be monitored. All follow-up visits and procedures, as outlined in the SoA in Section 1.3.1, should be completed.

7.2 Participant Withdrawal From the Study

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

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as outlined in the SoA in Section 1.3.2 (Early Withdrawal from Study visit), 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 decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The volume of blood collected from a participant over the duration of the study is provided in Table 11 (US and Israel) and Table 12 (South Africa). Participants who provide documented informed consent to participate in the PBMC Substudy will have additional blood collected over the duration of the study as noted in Table 11 and Table 12.
- Repeat or unscheduled samples may be taken for safety reasons, for technical issues with the samples, or may be required for participants who are rescreened. Therefore, the total amount of blood collected for a participant may be changed beyond what is listed in Table 11 and Table 12.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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

Specifics about the study and the study population are to be included in the ICF.

The participant (or their 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.

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.

8.1.1.3 Consent for PBMC Subset

Participation in the PBMC Subset will be optional. The investigator or medically qualified designee will explain the PBMC Subset consent to the participant, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to the PBMC Subset. Participants who consent to participate in the PBMC Subset will have additional weekly visits between Day 2 and Week 4 and 1 additional follow-up visit (Follow-up Week 6) (Section 1.3.1). A copy of the ICF will be given to the participant.

If a participant withdraws consent for the PBMC Subset during the study, the participant does not need to be discontinued. In this situation, the site should revert the participant to the visits and procedures applicable for participants not in the PBMC Subset, for the remainder of the study.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

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 30 days before the first dose of study intervention.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after

randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.8 Study Intervention Administration

All study intervention will be administered at the clinic/investigative site QM per the SoA (Section 1.3). Administration of study intervention will be witnessed by the investigator and/or study staff. There are no meal restrictions for dosing; therefore, all dosing can occur without regard to food.

At each monthly dosing visit, 4 bottles of blinded study intervention will be dispensed per participant, each containing 1 capsule (MK-8527 or placebo; Section 6.1). All participants will take a total of 4 capsules, swallowed whole, for the assigned dose as follows:

- Group 1 (MK-8527 3 mg): participants will receive 1 capsule of MK-8527 (3 mg) and 3 capsules of matching placebo.
- Group 2 (MK-8527 6 mg): participants will receive 2 capsules of MK-8527 (3 mg) and 2 capsules of matching placebo.
- Group 3 (MK-8527 12 mg): participants will receive 4 capsules of MK-8527 (3 mg).
- Group 4 (Placebo): participants will receive 4 capsules of matching placebo.

All 4 capsules should be taken together, and the actual dosing time will be recorded on the eCRF.

8.1.8.1 Timing of Dose Administration

Participants will receive 6 observed QM doses of oral MK-8527 or matching placebo, starting at Day 1 with a final dose at Week 20 per the following dosing guidelines:

- Participants should take the QM dose of MK-8527/placebo within ±2 days (Week 4) or ±7 days (Weeks 8, 12, 16, 20) of the ideal dosing day (calculated based on Day 1).

- If a participant is late for a QM dose of MK-8527/placebo and it is outside the dosing window (Table 4) for that study visit, the QM dose should be skipped/missed, and the normal dosing schedule resumed (based on the ideal dosing day) at the next dosing visit.

Note: This guidance may be modified after consultation with the study Sponsor. Participants should not double the next dose to compensate for what has been missed.

Table 4 Study Intervention Administration Schedule

Study Dosing Visits	Ideal Dosing Day	Study Visit Window per SoA	Dosing Window
Day 1	Day 1	N/A	N/A
Week 4	Day 29	±2 days Day 27 to Day 31	±2 days Day 27 to Day 31
Week 8	Day 57	±7 days Day 50 to 64	±7 days Day 50 to 64
Week 12	Day 85	±7 days Day 78 to 92	±7 days Day 78 to 92
Week 16	Day 113	±7 days Day 106 to 120	±7 days Day 106 to 120
Week 20	Day 141	±7 days Day 134 to 148	±7 days Day 134 to 148
N/A=not applicable; SoA=Schedule of Activities.			

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the final dose at Week 20 should return to the clinic for an EOT visit (Visit 11) and should be encouraged to continue to be followed as outlined in the SoA (Sections 1.3.1 and 1.3.2) and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the "Early Withdrawal from Study" visit (Section 1.3.2) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 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

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.11 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.

8.1.12 HIV Risk Reduction

Participants will be offered condoms, lubricants, and HIV risk reduction counseling.

8.2 Efficacy Assessments

There are no efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study, including approximate blood volumes drawn by visit and by sample type per participant, can be found in the Appendix 2.

Note: External circumstances (eg, rescreening, hemolysis) may necessitate repeat testing, which may change the total amount of blood collected for a participant beyond what is listed in Appendix 2.

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

8.3.1 Physical Examinations

At the screening visit, a complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. The complete physical examination will include examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system).

At subsequent visits as per the SoA, a brief directed 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 at the visits specified in the SoA (Section 1.3).

8.3.2 Vital Signs

Vital signs will be measured after approximately 5 to 10 minutes of rest and will include temperature, pulse, respiratory rate, and systolic and diastolic blood pressure.

Note: Oral temperatures should be taken. If an oral temperature measurement is not possible, a temporal, tympanic, rectal, or axillary temperature measurement may be taken and should be recorded appropriately.

8.3.3 Electrocardiogram

Procedures for printing, archiving, and review of ECGs will be specified by the central vendor.

Sites will receive an immediate, machine-read QTcF value when the ECG is performed using the central vendor supplied machine. This value may change on the final cardiologist-read ECG report; therefore, sites should use only the final ECG report QTcF value from the screening visit to determine participant eligibility.

In some instances, the Sponsor may request that the site do a repeat ECG to further evaluate a potentially clinically significant ECG finding.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove their bra. Participants should be resting in the semirecumbent position for at least 10 minutes prior to each ECG measurement.

8.3.4 Sexually Transmitted Infections

8.3.4.1 HIV Infection

Participants who have a positive HIV-1/2 screen test while on study intervention will return to the site for a confirmatory HIV-1 RNA PCR test and collection of a viral drug resistance sample, as soon as possible and no later than 14 days after receiving the positive HIV-1/2 screen test result. If HIV-1 infection is confirmed and the HIV-1 RNA PCR results meet the criteria for testing (HIV-1 RNA ≥200 copies/mL) genotypic and phenotypic viral drug resistance testing will be performed on collected plasma samples (by the central laboratory).

Participants with confirmed HIV-1 infection will be discontinued from study intervention and referred to local medical providers for HIV care and treatment; they should remain in the study and continue to be followed as outlined in the SoA (Section 1.3). No poststudy ART will be provided.

8.3.4.2 Other STIs

Testing for GC/CT, syphilis, and trichomoniasis (females only) will be performed at Screening as described in the SoA (Section 1.3.1). Participants with a confirmed STI at screening are not eligible for the study and should be referred for treatment as per local guidelines.

Participants with a positive syphilis test result and with documentation of adequate antibiotic treatment for the syphilis infection (>12 months prior to screening or rescreening [if applicable]) may be considered eligible for the study after consultation between the investigator and Sponsor Clinical Director.

During the study, symptomatic testing for STIs will be at the study investigators discretion. Participants with a confirmed STI while on study intervention may be required to discontinue study intervention but will be followed in the study as outlined in the SoA (Section 1.3).

Sites should report STIs as per local reporting requirements.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Renal Function Assessment

Blood samples will be collected to evaluate renal function as measured by key indicators such as serum creatinine and serum cystatin-C (Appendix 2) and CrCl (Appendix 9).

8.3.6 HIV Risk Evaluation

At screening and again at Day 1 prior to randomization, a participant's risk status should be evaluated based on Inclusion Criterion #2 (Section 5.1). A participant that does not meet all elements of Inclusion Criterion #2 should not be randomized. After randomization (Day 1), at each treatment and follow-up visit as specified in the SoA (Sections 1.3.1 and 1.3.2), participants will be screened by appropriate study-site personnel for changes in HIV risk behaviors based on the list of questions included in Appendix 8.

Any participant who develops a risk for HIV infection at any time during the study should be brought to the attention of the Sponsor. No further study intervention should be administered from the time the site is made aware of the change in risk status until the Sponsor has provided guidance.

Upon assessment of the increase in risk status, the Sponsor will determine: a) the appropriateness of continuing study intervention and/or b) the necessity to refer the participant for applicable services (eg, substance use, mental health, PrEP).

8.3.7 Pregnancy Testing

POCBP are required to use contraception to prevent pregnancy during the study and will be tested for pregnancy at each visit as outlined in Section 1.3, Section 5.1, and Appendix 5.

Participants who are not on contraception at screening should be counseled about available options and directed to start their chosen method prior to randomization.

Participants should be asked at study visits per the SoA to verbally confirm their use of contraception since the prior visit, according to the Contraceptive Guidance in Appendix 5. Confirmation should be noted in the source documents for each visit.

Pregnancy testing using a highly sensitive urine β-hCG pregnancy test kit will be performed at the study site. In the event of a positive urine pregnancy test result, a confirmatory highly sensitive serum β-hCG pregnancy test will be performed. If a participant becomes pregnant, refer to Section 8.11.3. Once a continuing pregnancy has been confirmed, monthly urine pregnancy tests should be deferred until 1 month following the end of the pregnancy.

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 randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the

event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through study duration, 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 5.

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

Table 5 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 (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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 (spontaneously reported to the investigator or their designee) that occurs in a participant 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

This section is 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. 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).
2. A lymphocyte count that meets DAIDS criteria for Grade 3 (<500 cells/mm^3) or higher grade, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing at any time during the study.
3. A CD4+ T-cell count that meets DAIDS criteria for Grade 3 (<200 cells/mm^3) or higher grade, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing at any time during the study.

8.5 Treatment of Overdose

In this study, an overdose is defined as a participant taking more than 1 dose (>4 capsules) within 14 days.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Refer to the SoA in Section 1.3.1 and Table 6, Table 7, Table 8, and Table 9 for the list of PK sample collection timepoints. For participants who withdrawal consent or require an HIV Infection Confirmation visit, refer to PK sample collection details in Section 1.3.2 of the SoA and Section 8.6.4.

The decision as to which samples collected will be measured for evaluation of PK 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. Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Plasma MK-8527 (All Participants)

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

PK samples will be collected from all participants as outlined in Table 6. The exact time of dosing of study intervention prior to the sample collection and the time of PK sample collection will be recorded on the appropriate source documentation.

Table 6 Timepoints for Collection of Plasma MK-8527 Samples (All Participants)

Study Visit (Day/Week)	**Time Relative to Dose[a]**
Day 1	One sample to be collected predose One sample to be collected 30 min (±15 min) postdose One sample to be collected 4 hours (±30 min) postdose
Day 2	One sample to be collected 24 hours (±6 hours) after Day 1 dose
Week 20/EOT (Visit 11)	If Week 20: One sample to be collected 30 min (±15 min) postdose One sample to be collected 4 hours (±30 min) postdose
	If EOT: One sample to be collected at any time during the visit
Follow-up Day 1	One sample to be collected 24 hours (±6 hours) after the Week 20 dose. If Visit 11 was performed as an early EOT visit (no study intervention dosing), then one sample can be collected at any time during the visit.

EOT=End of Treatment.
[a] Indicates time relative to monthly oral capsule administration up to and including the Week 20 dose.

8.6.2 Blood Collection of PBMC Samples (PBMC Subset Only)

Sample collection, storage, and shipment instructions for PBMC samples will be provided in an Operations/Laboratory Manual.

Participating sites will be trained on sample collection and processing procedures. The exact time of dosing of study intervention prior to the sample collection and the time of PK sample collection will be recorded on the appropriate source documentation.

Timepoints for the collection of these samples are provided in Table 7.

Table 7 Timepoints for Collection of PBMC Samples (PBMC Subset Only)

Study Visit (Day/Week)	**Time Relative to Dose[a]**
Day 1	One sample to be collected predose One sample to be collected 4 hours (±30 min) postdose
Day 2	One sample to be collected 24 hours (±6 hours) after Day 1 dose
Week 1	One sample to be collected at any time during the visit
Week 2	One sample to be collected at any time during the visit
Week 3	One sample to be collected at any time during the visit
Week 4	One sample to be collected predose
Week 8	One sample to be collected predose
Week 12	One sample to be collected predose
Week 16	One sample to be collected predose
Week 20/EOT (Visit 11)	If Week 20: One sample to be collected predose One sample to be collected 4 hours (±30 min) postdose
	If EOT: One sample to be collected at any time during the visit
Follow-up Day 1	One sample to be collected 24 hours (±6 hours) after the Week 20 dose. If Visit 11 was performed as an early EOT visit (no study intervention dosing), then one sample can be collected at any time during the visit.
Follow-up Week 4	One sample to be collected at any time during the visit
Follow-up Week 6	One sample to be collected at any time during the visit
Follow-up Week 8	One sample to be collected at any time during the visit

EOT=End of Treatment; PBMC=peripheral blood mononuclear cell.
[a] Indicates time relative to monthly oral capsule administration up to and including the Week 20 dose.

8.6.3 Blood Collection of Venous Microsampling (Mitra®/VAMS) (All Participants)

The VAMS blood collection technique will be used to obtain venous blood samples from all study participants; however, the timepoints for collection are different for participants in the PBMC Subset (Table 8) and those not in the PBMC Subset (Table 9).

Sites will be trained on sample collection and processing procedures. The exact time of dosing of study intervention prior to the sample collection and the time of PK sample collection will be recorded on the appropriate source documentation.

Further instructions on use of the device, which follow VAMS blood collection technique will be provided in a Laboratory/Operations Manual.

Timepoints for the collection of VAMS samples in PBMC Subset participants are provided in Table 8.

Table 8 Timepoints for Collection of Venous Microsampling (Mitra®/VAMS) PK Samples (PBMC Subset Only)

Study Visit (Day/Week)	**Time Relative to Dose[a]**
Day 1	One sample to be collected predose[b]
Day 2	One sample to be collected 24 hours (±6 hours) after Day 1 dose
Week 1	One sample to be collected at any time during the visit
Week 2	One sample to be collected at any time during the visit
Week 3	One sample to be collected at any time during the visit
Week 4	One sample to be collected predose
Week 8	One sample to be collected predose
Week 12	One sample to be collected predose
Week 16	One sample to be collected predose
Week 20/EOT (Visit 11)	If Week 20: One sample to be collected predose[b]
	If EOT: one sample to be collected at any time during the visit
Follow-up Day 1	One sample to be collected 24 hours (±6 hours) after the Week 20 dose. If Visit 11 was performed as an early EOT visit (no study intervention dosing), then one sample can be collected at any time during the visit.
Follow-up Week 4	One sample to be collected at any time during the visit
Follow-up Week 6	One sample to be collected at any time during the visit.
Follow-up Week 8	One sample to be collected at any time during the visit

EOT=End of Treatment; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; VAMS=volumetric absorptive microsampling.
[a] Indicates time relative to monthly oral capsule administration up to and including the Week 20 dose.
[b] No VAMS sample is required to correspond with the 4-hour postdose PBMC sample collection.

Timepoints for the collection of VAMS samples in participants not in the PBMC Subset are provided in Table 9.

Table 9 Timepoints for Collection of Venous Microsampling (Mitra®/VAMS) PK Samples (Participants Not in the PBMC Subset)

Study Visit (Day/Week)	Time Relative to Dose[a]
Week 4	One sample to be collected predose
Week 8	One sample to be collected predose
Week 12	One sample to be collected predose
Week 16	One sample to be collected predose
Week 20/EOT	If Week 20: One sample to be collected predose
	If EOT: One sample to be collected at any time during the visit

EOT=End of Treatment; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; VAMS=volumetric absorptive microsampling.
[a] Indicates time relative to monthly oral capsule administration up to and including the Week 20 dose.

8.6.4 Collection of PK Samples in Participants Who Withdraw Consent or Require an HIV Infection Confirmation Visit

This section outlines the PK sample collection requirements for participants that withdraw consent or require an HIV Infection Confirmation visit. Refer to the SoA in Section 1.3.2 for additional details.

Participants that Withdraw Consent

Participant should have an "Early Withdrawal From Study" visit as per the SoA in Section 1.3.2. At this visit:

- All participants will have 1 plasma PK sample collection (if the participant has not yet completed the Follow-up Day 1 visit) at any time during the visit.
- In addition, participants in the PBMC Subset will have 1 PBMC sample and 1 VAMS venous sample collected, at any time during the visit.

Participants that Require an HIV Infection Confirmation Visit

Participant should have an HIV Infection Confirmation visit as per the SoA in Section 1.3.2. At this visit:

- All participants will have 1 plasma PK sample collection (if the participant has not yet completed the Follow-up Day 1 visit) at any time during the visit.
- In addition, participants in the PBMC Subset will have 1 PBMC sample and 1 VAMS venous sample collected, at any time during the visit.

Refer to Section 8.11.4 for details on the management of participants in the study based on the results of the HIV infection confirmation testing.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

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 planned 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.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. 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 specimens listed in Section 8.8.

8.10 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/Rescreening

Approximately 45 days before intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

8.11.1.1 Screening

The screening window, which is a ≤45-day window prior to randomization, will begin on the date of the documented main study consent for the participant. During the screening window, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Select screening procedures may be repeated after consultation with the Sponsor. If a participant has passed the 45-day screening window, the participant may be allowed to rescreen.

8.11.1.2 Rescreening

If the 45-day screening window has been exceeded, participants are allowed to rescreen 1 time. Once a participant has started the rescreening process, a new screening period (ie, an additional ≤45-day window) will begin, during which time screening procedures may be repeated and are expected to be completed within this new 45-day window.

Documented informed consent (for the main study, FBR [if applicable], PBMC Subset [if applicable] and all other locally applicable study consent forms [eg, Greenphire]) obtained during the original screening period should be reviewed with the participant, including any screening procedures that need to be repeated, and a verbal reconsent to continue in the study should be documented.

Evaluation of eligibility will be determined through repeating select screening procedures during the rescreening process to ensure that participants are still at low-risk for HIV-1 infection and in generally good health, as outlined below. If a procedure is required to be repeated at rescreening, that result will be used to confirm eligibility.

All Participants

The following assessments must be repeated for all participants during rescreening:

- Register the rescreening in the IRT system
- Review medical history, HIV infection risk, prior/concomitant medications use, and contraceptive use
- Review AEs
- 12-lead ECG
- Complete physical examination
- Complete set of vital signs, including height and weight
- HIV-1 and HIV-2 testing
- HBV and HCV testing
- Serum pregnancy test
- Hematology, chemistry, CrCl, cystatin-C, TBNK Panel, and PT/INR

The following assessments do not need to be repeated at rescreening if the participant had a negative test result at the original screening visit, ≤60 days have passed since the date of the original sample collection, and the participant does not report an increase in risk for HIV infection; however, testing must be performed at rescreening if any of the above criteria are not met:

- Syphilis serologic testing
- Urine GC/CT & trichomoniasis testing (females only)
- Urine GC/CT testing (males only)

8.11.2 Intervention Period

During the intervention period, participants will receive a total of 6 oral doses of the assigned blinded study intervention (MK-8527 [3 mg, 6 mg, or 12 mg] or placebo) per the SoA. Administration of study intervention will be witnessed by the investigator and/or study staff approximately every 4 weeks starting on Day 1. The final dose will be administered at the Week 20 visit.

After Day 2, participants in the PBMC Subset will return to the site at Weeks 1, 2, and 3 for additional required assessments, per the SoA (Section 1.3.1).

8.11.2.1 AE Assessment Phone Call (Week 2)

A phone call to collect safety information will be made at Week 2 for participants not in the PBMC Subset. The investigator is responsible for ensuring that all telephone contacts are performed by a staff member who is a health care professional qualified to elicit a discussion with the participant that will lead to a clinically meaningful disclosure on the participant's well-being. Telephone contacts are to be documented in the source documents and in the EDC tool (if required) and the investigator must review the entry within 2 days. However, if the participant reports any clinically concerning events (eg, SAEs, ECIs) during a telephone call, then the investigator must be promptly notified. The investigator will contact the participant to determine if a clinic visit is warranted.

If the participant cannot be reached by telephone at the regularly scheduled time, the site should make at least 3 attempts (in addition to the initial phone call) to contact the participant within 48 hours of the missed scheduled time. The participant's reliable contact person should be called if attempts to contact the participant are not successful. All phone contacts and attempts should be recorded in source documents.

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

Participants who discontinue study intervention before the final dose at Week 20 should complete an EOT visit (Visit 11) (Section 1.3.1), and then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period as listed in the SoA (Section 1.3.1) and further described in Section 8.11.6.

For the EOT visit, the site should perform all procedures, as listed in the SoA (Section 1.3.1) for Visit 11 (Week 20/EOT), except for the following procedure modifications:

1. No study intervention should be dispensed via the IRT or administered to the participant. The site should call the IRT to register the EOT visit.
2. One sample for plasma MK-8527 PK collected, at any time during the visit.
3. If in the PBMC Subset: only 1 PBMC sample and 1 VAMS venous sample should be collected, at any time during the visit.

If a participant discontinues study intervention before the final dose at Week 20, the EOT visit (Visit 11) should be performed in place of the next study visit. If a participant discontinues study intervention and also withdraws from the study before the final dose at Week 20, then only the EOT visit (Visit 11) should be performed in place of the next study visit. If a participant receives the final Week 20 dose of study intervention and then withdraws from the study, an "Early Withdrawal From Study" visit should be performed as the final study visit as outlined in Section 1.3.2 of the SoA.

8.11.3.1 Management of Participants with Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Counts

Participants discontinued from study intervention (prior to the final dose at Week 20) due to confirmed decreases in total lymphocyte count or CD4+ T-cell count (Section 7.1 and Table 3) should undergo assessments for the EOT visit (Visit 11) as specified in the SoA in Section 1.3.1. To meet the protocol-defined discontinuation criteria, participants must have a confirmed total lymphocyte count or CD4+ T-cell count that indicates a specified decrease on 2 consecutive measurements 1 to 4 weeks apart (Table 3). Note: The time frame for confirmation of decreases in total lymphocyte count or CD4+ T-cell count may be extended in the setting of intercurrent illness, immunization, or study intervention dosing interruptions (due to missed study visits). Allow approximately 4 weeks following resolution of illness, immunization, or study intervention dosing interruptions before collecting the confirmation sample to allow for evaluation of a potential other causal effect. Consult with the Sponsor prior to discontinuation if the investigator believes there is an alternative explanation for the result (eg, COVID-19).

After discontinuation from study intervention, participants should continue to be followed in the study, by completing the follow-up visits as outlined in the SoA in Section 1.3.1.

Total lymphocyte counts and CD4+ T-cell counts will also be monitored during follow-up (after last dose at Week 20). If a participant has a confirmed decrease in total lymphocyte count or CD4+ T-cell count as per Section 7.1, Table 3, after the last dose at Week 20, participants should continue to be followed in the study, by completing the follow-up visits as outlined in the SoA in Section 1.3.1.

If at the Follow-up Week 8 visit the participants total lymphocyte count and/or CD4+ T-cell count has not returned to ≥1000 cells/mm^3 or ≥500 cells/mm^3, respectively, on 2 consecutive measurements, the participants should continue to be followed in the study with approximately monthly unscheduled visits. At the unscheduled visit, the site should complete

an AE assessment and collect hematology and TBNK Panel/CD4+ T-cell samples for evaluation by the central laboratory. Participants should continue with the unscheduled visits until the total lymphocyte count and/or CD4+ T-cell count has returned to ≥1000 cells/mm^3 or ≥500 cells/mm^3, respectively, on 2 consecutive measurements.

8.11.3.2 Participants Who Become Pregnant

If a participant becomes pregnant prior to the last dose of study intervention at Week 20, an EOT visit (Visit 11) as per the SoA in Section 1.3.1 should be performed. If the pregnancy is reported at a scheduled study visit (eg, Week 8), the assessments/procedures for the EOT visit (Visit 11) should be conducted at that time. The participant will then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period (Follow-up Day 1, Follow-up Week 4, etc) as listed in the SoA in Section 1.3.1.

If the participant becomes pregnant after the last dose of study intervention at Week 20 or during the "Follow-up (Blinded)" study period they should continue with the protocol-specified follow-up visits listed for this period in the SoA in Section 1.3.1.

All reported pregnancies will be followed to the completion/termination of the pregnancy (Section 8.4.5).

8.11.4 HIV Infection Confirmation

Participants who have a positive HIV-1/2 screen test should return to the site for an "HIV Infection Confirmation" visit within 14 days of the site receiving the positive test result and have procedures performed as specified in the SoA in Section 1.3.2, including collection of an HIV-1 RNA PCR sample.

- If the positive HIV-1/2 screen test is prior to the last dose of study intervention at Week 20, and the HIV confirmation and differentiation test is negative, the participant may continue study intervention while waiting for the results of the HIV-1 RNA PCR test.
  - If the HIV-1 RNA PCR test is negative, the participant can continue to take study intervention.
  - If the HIV-1 RNA PCR test is positive, the participant should complete an EOT visit (Visit 11), and then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period as listed in the SoA in Section 1.3.1. The participant should be referred to local medical providers for HIV care and treatment. No poststudy ART will be provided by the study.
- If the positive HIV-1/2 screen test is prior to the last dose of study intervention at Week 20, and the HIV confirmation and differentiation test is positive, the participant should **not** receive additional doses of study intervention while waiting for the results of the HIV-1 RNA PCR test.
  - If the HIV-1 RNA PCR test is negative, the participant may be able to resume study intervention after consultation with the Sponsor.

  - If the HIV-1 RNA PCR test is positive, the participant should be permanently discontinued from study intervention and complete an EOT visit (Visit 11), and then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period as listed in the SoA in Section 1.3.1. The participant should be referred to local medical providers for HIV care and treatment. No poststudy ART will be provided by the study.
- If the positive HIV-1/2 screen test is after the last dose of study intervention at Week 20 or during the "Follow-up (Blinded)" study period, the participant should continue with the protocol-specified visits listed for this period in the SoA in Section 1.3.1.
  - The study investigator should utilize the results of the HIV confirmation and differentiation test and HIV-1 RNA PCR to determine the appropriate follow-up care for the participant.

If a participant has repeated positive HIV-1/2 screening tests which the investigator considers to be false positive results (due to the biology of the participant), after consultation between the site and the Sponsor, and written documentation of the collaborative decision, HIV RNA testing can be performed at each scheduled visits to avoid the participant needing to return for an HIV confirmation visit with each false positive screening test result.

8.11.5 Participants Who Withdraw Consent

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the "Early Withdrawal From Study" visit (Section 1.3.2) at the time of withdrawal.

8.11.6 Follow-up Period

During the 8-week blinded follow-up period, all participants will complete 3 monthly follow-up visits: Follow-up Day 1, Follow-up Week 4, and Follow-up Week 8. PBMC Subset participants will have 1 additional follow-up visit at Follow-up Week 6.

The follow-up visits represent different study day/weeks for a participant that completes the final Week 20 dose and a participant that discontinues study intervention prior to Week 20, as outlined below.

A participant that completes the final Week 20 study intervention dose will return to the site for follow-up visits based on the following:

- **Visit 12/Follow-up Day 1 (all participants):** this visit should be completed ~24 hours after the Week 20 study intervention dose; PK samples must be collected 24 hours (±6 hours) after the Week 20 dose.
- **Visit 13/Follow-up Week 4 (all participants):** this visit should be completed 24 weeks (±7 days) from the Day 1 (Visit 2).
- **Visit 14/Follow-up Week 6 (PBMC Subset only):** this visit should be completed 26 weeks (±2 days) from the Day 1 (Visit 2).

- **Visit 15/Follow-up Week 8 (all participants):** this visit should be completed 28 weeks (±7 days) from the Day 1 (Visit 2).

A participant that discontinues study intervention prior to the Week 20 dose, will return to the site for follow-up visit based on the EOT (Visit 11) date:

- **Visit 12/Follow-up Day 1 (all participants):** this visit should be completed ~24 hours after the EOT visit (Visit 11).
- **Visit 13/Follow-up Week 4 (all participants):** this visit should be completed 4 weeks (±7 days) from the EOT visit (Visit 11).
- **Visit 14/Follow-up Week 6 (PBMC Subset only):** this visit should be completed 6 weeks (±2 days) from the EOT visit (Visit 11).
- **Visit 15/Follow-up Week 8 (all participants):** this visit should be completed 8 weeks (±7 days) from the EOT visit (Visit 11).

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the principal statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. To allow programmatic decisions, there will be an unblinded Sponsor team to review data on an ongoing basis for the duration of the study. The official, final database will not be locked until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The detailed list of unblinded Sponsor team is presented in section 6.3.3 of the protocol. All Sponsor personnel except for a blinded medical monitoring team will be unblinded after the last expected Follow-up Week 4 visit.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule for study treatment assignment.

9.2 Hypotheses/Estimation

There are no hypotheses to be tested in this study. Objectives of the study are stated in Section 3 of the protocol.

9.3 Analysis Endpoints

Safety and PK endpoints that will be evaluated for within- and between-treatment differences are listed below.

9.3.1 Safety Endpoints

The primary safety assessment will include all accumulated safety data through the last follow-up visit. AEs leading to discontinuation from study intervention are assessed until Week 20 (last dose received). Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory test results.

9.3.2 Pharmacokinetics Endpoints

The secondary PK endpoints for the study are MK-8527 $AUC_{0\text{-last}}$ and C_{max}.

Exploratory PK endpoints are:

- PBMC MK-8527-MP, MK-8527-DP, and MK-8527-TP: $AUC_{0\text{-last}}$, C_{max}, C_{trough}, concentrations at common time points
- MK-8527-TP $AUC_{0\text{-last}}$, C_{trough}, C_{max}, and $t_{1/2}$

9.4 Analysis Populations

9.4.1 Safety Analysis Population

Safety Analyses will be conducted in the APaT population, which consists of all randomized/allocated participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will generally be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

9.4.2 PK Analysis Population

The PK analysis population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR.

9.5 Statistical Methods

9.5.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results.

The overall safety endpoints include the number of participants with at least one AE, SAE, drug-related AE, drug-related SAE, Grade 3 to 4 AE, drug-related Grade 3 to 4 AE, discontinuation from study intervention due to an AE; and AE resulting in death.

The safety evaluation will include a summary by treatment group of the number and percentage of participants with each type of AE. For overall safety endpoints, point estimates and 95% CIs for the differences between MK-8527 and placebo in the percentages of participants with events will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985].

For continuous safety measures, such as change from baseline in laboratory values, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

9.5.2 Statistical Methods for Pharmacokinetics Analyses

Plasma MK-8527 endpoints will be summarized separately by dose level as appropriate, with geometric means and %GCV.

9.6 Interim Analyses

The siDMC will be responsible for an interim safety review as specified in the SAP. An interim safety analysis will be performed once 50% of the planned enrollment has reached Week 12 or discontinued from study intervention. Additional details will be specified in the SAP/siDMC charter.

Study enrollment may be ongoing at the time of the IA. Blinding to treatment assignment will be maintained at all investigational sites. The results of the IA will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an internal unblinded statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study. Details will be provided in the SAP/siDMC charter.

9.7 Multiplicity

No multiplicity adjustment is planned for this study.

9.8 Sample Size and Power Calculations

The sample size of this study will allow for the accumulation of approximately 150 person-years of safety data on MK-8527.

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

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the siDMC regarding the study.

10.1.4.2 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate internal DMC will monitor the interim data from this study. The internal DMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The internal DMC will monitor the study progress for evidence of any adverse effects of study intervention. The internal DMC will also make recommendations to the Sponsor study team regarding steps to ensure both participant safety and the continued ethical integrity of the study in the internal DMC charter.

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 safety laboratory tests detailed in Table 10 will be tested by a regional central laboratory in South Africa or by a global central laboratory in all other countries participating in the study. The differences in blood volumes between Table 11 and Table 12 are due to use of 2 different testing laboratories. PK samples will be tested by contract laboratories or the Sponsor's bioanalytical group.
- Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

  Note: External circumstances may require participants to have local laboratory testing performed in place of samples being sent to the central laboratory for evaluation. Allowance for the use of local labs must be determined collaboratively between the Sponsor and the investigator and the site IRB/EC will be notified. The local laboratory results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 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.
- The investigator (or medically qualified designee) must document their review of each laboratory safety report.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- If a participant is confirmed HIV-infected and is unblinded, results from HIV-1 drug resistance testing may be provided to site personnel.
- If a participant is confirmed HIV-infected and is not unblinded, results from HIV-1 drug resistance testing will not be provided to site personnel who are directly involved in supporting the study, as there is the potential for the data to unblind the participants intervention group. HIV-1 drug resistance testing may be provided to site personnel not associated with the study. HIV-1 resistance results will be blinded to the study team and site personnel associated with the study.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Pregnancy	Urine Pregnancy Test (POCBP only) (Highly sensitive urine) human chorionic gonadotropin (hCG) pregnancy test (performed locally)
	Positive urine pregnancy to be confirmed with serum pregnancy test - Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test

Laboratory Assessments	Parameters
PT/INR	Activated partial thromboplastin time (APTT) Prothrombin time (PT) International normalized ratio prothrombin time (INR)
Hematology	Hematocrit (Hct)
	Hemoglobin (Hb)
	Red blood cell (RBC) Count
	White blood cell (WBC) Count
	Platelet Count
	Mean Corpuscular Hemoglobin (MCH)
	Mean Corpuscular Hemoglobin Concentration (MCHC)
	Mean Corpuscular Volume (MCV)
	Mean Platelet Volume (MPV)
	Red Cell Distribution Width (RDW)
	CBC, Nucleated RBC (%, abs)
	WBC Differential, Basophils (%, abs)
	WBC Differential, Eosinophils (%, abs)
	WBC Differential, Immature Granulocyte (%, abs)
	WBC Differential, Lymphocytes (%, abs)
	WBC Differential, Monocytes (%, abs)
	WBC Differential, Neutrophils, Total (%, abs)
TBNK Panel/CD4+ T-Cell count	T and B Lymphocytes and Natural Killer Cell profile includes the following assessments:
	CD3+CD4+ Percent
	CD3+CD4+ Value/Absolute Count
	CD3+CD8+ Percent
	CD3+CD8+ Value/Absolute Count
	CD4/CD8 Ratio
	And the following exploratory assessments (which do not need to be evaluated by the investigator)
	CD3+ CD45+ Percent
	CD3+ CD45+ Value/Absolute Count
	CD3-CD19+ Percent
	CD3-CD19+ Value/Absolute Count
	CD3-CD16+CD56+ Percent
	CD3-CD16+CD56+ Value/Absolute Count
	CD3+CD4+CD8+ Percent
	CD3+CD4+CD8+ Value/Absolute Count

Laboratory Assessments	Parameters
Chemistry	Albumin
	Alkaline Phosphatase (ALP)
	Alanine Aminotransferase (ALT/SGPT)
	Aspartate Aminotransferase (AST/SGOT)
	Amylase
	Bicarbonate
	Bilirubin, Direct
	Bilirubin, Indirect
	Bilirubin, Total
	Calcium (Ca)
	Chloride (Cl)
	Cholesterol, Total
	Creatine Phosphokinase (CPK)
	Creatinine
	Creatinine Clearance (calculated)
	Cystatin-C
	Gamma Glutamyl Transferase (GGT)
	Glucose (fasting)
	Glucose (random)
	Lactate Dehydrogenase (LDH)
	Lipase
	Magnesium (Mg)
	Phosphorous
	Potassium (K)
	Protein, Total
	Sodium (Na)
	Triglycerides
	Urea Nitrogen, Blood (BUN)
	Uric Acid
Hepatitis screen (Screening)	Hepatitis B virus surface antigen (HBsAg)
	Hepatitis B Serology (HBsAb/HBcAb)
	Hepatitis C virus (HCV) antibody
	Plasma Hepatitis C virus PCR quantitative test (performed if Hepatitis C virus antibody is positive)

Laboratory Assessments	Parameters
Virology	HIV-1/2 antibody + antigen screening test
	HIV-1/2 confirmation and differentiation test
	HIV-1 RNA PCR – to be performed if participant has a positive HIV-1/2 screening test result (or upon request)
	HIV-1 drug resistance testing - to be performed if HIV-1 RNA is ≥200 copies/mL (or upon request)
STI Testing (Screening)	**All participants:** Syphilis testing will be performed based on an algorithm including the following tests: Syphilis antibody screen, rapid plasma reagin [RPR], RPR titer, *Treponema pallidum* IgG, *Treponema pallidum* IgG index
	Female testing: Urine for Trichomonas, Gonorrhea (GC), Chlamydia (CT)
	Male testing: Urine for GC/CT
PK Sampling	Plasma for MK-8527 PK
	Peripheral blood mononuclear cells (PBMC) for PK – **PBMC Subset only**
	Venous Microsampling (Mitra®/VAMS) for PK
Biomarkers	Genetic analysis

CBC=complete blood count; HIV=human immunodeficiency virus; IgG=immunoglobulin G; PCR=polymerase chain reaction; PK=pharmacokinetic; POCBP=participant of childbearing potential; RNA-ribonucleic acid; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; VAMS=volumetric absorptive microsampling.

Table 11 Blood Volumes For Samples Collected From Participants in the United States and Israel

Study Period	**Screening**	**Intervention (Blinded)**										**Follow-up (Blinded)**					**HIV Infection Conf**	**Early Withdrawal From Study**
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20 \EOT[c]	FD 1	FW 4	FW 6[a]	FW 8	**Totals**	Unscheduled	Unscheduled
All Participants																		
HIV-1/2 Screen HIV-1/2 Confirmation and Differentiation	Off HBV/ HCV/HIV	3.5					3.5	3.5	3.5	3.5	3.5		3.5		3.5	28		3.5
HBV/HCV/HIV (Serology)	5															5		
HCV RNA (only tested if AB+)	3.5															3.5		
Syphilis	4															4		
PT/INR	2.7															2.7		
Serum pregnancy test (β-hCG) (POCBP only)	Off Chem															0		
Hematology	2	2	2				2	2	2	2	2	2	2		2	22	2	2
TBNK Panel/CD4+ T-cell Count	6	6	6				6	6	6	6	6	6	6		6	66	6	6
Chemistry	4	4					4	4	4	4	4		4		4	36		4
Cystatin-C	2	2					2	2	2	2	2		2		2	18		2
Plasma PK sample collection		9	3								6	3				21	3[b]	3[b]
Venous Microsampling (eg, Mitra®/VAMS)							2.6	2.6	2.6	2.6	2.6					13		
HIV-1 RNA PCR																0	6	
HIV-1 drug resistance testing																0	12	
Blood for Genetic Analysis		8.5														8.5		
Total Blood Volume per Visit in mL (All Participants)	29.2	35	11	0	0	0	20.1	20.1	20.1	20.1	26.1	11	17.5	0	17.5	227.7	29	20.5
PBMC Substudy Only																		
PBMC sample		32	16	16	16	16	16	16	16	16	32	16	16	16	16	256	16	16
Venous Microsampling (eg, Mitra®/VAMS)		2.6	2.6	2.6	2.6	2.6						2.6	2.6	2.6	2.6	23.4	2.6	2.6
Hematology				2	2	2								2		8		
TBNK Panel/CD4+ T-cell Count				6	6	6								6		24		
Chemistry				4	4	4								4		16		
Cystatin-C				2	2	2								2		8		

Study Period	**Screening**	**Intervention (Blinded)**										**Follow-up (Blinded)**					**HIV Infection Conf**	**Early Withdrawal From Study**
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2 [a]	Week 3 [a]	Week 4	Week 8	Week 12	Week 16	Week 20 \EOT[c]	FD 1	FW 4	FW 6[a]	FW 8	**Totals**	Unscheduled	Unscheduled
Additional Blood Volume Collected per Visit in mL (Participants in the PBMC Subset)		34.6	18.6	32.6	32.6	32.6	16	16	16	16	32	18.6	18.6	32.6	18.6	335.4	18.6	18.6

β-hCG=beta human chorionic gonadotropin; EOT=End of Treatment; FD=follow-up day; FW=follow-up week; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; INR=International Normalized Ratio; PK=pharmacokinetic(s); PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; POCBP=participant of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; TBNK=T- and B-Lymphocyte and Natural Killer Cell.
a. Visits at Week 1, Week 2, Week 3, and Follow-up Week 6 are for participants who provide consent to participate in the PBMC Subset only.
b. Not collected if the participant is beyond Follow-up Day 1.
c. If performed as an EOT visit (as per Section 1.3.1), not all samples are required therefore the blood volume is reduced; refer to Section 8.11.3 for additional details.

Table 12 Blood Volumes for Samples Collected From Participants in South Africa

Study Period	**Screening**	**Intervention (Blinded)**										**Follow-up (Blinded)**					**HIV Infection Conf**	**Early Withdrawal From Study**
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20 \EOT[c]	FD 1	FW 4	FW 6[a]	FW 8	**Totals**	Unscheduled	Unscheduled
All Participants																		
HIV Elisa 4th Generation HIV Confirmatory Test (Bio Rad Geenius)	3.5	3.5					3.5	3.5	3.5	3.5	3.5		3.5		3.5	31.5		3.5
HBV/HCV/HIV (Serology)	3.5															3.5		
HCV RNA (only tested if AB+)	3.5															3.5		
Syphilis	3.5															3.5		
PT/INR	2.7															2.7		
Serum pregnancy test (β-hCG) (POCBP only)	Off Chem															0		
Hematology	4	4	4	-	-	-	4	4	4	4	4	4	4	-	4	44	4	4
TBNK Panel/CD4+ T-cell Count	4	4	4	-	-	-	4	4	4	4	4	4	4	-	4	44	4	4
Chemistry	5	5					5	5	5	5	5		5		5	45		5
Cystatin-C	3.5	3.5					3.5	3.5	3.5	3.5	3.5		3.5		3.5	31.5		3.5
Plasma PK sample collection		9	3								6	3				21	3[b]	3[b]
Venous Microsampling (eg, Mitra®/VAMS)							2.6	2.6	2.6	2.6	2.6					13		
HIV-1 RNA PCR																0	6	
HIV-1 drug resistance testing																0	12	
Blood for Genetic Analysis		8.5														8.5		
Total Blood Volume per Visit in mL (All Participants)	33.2	37.5	11	0	0	0	22.6	22.6	22.6	22.6	28.6	11	20	0	20	251.7	29	23
PBMC Substudy Only																		
PBMC sample		32	16	16	16	16	16	16	16	16	32	16	16	16	16	256	16	16
Venous VAMS Microsampling		2.6	2.6	2.6	2.6	2.6						2.6	2.6	2.6	2.6	23.4	2.6	2.6
Hematology				4	4	4								4		16		
TBNK Panel/CD4+ T-cell Count				4	4	4								4		16		
Chemistry				5	5	5								5		20		
Cystatin-C				3.5	3.5	3.5								3.5		14		
Additional Blood Volume Collected per Visit in mL (Participants in the PBMC Subset)		34.6	18.6	35.1	35.1	35.1	16	16	16	16	32	18.6	18.6	35.1	18.6	345.4	18.6	18.6

Study Period	**Screening**	**Intervention (Blinded)**										**Follow-up (Blinded)**					**HIV Infection Conf**	**Early Withdrawal From Study**
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1[a]	Week 2[a]	Week 3[a]	Week 4	Week 8	Week 12	Week 16	Week 20 \EOT[c]	FD 1	FW 4	FW 6[a]	FW 8	**Totals**	Unscheduled	Unscheduled

β-hCG=beta human chorionic gonadotropin; EOT=End of Treatment; FD=follow-up day; FW=follow-up week; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; INR=International Normalized Ratio; PK=pharmacokinetic(s); PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; POCBP=participant of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; TBNK=T- and B-Lymphocyte and Natural Killer Cell.
a. Visits at Week 1, Week 2, Week 3, and Follow-up Week 6 are for participants who provide consent to participate in the PBMC Subset only.
b. Not collected if the participant is beyond Follow-up Day 1.
c. If performed as an EOT visit (as per Section 1.3.1), not all samples are required therefore the blood volume is reduced; refer to Section 8.11.3 for additional details.

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."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.3 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/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE that changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
  - Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
  - Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
  - Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
  - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
- **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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
- **Rechallenge:** Was the participant reexposed to the study intervention 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; (2) the study is a single-dose drug study; or (3) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, 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 study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (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.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

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 to this study.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant 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.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal 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, Müllerian 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
  - 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 participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal 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.

Participants of Nonchildbearing Potential (PONCBP)

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, are considered PONCBP:

- Premenopausal 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, Müllerian 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
  - 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 participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant • IUS[a] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[c] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] IUS is a progestin releasing IUD [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [c] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[c]

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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable to this study.

10.8 Appendix 8: Risk Evaluation

At each treatment and follow-up visit as specified in the SoA (Section 1.3.1 and Section 1.3.2), participants will be screened by appropriate study-site personnel for changes in HIV risk behaviors. The following questions should be used based on the CDC Recommended Indications for PrEP [Centers for Disease Control and Prevention 2018]:

- Are you sexually active?
  - If no, no further questions.
  - If yes, are you in a mutually monogamous partnership with a recently tested/known to be HIV-negative partner?
    - If yes, no further questions.
    - If no, is one or more of the following true?

    1. You are in an ongoing sexual relationship with an HIV-positive partner.
    2. You infrequently use condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (defined as a person who injects drugs, a man who has sex with men, someone sexually active with other partners where the HIV incidence is >3% as per WHO guidelines for PrEP) [World Health Organization 2015].
    3. You have had anal sex without condoms (receptive or insertive) since last visit.
    4. You have had a bacterial STI (syphilis, gonorrhea in women or men) diagnosed or reported since last visit.

    Any response of 'YES' to the above questions 1 through 4 should be considered a change in HIV risk status and consultation with the Sponsor is required prior to dispensing further study intervention.

Changes in HIV risk status may be discovered by the interviewer-administered questions above, participant's self-reporting or as deemed by the study investigator or designee upon medical history and/or physical exam review.

Increases in a participant's HIV risk status at any time during the study should be brought to the attention of the Sponsor. No further study intervention should be administered from the time the site is made aware of the change in risk status until the Sponsor has provided guidance.

Upon assessment of the increase in risk status, the Sponsor will determine: a) the appropriateness of continuing study intervention and/or b) the necessity to refer the participant for applicable services (eg, substance use, mental health, PrEP).

10.9 Appendix 9: Calculation of Creatinine Clearance

Cockcroft-Gault equations for participants ≥18 years old:

- If male:

$$\text{CrCL (mL/min)} = \frac{(140\text{-age [y]}) \times \text{weight [kg]})}{72 \times \text{serum creatinine (mg/dL)}}$$

- If female:

$$\text{CrCL (mL/min)} = \frac{(140\text{-age [y]}) \times \text{weight [kg]}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	area under the concentration-time curve from dosing to the time of the last measured concentration
AZT	azidothymidine
BSEP	bile salt export pump
C_{168}	concentration at 168 hours
CDC	Centers for Disease Control and Prevention
CG	Cockcroft-Gault
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by the SARS-CoV-2 virus
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	chlamydia trachomatis
CTFG	Clinical Trial Facilitation Group
C_{trough}	concentration reached by a drug immediately before the next dose is administered
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction

Abbreviation	Expanded Term
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DP	diphosphate
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EFV	efavirenz
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	End of Treatment
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
FTC	emtricitabine
GC	*Neisseria gonorrhoeae*
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GERD	gastroesophageal reflux disease
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2

Abbreviation	Expanded Term
HRT	hormone replacement therapy
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
IC_{50}	concentration of a drug or inhibitor needed to inhibit a biological process or response by 50%
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IM	intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir, MK-8591
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JRCT	Japan Registry of Clinical Trials
M&N	Miettinen & Nurminen method
MP	monophosphate
NCT	Clinicaltrials.gov identifier
NDA	New Drug Application
NNRTI	non- nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B1	organic anion transporting polypeptide 1B1
OCT2	organic cation transporter 2
PBMC	peripheral blood mononuclear cell

Abbreviation	Expanded Term
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
POCBP	participant of childbearing potential
PONCBP	participant of nonchildbearing potential
PrEP	pre-exposure prophylaxis
QM	once monthly
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
RNA	ribonucleic acid
RT	reverse transcriptase
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
siDMC	Standing Internal Data Monitoring Committee
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TAF	tenofovir alafenamide
TBNK	T- and B-lymphocyte and natural killer cell
TDF	tenofovir disoproxil

Abbreviation	Expanded Term
TFV	tenofovir
TP	triphosphate
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number
VAMS	volumetric absorptive microsampling
WBC	white blood cell
WHO	World Health Organization
ZDV	zidovudine

11 REFERENCES

[Aziz, N., et al 2019]	Aziz N, Quint JJ, Breen EC, Oishi J, Jamieson BD, Martinez-Maza O, et al. 30-year longitudinal study of hematological parameters of HIV-1 negative men participating in Los Angeles Multicenter AIDS Cohort Study (MACS). Lab Med. 2019;50:64-72.	[086QPX]
[Aziz, N., et al 2019a]	Aziz N, Jamieson BD, Quint JJ, Martinez-Maza O, Chow M, Detels R. Longitudinal Intra- and Inter-individual variation in T-cell subsets of HIV-infected and uninfected men participating in the LA Multi-Center AIDS Cohort Study. Medicine (Baltimore). 2019 Oct;98(41):e17525.	[086RQC]
[Burger, D., et al 2005]	Burger D, van der Heiden I, la Porte C, van der Ende M, Groeneveld P, Richter C, et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol. 2005;61(2):148-54.	[057GSX]
[Centers for Disease Control and Prevention 2018]	Centers for Disease Control and Prevention. US Public Health Service: preexposure prophylaxis for the prevention of HIV infection in the United States - 2017 update: a clinical practice guideline. Atlanta (GA): U.S. Department of Health and Human Services (HHS); 2018 Mar. 77 p.	[056CXJ]
[Chimukangara, B., et al 2019]	Chimukangara B, Lessells RJ, Rhee SY, Giandhari J, Kharsany ABM, Naidoo K, et al. Trends in pretreatment HIV-1 drug resistance in antiretroviral therapy-naive adults in South Africa, 2000-2016: a pooled sequence analysis. EClinicalMedicine. 2019;9:26-34.	[08BRQX]
[Department of HIV/AIDS 2015]	Department of HIV/AIDS. Transgender people and HIV. Geneva (Switzerland): World Health Organization (WHO); 2015 Jul. 32 p.	[05BDGP]

[Giovannoni, G., et al 2018]	Giovannoni G, Wiendl H, Turner B, Umans K, Mokliatchouk O, Castro-Borrero W, et al. Circulating lymphocyte levels and relationship with infection status in patients with relapsing-remitting multiple sclerosis treated with daclizumab beta. Mult Scler. 2018;24(13):1725-36.	[0856K9]
[Hojilla, J. C., et al 2021]	Hojilla JC, Hurley LB, Marcus JL, Silverberg MJ, Skarbinski J, Satre DD, et al. Characterization of HIV preexposure prophylaxis use behaviors and HIV incidence among US adults in an integrated health care system. JAMA Netw Open. 2021 Aug 26;4(8):e2122692.	[0898MB]
[Joint United Nations Programme on HIV/AIDS 2023]	Joint United Nations Programme on HIV/AIDS. UNAIDS data 2023. Geneva (Switzerland): Joint United Nations Programme on HIV/AIDS (UNAIDS); 2023. 434 p.	[08HR90]
[McClung, R. P., et al 2022]	McClung RP, Oster AM, Ocfemia MCB, Saduvala N, Heneine W, Johnson JA, et al. Transmitted drug resistance among human immunodeficiency virus (HIV)-1 diagnoses in the United States, 2014-2018. Clin Infect Dis. 2022 Mar 15;74(6):1055-62.	[08BRR3]
[Merayo-Chalico, J., et al 2013]	Merayo-Chalico J, Gomez-Martin D, Pineirua-Menendez A, Santana-De Anda K, Alcocer-Varela J. Lymphopenia as risk factor for development of severe infections in patients with systemic lupus erythematosus: a case-control study. QJM. 2013;106:451-7.	[0856KJ]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O and Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Nadkarni, G. N., et al 2015]	Nadkarni GN, Patel AA, Yacoub R, Benjo AM, Konstantinidis I, Annapureddy N, et al. The burden of dialysis-requiring acute kidney injury among hospitalized adults with HIV infection: a nationwide inpatient sample analysis. AIDS. 2015;29(9):1061-6.	[08B4DF]

[National Institute of Allergy and Infectious Diseases 2017]	National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [Internet]. Bethesda, MD: NIAID; 2017. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2.	[04R7PK]
[O Murchu, E., et al 2022]	O Murchu E, Marshall L, Teljeur C, Harrington P, Hayes C, Moran P, et al. Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. BMJ Open. 2022;12:e048478.	[0898LV]
[Poteat, T., et al 2016]	Poteat T, Scheim A, Xavier J, Reisner S, Baral S. Global epidemiology of HIV infection and related syndemics affecting transgender people. J Acquir Immune Defic Syndr. 2016 Aug 15;72(suppl 3):S210-9.	[05BDHN]
[Rhee, S. Y., et al 2020]	Rhee SY, Kassaye SG, Barrow G, Sundaramurthi JC, Jordan MR, Shafer RW. HIV-1 transmitted drug resistance surveillance: shifting trends in study design and prevalence estimates. J Int AIDS Soc. 2020;23:e25611.	[08BRRF]
[Ribaudo, H. J., et al 2013]	Ribaudo HJ, Smith KY, Robbins GK, Flexner C, Haubrich R, Chen Y, et al. Racial differences in response to antiretroviral therapy for HIV infection: an AIDS Clinical Trials Group (ACTG) study analysis. Clin Infect Dis. 2013 Dec 1;57(11):1607-17.	[057GSZ]
[Spiezia, A. L., et al 2022]	Spiezia AL, Cerbone V, Molinari EA, Capasso N, Lanzillo R, Carotenuto A, et al. Changes in lymphocytes, neutrophils and immunoglobulins in year-1 cladribine treatment in multiple sclerosis. Mult Scler Relat Disord. 2022;57:103431.	[0856K6]

[Statland, B. E., et al 1978]	Statland BE, Winkel P, Harris SC, Burdsall MJ, Saunders AM. Evaluation of biologic sources of variation of leukocyte counts and other hematologic quantities using very precise automated analyzers. Am J Clin Pathol. 1978 Jan;69(1):48-54.	[086RQD]
[Subesinghe, S., et al 2020]	Subesinghe S, Kleymann A, Rutherford AI, Bechman K, Norton S, Galloway JB. The association between lymphopenia and serious infection risk in rheumatoid arthritis. Rheumatology. 2020;59:762-6.	[0856KK]
[Tetteh, R. A., et al 2017]	Tetteh RA, Yankey BA, Nartey ET, Lartey M, Leufkens HGM, Dodoo ANO. Pre-exposure prophylaxis for HIV prevention: safety concerns. Drug Saf. 2017;40:273-83.	[056Q8V]
[Warny, M., et al 2018]	Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. PLoS Med. 2018 Nov 1;15(11):e1002685.	[0856KD]
[Weintrob, A. C., et al 2009]	Weintrob AC, Grandits GA, Agan BK, Ganesan A, Landrum ML, Crum-Cianflone NF, et al. Virologic response differences between African Americans and European Americans initiating highly active antiretroviral therapy with equal access to care. J Acquir Immune Defic Syndr. 2009 Dec 15;52(5):574-80.	[0576P6]
[World Health Organization 2015]	World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva (CH). World Health Organization; 2015. 78 p.	[04BNTH]
[World Health Organization 2022]	World Health Organization [Internet]. Geneva (Switzerland): World Health Organization (WHO); c2023. HIV [press release]. 2022 Nov 9 [cited 2023 Apr 12]; [about 9 screens]. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids.	[0896S3]

[Wyatt, C. M., et al 2006] Wyatt CM, Arons RR, Klotman PE, Klotman ME. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. AIDS. 2006;20(4):561-5. [08B4CN]