Official Protocol Title:	A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8591 Once-Monthly in Participants at Low-Risk for HIV-1 Infection
NCT number:	NCT04003103
Document Date:	08-Dec-2021

Title Page

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Protocol Title: A Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral MK-8591 Once-Monthly in Participants at Low-Risk for HIV-1 Infection

Protocol Number: 016-03

Compound Number: MK-8591

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

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

Regulatory Agency Identifying Number(s):

IND	128,595

Approval Date: 08 December 2021

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 03	08-DEC-2021	The protocol was amended to add monitoring of lymphocytes and CD4+ T-cells in response to findings of decreases in lymphocytes (in studies of participants with or without HIV) and CD4+ T-cell counts (in studies of participants with HIV) in ISL clinical studies.
Amendment 02	18-NOV-2020	To extend the screening window; to allow rescreening of participants; and to modify the primary safety objective to include data through the last follow-up visit
Amendment 01	14-OCT-2019	To add NET-EN as a contraceptive option for participants in the Implant/Depot DDI PK Subset. To provide operational clarifications and make editorial corrections.
Original Protocol	19-JUN-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

The protocol was amended to add monitoring of lymphocytes and CD4+ T-cells in response to findings of decreases in lymphocytes (in studies of participants with or without HIV) and CD4+ T-cell counts (in studies of participants with HIV) in ISL clinical studies.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities for the Extended, Unblinded PK Follow-up for Participants on MK-8591 in the PBMC/PK Bridging Subset Appendix 2: Table 7	Added hematology and CD4+ T-cell count sample collection at FW 36 and FW 44 for participants in the PBMC/PK bridging subset who remain in the study. Added CD4 assessment to the list of clinical laboratory assessments.	To add safety monitoring in response to findings of decreases in lymphocyte and CD4+ T-cell counts in a study in participants with HIV receiving a combination of ISL and another investigational drug. As dosing of participants has been completed and only PK substudy participants remain in the study, collection of hematology samples was not added to study visits that had already been completed by all participants at the time of this amendment.
2.3 Benefit/Risk Assessment	Updated the benefit/risk assessment to include a summary of data related to decreased lymphocyte and CD4+ T-cell counts.	Updated to reflect findings relevant to PrEP population.
8 Study Assessments and Procedures Appendix 2: Table 9	Updated blood volume based on additional hematology and CD4+ T-cell sample collection.	To reflect blood volume changes resulting from protocol updates.

Section # and Name	Description of Change	Brief Rationale
Throughout	Editorial revisions.	Minor editorial changes to the text.

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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-8591 Once-Monthly in Participants at Low-Risk for HIV-1 Infection

Short Title: Safety and PK Study of Oral MK-8591 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 trial. The following objectives will be evaluated in adults at low-risk of HIV-1 infection:

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of 6 once-monthly doses of MK-8591 (60 mg and 120 mg) through the last follow-up visit.	- Adverse events - Adverse events leading to discontinuation of study intervention
Secondary Objectives	Secondary Endpoints
- To evaluate the safety and tolerability of 6 once-monthly doses of MK-8591 (60 mg and 120 mg) with follow-up of 4 weeks after the last dose.	- Adverse events - Adverse events leading to discontinuation of study intervention
To characterize the **plasma** pharmacokinetic profile of MK-8591	Pharmacokinetic parameters: MK-8591 $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, $t_{1/2}$

Overall Design:

Study Phase	Phase 2
Primary Purpose	Prevention
Indication	Pre-exposure prophylaxis of HIV-1 Infection
Population	Adults at low-risk for HIV-1 infection
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Masking	Investigator Participant Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 33 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 250 participants will be randomized in a 2:2:1 ratio to 1 of 3 intervention groups: Group 1: MK-8591 60 mg (N ~ 100); Group 2: MK-8591 120 mg (N ~ 100); Group 3: placebo (N ~ 50).

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Levels	Dose Frequency	Route of Administration	Intervention Period[a]
Group 1	MK-8591	60 mg	Once monthly	Oral	24 weeks
Group 2	MK-8591	120 mg	Once monthly	Oral	24 weeks
Group 3	Placebo[b]	Placebo	Once monthly	Oral	24 weeks

[a] Last dose is administered at the Week 20 visit; final dosing period ends at Week 24.

[b] Placebo product is created by the Sponsor to match the active product (30 mg capsule of MK-8591).

Total Number

3 intervention groups (2 active, 1 placebo)

Duration of Participation

Participants will be in the study for approximately 42 weeks (or 74 weeks if in the PBMC/PK Bridging Subset) 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, each participant will receive 6 once-monthly doses of assigned intervention with the final dose administered at Week 20. After the intervention period is complete (at Week 24), each participant will be followed for 12 weeks. Participants in the PBMC/PK Bridging Subset who received MK-8591 will also complete an extended, unblinded PK follow-up period for an additional 32 weeks, for a total duration of participation of 74 weeks. Participants who discontinue study intervention early will be followed for 12 or 44 weeks after ending study intervention.

Sponsor approval is required to allow participants to be in the study for a longer duration than originally estimated; these cases will be determined collaboratively between the Sponsor and the investigator. In such cases, the site IRB/EC will be notified.

Study Governance Committees:

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

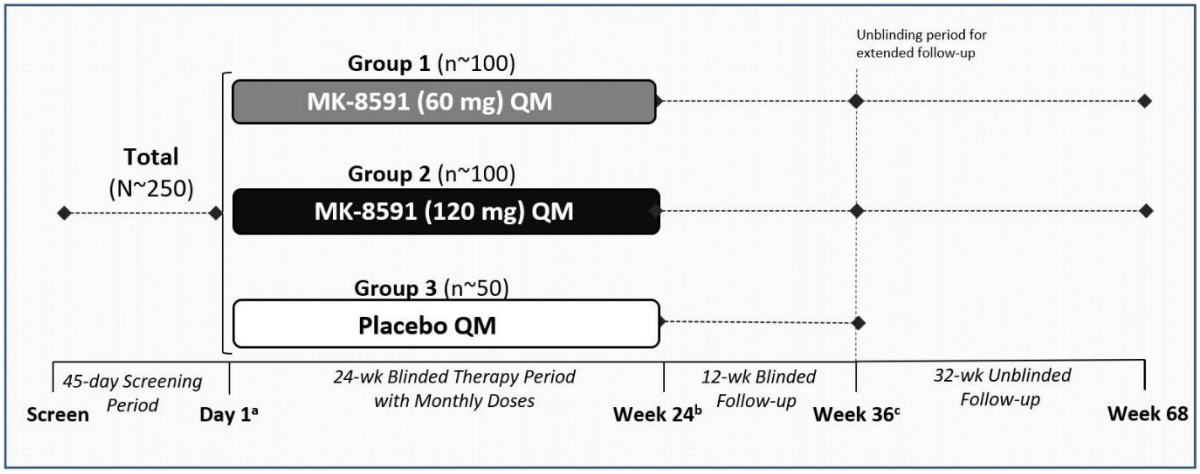
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



N=total number of participants in the study; n=number of participants in each treatment group; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; QM=once monthly; wk=week.

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

[b] *The Sponsor will be unblinded at Week 24. Participants and investigators/clinical site personnel will remain blinded up to Week 36.*

[c] *After Week 36, only participants in the PBMC/PK Bridging Subset who are randomized to receive MK-8591 will have an additional 32-week extended, unblinded PK follow-up through Week 68.*

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities (Base Study)

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
Administrative Procedures																					
Informed consent	X																				Providing documented informed consent for the main study will be considered the start of the screening window.
Informed consent for Future Biomedical Research	X																				
Participant identification card	X	X																			Add randomization number on Day 1.
Inclusion/ exclusion criteria (confirm eligibility)	X	X																			Review prior to dose on Day 1.
Register study visit in IRT	X	X	X	X	X	X	X	X	X	X	X				X						
Randomization		X																			
Dispense study intervention using IRT and administer		X					X	X	X	X	X										Directly observed dosing. Add randomization number and visit number to bottle at time of dispensing.

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
Offer condoms and lubricant		X					X	X	X	X	X				X			X	X		For sexually active participants. Document offer in participant chart.
Safety Procedures																					
Medical history	X	X																			
HIV-infection risk evaluation	X	X					X	X	X	X	X				X			X	X	X	Document in participant chart. Screening and Day 1 (prior to dose) based on Inclusion Criterion #3. Assess any changes in risk status and PrEP eligibility using Appendix 8 after randomization.
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Prior to dose on Day 1.
Contraceptive use confirmation	X	X					X	X	X	X	X				X			X	X	X	Prior to dose on Day 1. Document in participant chart.
Complete physical exam	X																				
Symptom-directed physical exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Prior to dose on Day 1.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Prior to dose on Day 1. Includes body temperature, pulse, respiratory rate, and systolic and diastolic blood pressure.
Height	X																				
Weight	X	X					X	X	X	X	X				X			X	X	X	Prior to dose on Day 1.
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Prior to and after dose on Day 1.

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
12-lead ECG	X										X										At Week 20, perform postdose.
DEXA scan for body composition and BMD (subset where allowed per country regulations)		X													X						Baseline scan can occur any time between confirmation of eligibility and before randomization (repeat baseline can be performed up to 14 days after randomization). Perform Week 24 scan ± 14 days of visit.
Laboratory Evaluations/Procedures																					
HIV-1 and HIV-2 Screen	X	X					X	X	X	X	X				X			X	X	X	Prior to dose on Day 1.
HBV and HCV testing	X																				
Syphilis serologic testing	X																				
Rectal swab GC/CT testing	X																				
Oropharyngeal swab GC/CT testing	X																				
Vaginal swab GC/CT & trichomoniasis testing (females only)	X																				
Urine GC/CT & trichomoniasis testing (males only)	X																				

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
Serum pregnancy test (β-hCG)	X																				Performed by the central laboratory per local regulations.
Urine pregnancy test (WOCBP only)		X					X	X	X	X	X				X			X	X	X	Performed by the local laboratory (kits provided) per local regulations. Prior to dosing on Day 1. Positive results to be confirmed with serum pregnancy test.[c]
Hematology	X	X					X	X	X	X	X				X			X	X	X	Collect Day 1 samples prior to dosing. Refer to Appendix 2 and laboratory manual for specific laboratory tests.
Chemistry	X	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	X	
Cystatin-C	X	X		X	X	X	X	X	X	X	X				X			X	X	X	
Urinalysis	X	X					X	X	X	X	X				X			X	X	X	
Urinary analytes		X							X						X					X	
Pharmacokinetics (All participants)																					
PK blood sample collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X						On Day 1 and Week 20, collect predose AND 30-min postdose. On Day 2 collect ~ 24 hours after Day 1 dose. On Weeks 4, 8, 12 and 16, collect predose.

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
Pharmacokinetics (PBMC/PK Bridging Subset)																					Participants are from pre-selected sites. Refer to laboratory/study operation manual for special collection and processing requirements.
Informed consent for PBMC/PK Bridging Subset sample collection	X																				
PBMC collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	At dosing visits, collect samples predose. On Day 2, collect ~ 24 hours after Day 1 dose. Mitra/VAMS™ venous sample at Day 1 and Week 20 are prepared from predose MK-8591 PK blood samples.
Mitra/VAMS™ collection-venous sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Pharmacokinetics (Tissue Biopsy Subset)																					Participants are from pre-selected sites. Refer to the laboratory/study operation manual for special collection and processing requirements.
Pap smear test (only females providing cervical biopsy sample)	X																				Not required if documented normal pap smear within 36 months of screening is available. Send to local laboratory before randomization.

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
Informed consent for Tissue Biopsy Subset sample collection	X																				
Pelvic and/or rectal examination	X			X			X								X				X		Perform rectal exam prior to rectal biopsy, and pelvic exam prior to cervical and/or vaginal biopsy. Document exam in participant chart.
Rectal, vaginal, cervical tissue sample collection				X			X								X				X		At Week 4, collect predose.
Post-biopsy contact (only participants providing biopsy sample)				X			X								X				X		Call within 48 hours of the biopsy and document in participant chart.
Pharmacokinetics (Implant/Depot DDI Subset)																					Participation is based on hormonal contraceptive use at screening (Section 8.6.4).
Informed consent for Implant/Depot DDI Subset sample collection	X																				
Blood sample collection for ENG, MPA, or NET levels	X	X		X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	On Day 1, Week 8 and Week 20, collect predose AND 30-min postdose. On Weeks 4, 12 and 16, collect predose.

Study Period	Screening	Intervention (Blinded)														Follow-up (Blinded)					Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2*	FW 2-3*	FW 4	FW 8	FW 12[a]	Calculate each visit from Day 1. * Only for PBMC/PK Bridging Subset
Visit Window (Days)	≤45 days	NA	+ 1 day	± 2 days				± 7 days				± 2 days							± 7 days		
Biomarkers/FBR																					
Blood for Genetic Analysis[b]		X																			Collect at predose from enrolled participants only.

AB=antibody; AE=adverse event; AG=antigen; β-hCG=beta human chorionic gonadotropin; BMD=bone mineral density; CG=Cockcroft-Gault; DDI=drug-drug interaction; DEXA=Dual X-ray Absorptiometry; DNA=deoxyribonucleic Acid; ECG=electrocardiogram; ENG=etonogestrel; FBR=future biomedical research; FW=follow-up week; GC/CT=Neisseria gonorrhoeae/Chlamydia trachomatis; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; MPA=medroxyprogesterone acetate; NA=not applicable; NET=norethisterone or norethindrone; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetics; PrEP=pre-exposure prophylaxis; WOCBP=a woman/women of childbearing potential.

[a] Participants who consent to participate in the PBMC/PK Bridging Subset and who are randomized to receive MK-8591 will have an additional 32-week extended, unblinded PK follow-up through Week 68 (FW 44 visit) (Section 1.3.2).

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

[c] For participants who become pregnant while receiving study intervention and consent to infant follow-up, their infant will have safety follow-up through approximately 1-year of age as outlined in the Schedule of Activities – Infant Safety Follow-up (Section 8.3.7).

1.3.2 Schedule of Activities for the Extended, Unblinded PK Follow-up for Participants on MK-8591 in the PBMC/PK Bridging Subset

Study Period	**Follow-up (Unblinded)**				Notes
Visit Number	21	22	23	24	
Scheduled Day/Week	FW 20	FW 28	FW 36	FW 44	Calculate each visit from Day 1.
Visit Window (Days)	±14 days				
HIV-infection risk evaluation	X	X	X	X	Document in participant chart. Assess any changes in risk status and PrEP eligibility (Appendix 8).
Concomitant medication review	X	X	X	X	
AE assessment [a]	X	X	X	X	
PBMC collection	X	X	X	X	
Hematology			X	X	
CD4+ T-cell count			X	X	

AE=adverse event; FW=follow-up week; HIV=human immunodeficiency virus; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; PrEP=pre-exposure prophylaxis; SAE=serious adverse event.

[a] During the extended, unblinded PK follow-up period (after FW 12 visit through FW 44 visit), only SAEs and nonserious AEs related to study procedures will be collected.

1.3.3 Schedule of Activities (HIV Infection Confirmation and Early Discontinuation)

Study Period	**HIV Infection Confirmation[a]**	**Early Discontinuation[b]**		**Notes**
Visit Number	Unscheduled			
Scheduled Day/Week	HIV Infection Confirmation	Early Discontinuation from Study Intervention	Early Withdrawal from Study	
Visit Window	Within 14 days of HIV-positive test	NA	NA	
Administrative Procedures				
Offer condoms and lubricant	X	X	X	For sexually active participants. Document offer in participant chart.
Register study visit in IRT		X		Only needed if discontinuation from study intervention occurs prior to the participant receiving the final dose at the Week 20 visit.
Safety Procedures				
HIV-infection risk evaluation	X	X	X	Document in participant chart. Assess any changes in risk status and PrEP eligibility (Appendix 8).
Concomitant medication review	X	X	X	
Contraceptive use confirmation	X	X	X	Document in participant chart.
Full physical exam		X	X	
Vital signs		X	X	Includes body temperature, pulse, respiratory rate, and systolic and diastolic blood pressure
Weight		X	X	
AE assessment	X	X	X	
12-lead ECG		X		Only needs to be performed once post randomization; should be done at the Early Discontinuation from Study Intervention visit for participants discontinuing from study intervention before the final dose at Week 20.

Study Period	**HIV Infection Confirmation[a]**	**Early Discontinuation[b]**		**Notes**
Visit Number	Unscheduled			
Scheduled Day/Week	HIV Infection Confirmation	Early Discontinuation from Study Intervention	Early Withdrawal from Study	
Visit Window	Within 14 days of HIV-positive test	NA	NA	
DEXA scan for body composition and BMD (subset where allowed per country regulations)		X	X	Only needs to be performed once post randomization, at the Early Discontinuation from Study Intervention visit for participants discontinuing from study intervention before the final dose at Week 20, or at the Early Withdrawal from Study visit for participants who withdraw from the study before the Week 24 study visit. Scans should preferably be performed within ±14 days of the discontinuation visit.
Laboratory Evaluations/Procedures				
HIV-1 and HIV-2 Screen		X	X	
HIV-1 RNA (real time PCR)	X			
HIV-1 drug resistance testing	X			
Hematology		X	X	Refer to Appendix 2 for list of specific laboratory tests.
Chemistry		X	X	
Creatinine clearance calculation (CG)		X	X	
Urinalysis		X	X	
Urinary analytes (if not done at Week 12 or 24)		X	X	
Urine pregnancy test (WOCBP only)		X	X	Conduct per local regulations. Positive results to be confirmed with serum pregnancy test.[c]
Pharmacokinetics (All participants)				
PK blood sample collection	X	X	X	Not required if participant is beyond Week 24.

Study Period	**HIV Infection Confirmation[a]**	**Early Discontinuation[b]**		**Notes**
Visit Number	Unscheduled			
Scheduled Day/Week	HIV Infection Confirmation	Early Discontinuation from Study Intervention	Early Withdrawal from Study	
Visit Window	Within 14 days of HIV-positive test	NA	NA	
Pharmacokinetics (PBMC/PK Bridging Subset)				Participants are from pre-selected sites. Refer to laboratory/study operation manual for special collection and processing requirements.
PBMC collection	X	X	X	
Mitra/VAMS™ sample collection- venous		X	X	Not required if participant is beyond Week 24.
Pharmacokinetics (Tissue Biopsy Subset)				Participants are from pre-selected sites. Refer to the laboratory/study operation manual for special collection and processing requirements.
Pelvic and/or rectal examination		X	X	Perform rectal exam prior to rectal biopsy, and pelvic exam prior to cervical and/or vaginal biopsy. Document exam in participant chart.
Rectal, vaginal, cervical tissue sample collection		X	X	
Post-biopsy contact (only participants who provided a biopsy)		X	X	Call **within 48 hours** of the biopsy and document in participant's chart.

Study Period	**HIV Infection Confirmation[a]**	**Early Discontinuation[b]**		**Notes**
Visit Number	Unscheduled			
Scheduled Day/Week	HIV Infection Confirmation	Early Discontinuation from Study Intervention	Early Withdrawal from Study	
Visit Window	Within 14 days of HIV-positive test	NA	NA	
Pharmacokinetics (Implant/Depot DDI Subset)				Participation is based on hormone contraceptive use at screening.
Blood sample collection for ENG, MPA, or NET levels		X	X	

blAB=antibody; AE=adverse event; AG=antigen; BMD=bone mineral density; CG=Cockcroft-Gault; DEXA=Dual X-ray Absorptiometry; ECG=electrocardiogram; ENG=etonogestrel; FW=follow-up; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; MPA=medroxyprogesterone acetate; NA=not applicable; NET=norethisterone or norethindrone; PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; WOCBP=a women/women of childbearing potential.

[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] For any participant who discontinues the study or study intervention early, follow-up should be conducted per Section 8.11.3.
An "Early Discontinuation from Study Intervention" visit is required if a participant discontinues study intervention before the final dose at Week 20. If a participant concurrently discontinues study intervention and withdraws from the study before the final dose at Week 20, then only the "Early Discontinuation from Study Intervention" visit needs to be performed.
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.

[c] For participants who become pregnant while receiving study intervention and consent to infant follow-up, their infant will have safety follow-up through approximately 1-year of age as outlined in the Schedule of Activities – Infant Safety Follow-up (Section 8.3.7).

2 INTRODUCTION

MK-8591 (also referred to as islatravir) is a novel, potent NRTTI being developed for treatment of HIV-1 infection and for prevention of HIV-1 infection in individuals currently uninfected with HIV-1 but who are at high risk of becoming infected.

2.1 Study Rationale

HIV-1 infection remains a worldwide epidemic with an estimated 36.9 million individuals infected globally [World Health Organization 2018]. Novel strategies to prevent HIV acquisition could help reduce the global burden. One proven biomedical intervention for the prevention of HIV-1 infection is PrEP. Despite FTC/TDF being approved in some countries for use as PrEP, in 2017 approximately 1.8 million new HIV-1 infections occurred worldwide [World Health Organization 2018]. The ongoing epidemic and new infection rate has resulted in a growing collective care burden, particularly as a chronic infection, with a risk for complications, that will require life-long treatment for each individual infected with HIV-1. Therefore, additional options for PrEP remain urgently needed.

Approval of FTC/TDF for PrEP was based on data from 2 Phase 3 studies, which demonstrated that efficacy is strongly correlated with adherence to daily therapy [Grant, R. M., et al 2010] [Baeten, J. M., et al 2012]; however, adherence to daily FTC/TDF had been shown to be suboptimal in many people at risk of HIV-1 infection [Marrazzo, J. M., et al 2015] [Hojilla, J. C., et al 2018].

MK-8591 is differentiated from other antiretrovirals based on its high potency, long half-life, favorable drug resistance profile, and broad pharmacologic distribution. Because of the long intracellular half-life of the active form of MK-8591-TP, a QM dosing regimen is being investigated. This dosing schedule is anticipated to facilitate adherence and be highly effective in preventing HIV-1 acquisition.

This Phase 2a study will evaluate the safety, tolerability, and PK of 2 doses of oral MK-8591 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 monthly dose of oral MK-8591 to be evaluated as PrEP in later efficacy studies.

2.2 Background

Refer to the IB for detailed background information on MK-8591.

2.2.1 Pharmaceutical and Therapeutic Background

MK-8591 is an antiretroviral agent, known as an NRTTI, which block HIV-1 reverse transcriptase by novel mechanisms of action. MK-8591 is an inactive nucleoside that is converted to the pharmacologically-active triphosphate form via endogenous intracellular kinases. It acts through multiple mechanisms, including both immediate chain termination by inhibiting translocation and delayed chain termination by preventing nucleotide excision [Michailidis E 2014].

MK-8591 is extremely potent at low doses and has a very long intracellular half-life. In a monotherapy, proof of concept study in treatment-naïve HIV-1-infected participants (MK-8591 Protocol 003), MK-8591, given in single doses as low as 0.5 mg, showed VL reductions greater than 1.0 $\log_{10}$ on average with no recrudescence for at least 7 days and no evidence of selection for any resistance-associated mutations. In healthy adult volunteers, MK-8591 has a plasma half-life of approximately 47 to 87 hours, while the active triphosphate (MK-8591-TP) demonstrates a half-life of approximately 120 to 210 hours in PBMCs. A rhesus macaque model demonstrated that levels of MK-8591-TP in rectal tissues were similar to those measured in vaginal tissues and both were at levels that suggest MK-8591 could be effective for prophylaxis against HIV-1 in both men and women [Grobler, J. A., et al 2017]. Similarly, at steady state with daily dosing, MK-8591-TP levels in rectal and vaginal tissues have been found to be generally similar to one another and to concurrent levels in PBMCs, at levels projected to be efficacious for treatment and prevention (MK-8591-009). Its high potency, long half-life and tissue distribution make MK-8591 a good candidate for further investigation as an HIV-chemoprophylactic agent.

2.3 Benefit/Risk Assessment

High potency against wild-type and resistant variants of HIV-1 virus, and a long half-life make ISL a suitable candidate for further development as a novel, long-acting PrEP agent. The comprehensive nonclinical safety evaluations of ISL, including developmental toxicity studies, have not revealed toxicities of concern. In a rhesus macaque SHIV intrarectal challenge model [Markowitz, M., et al 2019], ISL provided protection against infection at drug levels that are projected to be achieved with the dose regimen used in this study.

In a Phase 2 study (MK-8591-013) for once weekly HIV-1 treatment, decreases in lymphocyte and CD4+ T-cell counts from baseline were observed in the ISL 20 mg + MK-8507 treatment arms at Week 12 and Week 24. Decreases in lymphocytes were observed in all dosing arms of ISL + MK-8507 starting at Week 8 with further decreases continuing through Week 24. By Week 24, 20 of 58 participants on ISL + MK-8507 had a decrease in lymphocyte count of >30% (of which 9 had a >50% reduction). These reductions were more pronounced in the 2 higher MK-8507 dose arms (200 and 400 mg), potentially indicating a dose-response relationship. Dosing of ISL + MK-8507 in MK-8591-013 has been discontinued.

All clinical studies of ISL were evaluated for similar trends in lymphocytes and CD4+ T-cells across all indications and dosing regimens.

In 2 Phase 3 studies (MK-8591A-017 and MK-8591A-018) evaluating a switch to daily DOR/ISL in virologically suppressed participants, at Week 48 there were 10.6% and 8.5% mean decreases in lymphocyte counts from baseline in the DOR/ISL groups, compared with 2.27% and 3.46% increases from baseline in the comparator arms. In the same studies, DOR/ISL-treated participants experienced a mean change in CD4+ T-cell counts of -0.7% and 0.9%, compared with an increase of 8.7% in the baseline ART group and 12.8% in the BIC/FTC/TAF group. At this time, the data review support continuation of the Phase 3 clinical studies for the DOR/ISL daily HIV-1 treatment program.

Among participants in this study (MK-8591-016) at study Week 24, there was a 21% mean decrease in total lymphocytes observed in the 60 mg arm (the dose being evaluated in Phase 3 PrEP trials), a 36% decrease in total lymphocytes observed in the 120 mg arm, and a 4% increase in the placebo arm compared to baseline values. Less than 5% of the participants in the ISL 60 mg arm had a >50% reduction in total lymphocyte counts during the study with 3 of 95 participants reporting Grade 2 lymphocyte reductions and 1of 95 participants reporting a transient Grade 3 lymphocyte reduction (transient). Two (2 of 97) participants in the 120 mg arm had Grade 3 lymphocyte reductions. In this population of HIV-1 uninfected participants, the mean decreases in lymphocytes were in the normal range and there was no increase in clinical AEs related to infection. At this time, the data review support continuation of clinical studies for the ISL HIV-1 PrEP program with a dose of 60 mg monthly.

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. In this case, MK-8591 is being developed for the prevention of HIV-1 infection, and participants will be neither HIV-1–infected nor at high risk of infection, further reducing the potential for direct individual benefit.

Additional details regarding specific benefits and risks for participants 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 trial. The following objectives will be evaluated in adults at low-risk of HIV-1 infection:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of 6 once-monthly doses of MK-8591 (60 mg and 120 mg) through the last follow-up visit.	• Adverse events • Adverse events leading to discontinuation of study intervention
Secondary	
• To evaluate the safety and tolerability of 6 once-monthly doses of MK-8591 (60 mg and 120 mg) with follow-up of 4 weeks after the last dose.	• Adverse events • Adverse events leading to discontinuation of study intervention
• To characterize the **plasma** pharmacokinetic profile of MK-8591.	• Pharmacokinetic parameters: MK-8591 $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, $t_{1/2}$

Objectives	Endpoints
Exploratory	
• To characterize the intracellular pharmacokinetic profile of MK-8591-triphosphate in **peripheral blood mononuclear cells** up to 48 weeks after the last dose of 6 once-monthly doses of MK-8591 (60 mg and 120 mg).	• Pharmacokinetic parameters: MK-8591-triphosphate $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, $t_{1/2}$
• To evaluate the amount of MK-8591, MK-8591-triphosphate, and MK-8591-diphosphate in rectal, vaginal, and cervical tissue.	• MK-8591, MK-8591-triphosphate, and MK-8591-diphosphate tissue concentration
• To measure the plasma concentrations of etonogestrel, medroxyprogesterone acetate, and norethindrone among females who use an etonogestrel-releasing implant or injectable depot medroxyprogesterone acetate or injectable norethindrone enanthate.	• Plasma concentrations of etonogestrel, medroxyprogesterone acetate, and norethindrone
• 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

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of oral MK-8591 (also referred to as islatravir) administered QM in adults who are at low-risk of HIV-1 infection.

Approximately 250 participants will be randomized in a 2:2:1 ratio to 1 of 3 intervention groups (Group 1: MK-8591 60 mg; Group 2: MK-8591 120 mg; Group 3: placebo). At least 40% of the study population will be women, at least 80% will be 45 years or younger, and at least 30% will be enrolled in Africa. Randomization will be stratified by sex (female, male) and region (Africa, non-Africa).

This study consists of a screening period (45 days), intervention period (24 weeks), and a follow-up period (12 or 44 weeks). Sponsor approval is required to allow participants to be in the study for a longer duration than originally estimated; these cases will be determined

collaboratively between the Sponsor and the investigator. In such cases, the site IRB/EC will be notified.

During the intervention period, participants will receive a total of 6 oral doses of the assigned blinded study intervention (MK-8591 [60 mg or 120 mg] or placebo), 1 dose every 4 weeks, starting on Day 1. The final dose will be administered at the Week 20 visit with the final dosing period through the Week 24 visit. All participants will complete a follow-up period for 12 weeks after the last dosing period (ie, for 12 weeks beyond Week 24). Participants who consent to participate in the PBMC/PK Bridging Subset and are randomized to receive MK-8591 will have extended unblinded PK follow-up through Week 68 (ie, FW 44 visit) (Section 1.3.2) and participants who discontinue study intervention early will be followed for 12 or 44 weeks after stopping study intervention, respectively.

The primary safety assessment will include all accumulated safety data during the intervention and follow-up period. AEs leading to discontinuation from study intervention are assessed until Week 20 (last dose received). During the extended, unblinded PK follow-up period (after FW 12 visit through FW 44 visit), only SAEs and nonserious AEs related to study procedures will be collected. The Sponsor will perform ongoing comprehensive review of all relevant safety parameters including AEs and laboratory values to assess for overall trends and outliers in reported AEs and event toxicities per standard monitoring procedures.

All participants will also be evaluated for plasma PK drug levels. Participants may also agree to participate in the following optional PK subsets:

- PBMC/PK Bridging Subset (approximately n = 80): Participants will have PBMCs collected to measure MK-8591 and analyte drug levels. In parallel, blood samples will be collected using the Mitra/VAMS™ PK collection method to assess concordance between these 2 different sampling methods.

- Tissue Biopsy Subset (approximately n = 40): Participants will have rectal, cervical and/or vaginal tissues biopsies collected to analyze MK-8591 and analyte drug levels in tissue.

- Implant/Depot DDI Subset (approximately n = 30): Female participants who are using an ENG-releasing implant (ie, Nexplanon® or Implanon NXT®) or injectable-MPA or injectable-NET-EN (eg, Noristerat, Syngestal) will have blood samples collected to measure plasma concentrations of these hormonal contraceptives.

At Week 24, the Sponsor will be unblinded but participants and investigators/clinical site personnel will remain blinded up to Week 36 (FW 12 visit). Participants in the PBMC/PK Bridging Subset will be unblinded to MK-8591/placebo after Week 36 (FW 12) and prior to Week 44, but will remain blinded, along with their respective investigators/clinical site personnel, to MK-8591 dose (60 mg versus 120 mg). Only participants assigned to MK-8591 in the PBMC/PK Bridging Subset will continue in the 32-week extended, unblinded PK follow-up period through Week 68 (FW 44 visit). Refer to the study binder for more details on the unblinding procedure.

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

4.2 Scientific Rationale for Study Design

The main objective of this study is to characterize the safety, tolerability, and PK of MK-8591 in a larger and more diverse population than studied to date. The study will enroll participants who are at low-risk of HIV-1 infection, and as such, this is not an efficacy study. 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 is an approved product (FTC/TDF).

Based on population PK predictions for QM administration from clinical experience to date, MK-8591 doses of 60 mg and 120 mg QM are predicted to achieve threshold levels for HIV-1 prevention that would last more than 4 weeks. Further, simulations using a population PK model based on Phase 1 study data predict that after 1 dose of 60 mg or 120 mg, intracellular MK-8591-TP levels may persist above the threshold concentration for more than 8 weeks (Section 4.3). Therefore, in this study, participants will be followed for 12 to 44 weeks after the last dosing period of MK-8591 is completed at Week 24 to allow full characterization of the MK-8591-TP PK profile.

The number of participants (N ~ 250) and the 24-week intervention period duration allows characterization of the safety profile of MK-8591 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, ≥80% of the participants enrolled in this study will be ≤45 years, ≥40% will be women, and ≥30% will be enrolled in Africa.

4.2.1 Rationale for Endpoints

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 (hematology, chemistry, and urinalysis) 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.

Lipodystrophy and decreases in BMD have been reported in HIV-1-infected individuals taking some antiretroviral agents [AIDS info 2017] [Brown, T. T. 2006]. Based on the preclinical and clinical data to date, MK-8591 has not been associated with lipodystrophy or BMD issues. This study provides a greater opportunity to assess whether MK-8591 has any effect on body fat distribution or BMD because, unlike in HIV-1 treatment studies, participants are neither infected with HIV nor on any other antiretroviral agents. Assessments

of spine and hip BMD, as well as distribution of peripheral and trunk fat, will be conducted with DEXA scans per the SoA (Section 1.3) to evaluate if changes are observed with the use of 60 mg and 120 mg MK-8591 compared to each other and to placebo.

Additionally, 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 [Tetteh, R. A., et al 2017]. This study provides the opportunity to evaluate the impact of MK-8591 on renal functions as measured by laboratory markers, such as urinary (eg, albumin, protein, creatinine, B-2M/Cr, RBP/Cr) and serum (eg, creatinine, cystatin-C, and creatinine clearance) analytes and calculations.

4.2.1.2 Pharmacokinetic Endpoints

Sparse plasma PK samples will be collected from all participants and the data will be used in a population PK model for MK-8591 and MK-8591-TP levels (Section 8.6).

4.2.1.2.1 PBMC/PK Bridging Subset

The PBMC data collected from the PBMC/PK Bridging Subset will be used as part of the population PK model for MK-8591 and MK-8591-TP levels (Section 8.6). The Mitra/VAMS™ venous PK samples will not be used to evaluate the MK-8591 doses but rather to establish a correlation between this sampling method to more standard in-clinic PK sample collection methods (venipuncture) for potential use in future studies.

4.2.1.2.2 Tissue Biopsy Subset

Tissue biopsies will be performed at 4 different timepoints to collect rectal, vaginal, and/or cervical tissue samples to measure the tissue concentrations of MK-8591, MK-8591-TP, and MK-8591-DP as described in the SoA (Section 1.3) and Section 8.6. The reason for including the MK-8591-DP in tissue concentrations measurement is to confirm and cross validate the MK-8591-TP to MK-8591-DP ratio. Moreover, this will also confirm stabilization of the tissue samples. The extent of antiretroviral penetration into genital tract mucosa may have implications for the prevention of sexual transmission of HIV. Therefore, the extent of MK-8591 penetration to genital tract tissue will be measured in rectal (males and females) and vaginal and cervical mucosal tissue (females only). In addition, there is evidence that HIV may reside within anatomical “sanctuary sites,” where local drug exposure and viral dynamics may differ from those in the systemic compartment [Else, L. J., et al 2011]. Poor penetration of antiretrovirals into the mucosa of the genital tract might lead to suboptimal antiretroviral concentrations in these areas, leading to compartmentalized viral replication and re-entry of wild-type or drug-resistant strains into the systemic circulation [Else, L. J., et al 2011].

4.2.1.2.3 Implant/Depot DDI Subset

Plasma samples to measure concentrations of ENG, MPA, or NET will be collected as described in the SoA (Section 1.3) and Section 8.6. Although a Phase 1 clinical pharmacology DDI study (MK-8591 Protocol 006) of oral contraceptive pills (levorgestrel

0.15 mg/ethinyl estradiol 0.03 mg) did not find any interactions with MK-8591, ENG-releasing implants, injectable-MPA, and injectable-NET-EN deliver and maintain relatively lower levels of systemic hormones compared to daily, oral contraceptives. Because ENG, MPA, and NET are metabolized via cytochrome P-450 3A4, which is the same metabolic pathway of levorgestrel and ethinyl estradiol, no DDIs are expected between ENG, MPA, or NET, and MK-8591. It is important, however, to evaluate these potential DDIs, as females who are at risk for sexual acquisition of HIV-1 infection may also be at risk for unintended pregnancy and want to prevent pregnancy with the use of implanted and injected hormones for contraception.

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 absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), 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 multi-study 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 future biomedical research 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 (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

The primary goal of the study is to evaluate the safety and tolerability of oral MK-8591 in a population with low-risk of HIV-1-infection. A placebo-controlled study will allow for a robust, unbiased evaluation of the safety and tolerability profile of MK-8591.

4.2.3 Rationale for Collecting Race and Ethnicity

Differential effects on safety and efficacy based on any demographic parameter, including race or ethnicity, cannot be predicted for a new investigational intervention. Therefore, it is important to collect race and ethnicity data to investigate such differential effects prospectively. Furthermore, it is important to record these demographic parameters to ensure the results observed in the clinical study will be applicable to and representative of the intervention's use in a broader patient population. As 1 example, non-Caucasian females and males were found to have higher plasma concentrations of EFV (an NNRTI) than their Caucasian counterparts. These findings could indicate an increased risk of EFV-induced toxicity in non-Caucasian patients [Burger, D., et al 2005]. As another example, among the population with HIV in the United States, those of African heritage have been found to be less likely to maintain virologic suppression compared to other groups and the factors contributing to this remain to be elucidated [Weintrob, A. C., et al 2009] [Ribaudo, H. J., et al 2013]. Thus, sub group analyses on race and ethnicity will be performed to better understand how these parameters may influence clinical outcome and toxicity.

4.2.4 Rationale for Collecting Infant Safety Follow-up Data

Although women who become pregnant during the study will be required to discontinue study intervention, it is important to collect information on infants born to participants who become pregnant while receiving MK-8591. Follow-up through 1-year of age for infants born to participants who become pregnant while receiving study intervention provides the ability to monitor growth and development as well as potential adverse effects that may be associated with prenatal drug exposure. Growth parameters (ie, length, weight, and head circumference) within normal range at approximately 1-year of age are key noninvasive indicators that a serious congenital malformation caused by in utero drug exposure is unlikely.

4.3 Justification for Dose

MK-8591 has been evaluated in 8 completed Phase 1 clinical studies and is currently being evaluated in 8 ongoing studies (2 Phase 1 studies, 2 Phase 2 studies [including the current study], and 4 Phase 3 studies).

In HIV-1 -infected and -uninfected adult participants, MK-8591 has demonstrated good tolerability when administered: as a single oral dose of up to 400 mg; as 3 once-weekly doses of up to 100 mg; as a daily dose of 5 mg for 6 weeks; and as 0.25 mg, 0.75 mg and 2.25 mg daily for at least 48 weeks (the treatment study of these doses is currently ongoing).

In a Phase 1 study (MK-8591 Protocol 003) among HIV-1-infected, treatment-naïve participants, MK-8591 0.5 mg × 1 resulted in plasma HIV-1 RNA reduction of more than 1.0 $\log_{10}$ copies/mL. In a rhesus macaque study, weekly administration of MK-8591 resulted in statistically significant protection against Simian/HIV infection with a MK-8591-TP EC_{90} of ≈ 24 fmol/10^6 PBMC (or 0.024 pmol/10^6 cells) [Markowitz, M., et al 2019]. Based on these and other data [Deeks, S. G., et al 1998] [Anderson, P. L., et al 2014] [Anderson, P. L., et al 2012], a conservative PK threshold of 0.05 pmol/10^6 cells was chosen, which is approximately 5- to 7-fold above the in vitro IC_{50} for MK-8591.

Based on preclinical data and Phase 1 population PK modeling, a 60-mg dose is anticipated to achieve the threshold concentration of 0.05 pmol/10^6 cells of MK-8591-TP required for HIV-1 prevention efficacy for at least 4 weeks following each dose. In addition, a 120-mg dose will exceed the threshold concentration for at least 4 weeks following each dose and will also provide additional safety data with longer-term dosing at this level. Furthermore, MK-8591-TP levels in rectal and vaginal tissues have been found to be generally similar to one another and to concurrent levels in PBMCs, at levels projected to be efficacious for treatment and prevention, suggesting protective levels will be maintained in anatomical sites of potential exposure to HIV-1 (MK-8591-009). This study will fully evaluate the duration of efficacious levels/concentrations with follow-up and evaluation through an extended PK washout of 12 to 44 weeks following the final dosing period.

Refer to the current IB for other preclinical and clinical data supporting dose selection for 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 (ie, the participant is unable to be contacted by the investigator).

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/clinical endpoints 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 due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/Female participants between the ages of 18 and 65 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is in general good health with laboratory values at screening within the acceptable ranges in the protocol.

    - Hemoglobin ≥10.5 g/dL for females and ≥11 g/dL for males
    - 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)
    - ALT and AST <1.25 x 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)

    Note: Chemistry and hematology parameters which do not meet the inclusion criteria above may be repeated once during the screening period.

2. 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.

3. 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;
    - 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 a 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 antiretroviral therapy for HIV-1 infection PrEP or post-exposure prophylaxis.

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

Demographics

4. Is male or female, from 18 years to 65 years of age inclusive, at the time of signing the informed consent.

Contraception/Pregnancy

Male Participants

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

Female Participants

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

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

   Is not a WOCBP

   OR

   Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 16 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.

   A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before the first dose of study 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 located in Appendix 2.

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

Informed Consent

6. The participant (or legally acceptable representative) provides documented informed consent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

For female participants, the following criteria must also be met to provide cervical biopsy samples in the Tissue Biopsy Subset:

7. Has an acceptable Pap result documented within 36 months prior to randomization. *Note: Acceptable results are described in Section 8.1.4.*

For female participants, the following criteria must also be met to enroll in the Implant/Depot DDI Subset:

8. Is currently using an ENG-releasing implant (ie, Nexplanon or Implanon NXT) or injectable-MPA or injectable-NET-EN.

5.2 Exclusion Criteria

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

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 30 days prior to Day 1 through the duration of the study.

   Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) will be 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 through the duration of the study.

7. Has previously been randomized in a study and received MK-8591.

Diagnostic Assessments

8. Has QTc interval (using Fridericia correction) >450 msec (for males) or >460 msec (for females) or deemed clinically abnormal by the investigator.

Other Exclusions

9. Is female and expecting to conceive or donate eggs at any time during the study.

   Note: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study intervention. Consistent with the recommendations for contraceptive use, it is recommended that all female participants refrain from egg donation for 16 weeks after their last dose of study intervention.

   Note: Donation of sperm should follow local guidelines for men who are participating in a clinical study of an investigational product.

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.

Additionally, a participant will be excluded from the Tissue Biopsy Subset, if the participant:

11. Is unwilling to abstain from the following prohibited therapies:

    - aspirin or NSAIDS for 7 days before biopsy.

      Note: Daily or as needed use of low-dose aspirin (no more than 81 mg) is permitted.

    - heparin, enoxaparin, warfarin, clopidogrel, factor Xa inhibitors, and any other drugs that are associated with increased risk of bleeding for 3 days before biopsy and for 7 days post-biopsy.

A participant will be excluded from providing a rectal, cervical and/or vaginal biopsy samples, if he or she:

12. Has carcinoma in situ of the cervix or invasive cervical cancer, rectal cancer, or abnormalities of the mucosa, or significant localizing symptom(s), including but not limited to presence of any unresolved injury, and infectious or inflammatory condition of the local mucosa.

A female participant will be excluded from providing cervical biopsy samples, if she:

13. Had a hysterectomy procedure and the cervix was removed (total hysterectomy).

5.3 Lifestyle Considerations

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

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 Consolidated Standards of Reporting Trials (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 interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name[a]	Arm Type	Intervention Name	Type	Dose Formulation[b]	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Intervention Period	Use	IMP/ NIMP[c]	Sourcing
Group 1	Experi-mental	MK-8591	Drug	Capsule	30 mg	60 mg QM	Oral	Day 1 to Week 24	Experimental	IMP	Central
Group 1	Experi-mental	Placebo	Drug	Capsule	0 mg	0 mg QM	Oral	Day 1 to Week 24	Placebo	IMP	Central
Group 2	Experi-mental	MK-8591	Drug	Capsule	30 mg	120 mg QM	Oral	Day 1 to Week 24	Experimental	IMP	Central
Group 3	Placebo Compar-ator	Placebo	Drug	Capsule	0 mg	0 mg QM	Oral	Day 1 to Week 24	Placebo	IMP	Central

IMP=investigational medicinal product; NIMP=non-investigational medicinal product; QM=once monthly.

[a] Each participant will take 4 capsules for each dose. Participants in Group 1 (60 mg MK-8591) will receive 2 capsules of 30 mg MK-8591 and 2 capsules of matching placebo; thus, these 2 types of study intervention are listed for Group 1.

[b] Capsules should be swallowed whole.

[c] Definition IMP and NIMP is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

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 interactive response technology (IRT) system. There are 3 study intervention arms. Participants will be assigned randomly in a 2:2:1 ratio to MK-8591 (60 mg), MK-8591 (120 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-8591 and matching placebo will be packaged identically so that blind is maintained.

The Sponsor will be unblinded at Week 24 to allow for an interim evaluation of safety. Participants and investigators/clinical site personnel will remain blinded up to Week 36 (FW 12 visit). Participants in the PBMC/PK Bridging Subset will be unblinded to MK-8591/placebo after Week 36 (FW 12) and prior to Week 44, but will remain blinded, along with their respective investigator/clinical site personnel, to MK-8591 dose (60 mg versus 120 mg). Refer to the study binder for more details on the unblinding procedure.

To allow timely completion of population PK modeling, Sponsor PK personnel will be unblinded for the duration of the study. No personnel directly associated with study conduct will be unblinded before Week 24. Before granting access to select personnel to unblinded drug concentration data and information relevant for population PK modeling (eg, including, but not limited to PK sampling schedules, dosing records, etc.), an official memo detailing the unblinding procedures and listing of the personnel who will have access (before database lock) to the unblinded PK and relevant data will be generated per Sponsor SOP.

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment of ≥1 monthly dose require consultation between the site and the Sponsor and written documentation of the collaborative decision on participant management.

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 from 30 days before receiving study intervention through the study duration for all participants:

- Investigational agents (including devices), except for study intervention(s)

  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 16-weeks from the last dose of MK-8591 Protocol 016 study intervention.

- Immune therapy agents, immune modulators, or other immunosuppressive therapies

  Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) is allowed.

In addition, for participants (at selected sites) enrolled in the Tissue Subset:

- Use of aspirin or NSAIDS is not permitted for 7 days before biopsy.

  Note: Daily or as needed use of low-dose aspirin (81 mg or less) is permitted.

- Use of heparin, enoxaparin, warfarin, clopidogrel, factor Xa inhibitors, and any other drugs that are associated with increased risk of bleeding is not permitted for 3 days before biopsy and for 7 days post-biopsy.

There are no restrictions identified for MK-8591 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 antiretroviral therapy 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). In the event that 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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified intervention period will still continue to participate in the study as specified in the SoA (Section 1.3) and Section 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.11.3.

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 has been unblinded before Week 24 by the investigator or through the emergency unblinding call center. If the participant's treatment assignment has been unblinded before Week 24 by the Sponsor, the need for the participant to be discontinued from study intervention should be discussed 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), 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 (eg, lymphoma) 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 Week 36 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 antiretroviral therapy will be provided by the study.

- The participant has 1 of the following events that are life-threatening AND assessed by the investigator to be study drug-related:

    - SAE

    OR

    - Grade 4 laboratory AE

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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 9.

See Appendix 2 for detailed list of blood volume collections per sample type and visit. As shown in Appendix 2, the amount of blood collected for a participant is dependent on which subset(s) the participant is included in. Participants who consent to participate in the PBMC/PK Bridging Subset and received MK-8591 will have extended, unblinded PK follow-up through Week 68 (FW 44 visit) including collection of an additional 80 mL of blood.

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 or restarted on study intervention after an extended off-drug period. Further, per this amendment, the OnDemand™ device and Mitra/VAMS™ fingerstick samples are no longer being collected in this study. Therefore, the total amount of blood collected for a participant may be changed beyond what is listed in Appendix 2.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research 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 future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

8.1.1.3 Consent for PBMC/PK Bridging Subset

The investigator or medically qualified designee will explain the PBMC/PK bridging consent to the participant, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to the PBMC/PK Bridging Subset. Participants who consent to participate in the PBMC/PK Bridging Subset and who are randomized to MK-8591 will have extended, unblinded PK follow-up through Week 68 (FW 44 visit) (Section 1.3.2). A copy of the informed consent will be given to the participant.

8.1.1.4 Consent for Tissue Biopsy Subset

The investigator or medically qualified designee will explain the tissue biopsy consent to the participant, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to the Tissue Biopsy Subset. A copy of the informed consent will be given to the participant.

8.1.1.5 Consent for Implant/Depot DDI Subset

The investigator or medically qualified designee will explain the implant/depot DDI consent to the participant, answer all of her questions, and obtain documented informed consent before performing any procedure related to the Implant/Depot DDI Subset. A copy of the informed consent will be given to the participant.

8.1.1.6 Consent for Infant Safety Follow-up

Depending on applicable laws and regulations, a separate informed consent may be required for participation in the infant safety follow-up period (Section 8.3.7). If a separate consent is required, the investigator or medically qualified designee will explain the infant safety follow-up consent to the participant (or their legally acceptable representative), answer all questions, and obtain documented informed consent before collecting any data related to the infant follow-up. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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.

For female participants (at selected sites) interested in providing a cervical biopsy sample as part of the Tissue Biopsy Subset, the following criteria need to be met prior to randomization:

- Documentation is available indicating acceptable Pap results in the 36 months before the screening date. An acceptable Pap result is defined as a biopsy consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, November 2007.

  OR

- A Pap test can be performed by the site (sent to local laboratory for processing) before randomization. If Pap testing is indicated and the participant declines, she can still provide a rectal and vaginal biopsy sample (assuming all other criteria are met) but are not eligible to provide a cervical biopsy sample during the study.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 30 days before first dose of study intervention.

For female participants in the Implant/Depot DDI Subset, the most recent date of an ENG-releasing implant insertion or MPA injection or NET-EN injection (before the first dose of study intervention) should be recorded in the appropriate eCRF.

8.1.5.2 Concomitant Medications

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

For female participants in the Implant/Depot DDI Subset, the dates of all ENG-releasing implant insertions or MPA injection or NET-EN injection received during the study, including the follow-up period, should be recorded in the appropriate eCRF.

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

All study intervention will be administered at the clinic/investigative site once per month 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, 2 bottles of blinded study intervention will be dispensed per participant, each containing 2 capsules (MK-8591 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-8591 60 mg): participants will receive 2 capsules of MK-8591 30 mg and 2 capsules of matching placebo.
- Group 2 (MK-8591 120 mg): participants will receive 4 capsules of MK-8591 30 mg.
- Group 3 (Placebo): participants will receive 4 capsules of matching placebo.

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

8.1.8.1 Timing of Dose Administration

Participants will receive 6 observed QM doses of oral MK-8591 or matching placebo, starting at Day 1 with a final dose at Week 20 per the following dosing guidelines:

- Participants should take the monthly dose of MK-8591/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 monthly dose of MK-8591/placebo and it is outside the dosing window (Table 2) for that study visit, the monthly 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 2 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 prior to completion of the final dose at Week 20 should return to the clinic for an "Early Discontinuation of Study Intervention" visit and should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3) and Section 8.11.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the "Early Withdraw from Study" visit should be performed (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 future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

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. Prior to 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 chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that 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.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician 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. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that 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.

8.2 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/tissue to be drawn/collected over the course of the study (from screening through follow-up visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in 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).

For participants interested in the Tissue Biopsy Subset, the complete physical examination at screening should include pelvic and/or rectal examination.

At all subsequent visits (Day 1 through FW 12), a brief symptom-directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, sign- and symptom-directed, and based on the participant's condition and circumstances. The investigator should note any changes in the participant's condition (body systems) since the last examination. This does not preclude examination of any of the body systems as clinically indicated.

For participants in the Tissue Biopsy Subset, at Week 1, Week 4, Week 24, and FW 8, a rectal exam should be performed prior to rectal biopsy, and a pelvic exam prior to cervical and/or vaginal biopsy.

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 Electrocardiograms

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 semi-recumbent position for at least 10 minutes prior to each ECG measurement.

8.3.4 DEXA Assessment

DEXA images should be collected from all participants/sites willing and able to have the test performed and according to country law. Participants will not be excluded from participation in the study if unwilling/unable to have DEXA images performed.

Only those participants who are confirmed eligible to be randomized will undergo DEXA images for BMD of the spine and hip, as well as peripheral and trunk fat. For baseline assessment, DEXA images should be performed any time after eligibility is confirmed and prior to randomization. If a repeat baseline DEXA image is required, it may be performed up to 14 days after randomization. The DEXA images at the Week 24 visit (both the original scan and a repeat, if necessary) should be performed ±14 days of the scheduled visit. Only participants with valid baseline DEXA images should have Week 24 DEXA images performed.

For a participant who discontinues study intervention early or withdraws from the study prior to Week 24, DEXA images should preferably be performed within ±14 days of the discontinuation visit if possible.

DEXA images will be evaluated by a BICR; these analyses are not performed in real time and will not be provided to the site. For clinical management of the participant, the baseline and Week 24 DEXA images should be reviewed and interpreted by a local radiologist. Clinically significant findings noted in the local interpretation of the baseline DEXA images (including those DEXA images that need to be repeated up to 14 days after randomization) should be recorded in the participant's medical history. Clinically significant findings noted in the local interpretation of the Week 24 DEXA images should be recorded appropriately.

Refer to the Site Imaging Manual for additional details regarding DEXA procedures, including participant preparation instructions to be considered prior to DEXA imaging.

8.3.5 Sexually Transmitted Infections

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), a plasma sample will be sent to the central laboratory for genotypic and phenotypic viral drug resistance testing.

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 for safety and PK as outlined in the SoA (Section 1.3).

Other STIs

Testing for GC/CT, syphilis, and trichomoniasis will be performed at Screening as described in the SoA (Section 1.3). Testing will be performed by the central laboratory. 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 for safety and PK as outlined in the SoA (Section 1.3).

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 #3 (Section 5.1). A participant that does not meet all elements of Inclusion Criterion #3 should not be randomized. After randomization (Day 1), 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 based on the list of questions included in Appendix 8.

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).

8.3.7 Infant Safety Follow-up Assessments

For participants who become pregnant while receiving study intervention (including the protocol-specified follow-up period) and consent to infant follow-up, their infant will have safety follow-up through approximately 1-year of age as outlined in Section 8.3.7.1. This infant safety follow-up data may be collected by phone call or during a participant's scheduled study visit if occurring within the specified data collection window. Length, weight, and head circumference measurements will be collected at birth and at 1-year of age.

Infant SAEs, including congenital anomalies identifiable on physical examination at birth or shortly after birth, will be collected per Section 8.4.1 and should be reviewed at the participant's scheduled study visits that occur during this time.

8.3.7.1 Schedule of Activities: Infant Safety Follow-up Through 1-Year of Age

Study Period	**Infant Safety Follow-up**	
Visit Name		Infant-Follow Up-1
Scheduled Day	At Birth	1-Year After Birth[a]
Visit Window	+90 days	+90 days
Administrative and Safety Procedures		
Informed Consent (if applicable)[b]	X	
Review pregnancy outcome[c]	X	
Length	X	X
Weight	X	X
Head Circumference	X	X
Review Infant Serious Adverse Events[d]	X----------X	

[a] If a participant withdraws from the study, data from 1-Year After Birth should be collected at the time of withdrawal.

[b] Depending on applicable laws and regulations, a separate informed consent may be required (Section 8.1.1.6).

[c] Collect and report pregnancy outcome (health of infant) per Section 8.4.5.

[d] Collect SAEs, including any congenital anomalies, per Section 8.4.1 and review at participant's regularly scheduled study visits.

8.3.8 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory/study operation 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 16 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.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

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 16 weeks after the last dose (FW 12 visit), all AEs, SAEs, and other reportable safety events must be reported by the investigator. For participants in the PBMC/PK Bridging Subset any nonserious AEs related to a study procedure and all SAEs must be reported by the investigator through Week 68 (FW 44 visit).

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

For infants born to participants who become pregnant while receiving study intervention and consent to infant follow-up, SAEs occurring (in these infants) from the time of birth through 1-year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy /Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

For infants born to participants who become pregnant while receiving study intervention and consent to infant follow-up, SAEs occurring (in these infants) from the time of birth through 1-year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

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

This section is not applicable to this study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

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 site in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Refer to Appendix 2 and the SoA for the list of PK sample collection to be performed, including the timing and frequency. The decision as to which samples collected will be assayed for evaluation of PK will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-8591

Blood sample collection, storage, and shipment instructions for plasma samples will be provided in a laboratory/study operation manual. Plasma samples will be used for MK-8591 PK analysis.

Plasma population PK samples will be collected from all participants as outlined in the SoA (Section 1.3). On Day 1 and Week 20 visits, 2 samples will be collected (predose and 30-minutes postdose). For all other dosing visits (Week 4, 8, 12 and 16), 1 predose sample is collected. On Day 2 (Visit 3) it is preferred that PK samples be collected approximately 24 hours after the Day 1 dose; however, this is not a requirement. For all other non-dosing visits, the sample can be collected at any time during the study visit.

The exact time the dose of study intervention was taken prior to the sample collection and the time of PK sample collection will be recorded on the appropriate eCRF.

8.6.2 Blood Collection for PBMC/PK Bridging Subset

Participating sites will be trained on sample collection and processing procedures. The exact time when study intervention was taken before the sample collection and the time of sample collection will be recorded on the appropriate eCRF.

Participants in the PBMC/PK Bridging Subset (n ~ 80) are also permitted to participate in the Tissue Biopsy Subset and the Implant/Depot DDI Subset.

8.6.2.1 Intracellular (PBMC) Samples

Blood sample collection, storage, and shipment instructions for PBMC samples will be provided in the laboratory/study operation manual. PBMC samples will be used for MK-8591 PK analysis.

PBMC samples will be collected in this subset of study participants at specific timepoints outlined in the SoA (Section 1.3). All PBMC samples should be collected predose on dosing visits (Day 1, Week 4, 8, 12, 16 and 20). On Day 2 (Visit 3) it is preferred that PBMC samples be collected approximately 24 hours after the Day 1 dose; however, this is not a requirement. For all other non-dosing visits, the sample can be collected at any time during the study visit.

Participants in the PBMC/PK Bridging Subset who received MK-8591 will also have PBMC samples collected across 4 additional visits through 48 weeks after last dose (44 weeks after the intervention period) as outlined in the SoA (Section 1.3.2).

8.6.2.2 Mitra/VAMS™ Blood Samples

The Mitra® device, powered by VAMS™; Neoteryx, LLC), is a blood collection tool that will be used to obtain venous blood samples. The Mitra/VAMS™ device will be used to absorb blood from a venous blood collection, which will then be analyzed for drug

concentrations. Further instructions on use of the Mitra/VAMS™ device will be provided in the laboratory/study operation manual.

Timepoints for the collection of these samples can be found in the SoA (Section 1.3) and Appendix 2. Mitra/VAMS™ venous samples at Day 1 and Week 20 are prepared from predose MK-8591 PK blood samples.

8.6.3 Tissue Collection for Tissue Biopsy Subset

Rectal, vaginal, and cervical tissue samples from mucosal biopsies will be collected for MK-8591 PK analysis in a subset of approximately 40 participants enrolled into the Tissue Biopsy Subset at trained sites selected by the Sponsor. Biopsy samples will be obtained only from participants who agree to participate in the subset and procedures. Participants, at the selected sites, who do not consent to participate in this subset are still eligible to participate in the study if they meet all eligibility criteria. Participants who do consent to the subset may opt-out of providing a biopsy sample at any time.

Participants included in the Tissue Biopsy Subset are strongly encouraged also to participate in the PBMC/PK Bridging Subset to allow for the collection of paired PBMC and tissue samples which will allow characterization of the relationship between concentrations of MK-8591-TP in PBMCs and concentration in tissues.

Participants in the Tissue Biopsy Subset may also participate in the Implant/Depot DDI Subset.

Male participants will provide rectal biopsy samples at timepoints specified in the SoA (Section 1.3). Female participants may choose to provide 1, 2 or all 3 tissue sample types (rectal, vaginal and cervical) at the timepoints specified in the SoA (Section 1.3). Tissue biopsy samples should be collected predose at Week 4. At the Week 1, Week 24 and Follow-up Week 8 visit, the tissue biopsy samples can be collected at any timepoint during the clinic visit. The exact time when study intervention was taken before the sample collection and the time of sample collection will be recorded on the appropriate eCRF.

Rectal, vaginal, and cervical tissue sample collection, storage, and shipment instructions for samples will be provided in a laboratory/study operation manual. Biopsy samples will be obtained by medical specialists who have expertise in the procedures and according to the instructions provided separately and based on local standard of care.

8.6.3.1 Rectal Tissue Sample

Participants undergoing the rectal biopsy will be administered a saline enema prior to the procedure. Immediately before the procedure, the medical specialist will examine the area around the anus and then carefully insert a gloved and lubricated finger into the anus to perform rectal examination for any abnormalities.

Biopsy samples of adequate size will be taken from participants. Details are provided in the laboratory/study operations manual. Use of any and all anesthesia or sedation should be

recorded in the concomitant medication section of the CRF. The site will follow-up with the participant within 48 hours after the rectal biopsy procedure to determine if any AEs have occurred since the procedure.

8.6.3.2 Vaginal Tissue Sample

Immediately prior to the start of the biopsy procedure, the medical specialist will insert a speculum in the vagina and check for any abnormalities. If the medical specialist feels that a vaginal infection may be present upon initial examination, the participant may have 1 or 2 vaginal swabs collected to assess the discharge. If the medical specialist feels there is any structural abnormality or lesion of the vagina that would preclude safe biopsy, the procedure should be deferred.

Biopsy samples of adequate size will be taken from participants. Details are provided in the laboratory/study operations manual. Use of any and all anesthesia or sedation should be recorded in the concomitant medication section of the CRF. The site will follow-up with all female participants within 48 hours after the biopsy procedure to determine if any AEs have occurred since the procedure.

8.6.3.3 Cervical Tissue Sample

Immediately prior to the start of the biopsy procedure, the medical specialist will insert a speculum in the vagina and check for any abnormalities of the cervix. If the medical specialist feels that an infection or other abnormality may be present upon initial examination, the participant may have 1 or 2 vaginal swabs collected to assess the discharge. If the medical specialist feels there is any structural abnormality or lesion of the cervix that would preclude safe biopsy, the procedure should be deferred.

Biopsy samples of adequate size will be taken from participants. Details are provided in the laboratory/study operations manual. Use of any and all anesthesia or sedation should be recorded in the concomitant medication section of the CRF. The site will follow-up with all female participants within 48 hours after the biopsy procedure to determine if any AEs have occurred since the procedure.

8.6.4 Blood Collection for Implant/Depot DDI Subset

Blood sample collection, storage, and shipment instructions for plasma concentrations of ENG, MPA, or NET will be provided in the laboratory/study operation manual. The exact time the dose of study intervention was taken prior to the sample collection and the time of plasma concentration sample collection will be recorded on the appropriate eCRF.

Plasma concentration samples will be collected from Implant/Depot DDI Subset participants (n ~ 30) as outlined in the SoA (Section 1.3). On Day 1, Week 8 and Week 20 visits, 2 samples will be collected (predose and 30-minutes postdose). For all other dosing visits (Week 4, 12 and 16), 1 predose sample is collected. For all other non-dosing visits, the sample can be collected at any time during the study visit.

Participants included in the Implant/Depot DDI Subset are also permitted to participant in the PBMC/PK Bridging Subset and the Tissue Biopsy Subset.

Participants who are interested in participating in the Implant/Depot DDI substudy but who have not received the hormonal contraceptive prior to the screening visit (Visit 1) may be consented for the substudy and administered the contraceptive at the screening visit and return for collection of the screening sample for ENG, MPA, or NET levels within approximately 7 days after the screening visit.

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 will be collected from all participants as specified in the SoA (Section 1.3) and Appendix 2:

- Urine and blood for renal function assessment
- Blood for planned genetic analysis

8.8.1 Laboratory Markers Associated with Clinical Outcome

Urine and blood samples will be collected to evaluate renal function as measured by key indicators, such as the following potential analytes and calculations:

- Urine: albumin, protein, creatinine, beta-2-microglobulin/creatinine ratio, and retinol binding protein/creatinine ratio
- Serum: creatinine, cystatin-C, and creatinine clearance

8.8.2 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

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

- Leftover DNA for future biomedical research

8.10 Health Economics Medical Resource Utilization and Health Economics

Health Economics OR 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

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. Participants who were previously screened and confirmed to be a screen failure will not be permitted to be rescreened.

8.11.1.2 Rescreening

If the 45-day screening window has been exceeded, participants are allowed to rescreen 1 time following approval from the Sponsor. 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 and substudies) 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 trial 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:

- 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, urinalysis

A DEXA scan does not need to be repeated at rescreening if the participant had acceptable images from the original screening period and ≤60 days have passed since the date of the original acceptable DEXA images; however, DEXA scans must be done at rescreening if either of the above criteria are not met.

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 done at rescreening if any of the above criteria are not met:

- Syphilis serologic testing
- Rectal swab GC/CT testing
- Oropharyngeal swab GC/CT testing
- Vaginal swab GC/CT & trichomoniasis testing (females only)
- Urine GC/CT & trichomoniasis testing (males only)

Participants in the Tissue Biopsy PK Subset

- A Pap smear must be obtained at rescreening if >36 months has passed since the participant's previous Pap smear.
- A pelvic and/or rectal examination must be performed at rescreening if the participant did not have this examination at the original screening visit.

Participants in the Implant / DDI Subset

- Current contraceptive use must be evaluated at rescreening for female participants in the DDI subset.
- A blood sample for ENG, MPA or NET levels should be collected at the rescreening visit.

8.11.2 Intervention Period

During the 24-week intervention period, participants will receive a total of 6 oral QM doses of the assigned blinded study intervention (MK-8591 [60 mg or 120 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, and the final dosing period will be from the Week 20 dosing visit until the Week 24 visit.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study intervention before the final dose at Week 20 should complete an "Early Discontinuation from Study Intervention" visit (Section 1.3.3), 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 if in the PBMC/PK Bridging Subset and randomized to MK-8591, the protocol-specified visits for the extended, unblinded PK follow-up period (Section 1.3.2).

When a participant should return for the follow-up visits (per Section 1.3.1) will be based on the date of last dose of study intervention.

- A participant in the PBMC/PK Bridging Subset should return for the first follow-up visit (FW 1-2) approximately 1 or 2 weeks after the last dose of study intervention and return for the subsequent follow-up visits as outlined in the SoA.
- A participant who is not in the PBMC/PK Bridging Subset should return for the first follow-up visit (FW 4) approximately 4 weeks after the last dose of study intervention and return for the subsequent follow-up visits as outlined in the SoA.

If it is not feasible, due to an external circumstance (eg, unforeseen emergency, natural disaster), to use the date of a participant's last dose of study intervention to calculate the follow-up visit schedule, the follow-up visit schedule for that participant will be determined collaboratively between the Sponsor and the investigator and documented in writing.

Participants who withdraw from the study during the "Intervention (Blinded)" period (prior to the last dose of study intervention at Week 20) should have an "Early Discontinuation from Study Intervention" visit (Section 1.3.1); an "Early Withdrawal from Study" visit is not required.

Participants who withdraw from the study between Week 20 (after the final dose of study intervention) and Week 24, or during the "Follow-up (Blinded)" phase (through FW 12 [Week 36]), should have an "Early Withdrawal from Study" visit (Section 1.3.3) at the time of withdrawal. An "Early Withdrawal from Study" visit is not required for participants who withdraw from study during the extended, unblinded PK follow-up period (Section 1.3.2).

8.11.3.1 Participants Who Become Pregnant

- If the participant becomes pregnant during the "Intervention (Blinded)" study period (prior to the last dose of study intervention at Week 20), she should have an "Early Discontinuation from Study Intervention" visit (Section 1.3.3). If the pregnancy is reported at a scheduled study visit, the assessments for the "Early Discontinuation from Study Intervention" visit should be conducted at that time. The participant will then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period listed in Section 1.3.1, using the guidance provided in Section 8.11.3 and, if in the PBMC/PK Bridging Subset, the protocol-specified visits for the extended, unblinded PK follow-up period (Section 1.3.2).
- If the participant becomes pregnant during the "Intervention (Blinded)" study period but after the last dose of study intervention at Week 20 or during the "Follow-up (Blinded)" study period (after Week 24 through Week 36 [FW 12 visit]), she should continue with the protocol-specified visits listed for this period in the SoA (Section 1.3.1), and if in the PBMC/PK Bridging Subset and randomized to MK-8591, the protocol-specified visits for the extended, unblinded PK follow-up period (Section 1.3.2).
- If the participant becomes pregnant during the extended, unblinded PK follow-up period (after Week 36 [FW 12 visit]), she should continue with the protocol-specified visits listed for this period in the SoA (Section 1.3.2).

All reported pregnancies will be followed to the completion/termination of the pregnancy (Section 8.4.5). Infants born to these participants will have safety follow-up data collected through approximately 1 year after birth (Section 8.3.7).

All reported pregnancies occurring after Week 36 (FW 12 visit) must be followed to the completion/termination of the pregnancy (Section 8.4.5). Infants born to these participants will not be followed.

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 Section 1.3.3, including collection of an HIV-1 RNA PCR sample.

- If the positive HIV- 1 /2 screen test is during the "Intervention (Blinded)" study period (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 may be able to resume study intervention after consultation with the Sponsor.
    - If the HIV-1 RNA PCR test is positive, the participant should complete an "Early Discontinuation from Study Intervention" visit, and then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period as listed in Section 1.3.1, and if in the PBMC/PK Bridging Subset and randomized to MK-8591, the protocol-specified visits for the extended, unblinded PK follow-up period in Section 1.3.2. The participant should be referred to local medical providers for HIV care and treatment. No poststudy antiretroviral therapy will be provided by the study.
- If the positive HIV- 1 /2 screen test is during the "Intervention (Blinded)" study period (prior to the last dose of study intervention at Week 20), **and the HIV confirmation and differentiation test is positive**, the participant should be immediately discontinued from 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 complete an "Early Discontinuation from Study Intervention" visit, and then continue with the protocol-specified visits for the "Follow-up (Blinded)" study period as listed in Section 1.3.1, and if in the PBMC/PK Bridging Subset and randomized to MK-8591, the protocol-specified visits for the extended, unblinded PK follow-up period in Section 1.3.2. The participant should be referred to local medical providers for HIV care and treatment. No poststudy antiretroviral therapy will be provided by the study.
- If the positive HIV- 1 / 2 screen test is during the "Intervention (Blinded)" study period but after the last dose of study intervention at Week 20 or during the "Follow-up (Blinded)" study period (after Week 24 through Week 36 [FW 12 visit]), the participant should continue with the protocol-specified visits listed for this period in the SoA (Section 1.3.1), and if in the PBMC/PK Bridging Subset and randomized to MK-8591, the protocol-specified visits for the extended, unblinded PK follow-up period (Section 1.3.2).

- 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.

8.11.5 Follow-up Period

During the 12-week blinded follow-up period, all participants will complete 3 monthly follow-up visits (ie, at FW 4, FW 8, and FW 12 visits) after the last dosing period (ie, at 4, 8, and 12 weeks beyond Week 24).

All participants who are enrolled in the PBMC/PK Bridging Subset will have 2 additional visits during the 12-week blinded follow-up period: at 1-2 weeks and 2-3 weeks (ie, FW 1-2 and FW 2-3 visits) after the last dosing period. Participants who are enrolled in the PBMC/PK Bridging Subset and who were randomized to receive MK-8591 60 mg or 120 mg will have another 4 visits, approximately every 2 months, during the extended, unblinded PK follow-up period (ie, FW 20, FW 28, FW 36, and FW 44 visits) after the last dosing period (Section 1.3.2).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.1 through 9.12.

Study Design Overview	A Phase 2a, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of oral MK-8591 QM in participants at low-risk for HIV-1 infection
Treatment Assignment	A total of approximately 250 participants will be randomized to Group 1 (60 mg MK-8591), Group 2 (120 mg MK-8591), or Group 3 (placebo) in a 2:2:1 ratio.
Analysis Populations	Safety: APaT
Primary Endpoint(s)	AEs AEs leading to discontinuation of study intervention
Key Secondary Endpoints	Plasma MK-8591 $AUC_{0\text{-}672hr}$, C_{max}, C_{trough} and $t_{1/2}$
Statistical Methods for Key Pharmacokinetic Analyses	Geometric means and 95% CIs will be provided for Plasma MK-8591 and PBMC MK-8591-TP $AUC_{0\text{-}672hr}$, C_{max} and C_{trough} by dose level.
Statistical Methods for Key Safety Analyses	95% CIs (Tier 2 endpoints) will be provided for between-group differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	There are no planned interim analyses for this study.

Multiplicity	No multiplicity adjustment is necessary as there are no hypothesis tests for this protocol.
Sample Size and Power	There are no hypotheses in this study. The primary objective will compare the 95% CI for between-group differences. Given the planned sample size of 250 participants (2:2:1), the study has 80% probability at an overall 2-sided 5% α-level to rule out an 18.4% risk difference in AEs from the placebo group assuming an underlying incidence of 10% in the placebo group. The study has an 80% probability to rule out a 15% risk difference in AE between MK-8591 120 mg and 60 mg groups assuming an underlying incidence of 10% in the MK-8591 60 mg group. Assuming plasma MK-8591 C_{max} has a true between-participant standard deviation (log-scale) of 0.25, given 100 participants receiving MK-8591 at one of the dose levels, it is 80% likely that the half-width of the 95% CI for the true arithmetic mean C_{max} on the log scale will be at most 0.0525.

9.2 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.

For clinical site personnel, participants, and the Sponsor's clinical team this study will be a double-blind study under in-house blinding procedures through Week 24. The Sponsor will be unblinded at Week 24.For the PBMC/PK Bridging Subset only, investigators/clinical site personnel and participants will be unblinded to MK-8591/placebo between Weeks 36 and 44 while remaining blinded to MK-8591 dose. For those participants not in the PBMC/PK Bridging Subset, participants and investigators/clinical site personnel will remain blinded for the duration of the study.

To allow timely completion of population PK modeling, Sponsor PK personnel will be unblinded for the duration of the study. No personnel directly associated with study conduct will be unblinded. Before granting select personnel access to unblinded drug concentration data and information relevant for population PK modeling (eg, including, but not limited to PK sampling schedules, dosing records, etc.), an official memo detailing unblinding procedures will be generated per Sponsor SOP. This memo will list the names of the personnel who will have access to unblinded PK and relevant data. 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.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

PK and safety endpoints that will be evaluated for between-group differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Safety Endpoints

Section 4 provides an initial description of safety measures.

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). In the extended, unblinded PK follow-up period (after FW 12 visit through FW 44 visit), only SAEs and nonserious AEs related to study procedures will be collected. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory values.

Adverse Events

The following AEs will be summarized: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 Grade 3 to 5 AE; 5) participants with at least 1 AE which is both serious and drug-related; 6) participants with at least 1 AE which is both Grade 3 to 5 and drug-related; 7) participants who discontinued study therapy due to an AE; and 8) participants with an AE which results in death. The percentage of participants with specific AEs by system organ class will also be summarized.

Predefined Limits of Change in Laboratory Parameters

Participants must have both a baseline and post-randomization on-treatment measurement to be included in the summaries of laboratory tests. Participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study therapy) will be classified as to whether or not they fall outside of the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The PDLC grading criteria are adapted from DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, Version 2.1. A listing of the participants who meet the PDLC grading criteria will be provided.

9.4.2 Pharmacokinetics Endpoints

There are no primary PK endpoints.

The secondary PK endpoints in the study are: Plasma MK-8591 PK parameters such as $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, and $t_{1/2}$.

Exploratory PK endpoints in the study are :PBMC MK-8591-TP PK parameters such as $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, and $t_{1/2;}$ tissue concentrations of MK-8591, MK-8591-TP and MK-8591-DP; as well as plasma concentrations of ENG, MPA, and NET (in a subset of participants).

9.5 Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included

in the group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the 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 group corresponding to the study intervention actually received.

PK analyses will be conducted in 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. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one dose will be included in the PK analysis dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

9.6.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

Safety analyses will be performed for the following between-group comparisons:

- MK-8591 (60 mg) vs placebo
- MK-8591 (120 mg) vs placebo
- MK-8591 (60 mg) vs MK-8591 (120 mg)

The analysis of safety results will follow a tiered approach (Table 4). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet PDLCs in laboratory parameters are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. There are no a priori clinical events of concern that have been identified; therefore, there are no Tier 1 events for this protocol

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CI provided for differences in the proportion of participants with events (also via the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]).

Membership in Tier 2 requires that at least 4 participants in any intervention group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when intervention groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any intervention group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a SAE, a Grade 3 to 5 AE, an AE which results in death, an AE which is both drug-related and serious, an AE which is both drug-related and Grade 3 to 5, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by intervention group are provided for Tier 3 safety parameters.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison[a]	Descriptive Statistics
Tier 2	Any AE[b]	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Grade 3 to 5 AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3 to 5 and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	AE which Results in Death	X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 participants in one of the intervention groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 participants in all of the intervention groups)		X

AE=adverse event; CI =confidence interval; SOC=System Organ Class; PDLC=Predefined Limit of Change; X=results will be provided.
[a] 95% CIs will be based on the method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].
[b] Indicates broad AE category of the number of participants reporting any AE.

9.6.2 Statistical Methods for Pharmacokinetics Analyses

Plasma MK-8591 $AUC_{0\text{-}672hr}$, C_{max}, C_{trough}, and $t_{1/2}$ will be summarized separately by dose level as appropriate, with geometric means and 95% CIs based on natural log-transformed endpoints and t-distribution.

PBMC MK-8591-TP $AUC_{0\text{-}672hr}$, C_{max}, C_{trough} and $t_{1/2}$ will be assessed with a similar method as above.

9.7 Interim Analyses

There are no planned interim analyses for this study.

9.8 Multiplicity

No multiplicity adjustment is planned for this study.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Probability Calculations for Safety Analysis

The sample size of this study was chosen to allow for the accumulation of approximately 100 person-years of safety data (200 participants × 0.5 years).

While not the basis of the sample size for this study, information on the probability of observing a difference between intervention groups is provided. If the underlying incidence of a particular AE is 1%, there is a 63.4% chance of observing at least 1 AE among 100 participants in either MK-8591 group. If no AE of that type is observed among the 100 participants in the MK-8591 group, this study provides 97.5% confidence that the underlying percentage of participants with that particular AE is <3.62% (1 out of every 27 participants).

The estimate of and the upper bound of the 95% CI for the underlying percentage of participants with a particular AE given various hypothetical observed number of participants with a particular AE within either MK-8591 group are provided in Table 5. These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 5 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Number of Participants With a Particular AE Among 100 Participants in Either MK-8591 Intervention Group

Hypothetical Number of Participants with a Particular AE	Estimate of Incidence	95% Upper Confidence Bound[a]
0	0%	3.6
3	3%	6.3
5	5%	11.3
10	10%	17.6
15	15%	25.5
20	20%	29.2

AE=adverse event.
[a] Based on the two-tailed exact confidence interval of a binomial proportion [Clopper, C. J. and Pearson, E. S. 1934].

Table 6 summarizes differences in the incidence of AEs between the 2 MK-8591 groups and for either MK-8591 group compared with placebo that can be ruled out with different probabilities and 95% confidence for a variety of hypothetical underlying incidences of an AE. These calculations assume 100 participants in each MK-8591 group and 50 participants in the placebo group and that the underlying incidence of AEs is the same for both groups. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. and Manning, G. 1990]; no multiplicity adjustments were made.

Table 6 Difference in Incidence of AEs (MK-8591 Intervention Group Minus Placebo) That Can Be Ruled Out

	Difference[a] in Percentage Points That Can Be Ruled Out with Target Probability Assuming the Underlying Incidence of the AE is:				
Target Probability	10%	20%	30%	40%	50%
Compare MK-8591 to placebo					
80	18.4	21.9	23.5	24.0	23.5
85	20.1	23.6	25.2	25.6	24.9
90	22.2	25.7	27.3	27.5	26.7
95	25.3	28.9	30.3	30.3	29.2
Compare MK-8591 intervention groups					
80	15.0	17.9	19.3	19.7	19.3
85	16.2	19.2	20.6	21.0	20.6
90	17.8	20.9	22.3	22.7	22.1
95	20.1	23.4	24.8	25.1	24.4

AE=adverse event.
[a] The upper bound of the two-sided 95% confidence interval [Farrington, C. P. and Manning, G. 1990] for the difference in AE incidences assuming the incidences are the same. Assuming 100 participants in the MK-8591 intervention groups and 50 participants in the placebo group.

9.9.2 Sample Size and Probability Calculations for PK Analysis

No estimates of variability for AUC_{672hr} or C_{trough} following monthly oral dosing are available. The precision of the estimates of plasma MK-8591 C_{max} can be assessed by calculating the half-width of the 95% CIs expected for the given sample size and assumed variability. The calculations for C_{max} are based on assumed true between-participant standard deviations (log-scale) of 0.25 as observed in MK-8591 Protocol 001 and take into account the sampling distribution of the observed sample variance as described in [Wang, Y., et al 2012]. For the given sample size (100 participants receiving MK-8591 at one of the dose levels) and assumed between-participant variability, it is 80% likely that the half-width of the 95% CI for the true arithmetic mean C_{max} on the log scale will be at most 0.0525 (the lower and upper 95% confidence limits for the true geometric mean C_{max} will be OBS/1.05 and OBS × 1.05, where OBS is the observed geometric mean).

9.10 Subgroup Analyses

To evaluate potential differential pharmacokinetics between groups, plasma MK-8591 will be assessed with a similar method as described in Section 9.6 within each category of the following classification variables:

- Sex (female, male)
- Race (white, non-white)
- Region (Africa, non-Africa)
- Age (≤45 years; >45 years)

9.11 Compliance (Medication Adherence)

Study intervention data for MK-8591 and placebo will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes the required number of pills from all containers provided for this study. A participant will have to take all 4 capsules per dose to be considered compliant.

For a participant who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last dose of study intervention.

For each participant, percent compliance will then be calculated using the following formula:

$$Percent\ Compliance = \frac{Number\ of\ Days\ on\ Therapy}{Number\ of\ Days\ Should\ be\ on\ Therapy} x\ 100$$

Summary statistics will be provided on percent compliance by intervention group for the APaT population.

9.12 Extent of Exposure

Each study participant is planned to be exposed to 6 doses of either 60 mg or 120 mg of MK-8591 or placebo over a 6-month period. The amount of intervention received by the participants during the study will be summarized.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations, and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.7 Data Quality Assurance

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

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

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

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

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

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

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

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

Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

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

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

10.1.9 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the central laboratory or by a referral laboratory as outlined in the PPD Central Laboratory Manual and the MK-8591 Protocol 016 Study Operations Manual.

- Local laboratory results are only required in the event that 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: for female participants requiring a Pap test, it must be performed locally based on the requirements outlined in Section 8.1.4.

  Note: External circumstances may require participants to have local lab 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 lab 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.
- 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.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 7 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters
Pregnancy	Serum β-human chorionic gonadotropin (hCG) test
	Urine β-human chorionic gonadotropin (hCG) test
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 Red Blood Cell (%, 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)
	CD4% and absolute CD4/lymphocytes
	CD8% and absolute CD8/lymphocytes
	CD4/CD8 ratio
Chemistry (non-fasting)	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[a]
	Gamma Glutamyl Transferase (GGT)

Laboratory Assessments	Parameters
	Glucose (random)
	Lactate Dehydrogenase (LDH)
	Lipase
	Magnesium (Mg)
	Phosphorous
	Potassium (K)
	Protein, Total
	Sodium (Na)
	Triglycerides
	Urea Nitrogen, Blood (BUN)
	Uric Acid
Urinalysis- MACROSCOPIC	Specific gravity
	Appearance
	Bilirubin
	Blood
	Color
	Glucose
	Ketones
	Leukocyte Esterase (LE)
	Nitrites
	pH
	Protein
	Urobilinogen
Urinalysis- MICROSCOPIC	Amorphous Crystals
	Bacteria
	Calcium Carbonate Crystals
	Calcium Oxalate Crystals
	Calcium Phosphate Crystals
	Cysteine Crystals
	Granular Casts
	Hyaline Casts
	Leucine Crystals
	Mucus
	RBC
	RBC Casts
	Renal Epithelial Cells
	Squamous Epithelial Cells
	Transitional Epithelial Cells
	Triple Phosphate Crystals
	Tyrosine Crystals
	Uric Acid Crystals

Laboratory Assessments	Parameters
	Waxy Casts
	WBC
	WBC Casts
	Yeast
Urinary analytes	Albumin
	Beta-2-microglobulin
	Beta-2-microglobulin/creatinine ratio (B-2M/Cr) (calculated)
	Creatinine
	Protein
	Retinol binding protein
	Retinol binding protein/creatinine ratio (RBP/Cr) (calculated)
Hepatitis screen (Screening)	Hepatitis B virus surface antigen
	Hepatitis B virus surface antibody
	Hepatitis C virus antibody
	Plasma hepatitis C virus polymerase chain reaction (PCR) quantitative test (performed if Hepatitis C virus antibody is positive)
Virology	Human immunodeficiency virus (HIV) 1&2 Antibody
	HIV 1/2 Geenius Confirmation
	HIV-1 viral RNA quantification (real time PCR)
	HIV-1 drug resistance testing
Sexually transmitted infection (STI) Testing (Screening)	Rectal swab Neisseria gonorrhoeae (GC)/Chlamydia trachomatis (CT) testing
	Oropharyngeal swab GC/CT testing
	Urine GC/CT/trichomoniasis testing (males)
	Vaginal swab GC/CT/trichomoniasis testing (females)
	Syphilis serologic testing (rapid plasma reagin [RPR], RPR with titer, treponema pallidum IgG, treponema pallidum IgG index value)
Pharmacokinetic (PK) Sampling	Plasma PK (all participants)
	Mitra/VAMS™ (subset of participants)
Tissue Sampling (for PK analysis)	Rectal tissue biopsy (subset of participants)
	Cervical tissue biopsy (subset of participants)
	Vaginal tissue biopsy (subset of participants)
Peripheral blood mononuclear cells (PBMC) (for PK analysis)	PBMC (subset of participants)
Plasma Hormone Measurement	Etonogestrel (subset of participants)
	Medroxyprogesterone acetate (subset of participants)
	Norethindrone (subset of participants)
Biomarkers	Genetic Analysis
[a] Test requires a separate sample	

The PK sampling timepoints are detailed Table 8. Plasma will be collected for all participants and other sampling will be based on enrollment in a particular subset. The priority of PK sample collection is as follows:

1. Plasma
2. PBMC
3. Tissue biopsy
4. ENG/MPA/NET plasma concentration
5. Mitra/VAMS™ venous

Table 8 PK Sample Collection Timepoints

Study Day/Week	PK Sample Type	PK Sample Collection Time *(exact time must be documented)*
Screening (non-dosing visit)	ENG/MPA/NET plasma concentration	Sample can be collected at any time during the study visit.
Day 1 (dosing visit)	Plasma	Sample to be collected predose and 30-minutes postdose.
	PBMC	Sample to be collected predose.
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	Sample to be collected predose and 30-minutes postdose.
Day 2 (non-dosing visit)	Plasma	Samples to be collected ~ 24 hours after Day 1 dose.
	PBMC	
	Mitra/VAMS™ Venous	
Week 1 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ Venous	
	Tissue Biopsy Sample(s)	
	ENG/MPA/NET plasma concentration	
Week 2 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ venous	
	ENG/MPA/NET plasma concentration	
Week 3 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	
Week 4 (dosing visit)	Plasma	Samples to be collected predose.
	PBMC	
	Mitra/VAMS™ Venous	
	Tissue Biopsy Sample(s)	
	ENG/MPA/NET plasma concentration	

Study Day/Week	PK Sample Type	PK Sample Collection Time *(exact time must be documented)*
Week 8 (dosing visit)	Plasma	Samples to be collected predose.
	PBMC	
	Mitra/VAMS™ venous	
	ENG/MPA/NET plasma concentration	Sample to be collected predose and 30-minutes postdose.
Week 12 (dosing visit)	Plasma	Samples to be collected predose.
	PBMC	
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	
Week 16 (dosing visit)	Plasma	Samples to be collected predose.
	PBMC	
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	
Week 20 (dosing visit)	Plasma	Sample to be collected predose and 30-minutes postdose.
	PBMC	Samples to be collected predose.
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	Sample to be collected predose and 30-minutes postdose.
Week 21 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	
Week 22 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ venous	
	ENG/MPA/NET plasma concentration	

Study Day/Week	PK Sample Type	PK Sample Collection Time *(exact time must be documented)*
Week 23 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ Venous	
	ENG/MPA/NET plasma concentration	
Week 24 (non-dosing visit)	Plasma	Samples can be collected at any time during the study visit.
	PBMC	
	Mitra/VAMS™ venous	
	Tissue Biopsy Sample(s)	
	ENG/MPA/NET plasma concentration	
Follow-Up Week 1-2 (non-dosing visit)[a]	PBMC	Sample can be collected at any time during the study visit.
Follow-Up Week 2-3 (non-dosing visit)[a]	PBMC	Sample can be collected at any time during the study visit.
Follow-Up Week 4 (non-dosing visit)	PBMC	Samples can be collected at any time during the study visit.
	ENG/MPA/NET plasma concentration	
Follow-Up Week 8 (non-dosing visit)	PBMC	Samples can be collected at any time during the study visit.
	Tissue Biopsy Sample(s)	
	ENG/MPA/NET plasma concentration	
Follow-Up Week 12 (non-dosing visit)	PBMC	Samples can be collected at any time during the study visit.
	ENG/MPA/NET plasma concentration	
Follow-up Week 20[b] (non-dosing visit)	PBMC	Sample can be collected at any time during the study visit.
Follow-up Week 28[b] (non-dosing visit)	PBMC	Sample can be collected at any time during the study visit.
Follow-up Week 36[b] (non-dosing visit)	PBMC	Sample can be collected at any time during the study visit.

Study Day/Week	PK Sample Type	PK Sample Collection Time *(exact time must be documented)*
Follow-up Week 44[b] (non-dosing visit)	PBMC	Sample can be collected at any time during the study visit.

ENG=etonogestrel; MPA=medroxyprogesterone acetate; NET=norethisterone or norethindrone; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; VAMS=volumetric absorptive microsampling.

- PBMC and Mitra/VAMS™ venous samples only collected in participants included in the PBMC/PK Bridging Subset.
- Tissue biopsy samples only collected in participants included in the Tissue Biopsy Subset.
- ENG/MPA/NET plasma concentration samples only collected in participants included in the Implant/Depot DDI Subset.

[a] Visits only required for participants in the PBMC/PK Bridging Subset.
[b] Visits only required for participants in the PBMC/PK Bridging Subset who received MK-8591.

Table 9 Blood Volumes

Study Period	**Screening**	**Intervention (Blinded)**													**Follow-up (Blinded)**							**HIV-Inf. Crm**	**Erly Disc Std Intvn**	**Erly Wth-draw Std**
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2[a]	FW 2-3[a]	FW 4	FW 8	FW 12	Totals	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																							
HBV/HCV/HIV (Serology)	3.5																							
HCV RNA (only tested if AB+)	6																							
Syphilis	4																							
Hematology	2	2					2	2	2	2	2				2			2	2	2			2	2
Chemistry	6	6		6	6	6	6	6	6	6	6				6			6	6	6			6	6
Cystatin-C	2	2		2	2	2	2	2	2	2	2				2			2	2	2			2	2
Serum pregnancy test (β-hCG)	Off Chem																							
HIV 1&2 Screen	Off HBV/ HCV/ HIV	2					2	2	2	2	2				2			2	2	2			2	2
HIV Confirmation (Geenius)	1	1					1	1	1	1	1				1			1	1	1			1	1
HIV RNA																						6		
HIV-1 drug resistance testing																						12		
PK blood sample collection (all participants)		8	4	4	4	4	4	4	4	4	8	4	4	4	4							4	4	4
Blood for Genetic Analysis		8.5																						
Total Blood Volume per Visit in mL (All Study Participants)	24.5	29.5	4	12	12	12	17	17	17	17	21	4	4	4	17	0	0	13	13	13	251	22	17	17

Study Period	**Screening**	**Intervention (Blinded)**														**Follow-up (Blinded)**						**HIV-Inf. Crm**	**Erly Disc Std Intvn**	**Erly Wth-draw Std**
Scheduled Day/Week	Screening	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 21	Week 22	Week 23	Week 24	FW 1-2[a]	FW 2-3[a]	FW 4	FW 8	FW 12	Totals	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																							
Pharmacokinetics (PBMC/PK Bridging Subset)[b]																								
PBMC sample		16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16		16	16	16
Additional Blood Volume Collected per Visit in mL (Participants in the PBMC/PK Bridging Subset)[b]		16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	304	16	16	16
Pharmacokinetics (Implant/Depot DDI Subset)																								
ENG or MPA sample	3	6		3	3	3	3	6	3	3	6	3	3	3	3			3	3	3	60		3	3
NET sample	6	12		6	6	6	6	12	6	6	12	6	6	6	6			6	6	6	120		6	6

AB=antibody; β-hCG=beta human chorionic gonadotropin; Crm=confirmation; Disc=discontinuation; ENG= etonogestrel; Erly=early; FW=follow-up week; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; Inf=infection; Intvn=intervention; MPA=medroxyprogesterone acetate; NET=norethisterone or norethindrone; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; RNA=ribonucleic acid; Std=study; WOCBP=a woman/women of childbearing potential; Wthdraw=withdrawal; VAMS=volumetric absorptive microsampling.

Note: All volumes are provided in mL.

[a] Visits are only required for participants in the PBMC/PK Bridging Subset.

[b] Participants in the PBMC/PK Bridging Subset and randomized to MK-8591 will have PBMC samples (16 mL) collected at FW 20, 28, 36 and 44 and hematology samples (2 mL) and CD4+ T-cell count samples (6 mL) collected at FW 36 and 44 (Total Additional Blood Volume = 80 mL).

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

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

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

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

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

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

Assessment of intensity

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

- 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 which 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 funtions with intervention indicated to prevent permanent impairment, persistent disability, or death.

    - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the 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.

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the 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.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implantc • Intrauterine hormone-releasing system (IUS)d • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *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 • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[e]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation d. IUS is a progestin releasing IUD. e. A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

13. References

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

Confidential

10.8 Appendix 8: Risk Evaluation

At each treatment and follow-up visit as specified in the SoA (1.3.1 and 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 1-4 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
AB	antibody
AE	adverse event
AG	antigen
ALT	alanine aminotransferase
APaT	All Participants as Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta human chorionic gonadotropin
B-2M/Cr	Beta-2- microglobulin/creatinine ratio
BICR	blinded independent central review
BMD	bone mineral density
BMI	body mass index
CDC	Centers for Disease Control
CI	confidence interval
CrCL	creatinine clearance
C_{max}	maximum (peak) observed drug plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CT	Chlamydia trachomatis
CTFG	Clinical Trial Facilitation Group
C_{trough}	Trough plasma concentration
DAIDS	Division of AIDS
DAO	Data-As-Observed
DDI	drug-drug interaction
DEXA	Dual-energy X-ray Absorptiometry
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DP	diphosphate
EC_{90}	90% effective concentration
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EFV	efavirenz
ENG	etonogestrel
FBR	Future biomedical research
FDA	Food and Drug Administration
FDC	fixed dose combination
FSH	follicle stimulating hormone
FTC	emtricitabine
FW	Follow up Week
GC	Neisseria gonorrhoeae
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein

Abbreviation	Expanded Term
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceutical for Human Use
I/E	Inclusion/Exclusion
IEC	Independent Ethics Committee
IND	Investigational New Drug
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISG	immediate switch group
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LDL	low-density lipoprotein
Mg	milligram
MPA	medroxyprogesterone acetate
MSD	Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	maximum tolerated dose
NA	Not applicable
NC=F	Non-Completer=Failure
NDA	New Drug Application
NET	norethisterone or norethindrone
NET-EN	norethindrone enanthate
NIMP	non-investigational medicinal product
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
NSAIDS	non-steroidal anti-inflammatory drugs
OBS	observed
OF	Observed Failure
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PDLC	predefined limit of change
PEP	post-exposure prophylaxis
PET	positron emission tomography
PK	pharmacokinetic
PP	Per Protocol
PrEP	pre-exposure prophylaxis
PRO	patient-related outcome
QM	once monthly
QP2	department of quantitative pharmacology and pharmacometrics
RBP/Cr	retinol binding protein/creatinine ratio
RNA	ribonucleic acid
RPR	rapid plasma reagin
SAC	Scientific Advisory Committee
SAE	serious adverse event

Abbreviation	Expanded Term
sCD-163	soluble CD-163
siDMC	standing internal Data Monitoring Committee
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SOC	System Organ Class
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
STI	sexually-transmitted infection
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal half-life
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TP	triphosphate
UDS	urine drug screen
ULN	upper limit of normal
USDHHS	United States Department of Health and Human Services
VAMS	volumetric absorptive microsampling
VL	viral load
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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