Official Protocol Title:	A Phase 3, Randomized, Active-Controlled, Double-blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir Once-Monthly as Preexposure Prophylaxis in Cisgender Women at High Risk for HIV-1 Infection
NCT number:	NCT04644029
Document Date:	02-AUG-2022

Title Page

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Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir Once-Monthly as Preexposure Prophylaxis in Cisgender Women at High Risk for HIV-1 Infection

Protocol Number: 022-04

Compound Number: MK-8591

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	128,595
EudraCT	2021-001289-39

Approval Date: 02 August 2022

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	02-AUG-2022	The protocol was amended to add Part 3 to the study to unblind each participant's Part 1 study intervention assignment, continue participants on FTC/TDF, and monitor safety.
Amendment 03	24-FEB-2022	Based on the laboratory findings of decreases in lymphocyte and CD4+ T-cell counts observed in clinical studies across the islatravir (ISL, MK-8591) program, as of 13-DEC-2021, sites were instructed to discontinue dosing of blinded study intervention and participants were given the option to receive daily FTC/TDF or for HIV prevention treatment while continuing the study. Screening and randomization of new participants have stopped. The purpose of this amendment is to define changes in study design and conduct implemented due to stopping of blinded study intervention, and to describe continued monitoring of participants.
Amendment 02	07-DEC-2021	The protocol was amended to increase frequency of monitoring of lymphocytes, add monitoring of CD4+ T-cells, and add discontinuation criteria 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 01	06-MAY-2021	The protocol was amended to modify the management of participants who become pregnant, to modify PK assessments for participants who become pregnant and remain on ISL, and to modify breastfeeding options for participants who become pregnant.
Original Protocol	20-OCT-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

The protocol was amended to add Part 3 to the study to unblind each participant's Part 1 study intervention assignment, continue participants on FTC/TDF, and monitor safety.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Part 3 added to study design:	
1.2 Schema 1.3 Schedule of Activities 2.1 Study Rationale 2.3 Benefit/Risk Assessment 3 Hypotheses, Objectives, and Endpoints 4 Study Design 6.1 Study Intervention(s) Administered	Participants, investigators, and all Sponsor personnel will be unblinded to the participants' original randomized study intervention group.	Continued blinding is unnecessary since all participants will be receiving open-label daily PrEP therapy with FTC/TDF and undergoing the same study procedures regardless of original assignment.
	Ongoing participants will continue to receive FTC/TDF.	The Sponsor will continue to offer ongoing participants FTC/TDF to fulfill its ethical duties toward study participants.
	No new participants will be screened or randomized during Part 3.	Since ISL is no longer being offered as a study intervention, there is no reason to screen or randomize any new participants.
	Ongoing participants will continue to be monitored for safety.	The Sponsor will continue to monitor safety to ensure the wellbeing of study participants and to provide greater clinical detail for monitoring total lymphocyte counts.

Section # and Name	Description of Change	Brief Rationale
6.3 Measures to Minimize Bias: Randomization and Blinding 6.4 Study Intervention Compliance 6.9 Standard Policies 8 Study Assessments and Procedures 9 Statistical Analysis Plan 10.2 Appendix 2: Clinical Laboratory Tests	PRO preference will not be performed during Part 3. PK samples will not be collected in Part 3. No further assessments will be made by the eDMC.	Since participants are no longer receiving study intervention with ISL, PRO preference, PK sampling, and eDMC oversight are no longer necessary.
1.1 Synopsis 3 Hypotheses, Objectives, and Endpoints 9 Statistical Analysis Plan	Note added to describe that evaluation of the percentage of participants with confirmed HIV-1 infections will no longer be considered a primary endpoint and that the only study objective is to evaluate the safety and tolerability of ISL QM based on review of the accumulated safety data.	Since ISL is no longer being offered as a study intervention, formal hypothesis tests and comparisons between study intervention groups will not be conducted.

Section # and Name	Description of Change	Brief Rationale
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Requirement for investigators to document if an SAE is associated with medication error, misuse, or abuse added.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	Definitions of medication error, misuse, and abuse added.	

Section # and Name	Description of Change	Brief Rationale
4.2.6 Rationale for Collecting Infant Safety Follow-up Data 8.1.1.5 Consent for Infant Safety Data Collection 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.4.5 Pregnancy and Exposure During Breastfeeding 8.11.3.2 Clinical Management of Participants Who Become Pregnant – Part 2 and Part 3 8.11.4 Infant Safety Data Collection	Updated infant safety follow-up procedures for Part 3.	Participants will not receive ISL during Part 3. Therefore, additional infant safety follow-up through 1 year of age will not be required for participants who become pregnant during Part 3. Standard AE reporting requirements will apply.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 6.1 Study Intervention(s) Administered	Study intervention 'Use' term updated from 'Experimental' to "Test product' and study intervention classification column heading updated to include 'AxMP'.	To align with the EU CTR.
4.4 Beginning and End of Study Definition	Clarification of what constitutes the beginning and end of the study added.	To align with the EU CTR.
5 Study Population	Text related to the collection of demographic data added.	To clarify the collection, use, and confidentiality of demographic data provided by participants.
10.2 Appendix 2: Clinical Laboratory Tests	Genetic analysis and blood for FBR were removed from the table of protocol-required laboratory assessments	These samples are not clinical laboratory tests and were placed there in error.
Title Page 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address changed.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

Section # and Name	Description of Change	Brief Rationale
8.1.9.1 Withdrawal From Future Biomedical Research 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Sponsor email address updated from @merck.com to @MSD.com.	To reflect the recent change in the Sponsor's email address.
Throughout as applicable	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir Once-Monthly as Preexposure Prophylaxis in Cisgender Women at High Risk for HIV-1 Infection

Short Title: Oral ISL QM as PrEP in Cisgender Women at High Risk for HIV-1 Infection

Acronym: Impower - 022

Hypotheses, Objectives, and Endpoints:

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

Note: As of Amendment -04, formal hypothesis tests and comparisons between study intervention groups will no longer be conducted; therefore, evaluation of the percentage of participants with confirmed HIV-1 infections will no longer be considered a primary endpoint. The only study objective is to evaluate the safety and tolerability of ISL QM based on review of the accumulated safety data. Updated analyses are described in Section 9.

The following objectives will be evaluated in female participants, 16 to 45 years of age inclusive, at high risk for HIV-1 infection.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of oral ISL QM compared to FTC/TDF QD for the prevention of HIV-1 infection as assessed by the incidence rate per year of confirmed HIV-1 infections • Hypothesis: ISL QM is superior to FTC/TDF QD as assessed by the incidence rate per year of confirmed HIV-1 infections	• Confirmed HIV-1 infection
• To evaluate the safety and tolerability of oral ISL QM compared with oral FTC/TDF QD as assessed by review of the accumulated safety data	• Adverse events • Adverse events leading to discontinuation of study intervention

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of oral ISL QM in reducing the incidence per year of HIV-1 infection relative to the background rate • Hypothesis: ISL QM reduces the incidence rate of confirmed HIV-1 infections compared with the background incidence rate	• Confirmed HIV-1 infection

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	HIV Preexposure prophylaxis
Population	Cisgender Women at high risk for HIV-1 infection
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active Control
Study Blinding	Double-blind

Blinding Roles	Participants or Subjects Investigator Sponsor In Part 2: Personnel not directly involved with blinded safety monitoring of participants' ongoing in the study will be unblinded to the participants' original randomized study intervention group. In Part 3: Participants, investigators, and all Sponsor personnel will be unblinded to the participants' original randomized study intervention group.
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact.

Number of Participants:

Approximately 4500 participants will be randomized. No participants will be randomized in Parts 2 or 3.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1 ISL QM Group	ISL	60 mg	QM	Oral	Visit 2 to (up to) Visit 37	Test Product
Part 1 ISL QM Group	Placebo to FTC/TDF	0 mg	QD	Oral	Visit 2 to (up to) Visit 37	Placebo
Part 1 FTC/TDF QD Group	FTC/TDF	200/245 mg	QD	Oral	Visit 2 to (up to) Visit 37	Test Product
Part 1 FTC/TDF QD Group	Placebo to ISL	0 mg	QM	Oral	Visit 2 to (up to) Visit 37	Placebo
Part 2 All Participants	FTC/TDF	200/245 mg	QD	Oral	QD for Part 2	Test Product
Part 3 All Participants	FTC/TDF	200/245 mg	QD	Oral	QD for Part 3	Test Product

FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); ISL=islatravir also known as MK-8591; PrEP=preexposure prophylaxis; QD=once daily; QM=once-monthly. Each FTC/TDF tablet contains 200 mg emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg tenofovir disoproxil fumarate or 291.22 mg tenofovir disoproxil phosphate).

Total Number of Intervention Groups/ Arms	2
Duration of Participation	After a screening phase of up to 45 days, each participant will be in the study for up to 3 years from the time the participant provides documented Informed Consent/assent through final contact. Because this is an endpoint-driven study, participation times will vary depending on when the participant is enrolled. Participants will be enrolled over an approximately 12-month period with study intervention administered for approximately 1 year and up to 3 years, based on estimated accrual of primary endpoint cases. Participants who discontinue study intervention, become pregnant, or decide to breastfeed will be followed as described in the protocol.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1. *Note: The Executive Oversight Committee and Data Monitoring Committee are not applicable in Part 3.*	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

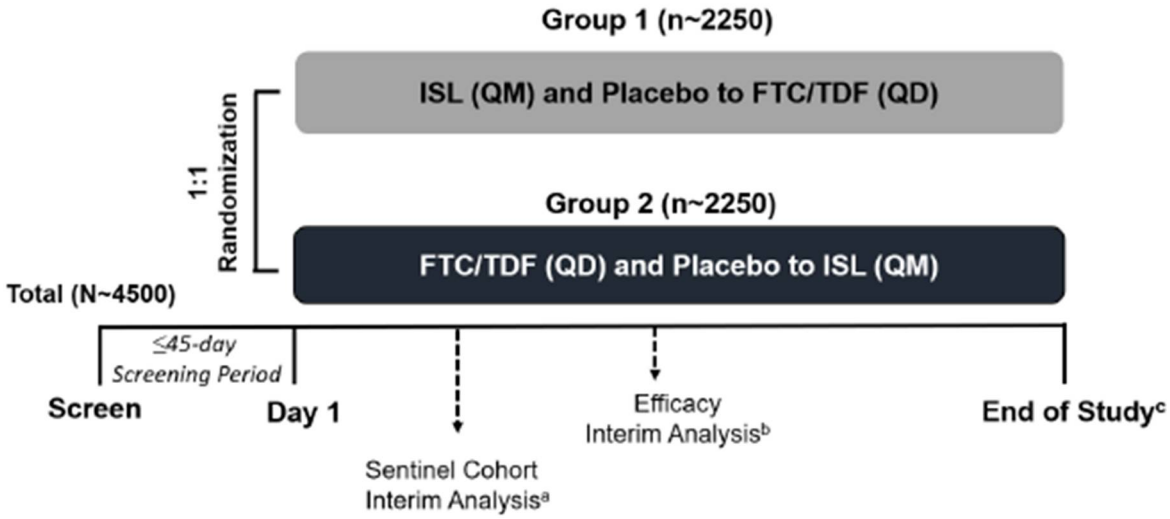
The study design is depicted in Figure 1 (Part 1), Figure 2 (Part 2), and Figure 3 (Part 3).

Blinded study intervention administration has been stopped; study assessments conducted prior to stopping blinded study intervention are designated as Part 1 (Figure 1).

During Part 2 (Figure 2), all participants were switched to PrEP therapy with FTC/TDF. No new participants will be screened or randomized during Part 2.

During Part 3 (Figure 3), all ongoing participants will continue to receive open-label PrEP therapy with FTC/TDF. No new participants will be screened or randomized during Part 3.

Figure 1 Study Schema – Part 1



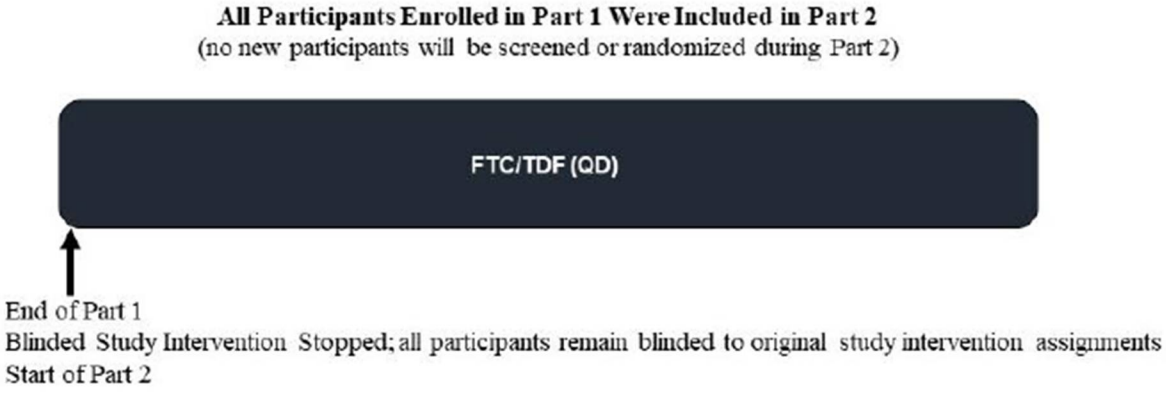
FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); ISL=islatravir; QD=once daily; QM=once-monthly

[a] Sentinel Cohort Interim Analysis (N=400) will be conducted 3 months after the last participant in the Sentinel Cohort has initiated study intervention.

[b] An efficacy Interim Analysis will be performed when 25 primary endpoint cases are observed.

[c] End of study includes the safety follow-up period of 42 days after the last dose of study intervention. End of Study will be determined based on estimated accrual of 40 primary endpoint cases. Participants will be enrolled over an approximately 12-month period with study intervention administered for approximately 1 year and up to 3 years.

Figure 2 Study Schema – Part 2



FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); QD=once daily.
Note: For Part 2, throughout the protocol, references to study intervention refer to FTC/TDF.

Figure 3 Study Schema – Part 3

FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); QD=once daily.
All participants will be unblinded to original study intervention assignments in Part 3.
No new participants will be screened or randomized during Part 3.
Note For Part 3, throughout the protocol, references to study intervention refer to FTC/TDF.

1.3 Schedule of Activities

Note: Blinded study intervention administration (Part 1) was stopped. During Part 2, all participants were switched to PrEP therapy with FTC/TDF and will maintain the visit schedule in Section 1.3.1. No new participants will be screened or randomized during Part 2. For Part 2, throughout the protocol, references to study intervention refer to FTC/TDF.

Note: At the start of Part 3, all participants will be unblinded to their Part 1 study intervention assignments and ongoing participants will continue to receive open-label daily PrEP therapy with FTC/TDF. No new participants will be screened or randomized during Part 3. For Part 3, throughout the protocol, references to study intervention refer to FTC/TDF.

1.3.1 Schedule of Activities for Part 1 and, Part 2, and Part 3

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Administrative Procedures															
Informed Consent/Assent	X														
Informed Consent/Assent for Future Biomedical Research	X														
Consent/Assent for Open-label FTC/TDF															For participants with a positive urine pregnancy test only. To occur at the time of the first positive urine pregnancy test.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Consent/Assent to Continue Study Participation after a Confirmed Continuing Pregnancy															For Part 1 participants with a confirmed continuing pregnancy only. To occur at the time a continuing pregnancy is confirmed. See Section 8.11.3 for details.
Consent/Assent to Continue Study Participation for Participants Who Choose to Breastfeed															For participants who choose to breastfeed during the study only. To occur before delivery. See Sections 8.11.3.1.1 and 8.11.3.2.1 for details.
Consent/Assent for Infant Safety Data Collection															For Part 1 and Part 2 participants with a confirmed continuing pregnancy only. To occur at any time after confirmation of continuing pregnancy (see Section 8.11.3).
Inclusion/Exclusion Criteria	X	X													Review prior to randomization on Day 1 to confirm no changes in eligibility.
Recency Assay	X	X													Samples will be analyzed in participants with confirmed HIV-1 infection at Screening or Day 1
Participant Identification Card	X	X													Randomization number will be added once the participant is randomized on Day 1.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Register study visit in IRT	X	X	X	X	X	X	X	X	X			X	X	X	
Medical History	X														
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X			X	X	X	
Intervention Randomization		X													
Assessment of acute retroviral syndrome	X														See Section 8.11.1
Dispense Study Intervention		X	X	X	X	X	X	X	X						During Part 1, in-clinic dosing of study intervention. The remaining supply of FTC/TDF or matching placebo will be dispensed at each visit. Do NOT dispense study intervention if the participant's Point-of-Care HIV test or urine pregnancy test is positive. During Part 2 and Part 3, participants will receive only FTC/TDF. Participants should stop FTC/TDF if Point-of-Care HIV test result is positive while further testing is conducted. No other study intervention is to be dosed.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Evaluation to receive continued study intervention												X			
Study Intervention Adherence Review		X	X	X	X	X	X	X	X			X			Reconcile doses, assess study intervention adherence, and offer adherence counseling.
Contraceptive use confirmation (WOCBP only)	X	X	X	X	X	X	X	X	X			X			Contraception to be provided to participants if needed.
HIV Risk Reduction	X	X	X	X	X	X	X	X	X			X			Completion of the sexual activity form, offer condoms, lubricants, and HIV risk reduction counseling.
PRO: HIV infection Risk		X			X			X		X		X			
PRO: Preference		X						X			X	X			Not applicable for Part 3.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Efficacy Procedures															
Point-of-Care HIV Testing	X	X	X	X	X	X	X	X	X			X			Performed at the study site. On Day 1, this testing should be performed prior to randomization and if positive, the participant should not be randomized. At all subsequent visits after Day 1, if this test result is positive, PK samples (both plasma and dried blood) should be collected, regardless of the PK sampling schedule. During Part 1, do NOT dispense study intervention if the participant's Point-of-Care HIV test is positive while further testing is conducted. During Part 2 and Part 3, participants should stop taking FTC/TDF if Point-of-Care HIV Test result is positive.
HIV-1/HIV-2 Antibody/Antigen Testing	X	X	X	X	X	X	X	X	X			X			

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	X	X	X	X	X			X			Samples will be collected at every visit and analyzed if Point-of-Care HIV test or HIV-1/HIV-2 antibody/antigen test is positive.
Whole Blood Collection for HIV-1 Resistance Testing		X													See Section 1.3.3 for additional requirements for participants who have an HIV Infection Confirmation Visit.
Safety Procedures															
Full physical examination	X														
Height	X							X			X				
Weight	X	X	X	X	X	X	X	X	X			X			
Symptom-directed Physical Examination		X	X	X	X	X	X	X	X			X			
Vital Signs	X	X	X	X	X	X	X	X	X			X			Includes pulse, blood pressure, body temperature, and respiratory rate.
Antenatal care record review			X	X	X	X	X	X	X			X			Only for participants who become pregnant in Parts 1 and 2 (see Sections 8.4.5 and 8.11.3).
Review of adverse events	X	X	X	X	X	X	X	X	X			X	X	X	
Review of social harm events		X	X	X	X	X	X	X	X			X	X	X	

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Laboratory Procedures															
Urine Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X			X			Conduct per local regulations and prior to administering/dispensing study intervention. Do NOT dispense study intervention if the participant's urine pregnancy test is positive. Confirm with serum test if urine test is positive[e].
Serum Pregnancy Test (WOCBP only)	X														
Hepatitis B Serology (HBsAb/HBcAb)	X														Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV.
HBsAg	X														
Syphilis Serologic Testing	X				X			X		X		X			
Vaginal swab for bacterial vaginosis testing	X				X			X		X		X			
Urine for Trichomonas	X				X			X		X		X			Collect the sample according to the laboratory manual.
Urine for GC/CT	X				X			X		X		X			Collect the sample according to the laboratory manual.
HSV-2 serology testing	X											X			
Hematology	X	X	X	X	X	X	X	X	X			X			

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
CD4+ T-cell count/Lymphocyte subset panel	X	X	X	X	X	X	X	X	X			X			
Chemistry	X	X			X			X		X		X			
Creatinine Clearance Calculation	X	X			X			X		X		X			See Appendix 9
Cystatin-C		X			X			X		X		X			
Pharmacokinetics															
Blood (Plasma) for PK[f]		X	X		X			X			X	X			**Not applicable for Part 3.** See Section 8.6.1 and Table 12. The sample must be collected irrespective of the planned PK collection schedule, if a participant has a positive Point-of-Care HIV test result at a visit. See Section 1.3.4 for participants who become pregnant and remain on ISL.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Blood (Plasma) for Investigational PK[g]				X							X				**Not applicable for Part 3.** During Part 1, investigational PK samples will be collected predose at Visit 4 (Month 2) and at any time during Visit 11 (Month 9) and every 6 months starting from Visit 11 (Month 9). During Part 2, investigational PK samples can be collected at any time during the visit. See Table 12. Samples will be stored and triggered for analysis by Sponsor, if needed. See Section 1.3.4 for participants who become pregnant and remain on ISL.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Dried Blood for PK[f]		X	X	X	X			X			X	X			**Not applicable for Part 3.** See Section 8.6.3, Table 12 and Table 13. The sample must be collected irrespective of the planned PK collection schedule, if a participant has a positive Point-of-Care HIV test result at a visit. See Section 1.3.4 for participants who become pregnant and remain on ISL.

Study Period	**Double-blind Study Intervention Period (Part 1) PrEP Therapy With FTC/TDF (Part 2 and Part 3)**												**Follow-up**		**Notes**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**	**39**	**40**	
Scheduled Day/Month	**Screening (N/A during Part 2)**	**Day 1 (N/A during Part 2 and Part 3)**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36/ EOT**	**14-Day Phone Call**	**42-Day Phone Call**	Each visit should be calculated from date of Day 1 and based on a 28-day month. A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Visit Window	≤45 days[d]	N/A	±7 Days												Visit windows for Part 3 are extended to ±14 Days
Biomarkers															
Blood for Genetic Analysis		X													See Section 8.8
Whole Blood for FBR		X													Optional participation, requires FBR Consent/assent.

EOT=End of treatment (not all participants will complete 36 months because this is a case-driven study); FBR=Future Biomedical Research; FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); GC/CT=*Neisseria gonorrhoeae/Chlamydia trachomatis*; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HSV=herpes simplex virus; IRT=Interactive Response Technology; ISL=islatravir (also known as MK-8591); N/A=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PRO=participant-reported outcome; RNA=ribonucleic acid; WOCBP=women of childbearing potential

[a] **Assessments noted in this column will be repeated every month from Month 7 through Month 35 (Visits 9 through 37).**

[b] **Additional assessments noted in this column will be repeated every 3 months until Month 35 – at the following visits:**
Month 9 (Visit 11), Month 12 (Visit 14), Month 15 (Visit 17), Month 18 (Visit 20), Month 21 (Visit 23), Month 24 (Visit 26), Month 27 (Visit 29), Month 30 (Visit 32), Month 33 (Visit 35)

[c] **Additional assessments noted in this column will be repeated every 6 months until Month 35 – at the following visits:**
Month 12 (Visit 14), Month 18 (Visit 20), Month 24 (Visit 26), Month 30 (Visit 32)

[d] A screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.

[e] Once a continuing pregnancy has been confirmed, monthly urine pregnancy tests should be deferred until 1 month following the end of the pregnancy.

[f] **Additional timepoints for Blood (plasma) and Dried blood PK collection**: Month 12 (Visit 14), Month 18 (Visit 20), Month 24 (Visit 26), Month 30 (Visit 32). PK samples will not be collected in Part 3.

[g] **Additional timepoints for Blood (Plasma) for Investigational PK collection**: Month 9 (Visit 11), Month 15 (Visit 17), Month 21 (Visit 23), Month 27 (Visit 29), Month 33 (Visit 35). PK samples will not be collected in Part 3.

1.3.2 Schedule of Activities – Participants Who Discontinue Study Intervention Early and/or Withdraw Consent/Assent

Study Period	**Early Discontinuation from Study Intervention**		**Notes**
Visit Number	**Unscheduled Visits**		
Scheduled Day/Week	Early Discontinuation of Study Intervention	Early Withdrawal from Study	
Visit Window	N/A	N/A	
Administrative Procedures			
Register study visit in IRT	X	X	No study intervention will be dispensed.
Concomitant medication review	X	X	
Contraceptive use confirmation (WOCBP only)	X	X	
PRO: HIV infection Risk	X	X	
PRO: Preference	X	X	Not applicable for Part 3
HIV Risk Reduction	X	X	Completion of the sexual activity form; offer condoms, lubricants, and HIV risk reduction counseling.
Efficacy Procedures			
Point-of-Care HIV-1 Testing	X	X	Performed at the study site.
HIV-1/HIV-2 Antibody/Antigen Testing	X	X	
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	Samples will be collected and analyzed if Point-of-Care HIV test or HIV-1/HIV-2 antibody/antigen test is positive.
Plasma for HIV-1 Drug Resistance Testing	X	X	Samples will be collected and analyzed if needed.
Safety Procedures			
Symptom-directed physical examination	X	X	
Vital signs	X	X	Includes pulse, blood pressure, body temperature, and respiratory rate.
Weight	X	X	
Review of adverse events	X	X	
Review of social harm events	X	X	
Laboratory Assessments			
Chemistry	X	X	

Study Period	**Early Discontinuation from Study Intervention**		**Notes**
Visit Number	**Unscheduled Visits**		
Scheduled Day/Week	Early Discontinuation of Study Intervention	Early Withdrawal from Study	
Visit Window	N/A	N/A	
Hematology	X	X	
CD4+ T-Cell Count/Lymphocyte subset panel	X	X	
Creatinine clearance calculation	X	X	See Appendix 9
Urine pregnancy test (WOCBP only)	X	X	Conduct per local regulations. Positive results to be confirmed with serum pregnancy test.
Cystatin-C	X	X	
HSV-2 Serology	X	X	
Pharmacokinetics			
Blood (Plasma) for PK	X	X	**Not applicable for Part 3.** PK samples should be collected at the time of discontinuation or withdrawal. For participants who do not withdraw consent/assent (ie, continuing to have study visits), PK samples will also be collected monthly for the next 3 months, after which the participant should resume the PK schedule outlined in Section 1.3.1.

Study Period	**Early Discontinuation from Study Intervention**		**Notes**
Visit Number	**Unscheduled Visits**		
Scheduled Day/Week	Early Discontinuation of Study Intervention	Early Withdrawal from Study	
Visit Window	N/A	N/A	
Dried blood for PK	X	X	**Not applicable for Part 3.** PK samples should be collected at the time of discontinuation or withdrawal. For participants who do not withdraw consent/assent (continuing to have study visits), PK samples will also be collected monthly for the next 3 months, after which the participant should resume the PK schedule outlined in Section 1.3.1.

HIV=human immunodeficiency virus; HSV=herpes simplex virus; IRT=Interactive Response Technology; ISL=islatravir (also known as MK-8591); PCR=polymerase chain reaction; PRO=participant-reported outcome; RNA=ribonucleic acid; WOCBP=women of childbearing potential

For details on the Early Discontinuation of Study Intervention visit, see Section 8.11.4.
For details on the Early Withdrawal from Study visit, see Section 8.11.5.

1.3.3 Schedule of Activities – Participants With a Positive HIV-1 Test Result

Study Period	**Follow-up after Seroconversion**				**Notes**
Visit Number	Unscheduled	Varies[a]			
Scheduled Day	HIV-1 Infection Confirmation	Follow-up Monthly Visits	Poststudy Intervention Follow-up Phone Call[b]		Each monthly visit will be based on a 28-day month.
Visit Window	Within 14 days of positive HIV-1 test	± 7 days	14 (+7) days after the last dose of study intervention	42 (+7) days after the last dose of study intervention	Visit windows for Part 3 Follow-up Monthly Visits are extended to ±14 Days.
Administrative Procedures					
Register study visit in IRT	X	X	X	X	Part 1, no study intervention will be dispensed. Part 2 and Part 3 participants should stop taking PrEP with FTC/TDF while further testing is conducted.
Link to HIV Treatment Services	X				Upon confirmed HIV-1 infection
Concomitant medication review	X	X	X	X	Including ART regimens
Contraceptive use confirmation (WOCBP only)	X				Contraception will be offered at monthly visits and confirmation of use is not required unless indicated.
HIV Risk Reduction	X	X			Completion of the sexual activity form, offer condoms, lubricants, and HIV risk reduction counseling
Efficacy Procedures					
Plasma HIV-1 RNA quantification (Real Time PCR)	X				
HIV-1/HIV-2 antibody/Antigen test	X				
Whole blood and plasma for HIV-1 drug resistance testing	X	X			Samples will be collected and analyzed every 3 months following HIV Infection Confirmation Visit

Study Period	**Follow-up after Seroconversion**				**Notes**
Visit Number	Unscheduled	Varies[a]			
Scheduled Day	HIV-1 Infection Confirmation	Follow-up Monthly Visits	Poststudy Intervention Follow-up Phone Call[b]		Each monthly visit will be based on a 28-day month.
Visit Window	Within 14 days of positive HIV-1 test	± 7 days	14 (+7) days after the last dose of study intervention	42 (+7) days after the last dose of study intervention	Visit windows for Part 3 Follow-up Monthly Visits are extended to ±14 Days.
Safety Procedures					
Symptom-directed physical examination	X				
Vital signs	X				Includes pulse, blood pressure, body temperature, and respiratory rate
Weight	X				
Review of adverse events	X		X	X	
Review of social harm events	X		X	X	
Hematology	X	X			
CD4+ T-cell count	X	X			
Chemistry	X				
HSV-2 Serology	X				
Pharmacokinetics					
Blood (Plasma) for PK	X	X			**Not applicable for Part 3.** PK samples should be collected at the time of HIV-1 infection confirmation visit, the first 3 monthly follow-up visits, and then every 3 months thereafter.
Dried Blood for PK	X	X			**Not applicable for Part 3.** PK samples should be collected at the time of the HIV-1 infection confirmation visit, the first 3 monthly follow-up visits, and then every 3 months thereafter.

Study Period	**Follow-up after Seroconversion**				**Notes**
Visit Number	Unscheduled	Varies[a]			
Scheduled Day	HIV-1 Infection Confirmation	Follow-up Monthly Visits	Poststudy Intervention Follow-up Phone Call[b]		Each monthly visit will be based on a 28-day month.
Visit Window	Within 14 days of positive HIV-1 test	± 7 days	14 (+7) days after the last dose of study intervention	42 (+7) days after the last dose of study intervention	Visit windows for Part 3 Follow-up Monthly Visits are extended to ±14 Days.
Biomarkers					
Whole blood for FBR	X				Optional participation, requires FBR consent/assent

ART=antiretroviral therapy; FBR=Future Biomedical Research; HIV=human immunodeficiency virus; HSV=herpes simplex virus; IRT=Interactive Response Technology; ISL=islatravir (also known as MK-8591); PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid; STI=sexually transmitted infection

[a] After the last completed visit prior to HIV-1 infection, the participant would start Follow-up Month 1 visit and monthly visits will align with the participant's date of randomization and will end at the Month 36 visit (ie, participants will not be in the study for >36 months).

[b] The 14-day and 42-day follow-up phone calls only need to be performed for participants who will not be completing the follow-up monthly visits after HIV-1 infection confirmation. During Part 2 and Part 3, phone calls should be performed based on the last dose of PrEP with FTC/TDF.

1.3.4 Schedule of Activities for Participants Who Become Pregnant and Remain on ISL

Note: This schedule is not applicable for Part 2 or Part 3 of the study.

Gestational Age	**≤12 Weeks**		**13-26 Weeks**		**≥27 Weeks**		**Postpartum**	**Notes**
Visit	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	Visits will begin when the pregnancy is confirmed and consent is obtained. Visits P1, P3, P5, and P7 should coincide with 1 planned monthly visit during the time period (see Section 1.3.1) and will include all planned procedures except urine pregnancy test. Visits P2, P4, and P6 should occur approximately 2 weeks after P1, P3, and P5, respectively.
Visit Window	**± 7 days**							
All procedures performed at recurring monthly visit	X		X		X		X	See Section 1.3.1
Administrative procedures								
Register study visit in IRT	X		X		X		X	
Concomitant medications	X	X	X	X	X	X	X	
Pharmacokinetics								
Blood (Plasma) for PK	X	X	X	X	X	X	X	See Section 8.6.4
Dried Blood for PK	X	X	X	X	X	X	X	See Section 8.6.4
Safety								
Antenatal care record review	X	X	X	X	X	X	X	See Sections 8.4.5 and 8.11.3
Weight	X	X	X	X	X	X	X	
Symptom-directed physical examination	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	
Review of adverse events	X	X	X	X	X	X	X	
Review of social harm events	X	X	X	X	X	X	x	
Collect blood sample for CrCl	X	X	X	X	X	X	X	Collect sample for CrCl if not collected as part of the planned monthly visit.
CrCl=creatinine clearance; IRT=Interactive Response Technology; PK=pharmacokinetic(s)								

2 INTRODUCTION

ISL (also known as MK-8591) is a novel and potent NRTTI being developed for HIV-1 PrEP administered as a monthly oral dose in individuals at high risk for HIV-1 infection.

2.1 Study Rationale

Part 1

HIV-1 infection remains a worldwide epidemic with an estimated 38 million individuals infected globally and 1.7 million new infections estimated to have occurred in 2019 [Joint United Nations Programme on HIV/AIDS 2020]. Novel strategies to prevent HIV acquisition are urgently needed.

One proven biomedical intervention for the prevention of HIV infection is PrEP. Although clinical study data have demonstrated that the effectiveness of TRUVADA™ (emtricitabine/tenofovir disoproxil [FTC/TDF], Gilead) QD for PrEP is strongly correlated with adherence to daily therapy [Grant, R. M., et al 2010] [Baeten, J. M., et al 2012], adherence to FTC/TDF QD is suboptimal in many individuals at risk for HIV-1 infection [Marrazzo, J. M., et al 2015] [Hojilla, J. C., et al 2018]. In particular, women in subSaharan Africa have an ongoing unmet medical need for alternatives to FTC/TDF QD for PrEP. This population continues to have a high HIV-1 incidence rate and clinical studies have shown great variability in the effectiveness of FTC/TDF QD for PrEP, related, in part, to challenges associated with adhering to this daily regimen [Van Damme, L., et al 2012] [Marrazzo, J. M., et al 2015].

Long-acting agents, such as a monthly pill, have the potential to reduce the risk of HIV-1 acquisition without relying on adherence to a daily regimen. In the same way that long-acting reversible contraceptives have provided important options and increased acceptability and uptake of contraception among women [Ross, J. 2013], expanded choices for HIV-1 prevention may increase utilization, adherence, and effectiveness.

ISL has the potential to be an effective agent for HIV-1 PrEP due to its potent antiviral activity, long half-life, and favorable safety profile as demonstrated in early phase clinical studies. The convenience and discretion of monthly oral administration of ISL may facilitate adherence and access to PrEP for women at high risk for HIV-1 infection, ultimately leading to greater effectiveness for HIV-1 prevention than what is currently observed with FTC/TDF QD.

Part 2 and Part 3

Decreases in total lymphocyte and CD4+ T-cell counts have been observed in studies with ISL alone or in combination (including ISL 60/120 mg QM in participants not infected with HIV, and DOR/ISL 100 mg/0.75 mg QD or ISL 20 mg + MK-8507 100/200/400 mg QW in participants with HIV-1). The decreases in lymphocytes and CD4+ T-cell counts appeared to be ISL-dose dependent. These laboratory changes were not associated with AEs in those receiving ISL or DOR/ISL. The long-term clinical impact of these laboratory changes is

unknown; however, the Sponsor is assessing the reversibility of the reductions in CD4+ T-cell and total lymphocyte counts.

Across the ISL clinical program, study protocols were amended to increase monitoring for decreases in total lymphocyte and CD4+ T-cell counts and to implement stopping rules for individuals who experience significant decreases in total lymphocytes and/or CD4+ T-cell counts.

In Part 3, participants, investigators, and all Sponsor personnel will be unblinded to the participants' original randomized study intervention group to provide greater clinical detail for monitoring total lymphocyte counts and continued safety monitoring of participants. Furthermore, since all participants will be receiving open-label daily PrEP (FTC/TDF) and undergoing the same study procedures regardless of original assignment, continued blinding unnecessary.

2.2 Background

Refer to the IB for detailed background information on ISL.

2.2.1 Pharmaceutical and Therapeutic Background

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

ISL is potent at low doses and has a long intracellular half-life [Markowitz, M. 2018]. In a rhesus macaque SHIV rectal-challenge prophylaxis-efficacy model, ISL provided complete protection against infection with weekly doses of 1.3 and 0.43 mg/kg [Markowitz, M., et al 2019]. Doses of 0.1 mg/kg afforded a 92% reduction of infection risk [Markowitz, M., et al 2019]. Studies in a rhesus macaque model demonstrated that ISL-TP concentrations were comparable in rectal and vaginal tissue, at levels predictive of prophylactic activity of ISL against HIV-1 in both men and women [Grobler, J., et al 2017]. Similarly, results from MK-8591 Protocol 009 indicate that at steady state with daily dosing, concurrent ISL-TP concentrations in human PBMCs, rectal and vaginal tissues were generally comparable, and observed to be at levels projected to be efficacious for treatment and prevention of HIV-1 infection. Based on intracellular concentrations of ISL-TP required to inhibit HIV-1 replication, the efficacy of ISL in the rhesus macaque SHIV challenge PrEP model, and associated exposures in animal models and human PK simulations, a QM regimen of ISL 60 mg QM has the potential to provide efficacious prophylaxis against HIV-1 infection (Sections 4.3.1 and 4.3.2).

2.2.2 Information on Other Study-related Therapy

FTC/TDF is currently the standard of care for prevention among individuals at high risk of HIV-1 infection. FTC/TDF was approved for use as PrEP in the US by the FDA in 2012. The USPSTF [Owens, D. K., et al 2019] recommends that clinicians offer PrEP for all persons at risk for HIV-1 infection, which includes men who have sex with men, women and men at risk through heterosexual contact, and people who inject drugs. FTC/TDF was approved for use as PrEP in Kenya and South Africa in 2015 [National AIDS and STI Control Program 2017] [AVAC: Global Advocacy for HIV Prevention 2015] making it available in some of the regions with the greatest burden of HIV worldwide. In 2015 the WHO [World Health Organization 2015] recommended that oral PrEP containing tenofovir disoproxil should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches, defining "substantial risk" as HIV incidence >3 per 100 person-years in the absence of PrEP. Furthermore, tenofovir disoproxil, along with 3TC (or FTC), is part of the WHO preferred first-line ART regimen recommended for adults, including pregnant women [World Health Organization 2017].

In this study, participants receiving FTC/TDF will be administered either TRUVADA™ (Gilead) or a generic product (emtricitabine/tenofovir disoproxil) at the approved marketed dose for prevention. The tenofovir disoproxil component of the generic product contains a different salt form (phosphate) compared with TRUVADA™ (fumarate), and is considered bioequivalent and is approved by the EMA. For simplicity, both TRUVADA™ and all generic versions are abbreviated as FTC/TDF throughout the protocol.

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 preclinical 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.

Decreases of total lymphocyte and CD4+ T-cell counts that appear dose dependent were observed in ongoing Phase 2 and Phase 3 studies with ISL alone or in combination with other antiviral agents.

In the Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and PK of 60 mg and 120 mg of ISL monthly for PrEP (conducted in participants at low risk of HIV-1 infection; MK-8591-016), after 6 monthly doses there was a 21% mean decrease in total lymphocytes observed in the 60-mg arm (the dose of ISL being evaluated in this study), a 36% decrease in total lymphocytes observed in the 120-mg arm, and a 4% increase in the placebo arm compared with baseline values. Approximately 35% of participants in the ISL 60-mg arm had a >30% reduction in total lymphocyte counts during the study, with 3 of 95 participants reporting Grade 2 lymphocyte reductions and 1 of 95 participants reporting a Grade 3 lymphocyte reduction (transient). Two of 97 participants in the 120 mg arm had Grade 3 lymphocyte reductions. In this population of participants not

infected with HIV-1, the mean lymphocyte counts remained in the normal range, and there were no increases in clinical AEs related to infection. With regard to the Phase 3 efficacy studies for PrEP, as of 13-DEC-2021, dosing (of 60 mg oral monthly ISL) has been stopped in all PrEP clinical studies.

In a Phase 2 study (MK-8591-013) for once-weekly HIV-1 treatment, decreases from baseline in lymphocyte and CD4+ T-cell counts were observed in the ISL 20 mg + MK-8507 treatment arms at Week 12 and Week 24. Decreases from baseline in total lymphocyte count were observed in all dosing arms of ISL + MK-8507 starting at Week 8, with further decreases continuing through Week 24, and the reduction appeared more pronounced in the 2 higher MK-8507 dose arms. Dosing of ISL + MK-8507 in MK-8591-013 has been discontinued.

In an interim analysis for 2 Phase 3 studies (MK-8591A-017 and MK-8591A-018) evaluating a switch to daily DOR 100 mg/ISL 0.75 mg for treatment of HIV-1 in virologically suppressed participants, mean decreases from baseline in total lymphocyte counts at Week 48 were 10.7% (MK-8591 A 017) and 8.5% (MK-8591 A 018) in the DOR/ISL groups, and mean decreases from baseline of CD4+ T-cell counts at Week 48 were approximately 60 cells/mm^3 relative to the comparator arms.

At this point, the long-term clinical impact of these laboratory changes is unknown, and the Sponsor is assessing not only the reversibility of the reductions in CD4+ T-cell and total lymphocyte counts, but also the potential impact on other immune cell types.

It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. The efficacy of ISL for HIV PrEP has not yet been demonstrated in humans. Participants who are randomized to the ISL QM group may be at risk of developing HIV-1 infection. To mitigate this risk, a monthly visit is required for HIV-1 testing at which time prevention counseling with distribution of lubricants and condoms will take place.

As of Amendment-03, all participants in the ISL 60-mg arm were switched to daily PrEP with FTC/TDF. There was monthly monitoring of lymphocyte and CD4+ T-cell counts to assess the reversibility of these laboratory changes, as well as ascertainment of any infections. As of Amendment-04, all ongoing participants will continue to receive open-label daily PrEP therapy with FTC/TDF.

Women have an increased risk of contracting HIV-1 infection during pregnancy and breastfeeding. Current guidelines recommend providing PrEP to pregnant and breastfeeding women to reduce the risk of HIV-1 infection in the woman and also the risk of subsequent mother-to-child transmission [World Health Organization 2017]. Nonclinical reproductive toxicity studies of ISL did not identify any clinically relevant concerns that would preclude continued dosing of ISL in participants who become pregnant during the study. The dosing of 60 mg ISL in pregnant women has been stopped while the Sponsor’s investigation is ongoing. Currently, there are no clinical data available to support or recommend against

breastfeeding by participants who have received ISL. Thus, women will not be permitted to continue ISL, but they may receive open-label FTC/TDF while breastfeeding.

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IBs and informed consent/assent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Note: As of Amendment -04, formal hypothesis tests and comparisons between study intervention groups will no longer be conducted; therefore, evaluation of the percentage of participants with confirmed HIV-1 infections will no longer be considered a primary endpoint. The only study objective is to evaluate the safety and tolerability of ISL QM based on review of the accumulated safety data. Updated analyses are described in Section 9.

The following objectives will be evaluated in female participants, 16 to 45 years of age inclusive, at high risk for HIV-1 infection.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of oral ISL QM compared to FTC/TDF QD for the prevention of HIV-1 infection as assessed by the incidence rate per year of confirmed HIV-1 infections • Hypothesis: ISL QM is superior to FTC/TDF QD as assessed by the incidence rate per year of confirmed HIV-1 infections	• Confirmed HIV-1 infection
• To evaluate the safety and tolerability of oral ISL QM compared with oral FTC/TDF QD as assessed by review of the accumulated safety data	• Adverse events • Adverse events leading to discontinuation of study intervention

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of oral ISL QM in reducing the incidence per year of HIV-1 infection relative to the background rate • Hypothesis: ISL QM reduces the incidence rate of confirmed HIV-1 infections compared with the background incidence rate	• Confirmed HIV-1 infection
Tertiary/Exploratory	
• To evaluate preferences for QM vs QD dosing	• Response for dosing preference
• To evaluate the pharmacokinetics of ISL QM	• Pharmacokinetic parameters
• To evaluate rates and patterns of adherence to FTC/TDF QD and ISL QM	• Pharmacokinetic-adherence relationship
• To evaluate the impact of ISL QM on renal function compared with FTC/TDF QD as measured by the change from baseline in renal biomarkers at Weeks 24 and 48	• Renal biomarkers
• To evaluate viral drug resistance in participants who seroconvert to HIV-1	• Viral resistance-associated substitutions

Objectives	Endpoints
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	• Germline genetic variation and association to clinical data collected in this study
• To evaluate the pharmacokinetics of ISL in pregnant participants	• Pharmacokinetic parameters

4 STUDY DESIGN

Blinded study intervention administration (Part 1), including ISL or its placebo, has been stopped. During Part 2, all participants were switched to PrEP therapy with FTC/TDF.

Study assessments conducted before stopping blinded study intervention are designated as Part 1. During Part 2 of the study, no new participants will be screened or randomized; participants already in the study will continue daily PrEP therapy with FTC/TDF, and samples for assessments will be collected at all monthly visits (Section 1.3.1). During Part 3 of the study, no new participants will be screened or randomized; ongoing participants will continue to receive open-label daily PrEP therapy with FTC/TDF and samples for assessments will be collected at all monthly visits (Section 1.3.1).

4.1 Overall Design

Part 1

This is a randomized, active-controlled, parallel-group, multisite, double-blind, double-dummy study to evaluate the safety and efficacy of ISL administered orally QM as PrEP in cisgender women who are at high risk for HIV-1 infection. The active comparator for this study (FTC/TDF) will be administered orally QD.

Approximately 4500 participants will be randomized (stratified by site and age) in a 1:1 ratio to receive either ISL or FTC/TDF for the duration of the study. Approximately 50% of the global study population will be <25 years of age.

The first approximately 400 participants ≥18 years of age enrolled will be identified as the Sentinel Cohort. An IA (hereafter referred to as the Sentinel Cohort IA) will be conducted by an external statistician 3 months after the last participant in the Sentinel Cohort has initiated study intervention. All available data will be submitted to an eDMC for a safety evaluation. Meanwhile, overall study enrollment will continue, but will be capped at no more than

1000 participants until safety and tolerability have been assessed. Enrollment for 16- or 17-year-old participants should begin upon completion of the Sentinel Cohort IA and review of IA results by the eDMC.

Samples for efficacy assessments will be collected at all monthly visits from participants receiving study intervention (Section 1.3.1). The primary efficacy analysis will be performed upon accrual of a total 40 primary endpoint cases of confirmed incident HIV-1 infections. An efficacy IA will be performed when 25 primary endpoint cases are observed. The study may be stopped early for demonstration of efficacy or futility in the efficacy IA. Consideration may also be given to stopping the study at approximately 3 years after the first participant has been randomized if 40 confirmed incident HIV-1 infections have not yet been accrued by this time (Section 9.6.1). Participants will be enrolled over an approximate 12-month period with study intervention administered for approximately 1 year and up to 3 years, based on estimated accrual of primary endpoint cases.

Any participants with confirmed HIV infection will be discontinued from study intervention, referred for and linked to treatment per local standard of care. Any participants with seroconversion will be followed as outlined in Section 1.3.3 and assessed for viral drug resistance.

If a participant becomes pregnant (has a positive serum pregnancy test) while receiving study intervention, the participant, investigator, and Sponsor will assess if the participant should continue study intervention (Section 8.11.3).

Safety assessments will include all accumulated safety data until the end of study, which includes the safety follow-up period of 42 days after the last dose of study intervention.

Participant safety and overall conduct of the study will be monitored by an independent eDMC through periodic review of safety and efficacy data throughout study duration.

Part 2

Blinded study intervention administration in Part 1, including ISL or its placebo, will be stopped, as noted above. During Part 2, all participants will be switched to PrEP therapy with FTC/TDF.

During Part 2 of the study, no new participants will be screened or randomized; participants already in the study will continue daily PrEP therapy and samples for assessments will be collected at all monthly visits (Section 1.3.1).

The participant, the investigator, and Sponsor personnel or delegate(s) directly involved in the clinical monitoring or evaluation of participants will remain blinded to the participants' original randomized study intervention group. Sponsor personnel or delegate(s) not directly involved in clinical monitoring or evaluation of the participants will be unblinded to the participants' original randomized study intervention group.

Part 3

In Part 3 of the study, participants, investigators, and all Sponsor personnel will be unblinded to the participants' original randomized study intervention group. No new participants will be screened or randomized; participants already in the study will continue to receive open-label daily PrEP therapy with FTC/TDF and samples for assessments will be collected at all monthly visits (Section 1.3.1). As of Part 3, no further evaluations will be conducted by the eDMC.

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

4.2 Scientific Rationale for Study Design

Part 1

The randomized, double-blinded, active-controlled, superiority study design is consistent with FDA regulatory guidance [Food and Drug Administration 2019]. A superiority design is recommended for studies of PrEP in at risk cisgender women to mitigate risks associated with NI margin prespecification because of variable historical evidence of HIV prevention efficacy in this population [Food and Drug Administration 2019] [Van Damme, L., et al 2012] [Marrazzo, J. M., et al 2015].

This study design is deemed appropriate to provide safety and efficacy data in cisgender women at high risk for HIV-1 infection to demonstrate whether oral ISL QM is an effective option for HIV-1 PrEP in this population. Because of the long intracellular half-life of the pharmacologically active triphosphate (ISL-TP) form of ISL, a QM dosing regimen is being investigated. This dosing schedule is anticipated to facilitate adherence and be effective in preventing infection with HIV-1.

Cisgender women 16 to 45 years of age, inclusive, at the time of screening, will be eligible to participate in the study. Global surveillance data demonstrate that cisgender women are at highest risk of infection between 16 to 45 years of age and therefore, this study will focus on this demographic where demonstrated protective benefit is most needed [Balkus, J. E., et al 2016] [de Oliveira, T., et al 2017].

Part 2

Given the findings of downward trends of total lymphocyte counts and CD4+ T-cell counts in studies with ISL alone or in combination with other antiviral agents, ISL will be stopped in this study, and all participants will be switched to PrEP therapy with FTC/TDF. Participants will have intensified monitoring of laboratory parameters, including lymphocyte subset panels, and will continue to be monitored on a monthly basis for AEs. This will allow for study continuity and blinded monitoring of AEs and laboratory parameters.

Part 3

To allow for study continuity and monitoring of AEs and laboratory parameters.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint will be the rate of confirmed HIV-1 infection, as assessed per a predefined algorithm for HIV-1 testing and diagnosis in recipients of PrEP. The algorithm was developed based on WHO-recommended strategies for point-of-care testing and takes into account the challenges of accurate detection of acute HIV infection in participants receiving ART for PrEP [Elliott, T., et al 2019] [Peluso, M. J., et al 2020]. The study site guidance for assessment and confirmation of HIV-1 infection based on this algorithm can be found in Appendix 11.

This study will be conducted at study sites with evidence of access to high risk individuals. To provide context for interpreting the results of the study, 2 methods will be utilized to estimate the background incidence of HIV-1 infection from the same site areas/time period in the screened population, which will include all individuals who come in for a screening visit for this study at one of the sites. One method will use local data on new HIV diagnoses to estimate incidence, while the second method will calculate HIV incidence based on a recency assay (assessment of recent infection biomarkers) [Murphy, G., et al 2017]. Recency assays distinguish between recent and nonrecent infection, thus cross-sectional surveys in a single population can be used for incidence estimation. These data will be referenced as an external benchmark to contextualize the study data and characterize the natural history of HIV acquisition in the community at large versus the enrolled population.

Frequent testing for HIV-1 acquisition during the study period (at all scheduled study visits) will help prevent dosing with the study intervention in a participant who may have acquired HIV infection, minimizing the risk of viral resistance and facilitating linkage to care. In addition, if a participant has signs or symptoms consistent with acute retroviral syndrome, or expresses a concern about recent HIV acquisition, HIV testing may be performed using an RNA test to detect early HIV-1 infection.

4.2.1.2 Safety Endpoints

Safety evaluations will include physical examinations (including vital signs) and laboratory tests (hematology and chemistry) performed per the SoA in Section 1.3. AEs and Social Harm events will be evaluated at each visit and assessed according to the guidelines in Section 8.4 and Appendix 3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

4.2.1.3 Participant-reported Outcomes

PROs provide a unique opportunity to acquire information on the impact of HIV PrEP in the lives of individuals who receive it. In conjunction with efficacy and safety, capturing data

from the participant's perspective may help clinicians, policy-makers, and individuals at risk for HIV infection make informed decisions when selecting a PrEP regimen.

Participants in this study will be administered 2 unvalidated questionnaires that measure preference and HIV infection risk, respectively. Each item on each questionnaire will be assessed independently. A 1-item preference questionnaire will be used to assess preference for daily or monthly dosing or no preference for HIV PrEP medication (not applicable in Part 3). The HIV infection risk questionnaire will be used to measure changes in participants' or their intimate partners' risks for HIV due to changes in behavior. HIV infection risk questionnaire will not be administered in participants with a positive HIV-1 test. All items will be analyzed descriptively.

4.2.1.4 Renal Biomarkers

Impaired kidney function (usually mild or moderate) may occur in a small proportion of individuals who take FTC/TDF for PrEP, especially in those with other risk factors for impairment of renal function [Tetteh, R. A., et al 2017]. This study provides an opportunity to compare the impact of ISL on renal functions to that of FTC/TDF as measured by creatinine, cystatin-C, and creatinine clearance.

4.2.1.5 Pharmacokinetic Endpoints

The PK samples collected from all participants as described in SoA and Section 8.6 will be used to evaluate PK concentrations of ISL, and as appropriate, exploratory PK-efficacy, PK-AE, and PK-adherence relationships of ISL. Additionally, TFV concentrations will be measured and analyzed (in a subset of study participants), as needed and may be used for exploratory study intervention adherence assessments.

Additional sparse PK samples from participants who become pregnant during the study and continue ISL treatment, will be collected as described in Section 1.3.4 and Section 8.6.4. These sparse PK samples will be used to explore and quantify the PK of ISL in pregnant participants compared with nonpregnant participants.

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 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.

4.2.1.7 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

Part 1

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidance E10 on Choice of Control Group and Related Issues in Clinical Trials (ICH E10) states that in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. HIV-1 infection can lead to serious harm in the study population and FTC/TDF has been demonstrated to reduce the risk of sexually acquired HIV-1 infection; therefore, a placebo control would not be appropriate for this study. Thus, rather than comparing the efficacy of oral ISL QM to placebo, the primary objective of this study will be to evaluate the efficacy of oral ISL QM compared with FTC/TDF QD for the prevention of HIV-1 infection. The active comparator for this study (FTC/TDF) is approved in many countries as PrEP and is currently standard of care for individuals at high risk for HIV-1 infection.

Matching placebo will be used in both study arms to provide a robust evaluation of the safety and tolerability profile of ISL by maintaining double-blind, double-dummy study intervention.

Part 2

Blinded study intervention administration in Part 1, including ISL, its placebo, or placebo to FTC/TDF, was stopped; all participants were switched to PrEP therapy with FTC/TDF.

Part 3

All participants will receive open-label FTC/TDF in Part 3. No comparator/placebo or ISL/placebo will be administered.

4.2.3 Rationale for Estimating Background HIV Incidence Rate

Because this study includes 2 active study intervention arms, it will not be possible to assess the relative reduction in HIV-1 infection risk compared with that in the corresponding communities where PrEP is generally available according to local standard of care. Thus, a key secondary objective of this study will be to evaluate the efficacy of oral ISL QM in reducing the incidence per year of HIV-1 infection relative to the background rate.

Several methods exist for estimating population-level HIV incidence: direct observation of HIV incidence through longitudinal follow-up of persons at risk for new HIV infection, indirect measurement of HIV incidence using data on HIV prevalence in a defined population (such as women attending antenatal clinics) and estimates of HIV incidence through the use of tests that can differentiate "recent" from "nonrecent" infections based on biomarkers from cross-sectional specimens [Mastro, T. D., et al 2010]. Directly observing new infections in cohorts of HIV-negative individuals followed up over time are costly and logistically challenging, and indirect measurements of incidence have significant limitations and may not provide data that are representative of the study population; therefore, in this study the background incidence of HIV-1 infections in the population will be estimated using tests based on biomarkers that can differentiate "recent" from "nonrecent" infections in the population screened for this study.

Cross-sectional incidence estimation uses biomarkers to identify individuals who are likely to have recent HIV infection. Most methods include serologic assays that measure the antibody response to HIV infection [Busch, M. P., et al 2010]. Use of a single assay approach to estimate HIV incidence has been problematic, since viral suppression, advanced HIV disease, uncontrolled viremia, immune-suppression, and immune-dysregulation can cause these tests to have values that are associated with recent infection when the person does not have a recent infection ("false-recency") [Brookmeyer, R., et al 2013], which can lead to an over-estimation of the HIV incidence rate [Gonese, E., et al 2020]. In contrast, Recent Infection Testing Algorithms that combine serologic and nonserologic assays, such as viral load [Kassanjee, R., et al 2016] [Sun, X., et al 2020], have been identified that provide accurate incidence estimates in several studies. Various algorithms have been used to estimate HIV incidence in clinical trials and cohort studies [Brookmeyer, R., et al 2013] [Eshleman, S. H., et al 2013] [Laeyendecker, O., et al 2013] [Gonese, E., et al 2019] [Shah, N. S., et al 2017]. A limiting antigen avidity assay (HIV-1 LAg) [Duong, Y. T., et al 2019] is now widely used for HIV incidence estimation in surveillance and research studies. The manufacturers of the LAg Avidity assay recommend using the assay in an algorithm where individuals with VL

<1000 copies/mL are classified as having nonrecent infection [Sedia Biosciences Corporation 2016] [Maxim Biomedical, Inc. 2019]. This algorithm is widely used to estimate HIV incidence in cross-sectional surveys [Rehle, T., et al 2015] [Szwarcwald, C. L., et al 2016] and is currently being used in large surveys conducted as part of the PEPFAR-supported Population-based HIV Impact Assessment.

Kassanjee, et al, have developed an estimator, based on these principles, that substantially increases the robustness of incidence estimation based on cross-sectional surveys using tests for recent infection. This methodology will be used to estimate the background HIV incidence rate in this study [Kassanjee, R., et al 2012].

4.2.4 Rationale for Collecting Specific Data

Rationale for Collecting Behavioral Assessment Data

Risk of HIV infection is correlated with behavior [Centers for Disease Control and Prevention 2020]. Adherence to PrEP is one type of behavior inversely associated with risk of acquiring HIV. There are many other behaviors that have been identified to be associated with the risk of HIV, such as substance use, number of sexual partners and consistent condom use. Understanding and quantifying ongoing risk behavior may identify segments of the population in which these behaviors are prevalent and may provide support for targeted risk reduction interventions, including prioritization of PrEP for certain groups. Furthermore, there has been concern that use of PrEP may result in behavioral disinhibition, that is, those who are taking PrEP may not take other protective measures because they believe that PrEP alone can protect against HIV [Golub, S. A., et al 2010]. Therefore, in support of broader HIV prevention efforts, behavioral data will be collected throughout this study.

4.2.5 Rationale for Continuing Study Intervention During Pregnancy

It is important for women to remain on PrEP during pregnancy because of an increased risk of HIV acquisition during pregnancy and in the peripartum period [Thomson, K. A., et al 2018]. Per WHO guidelines, in women who desire pregnancy or become pregnant while taking PrEP, continuing PrEP during pregnancy and breastfeeding should be considered if they continue to be at substantial risk of HIV-1 infection [World Health Organization 2017]. Similarly, the CDC recommends PrEP as an option to help protect women and their infants from acquiring HIV infection while a woman tries to get pregnant, during pregnancy, or while breastfeeding [Centers for Disease Control and Prevention 2018].

Additionally, clinicians need timely information on the extent of drug exposure to mothers and infants during pregnancy [Eke, A. C., et al 2020] as well as the safety and tolerability of antiretrovirals used for PrEP in this population.

Note: During Part 2 or Part 3 of this study, dosing of ISL during pregnancy is not applicable. Any participant who becomes pregnant during Part 2 or Part 3 of the study has the option to remain on PrEP therapy with FTC/TDF (Section 8.11.3).

Nonclinical developmental and reproductive toxicology studies have not demonstrated any teratogenicity or other clinically relevant concerns, supporting continued dosing of ISL in participants who become pregnant and provide consent/assent to continue study intervention (Sections 8.1.1.3 and 8.11.3). Study intervention will be unblinded for participants with a confirmed continuing pregnancy.

For Part 1, only participants who were randomized to ISL will have the option to remain on open-label ISL or to transition to open-label FTC/TDF. Participants who were randomized to FTC/TDF may remain on open-label FTC/TDF.

There are no clinical data currently available to support breastfeeding by participants who are receiving ISL. Therefore, women who choose to breastfeed will not be permitted to continue ISL, but may receive FTC/TDF while breastfeeding.

4.2.6 Rationale for Collecting Infant Safety Follow-up Data

It is important to collect information on infants born to participants who become pregnant while receiving ISL. 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.

Participants will not receive ISL during Part 2 or Part 3. Therefore, additional infant safety follow-up through 1 year of age, as described above, will not be required for participants who become pregnant during Part 3. Standard AE reporting requirements per Section 8.4 will apply.

4.3 Justification for Dose

4.3.1 Rationale for ISL QM Efficacious Exposure

Part 1

The lower efficacious exposure threshold for ISL PrEP efficacy is set at 0.05 pmol/10^6 cells in PBMCs to prevent HIV-1 infection. This conservative threshold is approximately 5-fold above the in vitro IC_{50} (≈ 0.00974 pmol/10^6 cells) of ISL-TP against wild-type HIV-1 virus and 2-fold above the EC_{90} (≈0.024 pmol/10^6 cells) in rhesus macaques [Grobler, J., et al 2019]. Please refer to the IB for additional details.

In the Phase 1 proof-of-concept clinical study (MK-8591 Protocol 003) with HIV-1-infected, treatment-naïve participants; a single dose of ISL as low as 0.5 mg resulted in plasma HIV-1 RNA reduction of median 1.26 log10 copies/mL as measured 7 days after a single dose, which compared favorably to a similar monotherapy study of daily tenofovir disoproxil [Schurmann, D., et al 2020]. At this dose, the geometric mean ISL-TP C_{168hr} was 0.116 pmol/10^6 cells, with the lowest concentration associated with antiviral efficacy at 0.0513

pmol/10^6 cells. This lowest observed ISL-TP concentration was associated with >1 log viral load reduction from baseline. Thus, the geometric mean ISL-TP C_{168hr} is approximately 12-fold above the in vitro IC_{50} of ISL-TP against wild-type HIV-1.

In a rhesus macaque SHIV challenge study, weekly administration of ISL at very low doses (0.43 mg/kg and 0.1 mg/kg) resulted in statistically significant protection for male rhesus macaques against infection following repeated rectal challenges with SHIV109CP3 [Markowitz, M., et al 2019]. In this model, ISL was completely protective at ≥ 0.43 mg/kg and highly protective (92%) at 0.1 mg/kg, a dose that corresponds to ISL-TP EC_{90} of ≈ 0.024 pmol/10^6 cells. Thus, this EC_{90} ISL-TP concentration is approximately 2-fold above the in vitro ISL-TP IC_{50} against wild-type HIV-1.

In comparison, the prophylactic TFV-DP EC_{90} associated with 90% risk reduction in rhesus macaques is 0.023 pmol/10^6 cells in PBMCs [Anderson, P. L., et al 2014]. In an intravaginal challenge study in female rhesus macaques using FTC/TAF, the observed minimum protective TFV-DP concentration was 0.123 pmol/10^6 cells [Massud, I., et al 2018]. This efficacious exposure is approximately ~3 fold above the in vitro TFV-DP IC_{50} against wild-type HIV-1 [Grobler, J., et al 2019]. Moreover, in the iPrEx efficacy study of FTC/TDF as PrEP, which was conducted among men who have sex with men, the estimated TFV-DP-EC_{90} was 0.016 pmol/10^6 cells [Anderson, P. L., et al 2012]. Overall, these prophylactic TFV-DP concentrations are approximately ~1-3 fold above the in vitro TFV-DP IC_{50} of wild-type HIV-1[Grobler, J., et al 2019].

In summary, integrating data from in vitro activity of ISL-TP against wild-type HIV-1, a rhesus macaque SHIV challenge study, a proof-of-concept study conducted in treatment-naïve participants infected with HIV-1, and relevant data from the literature regarding the prophylactic concentrations of TFV-DP, 0.05 pmol/10^6 cells in PBMCs has been determined to be a conservative, efficacious PrEP PK threshold.

Part 2

No study participants will receive ISL in Part 2 of the study.

Part 3

No study participants will receive ISL in Part 3 of the study.

4.3.2 Rationale for Dose Selection

Part 1

A 60-mg oral ISL QM dose is selected for this study to provide efficacious exposures for protection against HIV-1 (Section 4.3.1). Simulations predict that ISL 60 mg QM will achieve ISL-TP concentrations in PBMCs exceeding the PrEP PK exposure threshold of 0.05 pmol/10^6 cells within 24 hours of the first dose and will provide sustained, adequate exposures even in the event of a delayed or missed dose (ie, up to 8 weeks following a dose).

An IA of PK data from an ongoing Phase 2 study (MK-8591 Protocol 016) revealed that the observed concentrations for plasma ISL and ISL-TP in PBMCs were consistent with those from earlier MK-8591 Phase 1 and other Phase 2 studies. In this Protocol 016 IA, the PrEP PK exposure threshold of 0.05 pmol/10^6 cells in PBMCs was exceeded among all participants who received the 60-mg QM dose. The mean trough level of ISL-TP in PBMCs 4 weeks after a single 60-mg dose is 1.32 pmol/10^6 cells, which is ~136 fold above the in vitro ISL-TP IC_{50} against wild-type HIV-1and ~26 fold above the prespecified PK threshold of 0.05 pmol/10^6 cells in PBMCs, respectively. The ISL 60-mg QM simulations predict that at steady state the lower 2.5th percentile of the 95% prediction interval is ~0.17 pmol/10^6 cells in PBMCs. Thus, observations from Protocol 016 IA, (data not yet incorporated into the population PK model) together with the population PK simulations, support the selection of 60-mg QM oral dose for this Phase 3 efficacy study.

Additionally, limited cervical tissue concentration data from MK-8591 Protocol 016 show that the ratio of ISL plasma to ISL-TP in this tissue-type was comparable to the ratios of ISL plasma to ISL-TP in vaginal and rectal tissues observed in the Phase 1 study MK-8591 Protocol 009 [Matthews, R. P., et al 2018]. The estimated mean trough concentration in cervical tissue at Week 4, following a single oral dose of 60 mg ISL, was approximately 8.5 fmol/mg. These preliminary data suggest rapid, sustained and adequate tissue penetration of ISL-TP at sites of potential HIV acquisition.

From a safety perspective, oral ISL has been evaluated in 8 Phase 1 clinical studies that demonstrated good tolerability of ISL in healthy participants who were administered: a single oral dose of up to 400 mg; 3 once-weekly doses of up to 100 mg; or a daily dose of 5 mg for 6 weeks. In an ongoing Phase 2 HIV-1 treatment study (MK-8591 Protocol 011), ISL administered daily at 0.25 mg, 0.75 mg and 2.25 mg, in combination with DOR and 3TC, has been generally well tolerated through 96 weeks of dosing. Interim analysis of blinded data from Protocol 016 indicated that ISL administered monthly at 60 mg and 120 mg have been generally well tolerated. Overall exposures that result from the selected 60-mg QM oral dose are not expected to exceed those observed in Phase 1 and Phase 2 studies.

In summary, the 60-mg QM oral dose is expected to achieve a sufficient and adequate systemic threshold that will be efficacious as HIV-1 prophylaxis.

Part 2

No study participants will receive ISL in Part 2 of the study.

Part 3

No study participants will receive ISL in Part 3 of the 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/assent. The overall study ends when the last

participant completes the last study-related contact, withdraws consent/assent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/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, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Early study termination may also be considered based on interim analysis(es) or after review of accumulating efficacy and safety data by the eDMC (Section 9.7).

5 STUDY POPULATION

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

No new participants will be screened or randomized in Part 2 or Part 3.

Female participants who are at high risk of acquiring HIV-1 infection 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 confirmed HIV-uninfected based on negative HIV-1/HIV-2 test results before randomization.

   Note: If a positive result is obtained for any HIV test prior to randomization, the participant is not eligible for the study. Additional testing to confirm suspected HIV

infection during screening will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will be referred for appropriate care, as necessary.

2. Has been sexually active (vaginal and/or anal sex) with a male sexual partner in the 30 days prior to Screening.

3. Is at high risk for HIV-1 infection as defined by a risk score ≥5 using a VOICE risk score tool (sites in Africa) or meets criteria for PrEP eligibility in accordance with CDC guidance (sites in the US) (see Appendix 10).

Demographics

4. Was assigned female sex at birth, is cisgender, 16 years to 45 years of age, inclusive, at the time of providing informed consent/assent.

   Note: Participants 16 or 17 years of age must weigh ≥35 kg. Enrollment of 16- to 17-year-old participants will begin only after completion of the Sentinel Cohort IA and review of IA results by the eDMC.

Female Participants

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, as described in Appendix 5 during the intervention period and for at least 42 days after the last dose (corresponding to the time needed to eliminate any study intervention [approximately 5 terminal half-lives]).

   - 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.

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

Informed Consent

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

Additional Categories

7. Has no plans to relocate or travel away from the site for ≥4 consecutive weeks during study participation.

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. Findings of chronic HBV (HBsAg-positive) or past HBV (HBsAg-negative and HBcAb-positive) infection, which could indicate risk for hepatitis B reactivation.

   Note: Participants who do not demonstrate immunity to HBV are encouraged to be vaccinated against HBV.

3. Current or chronic history of liver disease (eg, nonalcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy), unless the participant has stable liver function tests and no significant hepatic synthetic dysfunction.

   Note: Hepatic synthetic dysfunction is defined as a serum albumin <2.8 g/dL or an INR>1.7 in the absence of another explanation for the abnormal laboratory value.

4. Has a history of malignancy within 5 years of screening except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

5. Has a history or current evidence of any condition (including active tuberculosis infection), 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 enroll.

Prior/Concomitant Therapy

6. Has taken cabotegravir, lenacapavir, or any other long-acting HIV prevention product at any time (past or current use).

7. Is currently receiving or is anticipated to require any prohibited therapies outlined in Section 6.5 from 30 days prior to Day 1 through the duration of the study.

   Note: Participants taking tenofovir-based PrEP at screening may continue their regimen until 1 day prior to Day 1. Also, any prior or current HIV PrEP medications taken by the participant, regardless of timing, are to be recorded as prior medications.

Prior/Concurrent Clinical Study Experience

8. 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.

   Note: Prior participation in a COVID-19 vaccine study is allowed provided the final vaccination occurred ≥30 days before Day 1 (ie, a participant still in a study for long-term follow-up assessments is permitted).

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

Diagnostic Assessments

9. Has exclusionary laboratory values within 45 days prior to Day 1 as listed in Table 1.

   Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected, but the repeat test results must be available within the 45-day screening window.

Table 1 Laboratory Exclusion Criteria

Laboratory Assessment	**Exclusionary Values**
Absolute neutrophil count	≤750 cells/mm^3
Alkaline Phosphatase	>3 × ULN
AST	>3 × ULN
ALT	>3 × ULN
Bilirubin	≥2.5 × ULN
Calculated CrCl	<60 mL/min[a] based on the Cockcroft-Gault equation (Appendix 9)
CD4+ T-cell count	<400 cells/mm^3
Hemoglobin	<10.0 g/dL
Lymphocyte count	<650 cells/mm^3
Platelet count	<100,000/mm^3

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; ULN=upper limit of normal.

[a] Although not protocol exclusionary, sites should carefully consider the advisability of enrolling participants with calculated CrCl between 60 to 70 mL/min, as limited changes in CrCl during study conduct will lead to protocol-mandated product holds and may alter the risk-benefit considerations of study participation.

Other Exclusions

10. Is 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 42 days following their last dose of study intervention.

5.3 Lifestyle Considerations

All participants should be counseled on safer sex practices to prevent acquisition of HIV or other STIs.

5.4 Screen Failures

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

Screen failures who are HIV-uninfected will be referred to locally available HIV prevention services.

Screen failures who are HIV-infected will be referred to and linked with locally available HIV treatment services.

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 of study interventions provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

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

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Part 1 ISL QM Group	Experimental	ISL	Drug	Tablet	60 mg	60 mg	Oral	QM from Visit 2 to (up to) Visit 37	Test Product	IMP	Central
Part 1 ISL QM Group	Experimental	Placebo to FTC/TDF	Drug	Tablet	0 mg	0 mg	Oral	QD from Visit 2 to (up to) Visit 37	Placebo	IMP	Central
Part 1 FTC/TDF QD Group	Active Comparator	FTC/TDF	Drug	Tablet	200/245 mg	200/245 mg	Oral	QD from Visit 2 to (up to) Visit 37	Test Product	IMP	Central/Local
Part 1 FTC/TDF QD Group	Active Comparator	Placebo to ISL	Drug	Tablet	0 mg	0 mg	Oral	QM from Visit 2 to (up to) Visit 37	Placebo	IMP	Central
Part 2 All Participants	Active Comparator	FTC/TDF	Drug	Tablet	200/245 mg	200/245 mg	Oral	QD in Part 2	Test Product	IMP	Provided centrally by Sponsor
Part 3 All Participants	Active Comparator	FTC/TDF	Drug	Tablet	200/245 mg	200/245 mg	Oral	QD in Part 3	Test Product	IMP	Provided centrally by Sponsor

EEA =European Economic Area; FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions); IMP=Investigational Medicinal Product; ISL=islatravir (also known as MK-8591); NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once daily; QM=once-monthly.

Each FTC/TDF tablet contains 200 mg emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg tenofovir disoproxil fumarate or 291.22 mg tenofovir disoproxil phosphate).

FTC/TDF may also be locally sourced.

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

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

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

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

Part 1

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to ISL QM and placebo to FTC/TDF QD, OR FTC/TDF QD and placebo to ISL QM.

Part 2

No new participants will be screened or randomized in Part 2. Blinded study intervention administration, including ISL or its placebo, was stopped, and all participants were switched to PrEP therapy with FTC/TDF.

Part 3

No new participants will be screened or randomized in Part 3. Ongoing participants will continue to receive open-label daily PrEP therapy with FTC/TDF.

6.3.2 Stratification

Part 1

Intervention randomization will be stratified according to the following factors:

Site

- All US sites as 1 stratum
- Ex-US sites as individual strata

Age (at Randomization)

- <25 years
- ≥25 years

Site is included as a stratification factor due to regional differences in linkages to care, likelihood of sexual partners knowing HIV status (infection or viral suppression) and the burden of untreated HIV-1 infection in the community and thus among potential sexual partners. Age is included since risk may also vary by age (with higher risk among younger participants). Stratification at randomization ensures that the intervention groups are well-balanced within each stratum level.

Part 2

No new participants will be screened or randomized; therefore, there is no stratification for Part 2.

Part 3

No new participants will be screened or randomized; therefore, there is no stratification for Part 3.

6.3.3 Blinding

Part 1

A double-blinding technique with in-house blinding will be used. ISL and FTC/TDF will be packaged identically to their matching placebos so that blind is maintained. 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.

To allow timely completion of population PK modeling, restricted early (before database lock) unblinding of PK and relevant clinical data may be requested. No personnel directly associated with study conduct will be unblinded before database lock. Before granting select personnel access to unblinded PK and relevant clinical data, 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 clinical data before database lock.

If a participant is confirmed HIV-infected, results from HIV-1 drug resistance testing will not be provided to site personnel who are directly involved in supporting the study, as there is the potential for the data to unblind the participant's intervention group. HIV Resistance results will be blinded to the study team and site personnel.

Part 2

All participants have been switched to PrEP therapy with FTC/TDF. The participant, the investigator, and Sponsor personnel or delegate(s) directly involved in the clinical monitoring or evaluation of participants will remain blinded to the participants' original randomized study intervention group. Sponsor personnel or delegate(s) not directly involved in clinical monitoring or evaluation of the participants will be unblinded to the participants' original randomized study intervention group.

Part 3

In Part 3, participants, investigators, and all Sponsor personnel will be unblinded to the participants' original randomized study intervention group.

6.4 Study Intervention Compliance

Part 1

In-clinic dosing of study intervention is required on the day of monthly study visits. Participants should be instructed to bring their bottle of FTC/TDF or matching placebo to their visits. At each visit, the site personnel will count the number of tablets of FTC/TDF or matching placebo remaining in the bottle. This information will be reviewed and recorded in source documentation. The results will be used to assess study intervention adherence. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant and the explanation must be documented in the source documents. Participants should be reminded of the importance of taking their study intervention as instructed for the entire duration of 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 treatment of ≥1 monthly dose OR, for daily dosing, ≥7 consecutive days, require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and adherence records. Intervention start and stop dates, including dates for intervention delays and/or any deviations from the prescribed dosage regimen will also be recorded in the CRF.

Part 2

All participants have been switched to PrEP therapy with FTC/TDF. At each visit, site personnel will review the participant's FTC/TDF dosing adherence. The dosing record will also be recorded in the CRF as instructed by the Sponsor.

Part 3

Ongoing participants will continue to receive open-label daily PrEP therapy with FTC/TDF. At each visit, site personnel will review the participant's FTC/TDF dosing adherence. The dosing record will also be recorded in the CRF as instructed by the Sponsor.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study and 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.

Use of cabotegravir, lenacapavir, or any other long-acting HIV prevention product at any time (prior or current) is prohibited.

The following are specific restrictions for prior and concomitant therapies not permitted from 30 days before receiving study intervention through the study duration (ie, up to 42 days following last dose of study intervention) for all participants:

- Pentostatin (an adenosine deaminase inhibitor that may increase ISL levels) – only applicable for Part 1.
- Any nonstudy antiretrovirals.

  Notes:
  - *PEP is permitted if clinically indicated and should be managed according to local standard of care. Any potential interactions of PEP with study intervention will be managed by the investigator.*
  - *Part 1-Participants taking tenofovir-based PrEP at screening may continue their regimen until 1 day prior to Day 1.*
  - *Part 2- All participants were switched to PrEP therapy with FTC/TDF.*
- Any nonstudy investigational agents (including devices)
- Any immune therapy agents, immune modulators, or other systemic immunosuppressive therapies

  Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) are allowed.
- Any prohibited (ie, contraindicated or not recommended) therapy(ies) as specified in the local product circular for FTC/TDF

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information, including dose and frequency (if known)

  Note: Vaccines for COVID-19 approved locally for Emergency Authorized Use, or equivalent, that do not have a known or anticipated DDI with ISL, are permitted.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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.

6.7 Intervention After the End of the Study

At the end of the study, provided development of ISL as PrEP for HIV-1 continues, the Sponsor is planning for a mechanism for eligible participants to continue receiving ISL.

Providing ongoing study medication for a woman who is pregnant at the time of her last study visit will be handled the same as any other participant.

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

Participants will be provided letter(s) specific to the placebo(s) in the image of the competitor's product actually received per the following options, as appropriate:

TRUVADA™ (US Source)

After unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice: "You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug/vaccine TRUVADA™ 200 mg/300 mg (emtricitabine/tenofovir disoproxil fumarate) as much as possible. You did not receive the active drug/vaccine TRUVADA™ 200 mg/300 mg (emtricitabine/tenofovir disoproxil fumarate) as manufactured by Gilead Sciences, Inc."

Emtricitabine/Tenofovir Disoproxil (EU Source)

After unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice: "You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug/vaccine emtricitabine/tenofovir disoproxil 200 mg/245 mg as much as possible. You did not receive the active drug/vaccine emtricitabine/tenofovir disoproxil 200 mg/245 mg as manufactured by Ratiopharm GmbH."

TRUVADA™ (EU Source)

After unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the competitor's product to provide the following advice: "You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug/vaccine TRUVADA™ 200 mg/245 mg (emtricitabine/tenofovir disoproxil) as much as possible. You did not receive the active drug/vaccine TRUVADA™ 200 mg/245 mg (emtricitabine/tenofovir disoproxil) as manufactured by Gilead Sciences, Ireland UC."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 8.11.4.

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 8.11.4.

A participant must be discontinued from study intervention, but continue to be monitored per Section 8.11.4 in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention, including in relation to dosing while pregnant.
- The participant has confirmed HIV-1 or HIV-2 infection.

  Note: Participants who become infected with HIV-1 or HIV-2 during the study will stop receiving study intervention and will be referred to and linked with a local medical provider for HIV care and treatment. No poststudy antiretroviral therapy will be provided by the study.

- The participant has a medical condition or personal circumstance, which in the opinion of the investigator, in consultation with the Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

  Note: In the case of certain new medical conditions, such as if the participant develops a malignancy (eg, lymphoma, or a condition requiring a contraindicated medication per the local label of FTC/TDF) after randomization, or if a participant requires treatment for active tuberculosis infection, consultation regarding management should take place with the Sponsor Clinical Director on a case-by-case basis.

- The participant has an SAE or Grade 4 laboratory AE that is assessed by the investigator to be related to study intervention AND that is life-threatening or results in prolonged hospitalization.
- The participant is breastfeeding (This is applicable for Part 1 only. For Part 2 and Part 3, see Section 8.11.3.2.1).

  Note: Participants may take open-label FTC/TDF during breastfeeding (Section 8.11.3.1.1). Participants who decide to not breastfeed their infants may continue on assigned study intervention (Part 1 Only).

  Note: Participants may take FTC/TDF while breastfeeding during Part 2 or Part 3 of the study (Section 8.11.3.2.1).

- The participant has 2 consecutive DAIDS Grade 3 (<500 cells/mm^3) or higher grade of lymphocyte count and/or 2 consecutive DAIDS Grade 3 (<200 cells/mm^3) or higher grade of CD4+ T-cell count (at least 3 weeks apart) while on study intervention at any time during the study, unless there is a clear alternative explanation for the result (eg, COVID-19). If a participant is discontinued from study intervention for this reason, discontinuation is considered "permanent," and they will not be allowed to restart study intervention.

  Note: If study intervention is discontinued for this reason, participants should stay in the study and may take open-label FTC/TDF, and continue to complete study assessments as outlined in the SoA (Section 1.3.1).

Unless otherwise noted above, participants may be allowed to begin study intervention again if deemed medically appropriate.

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/assent 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

Note: Blinded study intervention administration (Part 1) has been stopped. During Part 2, all participants were switched to PrEP therapy with FTC/TDF and will maintain the visit schedule in Section 1.3.1. No new participants will be screened or randomized during Part 2; therefore, assessments performed as part of screening and randomization (Day 1) will not be performed during Part 2.

Note: During Part 3, all ongoing participants will continue to receive open-label daily PrEP therapy with FTC/TDF and will maintain the visit schedule in Section 1.3.1. No new participants will be screened or randomized; therefore, assessments performed as part of screening and randomization (Day 1) will not be performed during Part 3.

- 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 medicaldecisions 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 maximum amount of blood collected from each participant over the duration of the study will be approximately 1110 mL, with an additional approximately 49 mL each for any unscheduled visits required for HIV confirmation, early discontinuation of study intervention, or early withdrawal from study (Table 13). Participants who become pregnant and remain on ISL, will have additional assessments resulting in approximately 21 mL of blood collected.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent/assent from each potential participant (or their legally acceptable representative) prior to participating in 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/assent is in place.

8.1.1.1 General Informed Consent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent 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/assent discussion.

- A copy of the signed and dated informed consent/assent 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 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/assent form or addendum to the original consent/assent form that captures the participant's or the participant's legally acceptable representative's dated signature.

- Specifics about the study and the study population are to be included in the study informed consent/assent form.
- Informed consent/assent 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/assent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent/assent before performing any procedure-related to future biomedical research. A copy of the informed consent/assent will be given to the participant before performing any procedure-related to future biomedical research.

8.1.1.3 Consent in the Event of a Positive Pregnancy Test

8.1.1.3.1 Consent for Open-label FTC/TDF

Part 1

Participants who have a first positive urine pregnancy test will stop taking all study intervention and provide a serum sample for confirmatory serum pregnancy test (Section 8.11.3). These participants will be given the option to receive open-label FTC/TDF until a continuing pregnancy is confirmed. For a participant to receive open-label FTC/TDF, additional consent/assent is required. The investigator or medically qualified designee will explain the consent/assent to the participant or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent/assent before dispensing open-label FTC/TDF. A copy of the informed consent/assent will be given to the participant.

Part 2 and Part 3

Participants who have a first positive urine pregnancy test will provide a serum sample for confirmatory serum pregnancy test (Section 8.11.3.2). These participants will be given the option to receive FTC/TDF following a positive pregnancy test. For a participant to receive FTC/TDF, additional consent/assent is required. The investigator or medically qualified designee will explain the consent/assent to the participant or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent/assent before dispensing FTC/TDF. A copy of the informed consent/assent will be given to the participant.

8.1.1.3.2 Consent for Continuation or Interruption of Study Intervention During Pregnancy- Part 1 Only

Participants who become pregnant during the study and are confirmed to have a continuing pregnancy will be unblinded and given the option to: 1) continue in the study and receive

unblinded study intervention, or 2) interrupt study intervention. Upon confirmation of a continuing pregnancy, as outlined in Section 8.11.3, study intervention assignment will be unblinded and the investigator or medically qualified designee will discuss with the participant the potential benefits and risks of continuing (or discontinuing) study intervention (Section 8.11.3). Documentation of a separate additional consent/assent is required for participants with confirmed continuing pregnancy who decide to continue receiving unblinded study intervention. The investigator or medically qualified designee will explain the consent/assent to the participant or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent/assent before the participant may continue in the study and receive unblinded study intervention during the pregnancy. A copy of the informed consent/assent will be given to the participant.

8.1.1.4 Consent for Continuing Study Participation for Participants Who Choose to Breastfeed

Part 1

Participants who choose to breastfeed during the study will not be permitted to continue ISL, but will be given the option to receive open-label FTC/TDF after providing consent/assent to continue study participation (Section 8.11.3.1.1). The investigator or medically qualified designee will explain the consent/assent to the participant or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent/assent before delivery, ideally within the last trimester of the pregnancy. A copy of the informed consent/assent will be given to the participant.

Part 2 and Part 3

Participants who choose to breastfeed during Part 2 and Part 3 of the study will be given the option to continue receiving FTC/TDF after providing documented informed consent/assent to continue study participation (Section 8.11.3.2.1).

8.1.1.5 Consent for Infant Safety Data Collection

Part 1 and Part 2:

The investigator or medically qualified designee will explain the infant safety data collection consent/assent to the participant or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent/assent before collecting any data related to infant safety. A copy of the informed consent/assent will be given to the participant.

Part 3:

Infant Safety Data (1-year follow-up after birth) will not be collected by the Sponsor for pregnancies that occur during Part 3 of the study. Therefore a consent/assent is not required.

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.

8.1.2.1 HIV Recency Assay Testing

Per Inclusion Criterion #1, all participants are to be confirmed HIV-uninfected based on negative HIV-1/HIV-2 test. Samples for recency assay testing will be collected from all participants at Screening and Day 1. For participants who are found to be HIV-1 infected at one of these 2 time points, samples will be analyzed to help estimate community-level HIV-1 incidence rates (based on assessment of recent versus long-standing HIV-1 infection).

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/assent. 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.

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.

Any prior or current HIV PrEP medications taken by the participant, regardless of timing, are to be recorded as prior medications.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study (ie, from Screening and up to 42 days after the last dose of study intervention).

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be 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 reassigned to another participant.

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

8.1.8 Study Intervention Administration

Part 1

Study intervention will be provided per Table 2 (Section 6.1) and dispensed through the IRT system at visits indicated in the SoA (Section 1.3.1).

Part 2 and Part 3

Participants will receive PrEP therapy with FTC/TDF per Table 2 (Section 6.1).

8.1.8.1 Timing of Dose Administration

Part 1

For dosing of once-monthly tablets, all dosing can occur without regard to food.

For dosing of once daily tablets, please refer to the local product label as to whether or not doses should preferably be taken with food.

The monthly dose of ISL or matching placebo will be administered at the clinic/study site per the SoA (Section 1.3). The first dose of FTC/TDF or matching placebo will be administered at the study site on Day 1. Subsequent dosing will be performed once daily by the participant (ie, unsupervised at her home) at approximately the same time each day.

Participants should take the monthly dose of ISL or matching placebo within ± 7 days of the ideal dosing day (calculated based on Day 1).

If a participant is late for a monthly dose of ISL or matching placebo (ie, beyond the 7-day dosing window), then the monthly dose should be skipped/missed, and the normal dosing schedule resumed (based on the ideal dosing day) at the next dosing visit. Participants should not double the next dose to compensate for what has been missed.

The guidance in the approved FTC/TDF label should be followed regarding missed doses of FTC/TDF or matching placebo.

Part 2 and Part 3

Participants will receive PrEP therapy with FTC/TDF. For dosing of once daily tablets, please refer to the local product label as to whether or not doses should preferably be taken with food.

If a participant misses a dose of FTC/TDF, guidance in the approved label should be followed.

8.1.8.2 HIV Risk Reduction

Site staff will administer the Sexual Activity Form to participants at visits per the SoA (Section 1.3). Participants will be offered condoms, lubricants, and HIV risk reduction counseling.

8.1.8.3 Participant-reported Outcomes

Site staff will administer 2 questionnaires to participants at visits per the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). The questionnaires will be administered in no particular order using an interview format. Participant responses will be captured in the electronic database by site staff.

8.1.8.4 Interruption of Study Intervention

The site should encourage participants to remain adherent to study intervention per-protocol. Participants who intentionally or inadvertently interrupt study intervention, without withdrawing consent/assent to participate in the study, should not be discontinued from the study. The investigator and site personnel should make every reasonable effort to contact the participant and should have a discussion with her regarding resumption of study intervention. The discussion should be noted in source documentation. Participants may continue with study visits and procedures regardless of study intervention adherence.

Interruptions from the protocol-specified treatment plan due to an AE, pregnancy, or any other physician-directed interruption require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Sections 1.3.1 and 1.3.2) and Section 8.11.4.

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

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent/assent for future biomedical research. Participants may withdraw consent/assent 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@MSD.com). Subsequently, the participant's consent/assent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

8.1.10 Participant Blinding/Unblinding

This section is not applicable during Part 3 of the study since all participants will be unblinded to study intervention assignment.

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant’s intervention assignment, the

investigator who is a qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

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

Once an emergency unblinding or unblinding due to pregnancy (8.11.3) has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

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

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

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 HIV-1 Testing

HIV-1 testing (Point-of-Care HIV test, HIV-1/HIV-2 Antibody/Antigen test, and RealTime PCR for HIV-1 RNA quantitation) will be conducted per the SoA (Section 1.3), and per a predefined algorithm for HIV-1 testing and diagnosis (Appendix 11).

Point-of-Care HIV testing should be performed using an FDA-approved kit prior to administering/dispensing study intervention and prior to randomization on Day 1. Participants who have a positive Point-of-Care test on Day 1 should not be randomized and should be considered as a screening failure. Plasma HIV-1 RNA quantification will be

performed using a RealTime PCR assay for all participants who have a positive Point-of-Care test, including screening failures.

Regardless of how many Point-of-Care tests are performed, if any (one or more) Point-of-Care test is positive, the full study-specified HIV testing algorithm should be followed.

After randomization, in a case where a participant has a positive Point-of-Care HIV test and/or HIV-1/HIV-2 Antibody/Antigen Test, study intervention must be withheld and an "HIV Infection Confirmation" visit (Section 1.3.3) completed as soon as possible on a subsequent visit day, and no later than within 14 days of the positive test.

After randomization, in a case where a participant has a positive Point-of-Care HIV test, PK samples (both plasma and dried blood) must be collected at that visit, regardless of the planned PK collection schedule. The collection of prespecified PK samples should also be conducted according to the collection schedule.

If the confirmatory HIV testing is negative, the participant may be able to resume study intervention after investigator consultation with the Sponsor.

If the confirmatory HIV testing is positive, the participant should complete a "Poststudy Intervention Follow-up" visit, and then continue with the monthly visits per Section 1.3.3 (if possible, the monthly visits should resume at the previous schedule). The participant should be referred to local medical providers for HIV care and treatment and the site should prioritize and facilitate this linkage to care. No poststudy antiretroviral therapy for the treatment of HIV infection will be provided by the Sponsor.

8.2.2 Whole Blood Collection for HIV-1 Resistance Testing

Whole blood and/or plasma samples collected per the SoA will be sent for genotypic and phenotypic HIV-1 drug resistance testing to assess resistance-associated substitutions as applicable during the study.

8.3 Safety Assessments

Details regarding specific safety assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study, including approximate blood volumes drawn by visit and by sample type per participant, can be found in 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). Height and weight will also be measured and recorded.

At all subsequent visits a brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Weight will also be measured and recorded.

Pelvic examination is not required at screening or subsequent visits unless symptom-directed.

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 Confirmation of Contraception and Pregnancy Testing

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

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

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

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

8.3.4 Sexually Transmitted Infections

Testing for GC/CT, syphilis, vaginal trichomonas infection, bacterial vaginosis, and HSV-2 serology will be performed at Screening and at visits as described in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). Participants with a confirmed STI diagnosed at screening or during the study should either be referred for treatment/management of the STI or provided treatment at the study site depending on antimicrobial availability and following applicable STI guidelines. Sites should report STIs as per local reporting requirements.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 42 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 Review of Social Harm Events

Social harm events are negative events occurring as a result of being involved in a research study, as reported by a participant. Examples of social harm events include unfair treatment, lack of acceptance by family and/or employer, or conflict with an intimate partner due to participation in an HIV prevention study, or due to potential stigma of being “at risk” for HIV infection. Social harm events will be collected and reported on CRFs during regular visits and every reasonable effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety and wellbeing of the participant. Social harm events will be followed for reporting of resolution status.

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent/assent, 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 42 days following cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside 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 (during Part 1 and Part 2) and consent/assent to infant safety data collection, SAEs (including perinatal HIV-1 infection) occurring through 1-year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event. This does not apply to infants born to participants who become pregnant in Part 3.

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:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/termination ; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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:
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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 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.

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

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

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

For infants born to participants who become pregnant (during Part 1 and Part 2) and consent/assent to infant safety data collection, SAEs (including perinatal HIV-1 infection) occurring through 1-year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event. The 1-year safety follow-up does not apply to infants born to participants who became pregnant in Part 3.

The clinical management of pregnancy (Section 8.11.3) and breastfeeding (Section 8.11.3.1 and Section 8.11.3.2) provide details on management of confirmed pregnancy and breastfeeding options for participants postpartum.

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

This section is not applicable to this study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

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

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

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

8.5 Treatment of Overdose

In this study, an overdose is >1 dose of ISL or matching placebo within 14 days, or >2 doses of FTC/TDF or matching placebo on any single calendar day.

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

8.6 Pharmacokinetics

Note: PK samples will not be collected in Part 3 of the study.

8.6.1 Blood (Plasma) Collection for PK

Note: PK samples will not be collected in Part 3 of the study.

Venous blood samples will be collected for measurement of ISL and TFV. Bioanalysis of TFV blood (plasma) samples will be performed in selected subset of study participants. Sample collection, storage, and shipment instructions for plasma samples will be provided in a laboratory or operations manual.

PK samples will be collected from all participants as outlined in Table 4 and Table 12. The exact time of dosing of study intervention prior to the sample collection and the time of PK sample collection will be recorded on the appropriate source documentation.

Additional sparse plasma PK samples will be collected from participants randomized to ISL who become pregnant and consent to continue open-label ISL during Part 1 only (Section 8.6.4).

Table 4 Collection of Plasma PK Samples

Study Visit (Day/Month)	**Time Relative to Dose[a, b]**
Day 1	Predose
Month 1	One sample to be collected predose
Month 3	One sample to be collected at any time during the visit
Month 6	One sample to be collected predose
Month 12	One sample to be collected at any time during the visit
Month 18	One sample to be collected at any time during the visit
Month 24	One sample to be collected predose
Month 30	One sample to be collected predose
Month 36/EOT	One sample to be collected at any time during the visit

EOT=end of treatment (all participants may not complete 36 months because this is a case-driven study); PK=pharmacokinetic.

Note: PK samples will not be collected in Part 3 of the study.

[a] Indicates time relative to monthly oral tablet administration. Not applicable in Part 2.

[b] During Part 2, PK sample collection is irrespective of timing of dose.

Note: PK samples will not be collected in Part 3 of the study.

8.6.2 Blood (Plasma) for Investigational PK

Note: PK samples will not be collected in Part 3 of the study.

Blood (plasma) for investigational PK will be collected from all participants as outlined in the SoA (Section 1.3, Table 12 and Table 13). Analysis of the investigational samples will be triggered by the Sponsor, as needed. For Part 1, the investigational PK sample will be collected predose at Month 2 and at any time during the visit at Months 9, 15, 21, 27, and 33. For Part 2, investigational PK samples may be collected at any time during the visit.

Sample collection, storage, and shipment instructions for plasma samples will be provided in a laboratory or study operations manual.

8.6.3 Dried Blood Collection for PK

Note: PK samples will not be collected in Part 3 of the study.

The VAMS blood collection technique will be used to obtain dried blood. Further instructions on use of device, which follow VAMS blood collection technique will be provided in the laboratory/operations manual. Timepoints for the collection of these samples are provided in Table 5 and Table 12.

Additional sparse dried blood samples will be collected from participants randomized to ISL who become pregnant and consent to continue open-label ISL (Section 8.6.4) in Part 1 only.

Table 5 Collection of Dried Blood PK Samples

Study Visit (Day/Month)	**Time Relative to Dose[a, b]**
Day 1	Predose
Month 1	One sample to be collected predose
Month 2	One sample to be collected predose
Month 3	One sample to be collected at any time during the visit
Month 6	One sample to be collected predose
Month 12	One sample to be collected at any time during the visit
Month 18	One sample to be collected at any time during the visit
Month 24	One sample to be collected predose
Month 30	One sample to be collected predose
Month 36/EOT	One sample to be collected at any time during the visit

EOT=end of treatment (all participants may not complete 36 months because this is a case-driven study).

Note: PK samples will not be collected in Part 3 of the study.

[a] Indicates time relative to monthly oral tablet administration. Not applicable in Part 2.

[b] During Part 2, PK sample collection is irrespective of timing of dose.

Note: PK samples will not be collected in Part 3 of the study.

8.6.4 Collection of PK Samples in Participants Who Become Pregnant and Continue ISL (Only Applicable for Part 1)

Note: PK samples will not be collected in Part 3 of the study.

Participants who were randomized to ISL and consent to continue ISL during pregnancy will undergo additional PK sampling (participants who were randomized to FTC/TDF do not need additional PK sampling, and should continue to follow the sampling schedule in SoA 1.3.1). These PK samples will be used to evaluate how physiological changes that occur during pregnancy may affect ISL PK. The timing PK sampling relative to ISL dosing may vary based on trimester of pregnancy and the timing of collections must be recorded on the appropriate source documentation. Refer to Section 1.3.4 and Table 6 for detailed time points relative to ISL dosing.

Table 6 Collection of Population PK Samples in Participants Who Become Pregnant and Continue ISL

Gestational Age	Study Visit[a]	Time Relative to Dose[a]	PK Sample Types
≤12 Weeks	P1	• One sample collected predose • One sample collected 0.5-2 hours postdose	• Plasma • Dried blood (using VAMS)
	P2	• One sample collected at any time during the visit	
13-26 Weeks	P3	• One sample collected predose • One sample collected 0.5-2 hours postdose	
	P4	• One sample collected at any time during the visit	
≥27 Weeks	P5	• One sample collected predose • One sample collected 0.5-2 hours postdose	
	P6	• One sample collected at any time during the visit	
Postpartum	P7	• One sample collected predose • One sample collected 0.5-2 hours postdose	

PK=pharmacokinetic; VAMS=volumetric absorptive microsampling.

[a] Study visits P1, P3, P5, and P7 should coincide with 1 planned monthly visit during the time period (See Section 1.3.1). Study visits P2, P4, and P6 should occur approximately 2 weeks after study visits P1, P3 and P5, respectively. See Section 1.3.4 for more details.

Note: PK samples will not be collected in Part 3 of the study.

8.6.5 Collection of PK Samples in Participants Who Discontinue Study Intervention Early, Withdraw Consent/Assent, or Have a Positive HIV-1 Test

Note: PK samples will not be collected in Part 3 of the study.

Blood (plasma) PK and dried blood PK samples should be collected at the discontinuation visit, withdrawal visit, and/or HIV-1 infection confirmation visit, as applicable. For participants who do not withdraw consent/assent (ie, continuing to have study visits), both types of PK samples will also be collected monthly for 3 months, after which the participant should resume the PK schedule outlined in Section 1.3.1. All samples are to be collected at any time during the visit. For participants who have a positive HIV-1 test result, both types of PK samples should be collected at the time of the HIV-1 infection confirmation visit, the first 3 monthly follow-up visits, and then every 3 months thereafter.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of the following samples for biomarker research will be per the SoA (Section 1.3) and Appendix 2.

8.8.1 Planned Genetic Analysis Sample Collection

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

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

8.8.2 Renal Biomarkers

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

8.9 Future Biomedical Research Sample Collection

If consent/assent is provided for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future biomedical research
- Whole blood for future biomedical research

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening/Rescreening

Approximately 45 days prior to intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor. Individuals with

symptoms that could be consistent with acute retroviral syndrome at the time of Screening may proceed with screening procedures, including laboratory and HIV RNA testing, but will be asked to return after symptoms have resolved (and within 1 month) for repeat laboratory testing, as needed, and referred for local HIV testing and/or treatment as deemed appropriate.

The date of the participant's most recent HIV test prior to screening will be collected, if known.

Rescreening

If the screening window has been exceeded, after approval from the Sponsor, participants may be allowed to rescreen 1 time. Once a participant has started the rescreening process, a new Screening period (ie, an additional ≤45-day window) will begin.

The following assessments must be repeated for participants who are rescreened:

- Vital signs, weight, and directed physical examination
- Review medical history and prior/concomitant medication for new information
- All laboratory assessments
- Review of AEs

If the informed consent/assent has been updated, participants should be reconsented before rescreening. If no updates have been made, documented informed consent/assent during the original Screening period should be reviewed with the participant and a verbal reconsent to continue in the study should be documented.

8.11.2 Treatment Period

All procedures and their timing should be completed as per the SoA (Section 1.3.1).

8.11.2.1 Off-site Visits

Visits are to be completed at the study site unless otherwise noted in Section 1.3. Under certain circumstances, in lieu of a participant traveling to the study site, an at home (or community-based location) visit by a health care provider (eg, site personnel, home health care company, visiting nurse, etc.) may be appropriate. Upon Sponsor approval (where available and when permitted by local regulations and IRB/IEC), off-site services may be used to collect study data and samples and dispense study interventions at any visit per the SoA (Section 1.3) after a participant is enrolled. Additionally, in such cases, the investigator should contact the participant by telephone on the same day as the off-site visit, or as soon as possible, to perform an investigator AE assessment.

8.11.3 Clinical Management of Participants Who Become Pregnant

8.11.3.1 Clinical Management of Participants Who Become Pregnant - Part 1

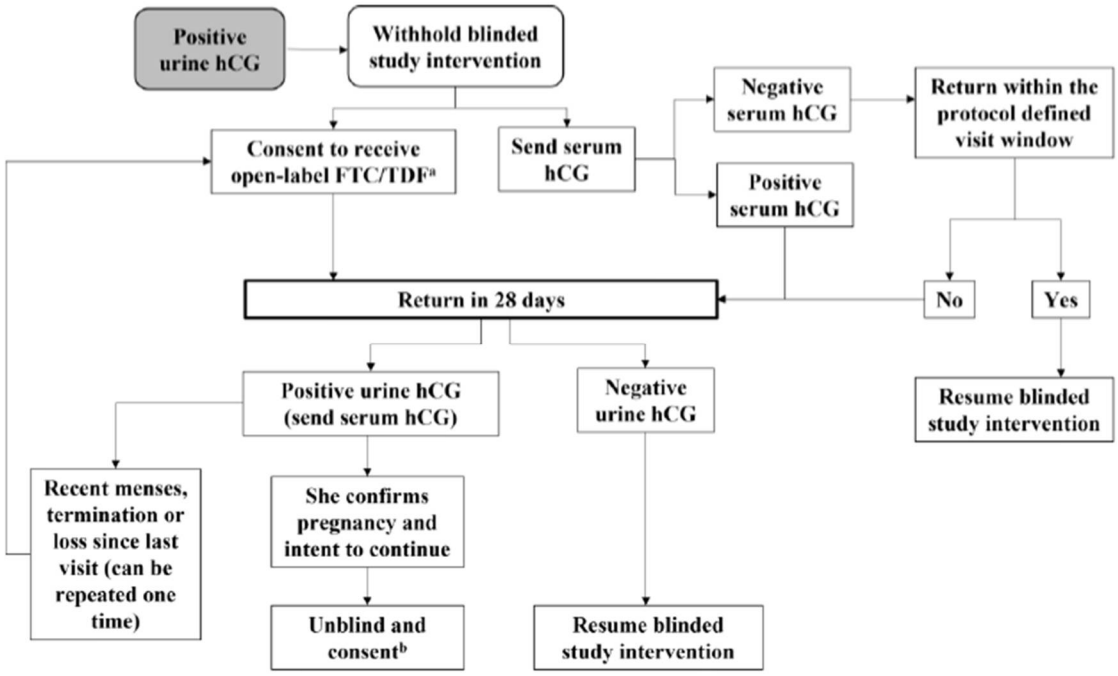
In the event of a first positive urine pregnancy test, the following steps should be taken with the participant (Figure 4):

- Hold administration/dispensation of all study intervention.
- Obtain a venous blood sample for confirmatory testing of serum hCG.
- Give the participant the option to receive open-label FTC/TDF while a continuing pregnancy is being confirmed. If the participant consents to receive open-label FTC/TDF, dispense a locally sourced 1-month supply of open-label FTC/TDF. Note that open-label FTC/TDF is considered to be an NIMP during this period and should be recorded as a concomitant medication on the appropriate eCRF. In this scenario the FTC/TDF will not be dispensed through the IRT system.
- If the serum hCG test is negative and the participant is able to return to the site within the permitted window for that visit, resume regular dispensing of blinded study intervention.
  - If the serum hCG test is positive, the participant should return for her next regular monthly study visit, as follows below.
- Participant returns for her next regular monthly study visit (approximately 28 days later) and a urine pregnancy test is repeated.
  - If urine pregnancy test is negative, return to regular dispensing of blinded study intervention.
  - If urine pregnancy test is positive, the participant should be unblinded and consented, as below. If, however, the urine pregnancy test is positive, but the participant reports menses or termination or loss of pregnancy since her last visit, or asserts a planned termination of the pregnancy within the next month, the above procedures should be repeated and a second month supply of open-label FTC/TDF should be dispensed. In these cases, the investigational product should not be resumed until serum hCG decreases to nonpregnant levels. Note that open-label FTC/TDF is considered to be an NIMP during this period and should be recorded as a concomitant medication on the appropriate eCRF. The FTC/TDF will not be dispensed through the IRT system.

Note: At each and every visit where there is a positive urine pregnancy test, a serum hCG test should be sent.

Note: A participant considered to have a nonviable pregnancy (eg, ectopic pregnancy or retained products of conception) may be allowed to resume blinded study intervention after consultation with the Sponsor.

Figure 4 Pregnancy Confirmation Flow Chart (Only applicable for Part 1)



FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions); hCG=human chorionic gonadotropin.

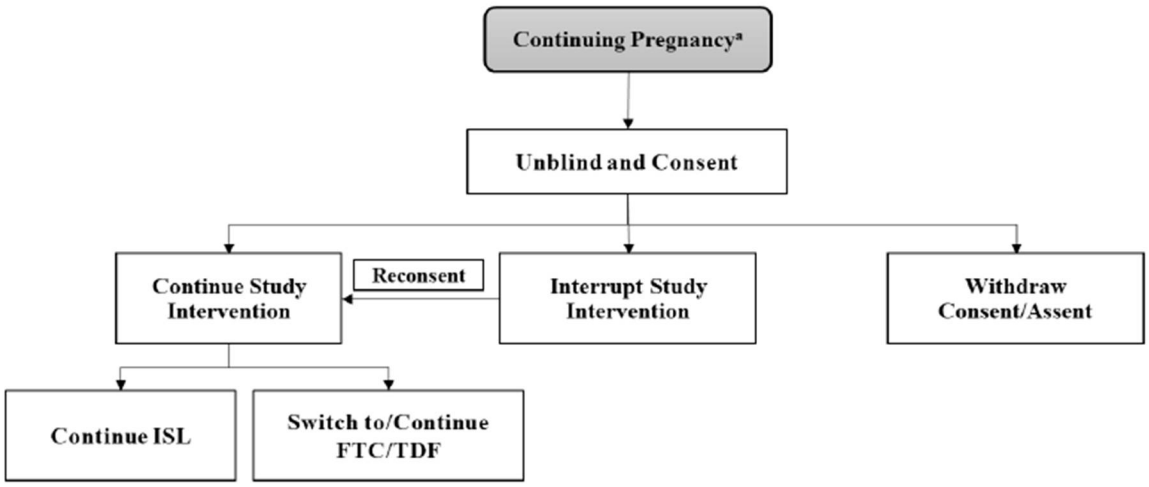
[a] Participants are not required, but strongly encouraged to receive open-label FTC/TDF while blinded study intervention is held pending confirmation of continuing pregnancy.

[b] Please refer to Figure 5 for next management steps.

Once a continuing pregnancy is confirmed (Figure 4), the participant must be unblinded to identify the study intervention to which they were randomly assigned, and monthly urine pregnancy tests should be deferred until 1 month following the end of the pregnancy. The participant will be counseled by the investigator or medically qualified designee regarding the potential risks and benefits of continuing and discontinuing study intervention. The participant, investigator, and Sponsor should assess the appropriateness of continuing study intervention based on available data and local standard of care guidelines. The final decision to continue study intervention (where allowed by local regulations) will be made by the participant and the investigator in consultation with the antenatal care provider. If the participant would like to consult with an antenatal care provider after unblinding and before making a decision about treatment, they may continue on FTC/TDF open-label until after the discussion takes place and a decision is made. The participant will provide documented consent and indicate their decision (Section 8.1.1.3.2). The following options will be available to participants with a continuing pregnancy (Figure 5):

- **Continue Study Intervention**: Participants with a confirmed, continuing pregnancy and consent/assent to continue study intervention (Section 8.1.1.3.2) should complete all remaining protocol-specified visits and procedures per the regular schedule in the SoA (Section 1.3.1).
  - Participants who were randomized to ISL may choose to remain on ISL (open-label) or opt to switch to FTC/TDF (open-label) for the duration of the pregnancy.
    - Those who choose to remain on ISL will have additional assessments as outlined in the SoA for participants who become pregnant and remain on ISL (Section 1.3.4 and Section 8.6.4).
  - Participants who were randomized to FTC/TDF may remain on FTC/TDF.
  - FTC/TDF and ISL are dispensed through the IRT system and recorded as study intervention on the appropriate eCRF.
  - Participants who choose to breastfeed should follow Section 8.11.3.1.
- **Interrupt Study Intervention**: If the decision is made to interrupt study intervention at any time during pregnancy, the participant should not be withdrawn from the study. The participant will continue with the protocol-specified visits per the regular schedule in the SoA (Section 1.3.1). Participants may resume study intervention at any time during or after pregnancy after consultation with the investigator and Sponsor. Participants resuming any study intervention after an interruption due to pregnancy should be reconsented (Section 8.1.1.3.2).
- **Withdraw Consent/Assent**: At any time, participants who become pregnant may choose to withdraw consent/assent for the study. The Early Withdrawal from Study visit should be completed (Section 8.11.9).

Figure 5 Clinical Management of Participants Who Become Pregnant (Only applicable for Part 1)



FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions); ISL=islatravir.

[a] Processes following completion of steps in Figure 4.

Active linkage to antenatal care will be made for participants who become pregnant. The investigator should review records from antenatal care at each study visit (see Sections 1.3.1 and 1.3.4 for those who remain on ISL). The participant's medical records will be collected and reviewed by the study site for:

- Clinical safety laboratory assessments
- Estimation of gestational age
- Results of ultrasound(s)
- Any complications associated with the pregnancy
- Outcome of pregnancy
- Information that could indicate congenital abnormalities

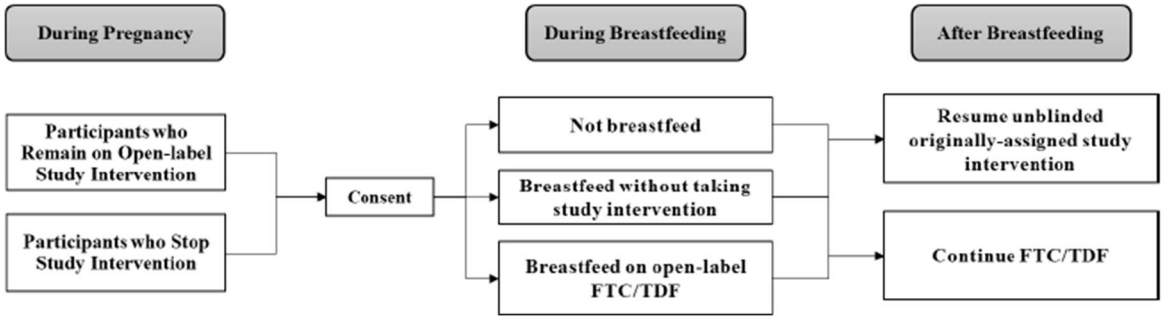
The site will also confirm breastfeeding status with the participant.

All reported pregnancies will be followed to the completion or termination of the pregnancy (Section 8.4.5). For any participant who is pregnant at the last scheduled study visit and reconsents to continue with study intervention (Section 6.7), the pregnancy will be followed to completion/termination with outcome reported in this original study. Infants born to these participants will have safety data collection through approximately 1-year of age (Section 8.11.4). Exposure to antiretroviral therapy during pregnancy will be reported by the site to relevant registries.

8.11.3.1.1 Clinical Management of Participants Who Choose to Breastfeed – Part 1

Participants who choose to breastfeed will not be permitted to continue ISL, but may receive FTC/TDF while breastfeeding after obtaining documented informed consent/assent to continuing study participation. Options for breastfeeding and study intervention during and after breastfeeding are shown in Figure 6.

Figure 6 Clinical Management of Participants Who Choose to Breastfeed – Part 1



FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions).

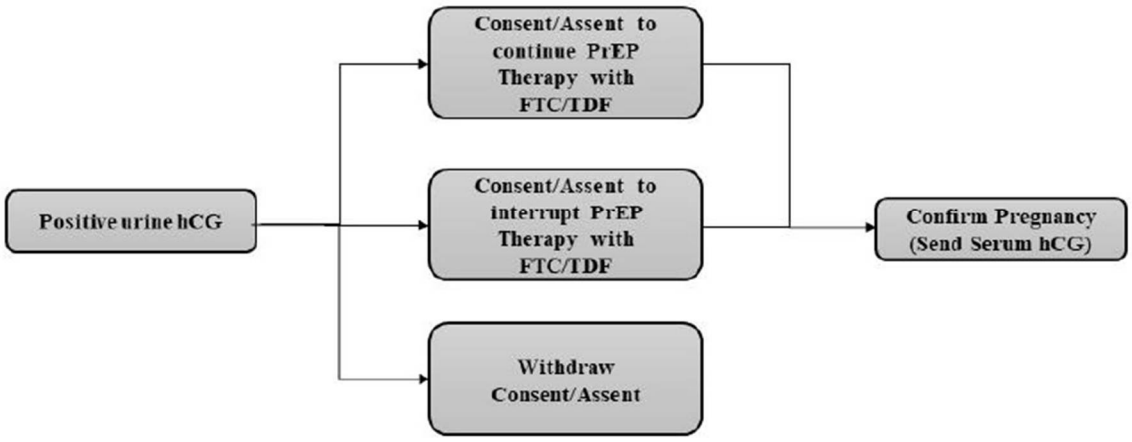
8.11.3.2 Clinical Management of Participants Who Become Pregnant – Part 2 and Part 3

Procedures for Part 2:

In the event of a first positive urine pregnancy test, the following steps should be taken with the participant (Figure 7):

- Obtain a venous blood sample for confirmatory testing of serum hCG.
- Give the participant the option to:
  - Consent to continue to receive PrEP therapy with FTC/TDF while the pregnancy is being confirmed/during a pregnancy. If the participant consents to receive PrEP therapy with FTC/TDF, dispense accordingly.
  - Consent to not receive PrEP therapy with FTC/TDF, but remain in the study.
  - Withdraw from the study.

Figure 7 Pregnancy Confirmation Flow Chart (Only applicable for Part 2)



Active linkage to antenatal care will be made for participants who become pregnant. The investigator should review records from antenatal care at each study visit (see Section 1.3.1). The participant's medical records will be collected and reviewed by the study site for:

- Clinical safety laboratory assessments
- Estimation of gestational age
- Results of ultrasound(s)
- Any complications associated with the pregnancy
- Outcome of pregnancy
- Information that could indicate congenital abnormalities

The site will also confirm breastfeeding status with the participant.

All reported pregnancies will be followed up to the completion or termination of the pregnancy (Section 8.4.5). Exposure to antiretroviral therapy during pregnancy will be reported by the site to relevant registries.

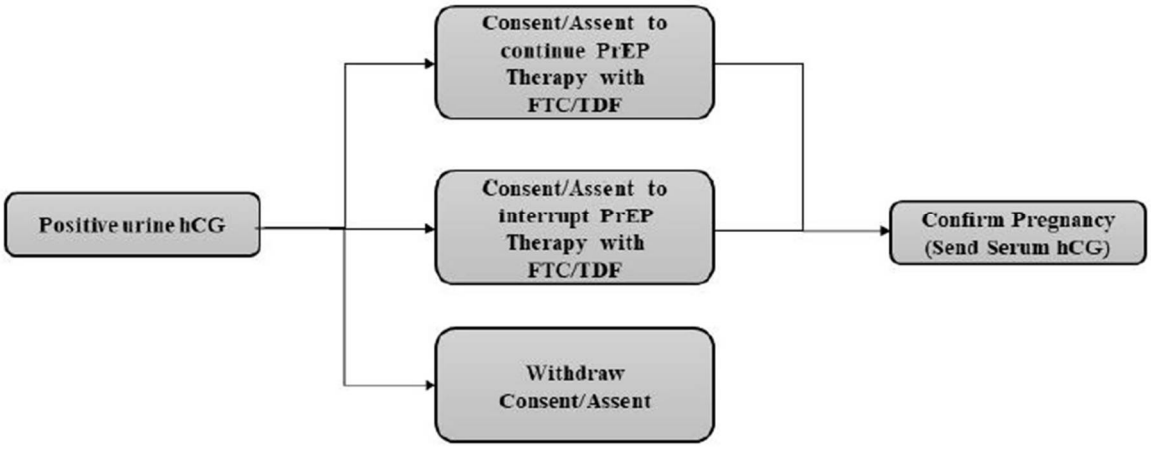
For any participant who is pregnant at the last scheduled study visit and reconsents to continue with FTC/TDF (Section 6.7), the pregnancy will be followed to completion/termination with outcome reported in this original study. Infants born to these participants will have safety data collection through approximately 1-year of age (Section 8.11.4). Exposure to antiretroviral therapy during pregnancy will be reported by the site to relevant registries.

Procedures for Part 3:

In the event of a first positive urine pregnancy test, the following steps should be taken with the participant (Figure 8):

- Obtain a venous blood sample for confirmatory testing of serum hCG.
- Give the participant the option to:
  - Consent to continue to receive PrEP therapy with FTC/TDF while the pregnancy is being confirmed/during a pregnancy. If the participant consents to receive PrEP therapy with FTC/TDF, dispense accordingly.
  - Consent to not receive PrEP therapy with FTC/TDF, but remain in the study.
  - Withdraw from the study.

Figure 8 Pregnancy Confirmation Flow Chart (Only applicable for Part 3)



Active linkage to antenatal care will be made for participants who become pregnant.

All reported pregnancies will be followed up to the completion or termination of the pregnancy (Section 8.4.5). Exposure to antiretroviral therapy during pregnancy will be

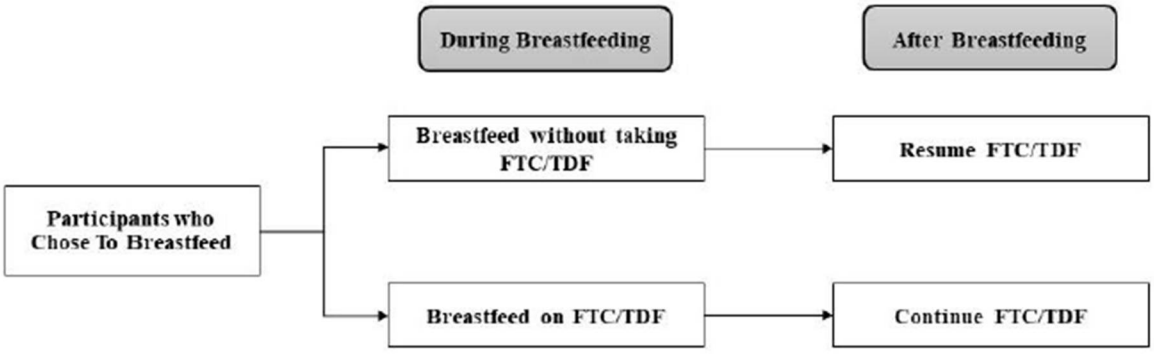
reported by the site to relevant registries. Any pregnancy-related complication should be reported as an AE.

For any participant who is pregnant at the last scheduled study visit and reconsents to continue with FTC/TDF (Section 6.7), the pregnancy will be followed to completion/termination with outcome reported in this original study. Infants born to these participants may have safety data collection through approximately 1 year of age (Section 8.11.4) for reporting by the site to relevant registries. Exposure to antiretroviral therapy during pregnancy will be reported by the site to relevant registries.

8.11.3.2.1 Clinical Management of Participants Who Choose to Breastfeed – Part 2 and Part 3

Participants who choose to breastfeed may receive FTC/TDF while breastfeeding after obtaining documented informed consent/assent to continue study participation. Options for receiving FTC/TDF during and after breastfeeding are shown in Figure 9.

Figure 9 Clinical Management of Participants Who Choose to Breastfeed – Part 2 & Part 3



8.11.4 Infant Safety Data Collection

Procedures for Part 1 and Part 2:

For participants who become pregnant while receiving study intervention, or within 42 days after the last dose of study intervention, the data in Section 8.11.4.1 should be obtained by the site within 12 weeks of each timepoint and entered the appropriate eCRF and source documentation. Study staff should also obtain results from any ultrasound studies performed per local standard of care.

Data for SAEs, including HIV-1 infection, reported for the infant will be collected as per Section 8.4.1 and should be reviewed at the participant's scheduled study visits that occur during this time.

If the infant's mother has completed her last scheduled study visit and consents to continue study intervention provided by the Sponsor (Section 6.7) before the completion of the

infant's 1-year follow-up, the infant will complete the 1-year follow-up with data reported within this original study.

8.11.4.1 Schedule of Activities: Infant Safety Collection

Timepoint	**At Birth[a]**	**1-Year After Birth[a,b]**
Visit Name	**N/A**	**Infant Follow-up-1**
Administrative and Safety Procedures		
Infant informed consent/assent		X[c]
Gestational age at birth	X	
Apgar scores	X	
Length	X	X
Weight	X	X
Head Circumference	X	X
Directed pediatric examination	X	
Concomitant medications review[d]	X	X
Review infant SAEs[e]	X	

HIV=human immunodeficiency virus; N/A=not applicable; SAE=serious adverse event.

[a] Data should be collected and entered at the site within 12 weeks of each timepoint.

[b] If a participant withdraws from the study, data from 1-year after birth should be collected at the time of withdrawal.

[c] Consent for infant safety data collection can be obtained from the mother at any time after confirmation of continuing pregnancy.

[d] Concomitant medications taken by the infant (for SAEs or HIV postpartum prophylaxis).

[e] Collect SAEs, including any congenital anomalies and HIV infection in the infant, per Section 8.4.1 and review at participant's regularly scheduled study visits.

Procedures for Part 3:

Aside from reporting pregnancy outcomes, no other infant follow-up procedures are required for pregnancies that occur in Part 3. Standard AE reporting requirements per Section 8.4 will apply.

8.11.5 Participants Who Discontinue Study Intervention

A participant must be discontinued from study intervention for any of the reasons listed in Section 7.1, but should be continued to be monitored during the study.

For discontinuations not related to pregnancy, including participants who discontinue study intervention due to decreased lymphocyte or CD4+ T-cell counts as described in Section 7.1, the participant should complete an Early Discontinuation of Treatment visit (Section 1.3.2) and be encouraged to complete remaining visits and assessments per the regular schedule in the SoA (Section 1.3.1), with the exception of dispensing study intervention.

If a participant becomes pregnant (has a positive serum pregnancy test) while receiving study intervention, the participant, investigator, and Sponsor will assess if the participant should continue study intervention (Section 8.11.3).

8.11.6 Participants Who Withdraw Consent/Assent

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

If the participant withdraws consent/assent within 28 days of completing the Early Discontinuation of Treatment visit (Section 1.3.2), the Early Withdrawal from Study visit is not required.

8.11.7 Follow-up Phone Calls

Participants who complete the protocol-specified treatment period or who discontinue study intervention due to seroconversion will be contacted via phone call at 14 days and 42 days post last dose of study intervention per the SoA (Sections 1.3.1 and 1.3.3).

The investigator is responsible for ensuring that all telephone contacts are performed by a staff member who is a health care professional qualified to elicit a discussion with the participant that will lead to a clinically meaningful disclosure on the participant's well-being. Telephone contacts are to be documented in the source documents and the investigator must review the entry within 2 days. However, if the participant reports any clinically concerning events (eg, SAEs, ECIs) during a telephone call, then the investigator must be promptly notified. The investigator will contact the participant to determine if a clinic visit is warranted.

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

9 STATISTICAL ANALYSIS PLAN

Note: As of Amendment-04, various subsections in Section 9 have been updated to clarify, which analyses will be performed and which will no longer be performed/applicable. Specific notes in relevant subsections have been inserted. No efficacy analyses will be performed. Safety data will be evaluated both for the blinded treatment period for most safety endpoints, and for the entire duration of the study to evaluate the recovery of total lymphocyte counts.

Note: Blinded study intervention administration (Part 1) has been stopped. During Part 2, all participants were switched to PrEP therapy with FTC/TDF. No new participants will be screened or randomized during Part 2. The participant, the investigator, and Sponsor personnel or delegate(s) directly involved in the clinical monitoring or evaluation of

participants will remain blinded to the participants' original randomized study intervention group. Sponsor personnel or delegate(s) not directly involved in clinical monitoring or evaluation of the participants will be unblinded to the participants' original randomized study intervention group. .During Part 3, ongoing participants will continue to receive open-label PrEP therapy with FTC/TDF. No new participants will be screened or randomized during Part 3. Participants, investigators, and all Sponsor personnel will be unblinded to the participants' original randomized study intervention group in Part 3.

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (eg, those specific to the analysis of PK data), will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Note: As of Amendment-04, no efficacy analyses will be performed. Safety data will be evaluated for the blinded treatment period for applicable safety endpoints, and for the entire duration of the study to evaluate the recovery of total lymphocyte counts. All safety data will be summarized descriptively.

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 3, Randomized, Active-Controlled, Double-blind Clinical Study to Evaluate the Efficacy and Safety of Oral Islatravir Once-Monthly as Preexposure Prophylaxis in Cisgender Women at High Risk for HIV-1 Infection
Treatment Assignment	A total of ~4500 participants will be randomized, stratified by site and age, in a 1:1 ratio to receive either ISL QM and placebo matched to FTC/TDF QD or FTC/TDF QD and placebo matched to ISL QM.
Analysis Populations	Efficacy: mFAS Safety: APaT
Primary Endpoint(s)	1. Confirmed HIV-1 infection 2. AEs and AEs leading to discontinuation of study intervention

Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing ISL QM to FTC/TDF QD with respect to incidence rate per year of confirmed HIV-1 infections. This comparison is done in terms of Prevention Efficacy (PE). The p-value for testing the null hypothesis that PE ≤0% versus the alternative that PE >0%, as well as the 95% CI estimate of PE, will be computed using the exact binomial method proposed by Chan and Bohidar[Chan, I. S. F. and Bohidar, N. R. 1998]. The statistical criterion for success requires that the lower bound of the 2-sided 95% CI for PE be >0%. If the target number of events are not observed by the time the last participant randomized has been in the study for approximately 2 years, consideration may be given to stopping the study early and conducting the analyses with all of the data collected up to that point.
Statistical Methods for Key Safety Analyses	Point estimates and 95% CIs will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] for the difference in proportions between intervention groups while ANCOVA will be used to provide point estimates and 95% CIs for the difference in change from baseline between intervention groups (ISL QM minus FTC/TDF QD).
Interim Analyses	The following interim analyses are planned. An external unblinded statistician will provide results to be reviewed by the eDMC. • Sentinel Cohort IA: This will be conducted 3 months after the last participant in the Sentinel Cohort initiates the study intervention. All available data will be submitted to the eDMC for a safety evaluation. • Efficacy IA: This will be performed when at least 25 confirmed incident HIV-1 infections in the combined ISL QM and FTC/TDF QD Groups have been accumulated. Inferential analyses for incidence rate per year of confirmed HIV-1 infections will be provided. • Continuous safety and efficacy monitoring throughout the study: Accumulating safety and efficacy data at regular intervals throughout the study duration will be reviewed.
Multiplicity	The primary efficacy hypothesis will be tested at an overall (over the interim and final analyses) 1-sided Type 1 error ≤ 2.5% and alpha will be controlled based on the exact calculations for binary data described by Jennison and Turnbull [Jennison, C. and Turnbull, B. W. 2000].
Sample Size and Power	Approximately 4500 participants will be randomized to enable the timely accrual of 40 confirmed incident HIV-1 infections which provide approximately 93% power to demonstrate that ISL QM is superior to FTC/TDF QD.

9.2 Responsibility for Analyses/In-house Blinding

Note: As of Part 2, Sponsor personnel not directly involved with blinded safety monitoring of participants ongoing in the study will be unblinded to the participants' original randomized study intervention group. As of Part 3, all Sponsor and site personnel as well as participants will be unblinded to the participants' original randomized study intervention assignment.

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

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment. Randomization will be implemented using IRT.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and between-group differences are listed below. Exploratory endpoints are stated in Section 3 and described in Section 4.2.1.

9.4.1 Efficacy Endpoints

Note: As of Amendment-04, this section is no longer applicable.

The primary efficacy objective will be assessed based on the incidence rate per year of confirmed HIV-1 infections.

9.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.

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

9.5 Analysis Populations

Note: As of Amendment-04, Section 9.5.1 is no longer applicable since no efficacy analyses will be performed. The APaT will be used for safety assessments.

9.5.1 Efficacy Analysis Population

The mFAS will serve as the primary population for the analysis of efficacy data in this study. This includes participants who were randomized and received at least 1 dose of study intervention and excludes participants who had confirmed HIV infections prior to or at randomization.

The screened population, which will include all individuals who come in for a screening visit for this study at one of the sites, will be used to estimate the background incidence rate.

9.5.2 Safety Analysis Population

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 intervention group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the intervention group corresponding to the study intervention actually received.

At least 1 laboratory measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to PK analysis and modeling will be described in a separate modeling and simulation plan authored by the department of Pharmacokinetics, Pharmacodynamics & Drug Metabolism - Quantitative Pharmacology and Pharmacometrics. Methods related to exploratory objectives will be described in the sSAP.

9.6.1 Efficacy Analyses

Note: As of Amendment -04, this section is no longer applicable.

The primary efficacy hypothesis will be addressed by testing the following:

$$H_0: PE \leq 0\%$$

$$H_1: PE > 0\%;$$

PE is the percent reduction in risk of becoming HIV-1 infected in the ISL QM group relative to the risk in the FTC/TDF QD group and is defined as,

$$PE = 100\%\{1-R_E/R_C\} \text{ where}$$

$$R_E = C_E/T_E \text{ and}$$

$$R_C = C_C/T_C$$

are the incidence rates of HIV-1 in the experimental (ISL QM) and control (FTC/TDF QD) groups, respectively. C_E is defined as the count of the HIV-1 infections in the ISL QM group

and T_E as total person-years of follow-up for efficacy in the ISL QM group. C_C and T_C are defined similarly for the FTC/TDF QD group.

The primary hypothesis that prevention efficacy is >0% will be tested by computing a 100*(1-α) % CI for PE with respect to the primary endpoint, denoted as (PE_L, PE_U). Success will be declared for the primary endpoint if PE_L >0%.

To construct the CI, assume that T_ER_E and T_CR_C are means of independent Poisson distributions. Given that there is a total of $n = C_E + C_C$ HIV-1 infections observed across the 2 treatment groups, $C_E \sim$ Binomial(n, π) with $\pi = T_ER_E/(T_ER_E + T_CR_C)$.

The probability π is a person-years-adjusted estimate of the probability that a participant who became HIV-1 infected belongs to the ISL QM group. The lower bound of the 100*(1-α) % exact CI for the probability π is obtained by searching for the proportion π_L such that the probability of observing C_E or more HIV-1 infections out n total HIV-1 infections is ≤α/2. Similarly, the upper bound of the 100*(1-α) % exact CI for the probability π is obtained by searching for the proportion π_U such that the probability of observing C_E or fewer efficacy endpoint infections out n total efficacy infections is ≤α/2 [Chan, I. S. F. and Bohidar, N. R. 1998]. PE_L and PE_U are then calculated from π_L and π_U as follows:

$$PE_L = 100\% *(1 - \pi_U (1+\theta))/(1- \pi_U)$$
$$PE_U = 100\% *(1 - \pi_L (1+\theta))/(1- \pi_L)$$

where $\theta = T_C/T_E$ is the ratio of the total person-years in the study in the FTC/TDF QD group over the ISL QM group.

If 40 confirmed HIV-1 infections are observed and ≤13 are in the ISL QM group, the primary efficacy hypothesis test would be successful and the efficacy of ISL QM relative to FTC/TDF QD would be demonstrated.

This study has an efficacy IA planned where the study may be stopped for efficacy or futility (Section 9.7). Moreover, the study may be stopped early if the number of events (25) needed to perform the IA is not accrued approximately 2 years from the time the last participant has been randomized, or if the IA was performed and the study continued, but the total number of events (40) needed to perform the final analysis is not accrued approximately 2 years from the time the last participant has been randomized.

The secondary efficacy objective will be addressed by comparing the incidence rate per year of confirmed HIV-1 infections in the ISL QM group to the background incidence rate using relative risk.

The relative risk, R, of becoming HIV-1 infected in the ISL QM group compared with the background population is defined as the ratio of the incidence rate per year of confirmed HIV-1 infections in the ISL QM group λ_1 to the background incidence rate λ_0,

$$R = \lambda_1/\lambda_0$$

The methodology proposed by Gao et al. [Gao, F., et al 2020], which specifies the asymptotic property of R and the testing scheme, will be used to test the secondary hypothesis.

The background incidence rate λ_0 will be estimated in the screened population using the methodology proposed by Kassanjee [Kassanjee, R., et al 2012]:

$$\hat{\lambda}_0 = \frac{n_R - n_+\hat{\beta}_T}{n_S(\hat{\Omega}_T - \hat{\beta}_T T)}$$

The incidence rate per year of confirmed HIV-1 infections in the ISL QM group λ_1 will be estimated as:

$$\hat{\lambda}_1 = \frac{n_{event}}{\tau}$$

Where,

n_R is the number of individuals in the screened population with HIV-1 infections and are identified as recent infections,

n_+ is the number of individuals in the screened population with HIV-1 infections,

n_S is the number of individuals in the screened population without HIV-1 infection,

n_{event} is the number of confirmed HIV-1 infections in the ISL QM group,

τ is the total person-years of treated participants in the ISL QM group,

$\hat{\beta}_T$ is the estimated false-recent rate (FRR) (the probability that a participant who is infected for longer than the prespecified cutoff time, T, will be identified as "recent"),

$\hat{\Omega}_T$ is the estimated mean duration of recent infections (MDRI) (the average time individuals were "recently infected" [the time they were infected within the defined cutoff time, T, after infection]), and

T is the cutoff time beyond which a "recent" result from the assay is considered to be falsely recent and is associated with the estimation of MDRI and FRR and generally defined as 2 years [Kassanjee, R., et al 2014].

For n_R, a participant is considered to be recently infected if all of the following criteria are met [Kassanjee, R., et al 2016] [Duong, Y. T., et al 2019]:

- The participant is HIV-1 seropositive at screening AND
- The normalized optical density (ODn) results from the Maxim HIV-1 LAg Avidity enzyme immunoassay are ≤1.5 AND
- The participant has HIV-1 RNA viral load with ≥1000 copies/mL.

In addition, participants who were HIV-1 seronegative at screening, but have confirmed HIV-1 infection at baseline (Day 1) prior to receiving any intervention, will be counted as recently infected.

MDRI (and FRR) will be based on the weighted average of estimated MDRIs (and FRRs) reported for the dominant subtypes at the various geographic locations, with the weighting based on the proportion of participants screened at the different sites. The estimated MDRIs (and FRRs) and their associated variances will be obtained from published reports for the subtypes using recency tests based on LAg Avidity (eg, [Kassanjee, R., et al 2014] or [Duong, Y. T., et al 2015]).

A 95% CI for the relative risk will be constructed based on Gao et al. [Gao, F., et al 2020]. The statistical criterion for success requires the upper bound of this 95% CI to be less than 1.

Analyses will be based on data as observed. Stratification variables will not be factored into the analyses.

Participants who discontinue study medication with no evidence of HIV-1 infection and do not withdraw consent/assent will be included in the analyses.

In the event that a participant becomes pregnant and treatment allocation is unblinded (Sections 8.11.3 and 8.11.4), data for that participant collected after unblinding will be excluded from efficacy analysis.

9.6.2 Safety Analysis

Note: As of Amendment-04, safety data will be evaluated for the blinded treatment period for applicable safety endpoints (Table 7), and for the entire duration of the study to evaluate recovery of total lymphocyte counts. All safety data will be summarized descriptively.

The analysis of safety results will follow a tiered approach. 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 PDLC in laboratory parameters will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event. The safety analysis strategy is summarized in Table 7.

Safety parameters or adverse events of interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. No a priori clinical events of concern have been identified for this study.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]). Membership in Tier 2 requires that at least 1% of participants in any treatment group exhibit the event. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals 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 PDLCs.

In addition to individual events that occur in at least 1% in any treatment group, the broad categories consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 to 4 AE, with an AE that is both drug-related and serious, with an AE that is both Grade 3 to 4 and drug-related, who discontinued study intervention due to an AE, who discontinued study intervention due to a drug-related AE, and with AE(s) leading to death will be considered Tier 2 endpoints. Safety endpoints that are not Tier 2 events are considered Tier 3 events. Only point estimates will be provided by treatment group for Tier 3 safety parameters.

Tier 2 endpoints also include the change from baseline in renal biomarkers at Weeks 24 and 48. The point estimate and 95% CI for change from baseline in treatment difference will be estimated between groups using ANCOVA models adjusted by baseline and intervention group (and any other participant characteristics that may be relevant).

For continuous measures such as change from baseline in laboratory parameters that are not prespecified as Tier 2 endpoints, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group in table format.

Participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study intervention) will be classified as to whether or not they fall outside the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3). A listing of the participants who meet the criteria will also be provided. Unless otherwise specified, missing safety parameters will not be imputed, and data will be used as observed. Change from baseline summaries require a baseline value. If a baseline value is missing, the latest pretreatment value will be used instead. If no pretreatment result is available, that participant will not be included in the summary.

For participants who become pregnant during the study, safety parameters assessed during the pregnancy period (estimated date of conception to date of conclusion of the pregnancy) may be summarized separately from the primary and secondary safety analyses. For continuous measures that are considered to be Tier 2 events, data collected after the estimated date of conception will be excluded from the analyses.

Infant safety data will be reported separately. Additional details on how pregnancy and infant data will be handled in safety analyses will be provided in the sSAP and/or CSR.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Difference	Descriptive Statistics
Tier 2	• The percentage of participants with an AE in each of the following categories: 1 or more AE(s); drug-related AE(s), SAE(s), Grade 3 to 4 AE(s), AE(s), which are both drug-related and serious, AE(s), which are both Grade 3 to 4 and drug-related, AE(s) leading to discontinuation of study intervention, AE(s), which are both drug-related and leading to discontinuation of study intervention, and AE(s) leading to death • The percentage of participants with specific AEs (preferred terms), SOCs, or PDLCs[a] occurring in ≥1% of participants in either treatment group • Change from baseline in renal biomarkers	X	X
Tier 3	• The percentage of participants with specific AEs (preferred terms), SOCs, or PDLCs[a] occurring in < 1% of participants in both treatment groups		X

AE=adverse event; CI=confidence interval; PDLC=predefined limit of change; SAE=serious adverse event; SOC=System Organ Class; X = results will be provided.

[a] Includes only those endpoints not already prespecified as Tier 2 endpoints.

9.6.3 Demographic and Baseline Characteristics

The comparability of the intervention groups for each relevant demographic and baseline characteristic will be assessed by tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, and prior and concomitant therapies will be summarized by intervention either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Note: As of Part 2, Sponsor personnel not directly involved with blinded safety monitoring of participants ongoing in the study will be unblinded to the participants' original randomized study intervention group. As of Part 3, no further assessments will be made by the eDMC.

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An eDMC will serve as the primary reviewer of the results of the interim efficacy and safety reviews and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Results from the interim analysis will be provided to the eDMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

The Sentinel Cohort IA will be conducted 3 months after the last participant in the Sentinel Cohort (defined in Section 4.1) has initiated study intervention. All available data for all participants enrolled by that time will be evaluated for safety at this interim analysis. The IA for efficacy and futility is planned when 25 confirmed incident HIV-1 infections in the combined ISL QM and FTC/TDF QD groups have been accumulated. If either the efficacy or futility criterion is met at the time of this IA, the study may be stopped based upon the recommendation of the eDMC. The proposed futility criterion is nonbinding and type I error is controlled.

The eDMC will also review accumulating safety and efficacy data at regular intervals throughout the study duration. The eDMC will recommend steps to ensure the safety of study participants and the integrity of the study and may make recommendations for protocol modifications or discontinuation of the study.

The method proposed by Jennison and Turnbull [Jennison, C. and Turnbull, B. W. 2000] will be used to control overall alpha. Table 8 shows the corresponding decision rules for the efficacy IA and final analyses. At the efficacy IA, the eDMC will review the data when at least 25 total confirmed HIV-1 infections have been accumulated. If 25 confirmed HIV-1 infections are observed and ≤6 are in the ISL QM group, the efficacy of ISL QM relative to FTC/TDF QD will be demonstrated. If ≥16 of the 25 confirmed HIV-1 infections are in the ISL QM group, futility would be declared. This criterion is based on declaring futility only if there is evidence that the ISL QM group has reduced efficacy relative to the FTC/TDF QD group. If >6 and <16 of the confirmed HIV-1 infections are in the ISL QM group so that neither superior efficacy nor reduced efficacy is demonstrated, the study would continue until a total of 40 confirmed HIV-1 infections are accumulated. If the true PE is 69%, then the

probability of meeting the efficacy criterion at the time of the IA is 62%, and if the true PE is -50%, then the probability of meeting the futility criterion at the time of the IA is 42%.

If the study does not stop at the IA, the study would continue until at least 40 confirmed HIV-1 infections have been accrued, and the final efficacy analysis would be conducted.

In the event that more than 25 confirmed HIV-1 infections are accrued at the time of the interim analysis, the boundaries for stopping rules will be adjusted so that the alpha spent is no more than originally planned. Further details will be provided in the eDMC Charter.

Table 8 Decision Rule and Corresponding Type 1 Error and Power for Testing the Primary Efficacy Hypothesis

Analysis Time Point	Total Infections	Critical Infections Split for ISL QM		Cumulative Type I Error (%)	True PE (%)		
		Efficacy	Futility/Failure	True PE=0%	-50%[a]	50%	69%[b]
					Cumulative Power (%)		
Interim	25	≤6	≥16	0.7	<0.1	22.1	61.6
Final	40	≤13	≥14	2.2	0.1	54.2	92.9

FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions); ISL=islatravir; PE=prevention efficacy; QD=once daily; QM=once-monthly.

Probabilities of meeting the futility criterion at the interim for true PEs of 0%, -50%, 50%, and 69% are 11%, 42%, 0.2%, and <0.1%, respectively

[a] The incidence rate in the ISL QM group is 50% higher compared with the FTC/TDC QD group.

[b] Corresponds to PE under alternative

9.8 Multiplicity

Note: As of Amendment -04, this section is no longer applicable.

The primary efficacy hypothesis will be tested at an overall (over the interim and final analyses) 1-sided Type 1 error ≤2.5%. Table 8 shows the decisions rules and details on alpha spent at the interim analysis. The method proposed by Jennison and Turnbull [Jennison, C. and Turnbull, B. W. 2000] will be used to control overall alpha.

9.9 Sample Size and Power Calculations

Note: As of Part 2 and continuing into Part 3, no new participants will be screened or randomized. The planned sample size was not reached, and this section is no longer applicable.

9.9.1 Sample Size and Power for Efficacy Analyses

Approximately 4500 participants will be randomized in a 1:1 ratio to either the ISL QM + FTC/TDF-matched placebo group or the FTC/TDF QD group + ISL QM-match placebo group.

The projected accrual of incident HIV-1 infections is based on the following assumptions:

- Background HIV-1 incidence, in the absence of any PrEP, is 2.5% per year.
- ISL QM has 87.5% efficacy (incidence rate of 0.3125% per year).
- FTC/TDF QD has 60% efficacy (incidence rate of 1.0% per year).
- Average participant time in the study is 1.5 years.
- Lost-to-follow-up/study discontinuation rate of 5% per year.

The assumed background rate is a conservative estimate based on 2 recent prospective studies (ECHO [Evidence for Contraceptive Options and HIV Outcomes Trial Consor 2019] and HVTN 702 [Joint United Nations Programme on HIV/AIDS 2020]) conducted in Africa where the overall yearly incidence rates among women were 3.8% and ~4% respectively. The assumption regarding ISL QM efficacy is a conservative estimate based on a rhesus macaque SHIV intrarectal challenge model [Markowitz, M., et al 2019] where ISL provided protection against infection at drug levels that are projected to be achieved with the dose regimen used in this study. The assumption regarding FTC/TDF QD efficacy is an approximation based on the wide range of reported efficacy of FTC/TDF QD in previous studies, from not better than placebo to 64% to 84% in Partners PrEP [Murnane, P. M., et al 2013]. The assumption regarding study discontinuation rate is consistent with HPTN 84 [HIV Prevention Trials Network 2019].

A total of 40 confirmed HIV-1 infections across the ISL QM and FTC/TDF QD groups will result in 93% power to demonstrate that ISL QM is superior to FTC/TDF QD if the true PE is 69% with 1-sided Type 1 error $\alpha \leq 0.025$.

For the secondary efficacy objective, given the above assumptions, the study has >99% power to demonstrate that ISL QM reduces the incidence of HIV-1 infections compared with the background rate, for background rates ranging from 2% to 4%.

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 of a particular type of AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population.

If the underlying percentage of participants with a particular AE is 0.1%, there is 89.5% chance of observing at least 1 AE among 2250 participants in a treatment group. If no AE of that type is observed among the 2250 participants in a treatment group, this study will

provide 97.5% confidence that the underlying percentage of participants with that particular AE is <0.2% (1 out every ~ 600 participants).

The estimate of, and the upper bound of the 95% CI for, the underlying percentage of participants with an AE given various hypothetical observed numbers of participants with the AE within each treatment group are provided in Table 9. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 9 Percentage of Participants With AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants With AEs (2250 Participants per Group)

Hypothetical Numbers of Participants With AE	Percentage	95% Upper Confidence Bound[a]
0	0.0%	0.2%
50	2.2%	2.9%
100	4.4%	5.4%
150	6.7%	7.8%
200	8.9%	10.1%

AE=adverse event; CI=confidence interval.

[a] Based on the 2-tailed exact CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. and Pearson, E. S. 1934]). In the 0-event case, the 95% CI is one sided (α=0.05 all in the upper tail).

Table 10 demonstrates the difference in the percentage of participants with an AE (ISL QM minus FTC/TDC QD) that can be ruled out with different power levels and 95% confidence when there are 2250 participants in each group. The underlying percentage of participants with the AE is assumed to be the same for the 2 intervention groups. For example, for an AE that occurs in 10% of participants in both groups, the study has 80% power to show with 95% confidence that the true difference between the treatment groups is no more than 2.6% percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 10 Difference in Percentage of Participants With AEs (ISL QM Minus FTC/TDC QD) That can be Ruled Out With 2250 Participants in Each Group

Target Power	Underlying Percentage of Participants with AE			
	1%	5%	10%	20%
80	1.0%	2.0%	2.6%	3.4%
85	1.1%	2.1%	2.8%	3.7%
90	1.2%	2.3%	3.1%	4.0%

AE=adverse event; CI=confidence interval; FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions); ISL=islatravir; QD=once daily; QM=once-monthly.

Note: The upper bound of the 2-sided 95% CI (Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]) for the difference in percentages of participants with AEs (ISL QM minus FTC/TDF QD) assuming the percentages are the same.

9.10 Subgroup Analyses

Note: As of Amendment-04, no between-group comparisons will be conducted and this section is no longer applicable.

To assess whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary efficacy endpoint will be calculated within each category of the following classification variables.

- Age category (<18, ≥18 years; <25, ≥25 years)
- Site (all US sites – 1 level, each ex-US site is a separate level)

9.11 Compliance (Medication Adherence)

Note: As of Amendment-04, this section will only apply to the blinded treatment period (Part 1).

Adherence to ISL QM or matching placebo will be recorded upon in-clinic dosing at each monthly visit. For each participant in the FTC/TDF QD or matching placebo group, the number of tablets remaining in study packaging will be counted, reviewed, and recorded by site personnel at regular intervals. These results will be used to calculate participant compliance.

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

$$\text{Percent Compliance} = \frac{\text{Number of Days Dose Taken}}{\text{Number of Days Dose Should be Taken}} \times 100$$

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

9.12 Extent of Exposure

Note: As of Amendment-04, this section will only apply to the blinded treatment period (Part 1).

The extent of exposure to study intervention will be evaluated by summary statistics by intervention group.

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 & Dohme LLC, Rahway, NJ, USA (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 (including all applicable data protection laws and 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 and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. 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, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and nonSponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 [Interim Analysis]) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Clinical Adjudication Committee (CAC)

A CAC will evaluate the following events for the purposes of confirming them according to the criteria in Section 9, as well as evaluating the presence of confounding factors.

1. Incident HIV infection

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.4.4 Executive Oversight Committee

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

10.1.4.5 Protocol Steering Committee

The Protocol Steering Committee provides scientific leadership for the study and is comprised of both Sponsor and external members such as:

- Sponsor personnel,
- Investigators participating in the study, and
- Consulting therapeutic-area experts and clinical trialists.

The Protocol Steering Committee will be responsible for scientific aspects of the study, maintaining effective and independent scientific oversight, and will ensure that study execution and management are of the highest quality. The Protocol Steering Committee will convene regularly to discuss and report on ongoing supervision of the study. The Protocol Steering Committee will provide guidance on the operational aspects of the study, evaluate recommendations from the DMC and discuss these recommendations with the EOC. The Protocol Steering Committee is responsible for oversight of all public and scientific communications and publications, and for overseeing the development of ancillary, scientific studies.

Specific details regarding responsibilities and governance of the Protocol Steering Committee will be described in a separate charter.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical 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.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation 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 Trials.

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be processed by a central laboratory in the US, or by a local/regional laboratory in Africa.
- Local laboratory results may be 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 the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
Pregnancy	Urine Pregnancy Test (WOCBP only) (Highly sensitive urine) human chorionic gonadotropin (hCG) pregnancy test
	Positive urine pregnancy to be confirmed with serum pregnancy test - Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test
Hematology	Hematocrit (Hct)
	Hemoglobin (Hb)
	RBC Count
	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)

Laboratory Assessments	Parameters
CD4+ T-Cell count/Lymphocyte subset panel	CD4 + T-cell count/lymphocyte subset panel includes, but is not limited to:
	CD3+ Percent
	CD3+ Value/Absolute Count
	CD3+CD4+ Percent
	CD3+CD4+ Value/Absolute Count
	CD3+CD8+ Percent
	CD3+CD8+ Value/Absolute Count
	CD3-CD19+ Percent
	CD3-CD19+ Value/Absolute Count
	CD16+CD56+ Percent
	CD16+CD56+ Value/Absolute Count
	CD3+CD4+CD8+ Percent
	CD3+CD4+CD8+ Value/Absolute Count
	CD4/CD8 Ratio
Chemistry	Albumin
	Alkaline Phosphatase (ALP)
	Alanine Aminotransferase (ALT/SGPT)
	Aspartate Aminotransferase (AST/SGOT)
	Amylase
	Bicarbonate
	Bilirubin, Direct
	Bilirubin, Indirect
	Bilirubin, Total
	Calcium (Ca)
	Chloride (Cl)
	Cholesterol, Total
	Creatine Phosphokinase (CPK)
	Creatinine
	Creatinine Clearance (calculated)
	Cystatin-C
	Gamma Glutamyl Transferase (GGT)
	Glucose (fasting)
	Glucose (random)
	Lactate Dehydrogenase (LDH)
	Lipase
	Magnesium (Mg)
	Phosphorous
	Potassium (K)

Laboratory Assessments	Parameters
	Protein, Total
	Sodium (Na)
	Triglycerides
	Urea Nitrogen, Blood (BUN)
	Uric Acid
Hepatitis screen (Screening)	Hepatitis B virus surface antigen (HBsAg)
	Hepatitis B Serology (HBsAb/HBcAb)
Virology	Point-of-Care HIV-1 test
	HIV-1/HIV-2 antibody/antigen testing
	Plasma HIV-1 viral RNA quantification (real time PCR) – to be performed if HIV-1 positive
	Whole blood HIV-1 drug resistance testing - to be performed only if viremia is detected
STI Testing (Screening)	Syphilis Serologic Testing (rapid plasma reagin [RPR], RPR with titer, *Treponema pallidum* IgG, *Treponema pallidum* IgG index value)
	Vaginal Swab for bacterial vaginosis
	Nucleic acid amplification from urine for Trichomonas
	Nucleic acid amplification from urine for Gonorrhea and Chlamydia
	HSV-2 Serology Testing
PK Sampling	Blood (Plasma) for PK
	Dried blood for PK
	Blood (Plasma) for Investigational PK
Biomarkers	HIV Recency Assay (Samples will be analyzed only in participants with confirmed HIV-1 infection at screening or Day 1)

Notes:

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

If a participant is confirmed HIV-infected, results from HIV-1 drug resistance testing will not be provided to site personnel who are directly involved in supporting the study, as there is the potential for the data to unblind the participants intervention group. HIV Resistance results will be blinded to the study team and site personnel.

PK data will be blinded to site and Sponsor personnel during the study (Section 6.3.3).

Table 12 PK Sample Collection Timepoints

Note: PK samples will not be collected in Part 3 of the study.

Visit Number	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 11**	**Visit 14**	**Visit 17**	**Visit 20**	**Visit 23**	**Visit 26**	**Visit 29**	**Visit 32**	**Visit 35**	**Visit 38**	**Notes**
Day/Month	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**	**Month 36/ EOT**	A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Blood (Plasma) for PK	X	X		X			X		X		X		X		X		X	See Section 8.6.1 The sample must be collected irrespective of the planned PK collection schedule, if a participant has a positive Point-of-Care HIV test result at a visit.
Blood (Plasma) for Investigational PK			X					X		X		X		X		X		See Section 8.6.2 During Part 1, investigational PK samples will be collected predose at Month 2 and at any time during the visit at Months 9, 15, 21, 27, and 33. During Part 2, investigational PK samples may be collected at any time during the visit. Samples will be stored and triggered for analysis by Sponsor, if needed.

Visit Number	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 11**	**Visit 14**	**Visit 17**	**Visit 20**	**Visit 23**	**Visit 26**	**Visit 29**	**Visit 32**	**Visit 35**	**Visit 38**	**Notes**
Day/Month	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24**	**Month 27**	**Month 30**	**Month 33**	**Month 36/ EOT**	A participant may have up to 40 visits, but may have fewer visits (endpoint-driven study).
Dried Blood for PK	X	X	X	X			X		X		X		X		X		X	See Section 8.6.3 The sample must be collected irrespective of the planned PK collection schedule, if a participant has a positive Point-of-Care HIV test result at a visit.

EOT=end of treatment (all participants may not complete 36 months because this is a case-driven study); HIV=human immunodeficiency virus; PK=pharmacokinetic.

Note: For participants who become pregnant and remain on ISL, see Section 1.3.4 and Section 8.6.4.

Table 13 Blood Volumes

Note: PK samples will not be collected in Part 3 of the study.

Study Period	**Screen**	**Study Intervention**														
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**		**HIV Infection Confirmation**	**Early Discontinuation of Study Intervention**	**Early Withdrawal from Study**
Scheduled Day/Month	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36**	**Totals**	**Unscheduled**	**Unscheduled**	**Unscheduled**
HBV/HIV (Serology)	6												6			
Syphilis Serologic Testing	4				4			4		36		4	52			
HSV-2 serology	2											2	4			
Hematology	6	6	6	6	6	6	6	6	174			6	228	6	6	6
CD4+ T-cell count/Lymphocyte subset panel	6	6	6	6	6	6	6	6	174			6	228	6	6	6
Chemistry	5	5			5			5		45		5	70	5	5	5
Cystatin-C		3.5			3.5			3.5		31.5		3.5	45.5		3.5	3.5
Serum pregnancy test (WOCBP only)	Off Chem	2	2	2		2	2		40				50			
Point-of-Care HIV Testing[d]	Not applicable; additional volume not required.															
HIV-1/HIV-2 Antibody/Antigen Testing	Off HBV/ HIV	3.5	3.5	3.5	3.5	3.5	3.5	3.5	101.5			3.5	129.5	3.5	3.5	3.5
Plasma HIV RNA (Real Time PCR)	6	6	6	6	6	6	6	6	174			6	228	6	6	6
HIV-1 Drug Resistance Testing		3											3	15 (180)[e]	12	12
HIV Recency Assay	4	4											8			

Study Period	**Screen**	**Study Intervention**														
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**		**HIV Infection Confirmation**	**Early Discontinuation of Study Intervention**	**Early Withdrawal from Study**
Scheduled Day/Month	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36**	**Totals**	**Unscheduled**	**Unscheduled**	**Unscheduled**
Blood (Plasma) for PK		3	3		3			3			12	3	27[f]	3	3	3
Blood (Plasma) for Investigational PK				3							15[g]		18			
Dried Blood for PK		from PK tube	from PK tube	from investi-gational PK tube	from PK tube			from PK tube			from PK tube	from PK tube	0	from PK tube	from PK tube	from PK tube
Blood for Genetic Analysis		8.5											8.5			
Whole blood for FBR		4											4	4		

Study Period	**Screen**	**Study Intervention**														
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Recurring Visits**			**38**		**HIV Infection Confirmation**	**Early Discontinuation of Study Intervention**	**Early Withdrawal from Study**
Scheduled Day/Month	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Every Month[a]**	**(Additional Assessments) Every 3 Months[b]**	**(Additional Assessments) Every 6 Months[c]**	**Month 36**	**Totals**	**Unscheduled**	**Unscheduled**	**Unscheduled**
Total Blood Volume per Visit in mL[f,h]	39	54.5	26.5	26.5	37	23.5	23.5	37	663.5	112.5	27 [e]	39	1109.5	48.5 (213.5)[e]	45	45

EOT=end of treatment (all participants may not complete 36 months because this is a case-driven study); FBR=future biological research; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HSV = herpes simplex virus; PK=pharmacokinetic; RNA=ribonucleic acid; WOCBP=a woman/women of childbearing potential

Notes: All volumes are provided in mL. Serum pregnancy testing may be conducted using sample collected for chemistry ("off chem") as indicated. HIV-1/HIV-2 Antibody/Antigen Testing may be conducted using sample collected for HBV/HIV testing ("off HBV/HIV") as indicated. Samples for PK may be used for dried blood testing for PK as indicated.

[a] Samples are collected at every monthly visit up to Month 36 (29 visits for those who complete 3 years in study)

[b] Samples are collected every 3 months up to Month 36 (9 additional visits for those who complete 3 years in study)

[c] Samples are collected every 6 months up to Month 36 (4 additional visits for those who complete 3 years in study)

[d.] Investigational PK is collected at one additional every 6 month visit due to different visit collection schedule

[e] Participants who become pregnant and remain on ISL, will have additional visits and PK samples amounting to approximately 21 mL total (not reflected in Table).

[f] Negligible blood volume amount as sample is collected from another tube or fingerstick.

[g] Blood volumes are calculated based on volume requirements at Central lab (US) and Regional lab (Africa). Slight variances may occur if a local lab is utilized.

[h] Whole blood and Plasma Samples for HIV-1 Drug Resistance will be collected and analyzed every 3 months following HIV Infection Confirmation Visit (up to 12 additional visit collections)

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

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

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity /toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf). In addition, DAIDS Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies) will be used as the primary grading table (and thus takes precedence over the main grading table) for obstetric and gynecologic AEs. Note exception to DAIDS Addendum 1: The presence of bacterial vaginosis detected by routine study collection is not considered an AE if, in the medical judgment of the investigator, it is not clinically significant (https://rsc.niaid.nih.gov/sites/default/files/addendum-1-female-genital-grading-table-v1-nov-2007.pdf). 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 functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
- Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure 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 Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 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 Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt 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 implant[c] • IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia 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
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 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 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[3, 4]

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

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

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

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

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

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

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

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

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

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

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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes 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[3, 4]

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[3, 4]

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@MSD.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[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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[3, 4]

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

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

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the

participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

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

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

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

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

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

There are no country-specific requirements.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
BMI	body mass index
C_{168hr}	concentration at 168 hours postdose
CAC	Clinical Adjudication Committee
CDC	Centers for Disease Control
CI	confidence interval
C_{max}	maximum serum concentration
CONSORT	Consolidated Standards of Reporting Trials
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Regulation
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravirine
DP	diphosphate
EC_{90}	90% effective concentration
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EFV	efavirenz
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FRR	false-recent rate
FSH	follicle-stimulating hormone
FSR	First Site Ready
FTC/TDF	emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions)
GCP	Good Clinical Practice
GC/CT	*Neisseria gonorrhoeae/Chlamydia trachomatis*
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HRT	hormone replacement therapy

Abbreviation	Expanded Term
HSV	herpes simplex virus
IB	Investigator's Brochure
IA	interim analysis
IC_{50}	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	Investigational Medicinal Product
IND	Investigational New Drug
iPrEx	Preexposure Prophylaxis Initiative
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir
LAg	Limiting Antigen
MDRI	mean duration of recent infections
mFAS	modified Full Analysis Set
NI	noninferiority
NIMP	Noninvestigational medicinal product
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PDLC	predefined limit of change
PE	prevention efficacy
PEP	postexposure prophylaxis
PEPFAR	President's Emergency Plan For AIDS Relief
PK	pharmacokinetic
PrEP	preexposure prophylaxis
PRO	participant-reported outcome
QD	once daily
QM	once-monthly
QW	Once-weekly
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SHIV	simian human immunodeficiency virus
SoA	schedule of activities
SOP	standard operating procedure
sSAP	supplemental Statistical Analysis Plan
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
TFV	tenofovir
TP	triphosphate
ULN	Upper limit of normal
US	United States
USPSTF	United States Preventive Services Task Force

Abbreviation	Expanded Term
VAMS	volumetric absorptive microsampling
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

10.9 Appendix 9: Calculation of Creatinine Clearance

Cockcroft-Gault equation (for female participants):

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

10.10 Appendix 10: Document to Support Assessment of HIV-1 Infection Risk/CDC Criteria for PrEP

10.10.1 Background

Inclusion Criteria 3 of Protocol MK-8591 P022 references 2 commonly used HIV risk assessments to be utilized by investigators or study staff at screening for this study (depending upon study location). This document provides supporting information regarding the 2 assessments.

- The VOICE risk score tool – to be used by sites in Africa
- The CDC criteria for PrEP eligibility – to be used by sites in the US

The Protocol team has assembled this document to provide links to the full guidance and a brief presentation of specific information appropriate for evaluation in the trial.

Protocol Inclusion Criteria:

3. Is at high risk for HIV-1 infection as defined by a risk score ≥5 using a VOICE risk score tool (sites in Africa) or meets the CDC criteria for PrEP eligibility (sites in the US).

10.10.2 VOICE Risk Score – Sites in Africa

The Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial was a randomized, placebo-controlled trial to assess oral tenofovir disoproxil fumarate (TDF), oral TDF-emtricitabine (FTC), or 1% tenofovir (TFV) vaginal gel as PrEP in women in South Africa, Uganda, and Zimbabwe (https://www.nejm.org/doi/full/10.1056/NEJMoa1402269). Of 12,320 women screened, 5,029 were enrolled. The rate of retention was 91% during 5,509 person-years of follow-up. A total of 312 HIV-1 infections occurred; the incidence of HIV-1 infection was 5.7 per 100 person-years. Although none of the drug regimens evaluated reduced the rates of HIV-1 acquisition in an intention-to-treat analysis, the data were used to develop: “An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in Africa Women,” (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911322/pdf/nihms761084.pdf) in which data from the VOICE trial were analyzed and a risk score was derived; 2 other randomized trials of biomedical HIV prevention interventions among African women, HPTN 035 of microbicide gel and FEM-PrEP of TDF-FTC, were used to validate this risk score.

10.10.2.1 VOICE Risk Score Tool

Per-Protocol MK-8591 P022: Is at high risk for HIV-1 infection as defined by a risk score ≥5.

Risk Factor	Points
Age <25	2
Not married or living with primary partner	2
Partner does NOT provide financial or material support	1
Primary partner has other partners, yes or maybe	2
Alcohol use in past 3 months	1
Curable sexually transmitted infection at screen	1
Herpes simplex virus-2 seropositive	2
Maximum possible Points	11

10.10.3 CDC Criteria for PrEP – Sites in the US

The US Public Health Service Centers for Disease Control issued a Clinical Practice Guideline entitled PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES-2017 UPDATE: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

The criteria for assessment of high risk for HIV-1 infection for enrollment of female participants in US sites for Protocol MK-8591 P022 inclusion criterion #3 is provided below (modified from the CDC Guidance for MK-8591 P022):

Not in a (mutually) monogamous partnership with a recently tested (within the past 6 months) HIV-negative partner

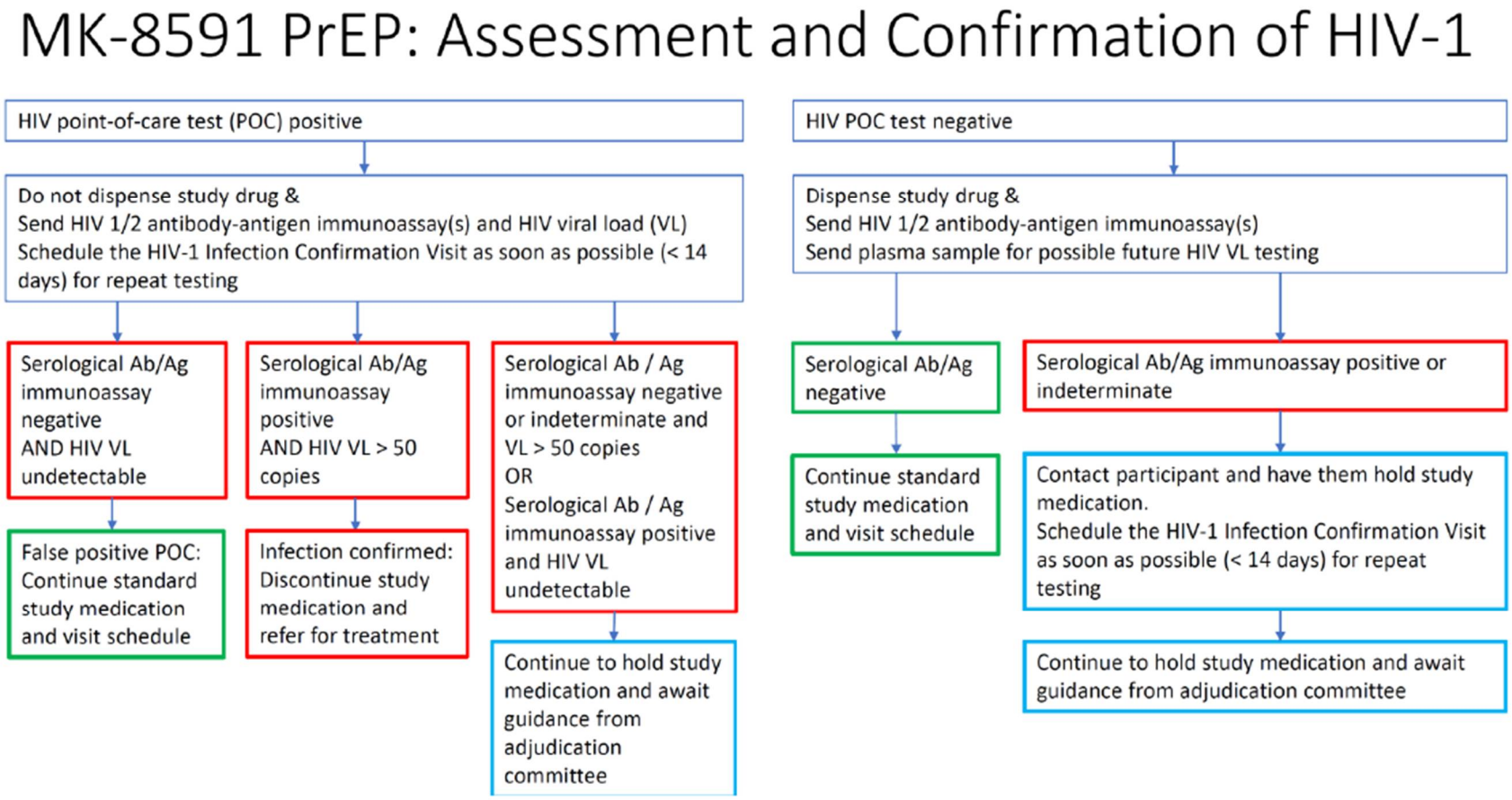
AND at least one of the following:

- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (person who injects drugs or has injected drugs within the past 6 months, or bisexual male partner) or has exchanged sex for commodities (eg, shelter, drugs, money) in the past 6 months
- Is in an ongoing sexual relationship with an HIV-positive partner
- A bacterial STI (syphilis, gonorrhea, chlamydia*) diagnosed or reported in past 6 months

* We are including chlamydia because the CDC guidelines also state “In addition, for all sexually active patients, clinicians may want to consider reports of diagnoses of bacterial STIs (chlamydia, syphilis, gonorrhea) during the past 6 months as evidence of sexual activity that could result in HIV exposure.”

Version Number	Date	Summary of Changes
1.0		Original Version (not originally a Protocol Appendix)
2.0	01-MAY-21	• Updated "Clinicians" to "investigators or study staff at screening" • Updated References of "Non-US Sites" and "Ex-US Sites" to "sites in Africa" • Updated References of "US Sites" to "sites in the US" • Updated the parenthetical statement in the first bullet in the table of recommended indications for PrEP use by heterosexually active women (MK-8591 P022 Specific). The statement formerly read "(Person Who Injects Drugs or bisexual male partner)" and was updated to "(person who injects drugs or has injected drugs within the last 6 months, or bisexual male partner)" • Removed an errant extra ")" in the table of recommended indications for PrEP use by heterosexually active women (MK-8591 P022 Specific).
3.0	DD-MMM-21	Updated the CDC Criteria for PrEP – Sites in the US as follows: • Revised text from Box B2 of the CDC Guideline provides Recommended Indications for PrEP Use by Heterosexually Active Men and Women. The criteria for assessment of high risk for HIV-1 infection for enrollment of female participants in US sites for Protocol MK-8591 P022 inclusion criteria #3 is provided below (modified for MK-8591 P022 to be appropriate specific to women in the study). Recommended indications for PrEP use by heterosexually active women (MK-8591 P022 Specific): To The criteria for assessment of high risk for HIV-1 infection for enrollment of female participants in US sites for Protocol MK-8591 P022 inclusion criteria #3 is provided below (modified from the CDC Guidance for MK-8591 P022). • Updated the first bullet in the criteria for assessment of high risk for HIV-1 infection to include "or has exchanged sex for commodities (eg, shelter, drugs, money) in the past 6 months."

10.11 Appendix 11: MK-8591 PrEP Program HIV Testing Algorithm



Ab=antibody; Ag=antigen; HIV=human immunodeficiency virus; POC=point-of-care; PrEP=preexposure prophylaxis; VL=viral load.

11 REFERENCES

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