

<b>Official Protocol Title:</b>	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 Men and Transgender Women Who Have Sex With Men, and Are at High Risk for HIV-1 Infection
<b>NCT number:</b>	NCT04652700
<b>Document Date:</b>	02-DEC-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 Men and Transgender Women Who Have Sex With Men, and Are at High Risk for HIV-1 Infection

**Protocol Number:** 024-05

**Compound Number:** MK-8591

**Sponsor Name:**

Merck Sharp & Dohme LLC  
(hereafter referred to as the Sponsor or MSD)

**Legal Registered Address:**

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Rahway, NJ 07065 USA

**Regulatory Agency Identifying Number(s):**

IND	128,595
EudraCT	2020-003309-79

**Approval Date:** 02 December 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 05	02-DEC-2022	The protocol was amended to extend the study duration from Month 24 to Month 30 to allow for additional safety follow-up.
Amendment 04	03-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 or FTC/TAF, and monitor safety.
Amendment 03	24-FEB-2022	<p>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 FTC/TAF for HIV prevention treatment while continuing the study. Screening and randomization of new participants have stopped.</p> <p>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.</p>
Amendment 02	06-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	07-JUN-2021	The protocol was amended to update the statistical methods for primary and secondary objectives, to add a blinded IA for sample size re-estimation, and to modify power assumptions.
Original Protocol	09-NOV-2020	Not applicable

## PROTOCOL AMENDMENT SUMMARY OF CHANGES

### Amendment: 05

#### Overall Rationale for the Amendments:

This amendment is to extend the study duration from Month 24 to Month 30 to allow for additional safety follow-up.

#### Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 4.1 Overall Design	The duration of participation was updated from “up to 2.5 years” to “approximately 2.5 years”.	To extend the study duration for additional safety follow-up
Section 1.3.1 Schedule of Activities for Part 1, Part 2, and Part 3	The table and footnotes ‘b’ and ‘c’ were updated to extend the study duration from Month 24 to Month 30.  The table footnote ‘f’ was added.	To extend the study duration for additional safety follow-up  For clarity of operational visit tracking
Section 1.3.3 Schedule of Activities – Participants Who Have A Positive HIV-1 Test	The table was updated to include lymphocyte subset panel in the CD4+ T-cell count.  Footnote ‘a’ was updated to extend the study duration from Month 24 to Month 30.	For clarity  To extend the study duration for additional safety follow-up
Section 8 Study Assessments and Procedures  Section 10.2 Clinical Laboratory Tests	The total volume of blood collected was updated in the text and in Table 14.	To reflect the volume of blood collected from the additional study visits

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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 Men and Transgender Women Who Have Sex With Men, and Are at High Risk for HIV-1 Infection

**Short Title:** Oral ISL QM as PrEP in MSM and TGW at High Risk for HIV-1 Infection

**Acronym:** Impower – 024

#### Hypotheses, Objectives, and Endpoints:

The hypothesis is 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 cisgender MSM and TGW  $\geq 16$  years of age who are at high risk for HIV-1 infection.

Primary Objectives	Primary Endpoints
<ul style="list-style-type: none"><li>- To evaluate the efficacy of oral ISL QM in reducing the incidence per year of HIV-1 infection relative to the background rate.</li></ul> Hypothesis: ISL QM reduces the incidence rate of confirmed HIV-1 infections compared to the background incidence rate.	<ul style="list-style-type: none"><li>- Confirmed HIV-1 infection</li></ul>
<ul style="list-style-type: none"><li>- To evaluate the safety and tolerability of oral ISL QM compared to FTC/TDF or FTC/TAF QD as assessed by review of the accumulated safety data.</li></ul>	<ul style="list-style-type: none"><li>- Adverse events</li><li>- Adverse events leading to discontinuation of study intervention</li></ul>
Secondary Objectives	Secondary Endpoints
<ul style="list-style-type: none"><li>- To compare the incidence rate per year of confirmed HIV-1 infections following administration of ISL QM and FTC/TDF or FTC/TAF QD.</li></ul>	<ul style="list-style-type: none"><li>- Confirmed HIV-1 infection</li></ul>

**Overall Design:**

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	HIV Preexposure prophylaxis
Population	Cisgender men and transgender women who have sex with men, are at least 16 years of age, and are 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 with in-house blinding
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 4 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 1500 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 Administration	Regimen/Treatment Period	Use
	Part 1 ISL QM group	ISL		60 mg	Once monthly	Oral	Day 1 through Month 24
Placebo to FTC/TDF or FTC/TAF			0 mg	Once daily	Oral	Day 1 through Month 24	Placebo
Part 1 FTC/TDF or FTC/TAF QD group	FTC/TDF or FTC/TAF <sup>a</sup>		200/245 mg <sup>b</sup> or 200/25 mg	Once daily	Oral	Day 1 through Month 24	Test Product
	Placebo to ISL		0 mg	Once monthly	Oral	Day 1 through Month 24	Placebo
Part 2 All Participants	FTC/TDF or FTC/TAF <sup>a</sup>		200/245 mg <sup>b</sup> or 200/25 mg	Once daily	Oral	Part 2	Test Product
Part 3 All Participants	FTC/TDF or FTC/TAF <sup>a</sup>		200/245 mg <sup>b</sup> or 200/25 mg	Once daily	Oral	Part 3	Test Product
FTC/TAF=emtricitabine/tenofovir alafenamide; FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); ISL=islatravir (also known as MK-8591); PrEP=preexposure prophylaxis. <sup>a</sup> FTC/TAF is only available for use as PrEP in the United States. If, during the course of the study, FTC/TAF is approved for use as PrEP in other countries, assignment is contingent upon availability of drug supply. <sup>b</sup> 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, participants will be in this study for approximately 2.5 years from the time the participant provides documented informed consent/assent through the final contact.						



**Study Governance Committees:**

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

**Study Accepts Healthy Volunteers: Yes**

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

## 1.2 Schema

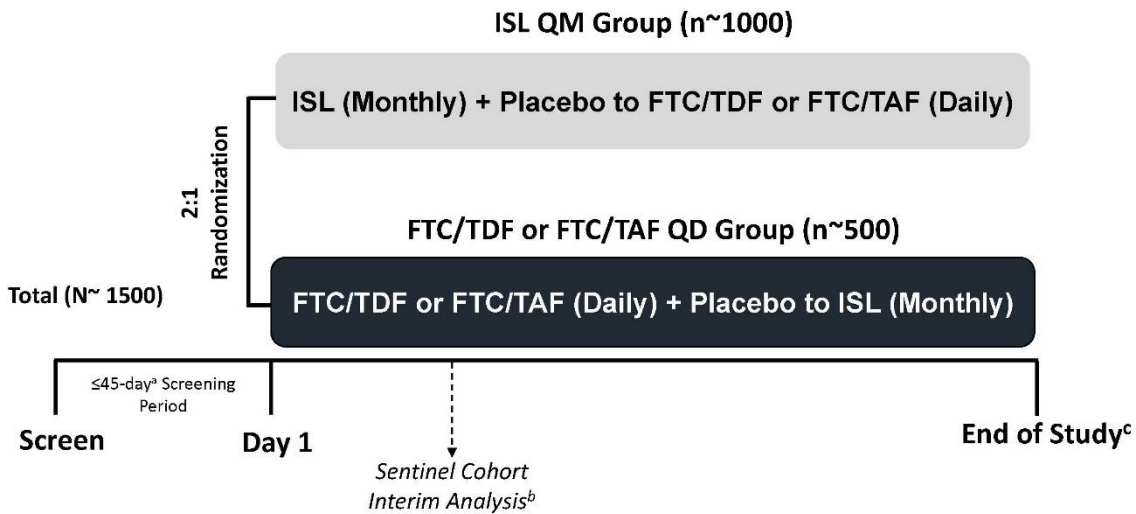
The study design is depicted in [Figure 1](#) (Part 1), [Figure 2](#) (Part 2), and [Figure 3](#) (Part 3).

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 or FTC/TAF. 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 or FTC/TAF. No new participants will be screened or randomized during Part 3.

Figure 1 Study Schema – Part 1



FTC/TAF=emtricitabine/tenofovir alafenamide; FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ [Gilead] and all generic versions); ISL=islatravir (also known as MK-8591); N=number of participants in the study; n=number of participants in each intervention group; QD=once daily; QM=once monthly.

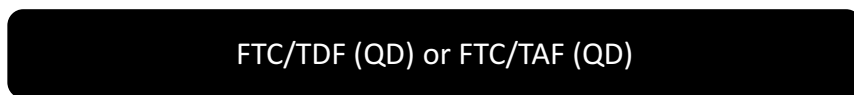
<sup>a</sup> Screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.

<sup>b</sup> Sentinel Cohort (first approximately 150 enrolled participants) interim analysis will be conducted 3 months after the last participant in the Sentinel Cohort has initiated study intervention.

<sup>c</sup> End of study includes the safety follow-up period of 42 days after the last dose of study intervention.

Figure 2 Study Schema – Part 2

**All Participants Enrolled in Part 1 Were Included in Part 2**  
(no new participants will be screened or randomized during Part 2)



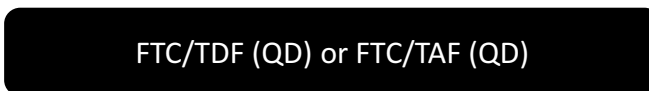
End of Part 1  
Blinded study intervention stopped; all participants remain blinded to original study intervention assignments  
Start of Part 2

FTC/TAF=emtricitabine/tenofovir alafenamide; 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 or FTC/TAF.*

Figure 3 Study Schema – Part 3

All Ongoing  
Participants



FTC/TAF=emtricitabine/tenofovir alafenamide; 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 or FTC/TAF.*

### 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 or FTC/TAF 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 or FTC/TAF.*

*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 or FTC/TAF. 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 or FTC/TAF.*

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

Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
Visit Window	≤45 days <sup>a</sup>	N/A	±7 Days													Visit windows for Part 3 are extended to ±14 Days.	
<b>Administrative Procedures</b>																	
Informed consent/assent	X																
Informed consent/assent for FBR	X																
Inclusion/exclusion criteria	X	X															Review prior to randomization on Day 1 to confirm no changes in eligibility.



Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
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
Register study visit in IRT	X	X	X	X	X	X	X	X	X <sup>f</sup>				X <sup>f</sup>		X <sup>f</sup>	X <sup>f</sup>	
Medical history	X																
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X				X	X	X	X	
Intervention randomization		X															
Assessment for acute retroviral syndrome	X																See Section 8.11.1.
Treatment Eligibility Assessment (TEA)	X																To be completed prior to randomization.

Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
Dispense study intervention		X	X	X	X	X	X	X	X <sup>f</sup>				X <sup>f</sup>				<p>During Part 1, in-clinic dosing of study intervention. The remaining monthly supply of FTC/TDF or FTC/TAF will be dispensed at each visit. Do NOT dispense study intervention if the participant's Point-of-Care HIV test is positive.</p> <p>During Part 2 and Part 3, participants will receive only FTC/TDF or FTC/TAF. Participants should stop FTC/TDF or FTC/TAF if Point-of-Care HIV Test is positive while further testing is conducted. No other study intervention is to be dosed.</p>

Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
Evaluation to receive continued study intervention														X			
Study intervention adherence review		X	X	X	X	X	X	X	X				X	X			Reconcile doses, assess study intervention adherence, and offer adherence counseling.
HIV Risk Reduction	X	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	X			
PRO: preference		X						X			X	X	X				Not applicable for Part 3.

Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
<b>Efficacy Procedures</b>																	
Point-of-Care HIV testing	X	X	X	X	X	X	X	X	X								<p>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.</p> <p>At all subsequent visits after Day 1, if the test is positive, PK samples (both plasma and dried blood) should be collected regardless of the PK sampling schedule.</p> <p>During Part 1, do NOT dispense study intervention if the participant's Point-of-Care HIV test is positive.</p> <p>During Part 2 and Part 3, participants should stop taking FTC/TDF or FTC/TAF if Point-of-Care HIV Test is positive while further testing is conducted.</p>
HIV-1/HIV-2	X	X	X	X	X	X	X	X	X				X	X			





Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
antibody/ antigen testing																	
Plasma HIV-1 RNA quantification (Real Time PCR)	X	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 for HIV-1 resistance testing		X															See Section 1.3.3 for additional requirements for participants who have an HIV Infection Confirmation Visit.
<b>Safety Procedures</b>																	
Full physical examination	X																
Height	X							X		X		X					
Weight	X	X	X	X	X	X	X	X	X			X	X				
Symptom-directed physical examination		X	X	X	X	X	X	X	X			X	X				
Vital signs	X	X	X	X	X	X	X	X	X			X	X				Includes pulse, blood pressure, temperature, and respiratory rate.
Review of adverse events	X	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	X		



Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
<b>Laboratory Assessments</b>																	
Hepatitis serology (HBsAb/HBcAb)	X																Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV.
HBsAg	X																
HCV testing	X									X			X				
Syphilis serologic testing	X				X			X		X			X	X			
Rectal swab for GC/CT testing	X				X			X		X			X	X			
Oropharyngeal GC/CT testing	X				X			X		X			X	X			
Urine GC/CT testing	X				X			X		X			X	X			Collect the sample according to the laboratory manual.
Hematology	X	X	X	X	X	X	X	X	X				X	X			
CD4+ T-cell count/Lymphocyte subset panel	X	X	X	X	X	X	X	X	X				X	X			
Chemistry	X	X			X			X		X			X	X			
Creatinine clearance calculation	X	X			X			X		X			X	X			See Appendix 9.
Cystatin-C		X			X			X		X			X	X			

Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
<b>Pharmacokinetics</b>																	
Blood (Plasma) for PK <sup>d</sup>		X	X		X						X	X	X				<p><b>Not applicable for Part 3.</b></p> <p>See Section 8.6.1 and <a href="#">Table 13</a></p> <p>The sample must be collected irrespective of the planned PK collection schedule, if a participant has a positive Point-of-Care HIV test at a visit.</p>
Blood (Plasma) for Investigational PK <sup>e</sup>					X												<p><b>Not applicable for Part 3.</b></p> <p>During Part 1, investigational PK samples will be collected predose at Month 2 and at any time during the visit at Months 9, 15, and 21. During Part 2, investigational PK samples can be collected at any time during the visit.</p> <p>See Section 8.6.2 and <a href="#">Table 13</a>. Samples will be stored and triggered for analysis by Sponsor, if needed</p>



Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.
Dried blood for PK <sup>d</sup>		X	X	X	X			X			X	X	X				<p><b>Not applicable for Part 3.</b></p> <p>See Section 8.6.3 and <a href="#">Table 13</a>.</p> <p>The sample must be collected irrespective of the planned PK collection schedule, if a participant has a positive Point-of-Care HIV test at a visit.</p>
<b>Biomarkers</b>																	
Blood for genetic analysis		X															See Section 8.8.1
Whole blood for FBR		X															Optional participation, requires FBR consent/assent.

Study Period	Double-blind Intervention Period (Part 1) PrEP Therapy With FTC/TDF or FTC/TAF (Part 2 and Part 3)													Follow-up		Notes	
	1	2	3	4	5	6	7	8	Recurring Visits	14	20	26	32	33	34		
Scheduled Day/Month	Screening (N/A during Part 2 and Part 3)	Day 1 (N/A During Part 2 and Part 3)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>b</sup>	(Addnl Assessments) Every 3 Months <sup>c</sup>	(Addnl Assessments) Month 12	(Addnl Assessments) Month 18	Month 24	Month 30	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.

Addnl=additional; DNA=deoxyribonucleic acid; FBR=Future Biomedical Research; FTC/TAF=emtricitabine/tenofovir alafenamide; 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; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; N/A=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PRO=participant-reported outcome; RNA=ribonucleic acid.

<sup>a</sup> Screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.

<sup>b</sup> **Assessments noted in this column will be repeated every month from Month 7 through Month 30 (Visits 9 through 32).** Note: The Month 24 (Visit 26) and Month 30 (Visit 32) monthly assessments are listed in stand-alone columns.

<sup>c</sup> **Additional assessments noted in this column will be repeated every 3 months through Month 30 – 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), and Month 30 (Visit 32). Note: The Month 24 (Visit 26) and Month 30 (Visit 32) every 3 month assessments are listed in stand-alone columns.

<sup>d</sup> **Additional timepoints for Blood (Plasma) and Dried Blood PK collection:** Month 12 (Visit 14), Month 18 (Visit 20), and Month 24 (Visit 26). PK samples will not be collected in Part 3.

<sup>e</sup> **Additional timepoints for Blood (Plasma) for Investigational PK collection:** Month 9 (Visit 11), Month 15 (Visit 17), and Month 21 (Visit 23). PK samples will not be collected in Part 3.

<sup>f</sup> After March 2023, study intervention will not be dispensed via the IRT system and scheduled study visits, including the follow-up phone calls, will not be registered in the IRT system (exceptions to this need to be discussed and agreed upon by the Sponsor).

### 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 from Study Intervention	Early Withdrawal from Study	
Visit Window	N/A	N/A	
<b>Administrative Procedures</b>			
Register study visit in IRT	X	X	No study intervention will be dispensed.
Concomitant medication review	X	X	
HIV Risk Reduction	X	X	Completion of the Sexual Activity Form; offer condoms, lubricants, and HIV risk reduction counseling.
PRO: HIV-infection Risk	X	X	
PRO: Preference	X	X	Not applicable for Part 3.
<b>Efficacy Procedures</b>			
Point-of-Care HIV 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 at every visit 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.
<b>Safety Procedures</b>			
Symptom-directed physical examination	X	X	
Weight	X	X	
Vital signs	X	X	Includes pulse, blood pressure, temperature, and respiratory rate.
Review of adverse events	X	X	

Study Period	Early Discontinuation from Study Intervention		Notes
Visit Number	Unscheduled Visits		
Scheduled Day/Week	Early Discontinuation from Study Intervention	Early Withdrawal from Study	
Visit Window	N/A	N/A	
Review of social harm events	X	X	
<b>Laboratory Assessments</b>			
Hematology	X	X	
CD4+ T-cell count/Lymphocyte subset panel	X	X	
Chemistry	X	X	
Creatinine clearance calculation	X	X	See Appendix 9.
Cystatin-C	X	X	
<b>Pharmacokinetics</b>			
Blood (Plasma) for PK	X	X	<b>Not applicable for Part 3.</b>  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.
Dried blood for PK	X	X	<b>Not applicable for Part 3.</b>  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.

<b>Study Period</b>	<b>Early Discontinuation from Study Intervention</b>		<b>Notes</b>
<b>Visit Number</b>	<b>Unscheduled Visits</b>		
<b>Scheduled Day/Week</b>	Early Discontinuation from Study Intervention	Early Withdrawal from Study	
<b>Visit Window</b>	N/A	N/A	
<p>HIV=human immunodeficiency virus; IRT=Interactive Response Technology; N/A=Not applicable; PCR=polymerase chain reaction; PRO=participant-reported outcome; RNA=ribonucleic acid.</p> <p>For details on the Early Discontinuation of Study Intervention visit, see Section 8.11.3.</p> <p>For details on the Early Withdrawal from Study visit, see Section 8.11.4.</p>			



### 1.3.3 Schedule of Activities – Participants Who Have A Positive HIV-1 Test

Study Period	Follow-up After Seroconversion				Notes
Visit Number	Unscheduled	Varies <sup>a</sup>			
Scheduled Day	HIV-1 Infection Confirmation	Follow-up Monthly Visits	Post-Study Intervention Follow-up Phone Call <sup>b</sup>		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	
<b>Administrative Procedures</b>					
Register study visit in IRT	X	X	X	X	Part 1, no study intervention will be dispensed. Part 2 and Part 3, participant should stop taking FTC/TDF or FTC/TAF while further testing is conducted.
Link to HIV Treatment Services	X				Upon confirmation of HIV-1 infection.
Concomitant medication review	X	X	X	X	Including ART regimens.
HIV Risk Reduction	X	X			Completion of the Sexual Activity Form, offer condoms, lubricants, and HIV risk reduction counseling.
<b>Efficacy Procedures</b>					
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-1 Infection Confirmation visit.
<b>Safety Procedures</b>					
Symptom-directed physical examination	X				

Study Period	Follow-up After Seroconversion				Notes
	Unscheduled	Varies <sup>a</sup>			
Visit Number	HIV-1 Infection Confirmation	Follow-up Monthly Visits	Post-Study Intervention Follow-up Phone Call <sup>b</sup>		
Scheduled Day					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.
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/Lymphocyte subset panel	X	X			
Chemistry	X				
<b>Pharmacokinetics</b>					
Blood (Plasma) for PK	X	X			<b>Not applicable for Part 3.</b>  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.
Dried Blood for PK	X	X			<b>Not applicable for Part 3.</b>  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 <sup>a</sup>			
Scheduled Day	HIV-1 Infection Confirmation	Follow-up Monthly Visits	Post-Study Intervention Follow-up Phone Call <sup>b</sup>		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.
<b>Biomarkers</b>					
Whole blood for FBR	X				Optional participation, requires FBR consent/assent.
<p>ART=antiretroviral therapy; FBR=Future Biomedical Research; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PRO=participant-reported outcome; RNA=ribonucleic acid.</p> <p><sup>a</sup> 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 30 visit (ie, participants will not be in the study for &gt;30 months).</p> <p><sup>b</sup> 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 FTC/TDF or FTC/TAF.</p>					

## 2 INTRODUCTION

ISL (also known as MK-8591) is a novel, 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-1 acquisition are urgently needed.

One proven biomedical intervention for the prevention of HIV-1 infection is PrEP. In late 2015, the WHO-recommended PrEP as an additional prevention option for people who are HIV-negative and at substantial risk for HIV [World Health Organization 2015]. 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 daily FTC/TDF is, however, suboptimal in many people at risk for HIV-1 infection [Marrazzo, J. M., et al 2015] [Hojilla, J. C., et al 2018]. An additional PrEP option, DESCOVY™ (emtricitabine/tenofovir alafenamide [FTC/TAF], Gilead) has been approved for use in certain populations in the United States, though it still requires daily dosing.

Globally, the risk of acquiring HIV is 26 times higher among MSM than among all adult men [Joint United Nations Programme on HIV/AIDS 2020] and novel strategies to prevent HIV acquisition in this population are urgently needed. Gay men and other MSM accounted for an estimated 17% of new HIV infections globally, including more than half of new HIV infections in western and central Europe, and North America; 40% in Latin America; 30% in Asia and the Pacific; 22% in the Caribbean; 22% in eastern Europe and central Asia; 18% in the Middle East and North Africa; and 17% in western and central Africa [Joint United Nations Programme on HIV/AIDS 2019]. Further, the risk of acquiring HIV is 13 times higher for transgender people [Joint United Nations Programme on HIV/AIDS 2020], defined as those whose gender identities and/or expressions differ from the sex assigned to them at birth. In terms of prevalence, TGW are approximately 49 times more likely to be living with HIV than other adults of reproductive age with an estimated worldwide HIV prevalence of 19%; in some countries the HIV prevalence rate in TGW is 80 times that of the general adult population [World Health Organization 2020].

Gay, bisexual, and other MSM are the population most affected by HIV in the US [Centers for Disease Control and Prevention 2020]. In 2018, adult and adolescent gay and bisexual men made up 69% (26,305) of the 37,968 new HIV diagnoses in the US and dependent areas [Centers for Disease Control and Prevention 2020]. In the US, the problem is particularly concentrated among African American MSM. Black/African American gay, bisexual, and other MSM are more affected by HIV than any other group in the US [Centers for Disease Control and Prevention 2020]. In 2018, black/African American gay and bisexual men

accounted for 26% (9,756) of the 37,832 new HIV diagnoses and 37% of new diagnoses among all gay and bisexual men in the US and dependent areas. In the US, >50% of new HIV diagnoses in the US were in the South and 69% of new HIV diagnoses were in black/African American and Hispanic/Latino MSM [Centers for Disease Control and Prevention 2018].

Adolescents and young people also represent a growing share of people living with HIV globally. In 2019 alone, 460,000 young people between the ages of 10 to 24 were newly infected with HIV, of whom 170,000 were adolescents between the ages of 10 and 19. Adolescents account for about 5% of all people living with HIV and about 10% of new adult HIV infections [United Nations Children's Fund 2020].

Although use and awareness of HIV PrEP in the MSM population have increased in the US, further improvements are needed [Finlayson, T., et al 2019]. In particular, uptake in the use of daily, oral PrEP in the black/African American MSM population has been significantly lower than in other at-risk groups [Ezennia, O., et al 2019]. Cisgender MSM and TGW have an ongoing unmet medical need for alternatives to FTC/TDF and FTC/TAF QD for PrEP, particularly from a long-term safety perspective and to expand options for alternative dosing regimens.

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. ISL has the potential to be an effective agent for HIV-1 PrEP due to its long half-life and favorable tolerability 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 in cisgender MSM and TGW who are at high risk for HIV-1 infection, ultimately leading to greater effectiveness for HIV-1 prevention than what is currently observed with FTC/TDF or FTC/TAF QD. Such a simplified regimen may also be of particular benefit to adolescents who typically have challenges with adherence.

### **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 therapy with FTC/TDF or FTC/TAF and undergoing the same study procedures regardless of original assignment, continued blinding is 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, that 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

Products containing emtricitabine and tenofovir are 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 MSM, 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.

FTC/TAF was approved for PrEP in high risk adults (excluding individuals at risk from receptive vaginal sex) in 2019 in the US.

FTC/TDF and FTC/TAF will be administered at the approved marketed dose. Refer to approved labeling for detailed information on FTC/TDF and FTC/TAF. See Appendix 7 for dosing instructions for Japan.

In this study, participants receiving FTC/TDF will be administered either TRUVADA™ or a generic product (emtricitabine/tenofovir disoproxil). The tenofovir disoproxil component of the generic product contains a different salt form (phosphate) compared to 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-8591A 017) and 8.5% (MK-8591A 018) in the DOR/ISL groups, and mean decreases from baseline of CD4+ T-cell counts at Week 48 were approximately 60 cells/mm<sup>3</sup> 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-1 PrEP has not yet been shown 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 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 or FTC/TAF. 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 or FTC/TAF.

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

### 3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The hypothesis is 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 cisgender MSM and TGW  $\geq 16$  years of age who are at high risk for HIV-1 infection.

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> <li>To evaluate the efficacy of oral ISL QM in reducing the incidence per year of HIV-1 infection relative to the background rate.</li> </ul> <p><b>Hypothesis:</b> ISL QM reduces the incidence rate of confirmed HIV-1 infections compared to the background incidence rate.</p>	<ul style="list-style-type: none"> <li>Confirmed HIV-1 infection</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of oral ISL QM compared to FTC/TDF or FTC/TAF QD as assessed by review of the accumulated safety data.</li> </ul>	<ul style="list-style-type: none"> <li>Adverse events</li> <li>Adverse events leading to discontinuation of study intervention</li> </ul>
Secondary	
<ul style="list-style-type: none"> <li>To compare the incidence rate per year of confirmed HIV-1 infections following administration of ISL QM and FTC/TDF or FTC/TAF QD.</li> </ul>	<ul style="list-style-type: none"> <li>Confirmed HIV-1 infection</li> </ul>
Tertiary/Exploratory	
<ul style="list-style-type: none"> <li>To evaluate preferences for QM vs QD dosing.</li> </ul>	<ul style="list-style-type: none"> <li>Response for dosing preference</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the pharmacokinetics of ISL QM.</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacokinetic parameters</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate rates and patterns of adherence to FTC/TDF QD, FTC/TAF QD, and ISL QM.</li> </ul>	<ul style="list-style-type: none"> <li>Pharmacokinetic-adherence relationship</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the impact of ISL QM on renal function compared to FTC/TDF or FTC/TAF QD as measured by the change from baseline in renal biomarkers at Weeks 24 and 48.</li> </ul>	<ul style="list-style-type: none"> <li>Renal biomarkers</li> </ul>

Objectives	Endpoints
<ul style="list-style-type: none"> <li>To evaluate the impact of ISL QM on weight and body mass index compared to FTC/TDF or FTC/TAF QD as measured by the change from baseline at Weeks 24 and 48.</li> </ul>	<ul style="list-style-type: none"> <li>Weight and body mass index</li> </ul>
<ul style="list-style-type: none"> <li>To assess viral drug resistance in participants who seroconvert to HIV-1.</li> </ul>	<ul style="list-style-type: none"> <li>Viral resistance-associated substitutions</li> </ul>
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Germline genetic variation and association to clinical data collected in this study.</li> </ul>

## 4 STUDY DESIGN

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

Study assessments conducted prior to 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 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 or FTC/TAF 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, double-blind, double-dummy study to evaluate the efficacy and safety of oral ISL QM as PrEP in cisgender MSM and TGW  $\geq 16$  years of age who have sex with men and who are at high risk of HIV-1 infection. The active comparator in this study will be based on local standard of care and will be either FTC/TDF or FTC/TAF QD, as selected by the investigator prior to randomization.

Approximately 1500 cisgender MSM and TGW uninfected with HIV-1 will be randomized in a 2:1 ratio to 1 of 2 intervention groups, the ISL QM group or the FTC/TDF or FTC/TAF

QD group. Randomization will be stratified by geographic region/race. The duration of participation will be approximately 2.5 years and has the following enrollment targets:

- Approximately 50% of the global study population will be <30 years of age
- Approximately 50% of participants in the US will be black/African American OR Hispanic or Latino

The first approximately 150 enrolled participants  $\geq 18$  years of age will be identified as the Sentinel Cohort. An IA (Sentinel Cohort IA) will be conducted by an external unblinded statistician 3 months after the last participant in the Sentinel Cohort has initiated study intervention. All available data for all participants enrolled by that time will be submitted to an independent eDMC for a safety evaluation. Enrollment will continue, but be capped at no more than 375 participants until safety and tolerability have been assessed. Upon completion of the Sentinel Cohort IA and review of IA results by the eDMC, enrollment for participants 16 or 17 years of age can begin.

An additional blinded IA will be conducted by the Sponsor when approximately 1000 individuals have been screened for the purpose of sample size re-estimation. The goal of this IA is to assess the estimated background incidence rate of HIV-1 infection and the screen failure rate, and to determine the need of sample size adjustment to ensure adequate power to meet the success criteria for the primary endpoint.

Samples for efficacy assessments will be collected at all monthly visits from participants receiving study intervention (Section 1.3.1). The primary efficacy and safety analysis will be performed after:

- All participants have either reached Week 48 or have discontinued prior to Week 48  
and
- 50% of participants have either reached Week 96 or have discontinued prior to Week 96.

Any participants with confirmed HIV infection will be discontinued from study intervention and 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.

Safety assessments will include all accumulated safety data until the end of the 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 the eDMC through review of accumulating safety and efficacy data at regular intervals throughout study duration.

## Part 2

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

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 or FTC/TAF 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, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

## 4.2 Scientific Rationale for Study Design

### Part 1

This study is designed to demonstrate the superiority of oral ISL QM compared to the background HIV-1 incidence rate as PrEP in MSM and TGW. The study design represents an efficient study design and is deemed appropriate to provide safety and efficacy data in cisgender males and TGW at high risk for HIV-1 infection to demonstrate oral ISL QM as an effective option for HIV-1 PrEP in this population [Murray, J. 2019].

A traditional NI design for evaluation of a new PrEP modality in this population would require an unfeasibly large study population [Murray, J. 2019]. The anticipated reduction in infection is dependent on the investigational agent, and for studies of FTC/TDF (or FTC/TAF) in men, there is little reason to expect an improvement in efficacy; recent studies demonstrated incidence rates of 0.16 infections per 100 person-years with the use of FTC/TAF and noninferiority to FTC/TDF [Mayer, K. H., et al 2020] and incidence rates of 0.41 infections per 100 person-years with the use of cabotegravir (administered via intramuscular injections) and superiority to FTC/TDF [Landovitz, R. J., et al 2020].

Depending on assumptions made, classic NI designs could potentially require up to hundreds of events to demonstrate NI [Murray, J. 2019] [Cutrell, A., et al 2017].

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 used to estimate the background incidence of HIV-1 infection from the same site areas/time period. The primary method will calculate HIV-1 incidence based on use of a recency assay (assessment of recent infection biomarkers) in the population at the Screening visit and prior to randomization in this study [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. This method will be used to estimate the background rate for the comparison in the primary objective. A second method will use local data on new HIV-1 diagnoses to estimate incidence. These data will be referenced as external benchmarks to contextualize the study data and characterize the natural history of HIV-1 acquisition in the population at large versus the enrolled population.

Because of the long intracellular half-life of the pharmacologically active TP (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.

Participants will be randomized in a 2:1 ratio to the ISL QM group OR FTC/TDF or FTC/TAF QD group to ensure maximum exposure to ISL and still allow for comparison between the ISL QM group and the FTC/TDF or FTC/TAF QD group.

## **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 was stopped in this study, and all participants have been switched to PrEP therapy with FTC/TDF or FTC/TAF. 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-1 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 10.

Frequent testing for HIV 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 SoA (Section 1.3). AEs 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-1 PrEP in the lives of individuals who are receiving 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-1 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-1 PrEP medication (not applicable in Part 3). The HIV infection risk questionnaire will have 15 items that 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 Laboratory and Weight Markers**

The study will compare mean changes in laboratory and weight markers from baseline in the intervention groups to evaluate the impact of ISL on the following:

##### **Renal Function**

Studies have shown that impaired kidney function (usually mild or moderate) may occur in a small proportion of people on FTC/TDF for PrEP, especially if they have other risk factors [Tetteh, R. A., et al 2017]. This study provides the opportunity to evaluate the impact of ISL on renal functions as measured by creatinine, cystatin-C, and creatinine clearance.

## **Weight**

Compared with other antiretroviral classes, use of integrase inhibitors as well as tenofovir alafenamide in patients with HIV-1 has been associated with greater increases in body weight [Hill, A., et al 2019] [Venter, W. D. F., et al 2019]. This study provides the opportunity to evaluate the impact of ISL on body weight and BMI.

### **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 (either from FTC/TDF or FTC/TAF) will be measured and analyzed (in a subset of study participants), as needed and may be used for exploratory study intervention adherence assessments.

### **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 on 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 and FTC/TAF have been shown 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 oral ISL QM to placebo, the primary safety objective of this study will be to evaluate the safety and tolerability of oral ISL QM compared to FTC/TDF or FTC/TAF QD for the prevention of HIV-1 infection. The comparison of efficacy of oral ISL QM to FTC/TDF or FTC/TAF is a secondary objective.

FTC/TDF is approved in many countries as PrEP and is currently standard of care for individuals at high risk for HIV-1 infection. In the US, FTC/TAF is used as PrEP in at risk adults and adolescents weighing at least 35 kg to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex [Tanner, M. R., et al 2020].

Matching placebo will be used in the ISL and FTC/TDF or FTC/TAF 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 or FTC/TAF has been stopped; all participants were switched to PrEP therapy with FTC/TDF or FTC/TAF.

##### **Part 3**

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



### 4.2.3 Rationale for Estimating Background HIV-1 Incidence Rate

The primary objective of this study is 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-1 incidence: direct observation of HIV-1 incidence through longitudinal follow-up of persons at risk for new HIV-1 infection, indirect measurement of HIV-1 incidence using data on HIV-1 prevalence in a defined population (such as women attending antenatal clinics), and estimates of HIV-1 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 over-estimation of the HIV incidence rate [Gonese, E., et al 2020]. In contrast, Recent Infection Testing Algorithms combining 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-1 incidence rate in this study.

#### 4.2.4 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 1 type of behavior inversely associated with risk of acquiring HIV. There are many other behaviors that have been identified as 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 Collecting Race and Ethnicity Data

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

It is also important to look at PROs, specifically preference, by race and ethnicity. Despite having higher incidences of HIV infection, black and Hispanic/Latino MSM are less likely to use HIV PrEP than white MSM [Goedel, W. C., et al 2018]. In addition, despite the increased risk of acquiring HIV, TGW are an underserved population in terms of HIV prevention [Marquez, S. 2016]. Analyzing preference data by ethnicity and race, may help to determine if differences in PrEP use are associated with racial and ethnic differences in preference.

### 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 as 0.05 pmol/10<sup>6</sup> cells in PBMCs to prevent HIV-1 infection. This conservative threshold is approximately 5-fold above the in vitro IC<sub>50</sub> (≈ 0.00974 pmol/10<sup>6</sup> cells) of ISL-TP against wild-type HIV-1 virus

and 2-fold above the EC<sub>90</sub> ( $\approx 0.024$  pmol/10<sup>6</sup> cells) in rhesus macaques [Grobler, J., et al 2019]. See the IB for additional details.

In the Phase 1 proof-of-concept clinical study (MK-8591 Protocol 003) with treatment-naïve participants infected with HIV-1, a single dose of ISL as low as 0.5 mg resulted in plasma HIV-1 RNA reduction of median 1.26 log<sub>10</sub> 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<sub>168h</sub> was 0.116 pmol/10<sup>6</sup> cells, with the lowest concentration associated with antiviral efficacy at 0.0513 pmol/10<sup>6</sup> cells. This lowest observed ISL-TP concentration was associated with >1 log viral load reduction from baseline. Thus, the geometric mean ISL-TP C<sub>168h</sub> concentration is approximately 12-fold above the in vitro IC<sub>50</sub> 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  $\geq 0.43$  mg/kg and highly protective (92%) at 0.1 mg/kg, a dose that corresponds to ISL-TP EC<sub>90</sub> of  $\approx 0.024$  pmol/10<sup>6</sup> cells. Thus, this EC<sub>90</sub> ISL-TP concentration is approximately 2-fold above the in vitro ISL-TP IC<sub>50</sub> of wild-type HIV-1.

In comparison, the prophylactic TFV-DP EC<sub>90</sub> associated with 90% risk reduction in rhesus macaques is 0.023 pmol/10<sup>6</sup> 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<sup>6</sup> cells [Massud, I., et al 2018]. This efficacious exposure is approximately ~3-fold above the in vitro TFV-DP IC<sub>50</sub> 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 MSM, the estimated TFV-DP-EC<sub>90</sub> was 0.016 pmol/10<sup>6</sup> 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<sub>50</sub> 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<sup>6</sup> 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<sup>6</sup> 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 results from earlier MK-8591 Phase 1 and other Phase 2 studies. In MK-8591 Protocol 016 IA, the PrEP PK exposure threshold of 0.05 pmol/10<sup>6</sup> 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<sup>6</sup> cells, which is ~136-fold above the in vitro ISL-TP IC<sub>50</sub> against wild-type HIV-1 and ~26-fold above the prespecified PK threshold of 0.05 pmol/10<sup>6</sup> cells in PBMCs, respectively. The ISL 60 mg QM simulations predict that at steady-state the lower 2.5<sup>th</sup> percentile of the 95% prediction interval is ~0.17 pmol/10<sup>6</sup> cells in PBMCs. Thus, observations from MK-8591 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.

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 MK-8591 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 sufficient and adequate systemic threshold that will be efficacious for 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 EEA, the local start of the study in the EEA is defined as 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 the Sentinel Cohort IA 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.

Male participants and TGW who are at high risk for 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 result 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. Is sexually active with male (assigned male sex at birth) or transgender female partners defined as having anal sexual intercourse with a man or TGW at least once in the past month.
3. Is at high risk for sexually acquiring HIV-1 infection based on self-report of at least 1 of the following:
  - Condomless receptive anal intercourse in the 6 months prior to screening occurring outside a mutually monogamous HIV seronegative concordant relationship
  - More than 5 partners (anal intercourse) in the 6 months prior to screening (regardless of condom use and HIV serostatus, as reported by the enrollee)
  - Any unprescribed stimulant drug use in the 6 months prior to screening
  - Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months prior to screening

### Demographics

4. Is cisgender male or transgender female (assigned male sex at birth), and  $\geq 16$  years of age at the time of providing informed consent/assent.

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

### Informed Consent/Assent

5. 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

6. Has no plans to relocate or travel away from the site for  $\geq 4$  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 component 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. Has known 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 evidence of 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 anal cancers.
5. Has a history or current evidence of any condition (including active tuberculosis infection), therapy, laboratory abnormality or other circumstance (including drug or alcohol abuse 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).
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 FTC/TDF or FTC/TAF for PrEP at screening may continue their regimen until 1 day prior to Day 1.*

- *Note: Any prior or current HIV-1 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 or prevention 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 in the study occurred  $\geq 30$  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	$\leq 750$ cells/mm <sup>3</sup>
Alkaline phosphatase	$> 3 \times$ ULN
ALT	$> 3 \times$ ULN
AST	$> 3 \times$ ULN
Total bilirubin	$\geq 2.5 \times$ ULN
Calculated CrCl	$< 60$ mL/min <sup>a</sup> based on the Cockcroft-Gault equation (use sex at birth for calculation; Appendix 9)
CD4+ T-cell count	$< 400$ cells/mm <sup>3</sup>
Hemoglobin	$< 10.0$ g/dL
Lymphocyte count	$< 650$ cells/mm <sup>3</sup>
Platelet count	$< 100,000$ /mm <sup>3</sup>
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; ULN=upper limit of normal. <sup>a</sup> 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.	



### **5.3 Lifestyle Considerations**

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

### **5.4 Screen Failures**

Screen failures are defined as participants who consent/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 Day 1 through Month 24	Test Product	IMP	Provided centrally by the Sponsor
Part 1 ISL QM group	Experimental	Placebo to FTC/TDF or placebo to FTC/TAF	Drug	Tablet	0 mg	0 mg	Oral	QD Day 1 through Month 24	Placebo	IMP	Provided centrally by the Sponsor
Part 1 FTC/TDF or FTC/TAF QD group	Active Comparator	FTC/TDF or FTC/TAF	Drug	Tablet	200/245 mg or 200/25 mg	200/245 mg or 200/25 mg	Oral	QD Day 1 through Month 24	Test Product	IMP	Provided centrally by the Sponsor
Part 1 FTC/TDF or FTC/TAF QD group	Active Comparator	Placebo to ISL	Drug	Tablet	0 mg	0 mg	Oral	QM Day 1 through Month 24	Placebo	IMP	Provided centrally by the Sponsor
Part 2 All Participants	Active Comparator	FTC/TDF or FTC/TAF	Drug	Tablet	200/245 mg or 200/25 mg	200/245 mg or 200/25 mg	Oral	QD in Part 2	Test Product	IMP	Provided centrally by the Sponsor
Part 3 All Participants	Active Comparator	FTC/TDF or FTC/TAF	Drug	Tablet	200/245 mg or 200/25 mg	200/245 mg or 200/25 mg	Oral	QD in Part 3	Test Product	IMP	Provided centrally by the Sponsor

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
<p>EEA =European Economic Area; FTC/TAF=emtricitabine/tenofovir alafenamide; 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; PrEP=preexposure prophylaxis; QD=once daily; QM=once monthly.</p> <p>FTC/TAF is only available in the United States for use as PrEP. If, during the course of the study, FTC/TAF is approved for use as PrEP in other countries, assignment is contingent upon availability of drug supply.</p> <p>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).</p> <p>FTC/TDF or FTC/TAF may also be locally sourced.</p> <p>For specific sourcing requirements in Japan, see Section 10.7.1.</p> <p>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.</p>											

All supplies indicated in [Table 2](#), [Table 3](#), and [Table 4](#) will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number 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 2:1 ratio to either ISL QM and placebo to FTC/TDF or FTC/TAF QD OR FTC/TDF or FTC/TAF QD and placebo to ISL QM, respectively.

#### **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 or FTC/TAF.

#### **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 or FTC/TAF.

### **6.3.2 Stratification**

#### **Part 1**

Intervention randomization will be stratified according to the following factor:

Geographic region/race:

- US (black/African American)
- US (nonblack/non-African American)
- Africa
- Other

Geographic region is included as a stratification factor due to regional differences in linkages to care, likelihood of sexual partners knowing HIV-1 status (infection or viral suppression), and the burden of untreated HIV-1 infection in sexual partners. Risk may also vary by race within the US [Centers for Disease Control and Prevention 2020]. Stratification 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 and FTC/TAF will be packaged identically relative 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 drug concentration data and information relevant for population PK modeling (eg, including, but not limited to PK sampling schedules, dosing records, etc.) may be requested. No clinical efficacy and safety data will be unblinded. No personnel directly associated with study conduct will be unblinded before database lock. Before granting select personnel access to unblinded PK and relevant 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 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 participants intervention group. HIV-1 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 or FTC/TAF. 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 FTC/TAF or matching placebo to their visits. At each visit, the site personnel will count the number of tablets of FTC/TDF or FTC/TAF 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  $\geq 1$  monthly dose OR, for daily dosing,  $\geq 7$  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 or FTC/TAF. At each visit, site personnel will review the participant's FTC/TDF or FTC/TAF 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 or FTC/TAF. At each visit, site personnel will review the participant's FTC/TDF or FTC/TAF 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 the 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 FTC/TDF or FTC/TAF for PrEP at screening may continue their regimen until 1 day prior to Day 1.*
- *Part 2: All participants have been switched to PrEP therapy with FTC/TDF or FTC/TAF.*
- Any nonstudy investigational agents (including devices)
- 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 or FTC/TAF

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 and therapeutics 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 (Escalation/Titration/Other)**

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.

### **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."

#### **DESCOVY™**

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 DESCOVY™ 200 mg/25 mg (emtricitabine/tenofovir alafenamide) as much as possible. You did not receive the active drug DESCOVY™ 200 mg/25 mg (emtricitabine/tenofovir alafenamide) 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 emtricitabine/tenofovir disoproxil 200 mg/245 mg as much as possible. You did not receive the active drug 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 TRUVADA™ 200 mg/245 mg (emtricitabine/tenofovir disoproxil) as much as possible. You did not receive the active drug 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 prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 8.11.3.

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

A participant must be discontinued from study intervention but continue to be monitored per Section 8.11.3 for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- 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 post-study 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 or FTC/TAF) 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 is life-threatening or results in prolonged hospitalization.
- The participant has 2 consecutive DAIDS Grade 3 (<500 cells/mm<sup>3</sup>) or higher grade of lymphocyte count and/or 2 consecutive DAIDS Grade 3 (<200 cells/mm<sup>3</sup>) 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 the participant 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 or FTC/TAF, 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 or FTC/TAF 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 or FTC/TAF 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 medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent/assent 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 909 mL, with approximately 45 to 49 mL each for any unscheduled visits for HIV-1 confirmation, early discontinuation of study intervention, or early withdrawal from the study (Table 14).

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

#### **8.1.2 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 the 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 prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

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

### **8.1.6.1 Treatment Eligibility Assessment Form**

A TEA form is included in this study to document the investigator assessment of participant suitability for potential treatment with FTC/TDF or FTC/TAF and the rationale. These data may be required to support reimbursement efforts for ISL QM .

The investigator must complete this form and provide rationale to document the choice of FTC/TDF or FTC/TAF prior to randomization.

## **8.1.7 Assignment of Treatment/Randomization Number**

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

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

## **8.1.8 Study Intervention Administration**

### **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).

The first dose of study intervention should begin on the day of randomization.

### **Part 2 and Part 3**

Participants will receive PrEP therapy with FTC/TDF or FTC/TAF 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 1.3.1). The first dose of FTC/TDF or FTC/TAF or their matching placebos will be administered at the study site on Day 1. Subsequent dosing of FTC/TDF or FTC/TAF or their matching placebos will be performed once daily by the participant (ie, unsupervised at his home) at approximately the same time each day.

Participants should take the monthly dose of ISL or matching placebo within  $\pm 7$  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.

If a participant misses a dose of FTC/TDF or FTC/TAF or their matching placebos, guidance in the approved label should be followed.

##### **Part 2 and Part 3**

Participants will receive PrEP therapy with FTC/TDF or FTC/TAF. 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 or FTC/TAF, guidance in the approved label should be followed.



### **8.1.8.2 Interruption of Study Intervention**

The site should encourage participants to remain compliant with the protocol-specified treatment plan. Participants who intentionally or inadvertently interrupt study intervention, without withdrawing consent/assent to participate in the study should not be discontinued from the study.

Interruptions from the protocol-specified treatment plan due to an AE 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 prior to 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 8.11.3.

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

#### **8.1.9.1 Withdrawal From Future Biomedical Research**

Participants may withdraw their consent/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 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.

### **8.1.12 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.

### **8.1.13 Participant-reported Outcomes**

Site staff will administer 2 questionnaires to participants at visits per the SoA (Section 1.3). 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.

## **8.2 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 10).

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-1 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 “Post-Study 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 post-study 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 (Section 1.3) 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 procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study, including approximate blood volumes drawn by visit and by sample type per participant, can be found in 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.

#### **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 Sexually Transmitted Infections**

Testing for GC/CT and syphilis will be performed at study visits as described in the SoA (Section 1.3.1). 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.

### 8.3.4 Clinical Safety Laboratory Assessments

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

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

### 8.3.5 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 their families 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 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.

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	<b><u>Reporting Time Period:</u></b> Consent to Randomization/ Allocation	<b><u>Reporting Time Period:</u></b> Randomization/ Allocation through Protocol-specified Follow-up Period	<b><u>Reporting Time Period:</u></b> After the Protocol- specified Follow- up Period	<b>Time Frame to Report Event and Follow-up Information to Sponsor:</b>
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)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

Information in this section is not applicable since participants are cisgender male or transgender female (assigned male sex at birth) and partner pregnancy/lactation information is not required.

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

This section is not applicable to the 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 lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*

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

2. A lymphocyte count that meets DAIDS criteria for Grade 3 (<500 cells/mm<sup>3</sup>) 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<sup>3</sup>) 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 FTC/TAF or matching placebo on any single calendar day.

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

#### 8.6 Pharmacokinetics

*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 13](#). The exact time of dosing of study intervention prior to the sample collection and the time of PK sample collection will be recorded on the appropriate source documentation.

Table 4 Collection of Plasma PK Samples

Study Visit (Day/Month)	Time Relative to Dose <sup>a,b</sup>
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 predose
Month 24	One sample to be collected at any time during the visit

<sup>a</sup> Indicates time relative to monthly oral tablet administration. Not applicable in Part 2.

<sup>b</sup> During Part 2, plasma 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 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, and 21. For Part 2, investigational PK sample collection is irrespective of timing of dose.

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 the 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 13](#).

Table 5 Collection of Dried Blood PK Samples

Study Visit (Day/Month)	Time Relative to Dose <sup>a,b</sup>
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 predose
Month 24	One sample to be collected at any time during the visit

<sup>a</sup> Indicates time relative to monthly oral tablet administration. Not applicable in Part 2.

<sup>b</sup> During Part 2, dried blood 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 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 the next 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, 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. 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 instructions for planned genetic analysis samples will be 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 (Table 12; 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**

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 last HIV test will be collected, if known.

## Rescreening

If the screening window has been exceeded, after approval from the Sponsor, participants are allowed to rescreen 1 time. Once a participant has started the rescreening process, a new screening period (ie, an additional  $\leq 45$ -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 consent 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 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 all discontinuations, including participants who discontinue study intervention due to decreased lymphocyte or CD4+ T-cell counts, the participant should complete an Early Discontinuation from Study Intervention 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.

#### 8.11.4 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 from Study Intervention visit (Section 1.3.2), the Early Withdrawal from Study visit is not required.

#### 8.11.5 Follow-up Phone Calls

Participants who complete the protocol-specified intervention period or who discontinue study intervention due to seroconversion will be contacted via phone call at 14 days and 42 days post the 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 for the blinded treatment period for applicable safety endpoints, and for the entire duration of the study to evaluate 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 or FTC/TAF. 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 or FTC/TAF. 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 recovery of total lymphocyte counts. All safety data will be summarized descriptively.*

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

<b>Study Design Overview</b>	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 Men and Transgender Women Who Have Sex With Men, and Are at High Risk for HIV-1 Infection
<b>Treatment Assignment</b>	A total of ~1500 participants will be randomized in a 2:1 ratio to receive either ISL QM and placebo matched to FTC/TDF or FTC/TAF QD, OR FTC/TDF or FTC/TAF QD and placebo matched to ISL QM. The randomization will be stratified by region/race.
<b>Analysis Populations</b>	Efficacy: mFAS Safety: APaT
<b>Primary Endpoint(s)</b>	1. Confirmed HIV-1 infection 2. AEs and AEs leading to discontinuation of study intervention
<b>Statistical Methods for Key Efficacy Analyses</b>	The primary objective will be assessed 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 [Gao, F., et al 2020]. The background incidence rate will be estimated in the screened population using the Kassanjee methodology [Kassanjee, R., et al 2012]. The statistical criteria for success require the point estimate of the relative risk of the incidence rate of confirmed HIV-1 infections in the ISL QM group compared to the background incidence rate to be at most 0.5 and the upper bound of the 95% CI for the relative risk to be less than 0.8.

<p><b>Statistical Methods for Key Safety Analyses</b></p>	<p>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 or FTC/TAF QD).</p>
<p><b>Interim Analyses</b></p>	<p>The following interim analyses are planned. An external unblinded statistician will provide results to be reviewed by the eDMC.</p> <ul style="list-style-type: none"> <li>• Sentinel Cohort IA: This will be performed 3 months after the last participant in the Sentinel Cohort has initiated study intervention. All available data for all participants enrolled by that time will be reviewed.</li> <li>• Continuous safety and efficacy monitoring throughout the study: Accumulating safety and efficacy data at regular intervals throughout the study duration will be reviewed.</li> </ul> <p>An additional blinded IA will be conducted by the Sponsor when approximately 1000 individuals have been screened in the study for the purpose of sample size re-estimation. The goal of this IA is to assess the estimated background incidence rate and the screen failure rate, and to determine the need of increasing the sample size to ensure that the study will have at least 90% power to meet the success criteria for the primary objective.</p>
<p><b>Multiplicity</b></p>	<p>No multiplicity adjustment is planned.</p>
<p><b>Sample Size and Power</b></p>	<p>Approximately 1500 participants will be randomized in a 2:1 ratio to either the ISL QM or FTC/TDF or FTC/TAF QD groups. With 1000 participants in the ISL QM group and assuming ISL QM has 87.5% efficacy, the average participant time in the study is 1.5 years and the lost-to-follow-up/study discontinuation rate is 15% per year, there is &gt;90% power to meet the success criteria for the primary objective for background incidence rates ranging from 3% to 4%.</p>

**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 group.*

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

This study will be conducted as a double-blind study under in-house blinding procedures. 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 Endpoint**

*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 population 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 with 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 intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the intervention group to which they are randomized. Participants who take incorrect study

intervention for the entire intervention 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 Analysis

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

The primary efficacy objective will be assessed in terms of relative risk by comparing the incidence rate per year of confirmed HIV-1 infections in the ISL QM group to the background incidence rate. The primary hypothesis can be written as the following:

$$H_0: R \geq 0.8 \text{ vs } H_1: R < 0.8$$

R is the relative risk of becoming HIV-1 infected in the ISL QM group compared to the population not taking any PrEP, defined as the ratio of the incidence rate per year of confirmed HIV-1 infections in the ISL QM group  $\lambda_1$  to the background incidence rate  $\lambda_0$ .

$$R = \lambda_1 / \lambda_0$$

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

The incidence rate per year of confirmed HIV-1 infections in the ISL QM group  $\lambda_1$  will be estimated by:

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

The background incidence rate  $\lambda_0$  will be estimated in the screened population using the methodology proposed by Kassanjee [Kassanjee, R., et al 2012]:

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

Where,

- $n_R$  is the number of individuals in the screened population with HIV-1 infection and who are identified as recent infections,
- $n_+$  is the number of individuals in the screened population with HIV-1 infection,
- $n_S$  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,
- $\tau$  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  $n_R$ , an individual is considered to be recently infected if all of the following criteria [Kassanjee, R., et al 2016] [Duong, Y. T., et al 2019] are met:

- The individual is HIV-1 seropositive at screening AND
- The normalized optical density (ODn) results from the Maxim HIV-1 LAg-Avidity enzyme immunoassay are  $\leq 1.5$  AND
- The individual has HIV-1 RNA viral load with  $\geq 1,000$  copies/mL

In addition, individuals 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 MDRI (and FRR) reported for the dominant subtypes at the various geographic locations, with the weighting based on the proportion of individuals screened at the different sites. The estimated MDRI (and FRR) and their associated variances will be obtained from published reports for the

subtypes using recency tests based on LAg-Avidity [Kassanje, R., et al 2014] [Duong, Y. T., et al 2015].

The point estimate of the relative risk will be calculated as

$$\hat{R} = \hat{\lambda}_1 / \hat{\lambda}_0$$

The primary hypothesis that the relative risk  $R < 0.8$  will be tested by computing the 95% CI of  $R$ , denoted as  $(R_L, R_U)$ . Success will be declared for the primary objective if the point estimate of the relative risk  $\hat{R} \leq 0.5$  and the upper bound of the 95% CI of the relative risk  $R_U < 0.8$ . The 95% CI will be constructed as follows:

$$R_U = \frac{\hat{\lambda}_1}{\hat{\lambda}_0} \exp\left(Z_{0.975} \sqrt{\hat{V}_1 + \hat{V}_0}\right)$$
$$R_L = \frac{\hat{\lambda}_1}{\hat{\lambda}_0} \exp\left(-Z_{0.975} \sqrt{\hat{V}_1 + \hat{V}_0}\right)$$

where  $\hat{V}_1$  and  $\hat{V}_0$  are the estimated variance of  $\log \hat{\lambda}_1$  and  $\log \hat{\lambda}_0$ , respectively [Gao, F., et al 2020].

The key secondary objective to compare the incidence rate of confirmed HIV-1 infections following administration of ISL QM and either FTC/TDF or FTC/TAF QD will be assessed by a 95% CI of the difference of the incidence rate of confirmed HIV-1 infections in the ISL QM group compared to the FTC/TDF or FTC/TAF QD group. The CI will be constructed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] based on the Poisson distribution. Success for the key secondary objective will be declared if the upper bound of the 95% CI is less than 0.8 per 100 person-years.

Imputation methods will not be used to replace missing data for HIV-1 infection and data will be used as observed.

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

## 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 6), 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 6.

Safety parameters or AEs 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 intervention group exhibit the event. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and safety parameters that meet PDLCS. In addition to individual events that occur in at least 1% in any intervention 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 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 intervention group for Tier 3 safety parameters.

Tier 2 endpoints also include the change from baseline in renal biomarkers, body weight, and BMI 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 intervention 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 they fall outside of 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, JUL-2017, version 2.1 (Appendix 3). A listing of the participants who meet the criteria will also be provided.

A descriptive presentation of the safety endpoints for ISL QM vs each of FTC/TDF QD and FTC/TAF QD 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.

Table 6 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Difference	Descriptive Statistics
Tier 2	<ul style="list-style-type: none"> <li>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</li> <li>The percentage of participants with specific AEs (preferred terms), SOCs, or PDLCS<sup>a</sup> occurring in <math>\geq 1\%</math> of participants in either intervention group</li> <li>Change from baseline in body weight and BMI</li> <li>Change from baseline in renal biomarkers</li> </ul>	X	X
Tier 3	<ul style="list-style-type: none"> <li>The percentage of participants with specific AEs (preferred terms), SOCs, or PDLCS<sup>a</sup> occurring in <math>&lt; 1\%</math> of participants in both intervention groups</li> </ul>		X
AE=adverse event; BMI=body mass index; CI=confidence interval; PDLCS=predefined limit of change; SAE=serious adverse event; SOC=System Organ Class; X=results will be provided. <sup>a</sup> 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 interim 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 has initiated study intervention. All available data for all participants enrolled by that time will be evaluated for safety at this interim analysis.

An additional blinded IA will be conducted by the Sponsor when approximately 1000 individuals have been screened in the study for the purpose of sample size re-estimation. The goal of this IA is to assess the estimated background incidence rate and the screen failure rate, and to determine the need of increasing the sample size to ensure that the study will have at least 90% power to meet the success criteria for the primary objective. The sample size can be increased up to 3000. The background incidence rate will be estimated using the Kassanjee method as described in Section 9.6.1. [Table 7](#) presents the possible sample size adjustments based on the blinded review of the estimated background incidence rate and the screen failure rate. [Table 8](#) in Section 9.9.1 displays the power to meet the primary objective as a reference for the sample size re-estimation. Any changes resulting from this analysis will be shared and discussed with the eDMC.

Table 7 Sample Size Adjustments Based on Interim Blinded Review of Background Incidence Rate of HIV-1 Infections

Screen Failure Rate	Background Incidence Rate of HIV-1 Infections	Total Sample Size (2:1 Randomization Ratio of ISL QM vs Active Control)	Power to Meet the Primary Objective
30%	4.0%	1500	99%
	3.5%	1500	98%
	3.0%	1500	95%
	2.5%	1800	94%
	2.0%	2100	90%
10%	4.0%	1500	98%
	3.5%	1500	95%
	3.0%	1500	91%
	2.5%	1800	90%
	2.0%	2550	92%

HIV=human immunodeficiency virus; ISL=islatravir (also known as MK-8591); QM=once monthly.

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.

## 9.8 Multiplicity

No multiplicity adjustment is planned for this study.

## 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 1500 participants will be randomized in a 2:1 ratio to either the ISL QM group or the active control (FTC/TDF or FTC/TAF) QD group. With 1000 participants in the ISL QM group, there is 90% power to meet the success criteria for the primary objective for background incidence rates ranging from 3% to 4%. The power calculation is based on the following assumptions:

- ISL QM has 87.5% efficacy



- Average participant time is 1.5 years
- Lost-to-follow-up/study discontinuation rate is 15% per year
- Screen failure rate is 30%
- HIV-1 subtypes in the screened population comprises of: 60% Type B, 22% Type C, 15% Type A/E, 3% Type A or D
- Weighted averages of prevalence, MDRI, FRR, and associated standard errors are calculated based on the proportions of each subtype expected to be screened [Grebe, E., et al 2019] [Gao, F., et al 2020]

Incidence rates of >3% have been reported among MSM in the US [Mera, R., et al 2019], South Africa [Lane, T., et al 2016], and Thailand [Centers for Disease Control and Prevention 2013]. The assumption regarding ISL QM efficacy is a conservative estimate based on a rhesus macaque SHIV intrarectal challenge model [Markowitz, M., et al 2019] in which 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 study discontinuation rate is consistent with HIV Prevention Trials Network 083 study [Landovitz, R. J., et al 2020] and allows for challenges in retention (eg, COVID-19 pandemic).

For background incidence rates <3%, the study power is less than 90% under the above assumptions. Also, if the screen failure rate is lower than the assumed 30%, the smaller number of screened individuals will lead to a decrease in power. As described in Section 9.7, the sample size may be increased based on the IA assessment of estimated background incidence rate and screen failure rate. [Table 8](#) displays the study power under various assumptions including background incidence rates ranging from 2% to 4%, screen failure rates of 30% and 10%, and under different total sample sizes of 1500, 1800, 2100, 2550, and 3000.

Table 8 Study Power With Various Sample Sizes Under Various Background Incidence Rates of HIV-1 Infection and Screen Failure Rates

Screen Failure Rate	Background Incidence Rate of HIV-1 Infections	Power with Various Total Sample Size (2:1 Randomization Ratio of ISL QM vs Active Control)				
		1500	1800	2100	2550	3000
30%	2.0%	77%	86%	90%	95%	98%
	2.5%	89%	94%	96%	98%	99%
	3.0%	95%	97%	99%	>99%	>99%
	3.5%	98%	99%	>99%	>99%	>99%
	4.0%	99%	>99%	>99%	>99%	>99%
10%	2.0%	72%	81%	87%	92%	95%
	2.5%	84%	90%	94%	97%	99%
	3.0%	91%	95%	98%	99%	>99%
	3.5%	95%	98%	99%	>99%	>99%
	4.0%	98%	99%	>99%	>99%	>99%

HIV=human immunodeficiency virus; ISL=islatravir (also known as MK-8591); QM=once monthly.  
 Power is calculated based on the success criteria that the upper bound of the 95% CI of the relative risk (ISL:background incidence rate) <0.8 and the point estimate of the relative risk is ≤0.5.  
 Estimated via simulations with 100,000 iterations.

Table 9 displays the power to meet the key secondary objective under various background incidence rates of HIV-1 infections for different sample sizes. The assumptions for the power calculations include: efficacy of 87.5% and 75% for ISL QM and active control, respectively, the same assumed average participant time and lost to follow-up rate as for the primary objective.

Table 9 Power to Meet the Secondary Objective With Various Sample Sizes Under Various Background Incidence Rates of Confirmed HIV-1 Infections

	<b>Power with Various Total Sample Size (2:1 Randomization Ratio of ISL QM vs Active Control)</b>				
<b>Background Incidence Rate</b>	<b>1500</b>	<b>1800</b>	<b>2100</b>	<b>2550</b>	<b>3000</b>
2.0%	93%	97%	99%	>99%	>99%
2.5%	91%	96%	98%	99%	>99%
3.0%	90%	95%	97%	99%	>99%
3.5%	89%	94%	97%	99%	>99%
4.0%	88%	94%	97%	99%	99%

HIV=human immunodeficiency virus; ISL=islatravir (also known as MK-8591); QM=once monthly.  
 Power is calculated based on the success criterion that the upper bound of the 95% CI of the risk difference < 0.8 per 100 person-years.  
 Estimated via simulations with 100,000 iterations.

### 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 a 63.2% chance of observing at least 1 AE among 1000 participants in the ISL group. If no AE of that type is observed among the 1000 participants in the ISL group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <0.37% (1 of every 270 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 the ISL group are provided in [Table 10](#). These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 10 Percentage of Participants With AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants With AEs (in the ISL QM Group With 1000 Participants)

Hypothetical Numbers of Participants With AE	Percentage	95% Upper Confidence Bound <sup>a</sup> (ISL QM group)
0	0.0%	0.4%
20	2%	3.1%
50	5%	6.5%
100	10%	12.0%
150	15%	17.3%

AE=adverse event; CI=confidence interval; ISL=islatravir (also known as MK-8591); QM=once monthly.  
<sup>a</sup> 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 ( $\alpha=0.05$  all in the upper tail).

Table 11 demonstrates the difference in the percentage of participants with an AE (ISL QM group minus FTC/TDF or FTC/TAF QD group) that can be ruled out with different power levels and 95% confidence when there are 1000 participants in the ISL QM group and 500 in the FTC/TDF or FTC/TAF QD group. The underlying percentage of participants with the AE is assumed to be the same for the 2 intervention groups. For example, for a reasonably common AE, which occurs in 20% of participants in both groups, the study has 80% power to declare with 95% confidence that the true difference between the intervention groups is no more than 6.4 percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 11 Difference in Percentage of Participants With AEs (ISL QM Group Minus FTC/TDF or FTC/TAF QD Group) That can be Ruled Out With 1000 Participants in the ISL QM Group and 500 Participants in the FTC/TDF or FTC/TAF QD Group

Target Power	Underlying Percentage of Participants with AE			
	1%	5%	10%	20%
80	2.1%	3.8%	5%	6.4%
85	2.3%	4.1%	5.4%	6.9%
90	2.5%	4.6%	5.9%	7.5%

AE=adverse event; CI=confidence interval; FTC/TAF=emtricitabine/tenofovir alafenamide; FTC/TDF=emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions); ISL=islatravir (also known as MK-8591); 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 the percentage of participants with AEs (ISL QM group minus FTC/TDF QD or FTC/TAF QD group) 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; <30, ≥30 years)
- Geographic regions (US, Africa, Other)
- Race (black, not black)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Circumcised (yes, no)
- Risk group (MSM, TGW)

## 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 will be recorded upon in-clinic dosing of ISL QM at each monthly visit. For each participant in the FTC/TDF or FTC/TAF QD 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 non-Sponsor 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 incident HIV-1 infection for the purposes of confirmation. Specific details regarding composition, responsibilities, and governance, including the roles of the various members and the Sponsor protocol team will be described in the Adjudication charter. 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.

#### **10.1.5 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](http://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 12](#) will be processed by a local/regional laboratory in Africa or by the central laboratory in all other countries participating in the study.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered 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 12 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters
<b>Hematology</b>	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 Granulocytes (% , abs)
	WBC Differential, Lymphocytes (% , abs)
WBC Differential, Monocytes (% , abs)	
WBC Differential, Neutrophils, Total (% , abs)	

Laboratory Assessments	Parameters
<b>CD4+ T-cell count/Lymphocyte subset panel</b>	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
	<b>Chemistry</b>
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	

Laboratory Assessments	Parameters
	Magnesium (Mg)
	Phosphorous
	Potassium (K)
	Protein, Total
	Sodium (Na)
	Triglycerides
	Urea Nitrogen, Blood (BUN)
	Uric Acid
<b>Hepatitis screen (Screening)</b>	Hepatitis B virus surface antigen (HBsAg)
	Hepatitis B Serology (HBsAb/HBcAb)
	Hepatitis C virus (HCV) antibody
	Plasma Hepatitis C virus PCR quantitative test (performed if Hepatitis C virus antibody is positive)
<b>Virology</b>	Point-of-Care HIV 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
<b>Sexually Transmitted Infection (STI) Testing</b>	Rectal swab <i>Neisseria gonorrhoeae</i> (GC)/ <i>Chlamydia trachomatis</i> (CT) testing
	Oropharyngeal GC/CT testing
	Nucleic acid amplification from urine for GC/CT
	Syphilis serologic testing (rapid plasma regain [RPR], RPR with titer, <i>Treponema pallidum</i> IgG, <i>Treponema pallidum</i> IgG index value)
<b>Pharmacokinetic (PK) Testing</b>	Blood (Plasma) for PK
	Dried blood for PK
	Blood (Plasma) for Investigational PK
<b>Biomarkers</b>	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-1 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 13 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	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	
Blood (Plasma) for PK	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 at a visit.
Blood (Plasma) for Investigational PK			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, and 21. During Part 2, investigational PK samples can be collected at any time during the visit. Samples will be stored and triggered for analysis by Sponsor, if needed.
Dried Blood for PK	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 at a visit.

Table 14 Blood Volumes

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

Study Period	Screen	Study Intervention														HIV-1 Infection Confirmation	Early Discontinuation of Study Intervention	Early Withdrawal from Study		
		1	2	3	4	5	6	7	8	Recurring Visits			14	20	26				32	
Scheduled Day/Month	Screening	Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>a</sup>	(Additional Assessments) Every 3 Months <sup>b</sup>	(Additional Assessments) Every 6 Months <sup>c</sup>	(Additional Assessments) Month 12	(Additional Assessments) Month 18	Month 24	Month 30	Totals	Unscheduled	Unscheduled	Unscheduled	
HCV/HBV/HIV (Serology)	9.5											9.5		9.5		28.5				
Syphilis Serologic Testing	4				4			4		24				4	4	44				
Hematology	6	6	6	6	6	6	6	6	132					6	6	192	6	6	6	
CD4+ T-cell count/Lymphocyte subset panel	6	6	6	6	6	6	6	6	132					6	6	192	6	6	6	
Chemistry	5	5			5			5		30				5	5	60	5	5	5	
Cystatin-C		3.5			3.5			3.5		21				3.5	3.5	38.5		3.5	3.5	
Point-of-Care HIV Testing <sup>d</sup>	Additional volume not applicable																			
HIV-1/HIV-2 Antibody/Antigen Testing	Off HCV/ HBV/ HIV	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	77			Off HCV/ HBV/ HIV		Off HCV/ HBV/ HIV	3.5	105	3.5	3.5	3.5
Plasma HIV RNA (Real Time PCR)	6	6	6	6	6	6	6	6	132					6	6	192	6	6	6	
HIV-1 Drug Resistance Testing		3														3	15 (135) <sup>e</sup>	12	12	
HIV Recency Assay	4	4														8				

Study Period	Screen		Study Intervention														HIV-1 Infection Confirmation	Early Discontinuation of Study Intervention	Early Withdrawal from Study
	1	2	3	4	5	6	7	8	Recurring Visits			14	20	26	32				
Scheduled Day/Month	Screening	Day 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Every Month <sup>a</sup>	(Additional Assessments) Every 3 Months <sup>b</sup>	(Additional Assessments) Every 6 Months <sup>c</sup>	(Additional Assessments) Month 12	(Additional Assessments) Month 18	Month 24	Month 30	Totals	Unscheduled	Unscheduled	Unscheduled
Blood (Plasma) for PK		3	3		3			3				3	3	3		21	3	3	3
Blood (Plasma) for Investigational PK				3						9						12			
Dried Blood for PK		from PK tube	from PK tube	from PK tube	from 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		
<b>Total Blood Volume per Visit in mL<sup>f</sup></b>	40.5	52.5	24.5	24.5	37.0	21.5	21.5	37.0	473	75	9	12.5	3	43.0	34	908.5	48.5 (168.5) <sup>e</sup>	45.0	45.0

DNA=deoxyribonucleic acid; FBR=Future Biomedical Research; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HCV=hepatitis C virus; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid.

Note: All volumes are provided in mL. HIV-1/HIV-2 Antibody/Antigen Testing may be conducted using sample collected for HCV/HBV/HIV testing (“off HCV/HBV/HIV”) as indicated. Samples for PK may be used for dried blood testing for PK as indicated.

<sup>a</sup> Samples are collected at every monthly visit up to Month 30 (22 visits for those who complete the study).

<sup>b</sup> Samples are collected every 3 months up to Month 30 (6 additional visits for those who complete the study).

<sup>c</sup> Samples are collected every 6 months up to Month 24 (3 additional visits for those who complete the study).

<sup>d</sup> Negligible blood volume amount as sample is collected from another tube or finger stick.

<sup>e</sup> 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 8 additional visit collections).

<sup>f</sup> Blood volumes are calculated based on volume requirements at Central lab (US) and Regional lab (Africa). In cases where different volume requirements between the Central and Regional laboratories exist, the higher of the 2 volumes is used. Slight variances may occur if a local lab is used.

### **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 [National Institute of Allergy and Infectious Diseases 2017]. 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**

This section is not applicable.

## **10.5 Appendix 5: Contraceptive Guidance**

This section is not applicable.

## 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.<sup>1</sup>
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.<sup>2</sup>
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.<sup>2</sup>
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research<sup>3,4</sup>

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<sup>3,4</sup>

#### 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<sup>3,4</sup>**

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<sup>3,4</sup>

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<sup>3,4</sup>

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<sup>3,4</sup>

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<sup>3,4</sup>**

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<sup>3,4</sup>**

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<sup>3,4</sup>**

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<sup>3,4</sup>**

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](mailto:clinical.specimen.management@MSD.com).

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## **10.7 Appendix 7: Country-specific Requirements**

### **10.7.1 Country-specific Request for Japan**

Although not approved in Japan for PrEP, FTC/TDF was administered as an active comparator at a dose per product label in Part 1.

In a letter to the study communication via Dear Investigator Letter dated 13-DEC-2021, it was announced that dosing of investigational product for all participants is to be stopped and that all participants will be offered open-label PrEP therapy with daily FTC/TDF. This decision is stipulated based on ethical consideration and safety and wellbeing of study population who are at high risk for HIV-1 infection, as abrupt interruption of treatment exposes participants to risk of infection. As FTC/TDF is not yet approved in Japan for PrEP indication nor are there any alternative approved medication that participants have access to, open-label FTC/TDF will be offered to study participants as part of this study protocol. Open-label FTC/TDF used in Part 2 and Part 3 is categorized as "product(s) used in the clinical trial other than test product(s)" in Japan local regulation.

### **10.7.2 Country-specific Request for France**

In France, only participants  $\geq 18$  years of age at the time of providing informed consent can be enrolled.

## 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 <sub>168h</sub>	concentration at 168 hours postdose
CAC	Clinical Adjudication Committee
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
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 <sub>90</sub>	90% effective concentration
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
EEA	European Economic Area
EFV	efavirenz
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic participant-reported outcomes
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FRR	false-recent rate

Abbreviation	Expanded Term
FSR	first site ready
FTC/TAF	emtricitabine/tenofovir alafenamide
FTC/TDF	emtricitabine/tenofovir disoproxil (including TRUVADA™ and all generic versions)
GCP	Good Clinical Practice
GC/CT	<i>Neisseria gonorrhoeae/Chlamydia trachomatis</i>
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IB	Investigator Brochure
IA(s)	interim analysis(es)
IC <sub>50</sub>	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
IND	Investigational New Drug
INR	international normalized ratio
iPrEx	Preexposure Prophylaxis Initiative
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir (also known as MK-8591)
LAg	limiting antigen
MDRI	mean duration of recent infections
mFAS	modified full analysis set
MSM	men who have sex with men
NI	noninferiority
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OD <sub>n</sub>	normalized optical density
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PDLC	predefined limit of change
PEP	postexposure prophylaxis
PEPFAR	President's Emergency Plan for AIDS Relief
PK	pharmacokinetic(s)
PrEP	preexposure prophylaxis
PRO	participant-reported outcome
QD	once daily
QM	once monthly

<b>Abbreviation</b>	<b>Expanded Term</b>
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
TEA	Treatment Eligibility Assessment
TFV	tenofovir
TGW	transgender woman/women
TP	triphosphate
US	United States
USPSTF	United States Preventive Services Task Force
VAMS	volumetric absorptive microsampling
VL	viral load
WHO	World Health Organization

## 10.9 Appendix 9: Calculation of Creatinine Clearance

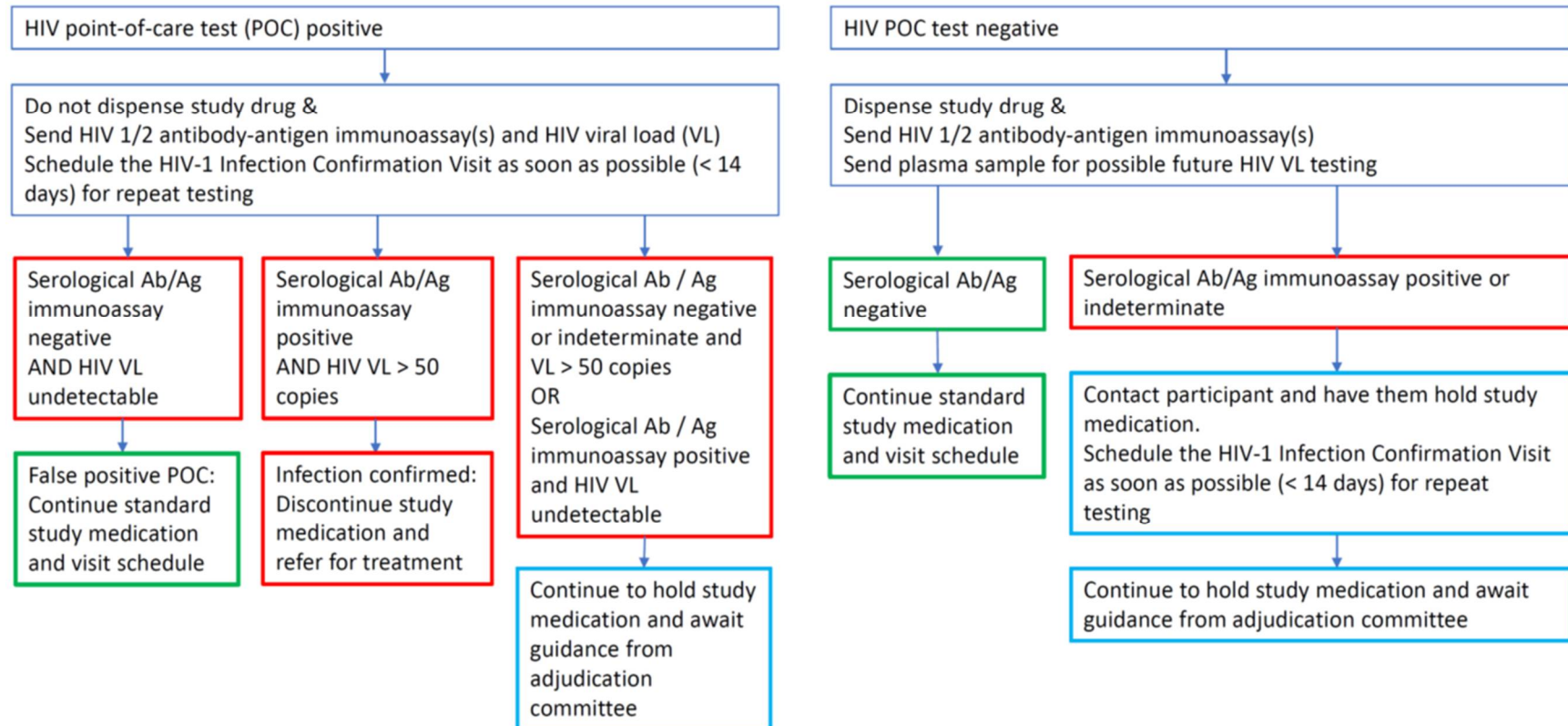
**Cockcroft-Gault** equation (for male participants):

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



### 10.10 Appendix 10: MK-8591 PrEP Program HIV Testing Algorithm

# MK-8591 PrEP: Assessment and Confirmation of HIV-1



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

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