Official Protocol Title:	A Phase 2b, Randomized, Active-Controlled, Double-Blind, Dose-Ranging Clinical Study to Evaluate a Switch to Islatravir (ISL) and MK-8507 Once-Weekly in Adults with HIV-1 Virologically Suppressed on Bictegravir/ Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) Once-Daily
NCT Number:	NCT04564547
Document Date:	20-Oct-2022

Title Page

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Protocol Title: A Phase 2b, Randomized, Active-Controlled, Double-Blind, Dose-Ranging Clinical Study to Evaluate a Switch to Islatravir (ISL) and MK-8507 Once-Weekly in Adults with HIV-1 Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) Once-Daily

Protocol Number: 013-04

Compound Number: MK-8591

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

EudraCT	2020-003071-18
IND	128,595

Approval Date: 20 October 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	20-OCT-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Additionally, the protocol was amended to clarify analysis visits during the unblinded safety monitoring and long-term unblinded safety monitoring periods to be relative to the last dose of study treatment.
Amendment 03	01-MAR-2022	The protocol was amended to expand lymphocyte analysis to include B-cells and NK cells (TBNK panel), to update the recovery to baseline criteria for total lymphocyte and CD4+ T-cell counts, to extend the follow-up period, and to clarify that the only study objective is to evaluate the safety and tolerability of ISL + MK-8507.
Amendment 02	01-DEC-2021	To make updates consistent with recommendations of the eDMC after an ad hoc review of the data; specifically, that all participants stop study intervention and participants receiving ISL + MK-8507 be followed. The study will continue so that participants who received ISL + MK-8507 can be followed for at least 6 months. After 6 months, participants with lymphocyte and CD4+ T-cell counts recovered to within 30% of baseline (Day 1) values for 2 consecutive visits and/or participants whose lymphocyte and CD4+ T-cell counts are stabilized in the opinion of the investigator can discontinue follow-up. Participants that have not met these criteria at 6 months should continue follow-up every 8 weeks for an additional 6 months for lymphocyte and CD4+ T-cell monitoring.
Amendment 01	26-FEB-2021	Country-specific amendment to add an additional study intervention discontinuation criterion that is required for France.
Original Protocol	30-JUL-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address. Additionally, the protocol was amended to clarify analysis visits during the unblinded safety monitoring and long-term unblinded safety monitoring periods to be relative to the last dose of study treatment.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Section 9.6.1.2	Refined “Day Range Rules” for analysis visits after the last dose to be every 4 weeks for the follow-up visits during the unblinded safety monitoring and every 12 weeks for the long-term unblinded safety monitoring period.	To clarify the analysis visits during the unblinded safety monitoring and long-term unblinded safety monitoring periods to be relative to the last dose of study treatment.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b, Randomized, Active-Controlled, Double-Blind, Dose-Ranging Clinical Study to Evaluate a Switch to Islatravir (ISL) and MK-8507 Once-Weekly in Adults with HIV-1 Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) Once-Daily

Short Title: Dose-Ranging, Switch Study of ISL and MK-8507 Once Weekly

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Note: As of Amendment 013-02, formal comparisons between study treatment arms will no longer be conducted; therefore, evaluation of the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 will no longer be considered a primary endpoint. Imaging, PROs, and biomarkers are no longer being collected. The only study objective is to evaluate the safety and tolerability of ISL + MK 8507 once-weekly as assessed by review of the accumulated safety data. Updated analyses are described in Section 9.

In participants ≥18 years of age with HIV-1 who have been virologically suppressed for ≥6 months on BIC/FTC/TAF:

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of ISL + MK-8507 once-weekly as assessed by review of the accumulated safety data.	- Adverse events - Adverse events leading to discontinuation of study intervention
- [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral activity of ISL administered with different doses of MK-8507 once-weekly after switching from BIC/FTC/TAF compared to continued treatment with BIC/FTC/TAF once-daily as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48.	- HIV-1 RNA

Secondary Objectives	Secondary Endpoints
- [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral activity following switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 48: HIV-1 RNA <50 copies/mL HIV-1 RNA <40 copies/mL	- HIV-1 RNA
- [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral activity following switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 24: HIV-1 RNA ≥50 copies/mL HIV-1 RNA <50 copies/mL HIV-1 RNA <40 copies/mL	- HIV-1 RNA
- [No longer an objective as of Amendment 013-02] To evaluate the sustained antiretroviral suppression in participants who switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 96: HIV-1 RNA ≥50 copies/mL HIV-1 RNA <50 copies/mL HIV-1 RNA <40 copies/mL	- HIV-1 RNA
- [No longer an objective as of Amendment 013-02] To evaluate the immunologic effect of switching to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as measured by change from baseline in CD4+ T-cell count at Weeks 24, 48, and 96.	- CD4+ T-cell count

- [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral suppression and immunologic effect of ISL + MK-8507 as assessed by the following at Week 144: Percentage of participants with HIV-1 RNA ≥50 copies/mL Change from baseline in CD4+ T-cell count	- HIV-1 RNA - CD4+ T-cell count
- [No longer an objective as of Amendment 013-02] To evaluate the development of viral drug resistance to any study intervention in participants who switch to ISL + MK-8507 and in participants who continue treatment with BIC/FTC/TAF.	- Viral resistance-associated substitutions

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	HIV-1 infection
Population	Participants ≥18 years of age with HIV-1 who have been virologically suppressed for ≥6 months on BIC/FTC/TAF.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study. **Note: As of Amendment 013-02, all participants have been unblinded and will be switched to non-study ART.**
Type of Control	Active Control **Note: As of Amendment 013-02, all participants have been unblinded, will be switched to non-study ART, and there will not be a control.**
Study Blinding	Double-blind with in-house blinding **Note: As of Amendment 013-02, all participants have been unblinded and will be switched to non-study ART.**

Blinding Roles	Participants or Subjects Investigator Sponsor **Note: As of Amendment 013-02, all participants, investigators, and the Sponsor have been unblinded and participants will be switched to non-study ART.**
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 2 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 140 participants will be randomized. As of Amendment 013-02, enrollment completed with 161 participants randomized into the study.

Intervention Groups and Duration:

Intervention Groups

Note: As of Amendment 013-02, all groups have stopped study intervention administration. All participants remaining in the study will be switched to non-study ART.

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Treatment Period	Use
Group 1 (n=35)	ISL	20 mg	QW	Oral	Parts 1, 2[a], and 3	Experimental
	MK-8507	100 mg	QW	Oral	Part 1	Experimental
	Placebo to MK-8507	0 mg	QW	Oral	Part 1	Placebo
	Placebo to BIC/FTC/TAF	0 mg	QD	Oral	Part 1	Placebo
	MK-8507	TBD	QW	Oral	Parts 2[a] and 3	Experimental
Group 2 (n=35)	ISL	20 mg	QW	Oral	Parts 1, 2[a], and 3	Experimental
	MK-8507	200 mg	QW	Oral	Part 1	Experimental
	Placebo to MK-8507	0 mg	QW	Oral	Part 1	Placebo
	Placebo to BIC/FTC/TAF	0 mg	QD	Oral	Part 1	Placebo
	MK-8507	TBD	QW	Oral	Parts 2[a] and 3	Experimental
Group 3 (n=35)	ISL	20 mg	QW	Oral	Parts 1, 2[a], and 3	Experimental
	MK-8507	400 mg	QW	Oral	Part 1	Experimental
	Placebo to BIC/FTC/TAF	0 mg	QD	Oral	Part 1	Placebo
	MK-8507	TBD	QW	Oral	Parts 2[a] and 3	Experimental
Group 4 (n=35)	Placebo to ISL	0 mg	QW	Oral	Part 1	Placebo
	Placebo to MK-8507	0 mg	QW	Oral	Part 1	Placebo
	BIC/FTC/TAF	50 mg/200 mg/25 mg	QD	Oral	Parts 1 and 2[a]	Experimental
	ISL	20 mg	QW	Oral	Part 3	Experimental
	MK-8507	TBD	QW	Oral	Part 3	Experimental

BIC=bictegravir; FTC=emtricitabine; ISL=islatravir; n=number enrolled in each group; QD=once daily; QW=once weekly; TAF=tenofovir alafenamide; TBD=to be determined based on dose selected in Part 1 of the study.

a. Part 2 will begin after the MK-8507 dose is confirmed based on the Week 48 data from all participants. Once Part 2 is initiated, participants will begin open-label study intervention at their next study visit. Participants who reach their next study visit (eg, Week 60, Week 72, etc.) before Part 2 initiates will continue taking blinded study intervention until their next visit after Part 2 initiation.

Total Number of Intervention Groups/ Arms	**Note: As of Amendment 013-02, all participants will be switched to non-study ART; therefore, there are no intervention groups/arms.** 4
Duration of Participation	**Note: As of Amendment 013-02, all study groups have stopped study intervention administration. All participants remaining in the study will be switched to non-study ART and will be followed for at least 6 months. Participants whose total lymphocyte and CD4+ T-cell counts have not recovered to within 10% of baseline should be followed until the recovery criteria are met.** Each participant will be in the study for approximately 156 weeks from the time the participant signs the Informed Consent Form through the final contact. After a screening period of up to 45 days, each participant will receive blinded study intervention for at least 48 weeks and then open-label study intervention through Week 144. Participants who discontinue study intervention will be followed as described in the protocol.

Study Governance Committees:

Note: As of Amendment 013-02, administration of study intervention for all treatment groups has been stopped based on Sponsor acceptance of the eDMC recommendation; therefore, there is no longer a need to convene these committees.

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Scientific Advisory Committee	Yes
Study governance considerations are outlined in Appendix 1.	

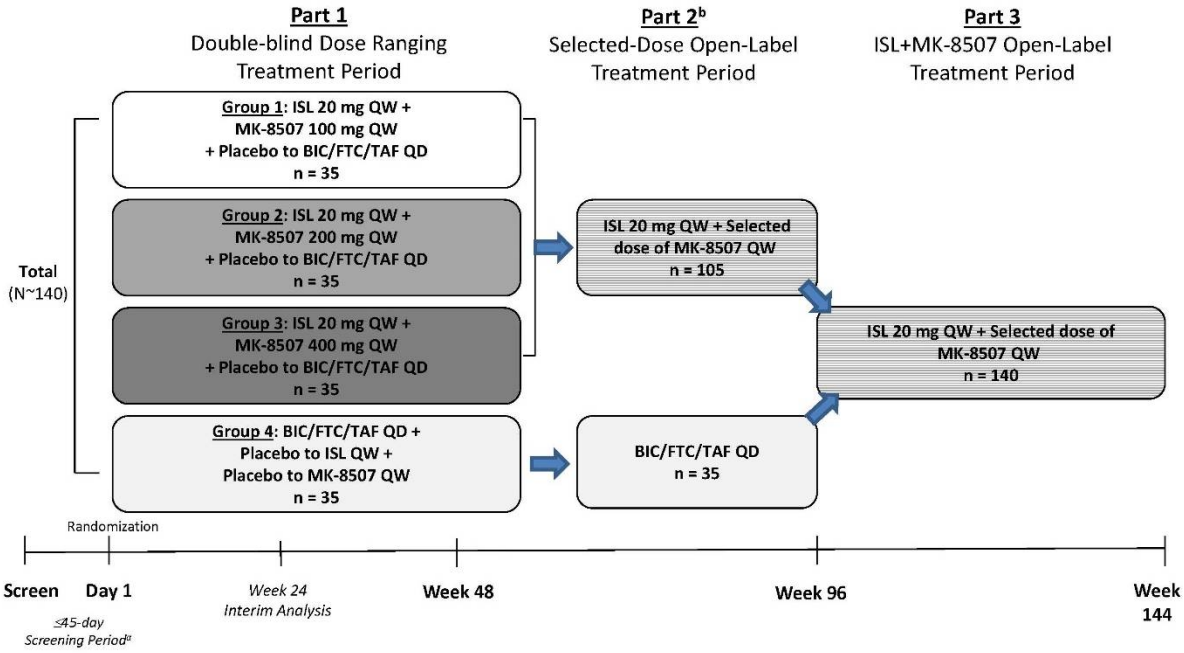
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The original study design is depicted in Figure 1. The revised study design as of Amendment 013-02 is depicted in Figure 2.

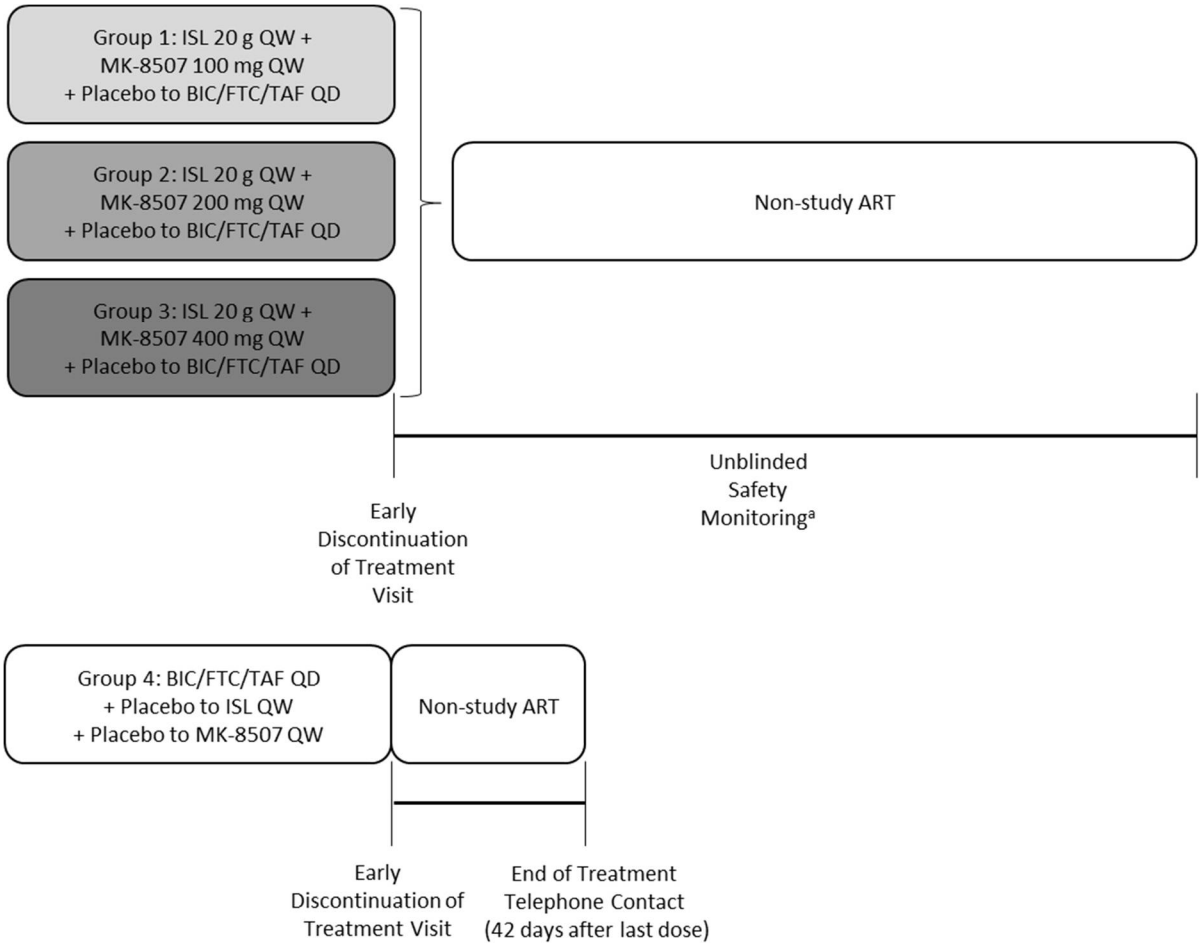
Figure 1 Study Schema and Treatment Plan (Original Study Design)



BIC=bictegravir; FTC=emtricitabine; ISL=islatravir; N=total number of participants in the study; n=total number of participants per group; QD=once daily; QW=once weekly; TAF=tenofovir alafenamide.

a. A screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.
b. Part 2 will begin after the MK-8507 dose is confirmed based on the Week 48 data from all participants. Once Part 2 is initiated, participants will begin open-label study intervention at their next study visit. Participants who reach their next study visit (eg, Week 60, Week 72, etc.) before Part 2 initiates will continue taking blinded study intervention until their next visit after Part 2 initiation.

Figure 2 Unblinded Safety Monitoring Study Schema – Amendments 02 and 03



ART=anti-retroviral therapy; BIC=bictegravir; FTC=emtricitabine; ISL=islatravir; QD=once daily; QW=once weekly; TAF=tenofavir alafenamide.

a. The Unblinded Safety Monitoring period will be 6 months for Groups 1-3 participants and will continue if total lymphocyte and CD4+ T-cell counts have not recovered to within 10% of baseline.

1.3 Schedule of Activities

1.3.1 Schedule of Activities

Note: As of Amendment 013-02, all participants should follow the SoA in Section 1.3.3 and Section 1.3.4.

Study Period:	**Screen**	**Part 1 Double-blind Dose-Ranging`**									**Part 2 Selected Dose Open-label[b]**				**Part 3 ISL + MK-8507 Open-Label**					**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]	13[b]	14[b,c]	15	16	17	18	19	
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 2	Week 4 (Fasting)	Week 8	Week 12	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 100	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Each visit should be calculated from date of Day 1. A visiting nurse may be used for visits after randomization per Section 8.11.2.2. Week 100 is only for participants in Group 4.
Visit Window	≤45 days[a]	NA	± 5 days								± 7 days				± 7 days					
Administrative Procedures																				
Informed Consent	X																			
Informed Consent for Future Biomedical Research	X																			
CCI																				
Inclusion/Exclusion Criteria	X	X																		Review prior to randomization on Day 1 to confirm changes in eligibility
Participant Identification Card	X	X																		At the time of randomization, site personnel will add the randomization number to the participant identification card

Study Period:	**Screen**	**Part 1 Double-blind Dose-Ranging`**									**Part 2 Selected Dose Open-label[b]**				**Part 3 ISL + MK-8507 Open-Label**					**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]	13[b]	14[b,c]	15	16	17	18	19	
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 2	Week 4 (Fasting)	Week 8	Week 12	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 100	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Each visit should be calculated from date of Day 1. A visiting nurse may be used for visits after randomization per Section 8.11.2.2. Week 100 is only for participants in Group 4.
Visit Window	≤45 days[a]	NA	± 5 days								± 7 days				± 7 days					
Medical History	X	X																		
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intervention Randomization		X																		All procedures should be completed prior to dose on Day 1
Dispense study intervention using IRT		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Evaluation to receive continued study intervention																			X	See Section 6.7
Study Intervention Compliance Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Reconcile doses and assess study intervention compliance
Administration of HIVTSQs and HAT-QoL Questionnaires		X												X					X	Administer prior to being seen by investigator and discussions about medical conditions or test results.
Administration of Treatment Preference Questionnaire														X					X	Week 96: Groups 1-3 only.
Administration of HIV Stigma Scale Questionnaire		X																		

Study Period:	**Screen**	**Part 1 Double-blind Dose-Ranging`**									**Part 2 Selected Dose Open-label[b]**				**Part 3 ISL + MK-8507 Open-Label**					**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]	13[b]	14[b,c]	15	16	17	18	19	
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 2	Week 4 (Fasting)	Week 8	Week 12	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 100	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Each visit should be calculated from date of Day 1. A visiting nurse may be used for visits after randomization per Section 8.11.2.2. Week 100 is only for participants in Group 4.
Visit Window	≤45 days[a]	NA	± 5 days								± 7 days				± 7 days					
Efficacy Procedures																				
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CD4+ T-cell Count/TBNK Panel	X	X				X		X	X	X		X		X			X		X	
Plasma for HIV Viral Drug Resistance Testing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Samples will be stored and used if needed
Safety Procedures																				
Full physical examination	X									X				X						
Height		X								X				X					X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Directed Physical Examination		X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse, bp, temp, and rr
12-lead ECG		X						X		X				X					X	
Contraceptive Use Confirmation (WOCBP Only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy Test (hCG; WOCBP only)	X																			
Urine Pregnancy Test (WOCBP only)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Confirm with serum test if urine test is positive

Study Period:	**Screen**	**Part 1 Double-blind Dose-Ranging`**									**Part 2 Selected Dose Open-label[b]**				**Part 3 ISL + MK-8507 Open-Label**					**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]	13[b]	14[b,c]	15	16	17	18	19	
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 2	Week 4 (Fasting)	Week 8	Week 12	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 100	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Each visit should be calculated from date of Day 1. A visiting nurse may be used for visits after randomization per Section 8.11.2.2. Week 100 is only for participants in Group 4.
Visit Window	≤45 days[a]	NA	± 5 days								± 7 days				± 7 days					
HIV-1 & HIV-2 Serology	X																			
Hepatitis Serology	X																			Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV
HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All participants at screening; only anti-HBc positive participants thereafter
HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Fasting is required at Day 1 and Weeks 4, 24, 48, 72, 96, 120, and 144.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting Lipids		X		X				X		X		X		X			X		X	
PT/INR	X																			
Urine fluoride and creatinine		X		X																Based on 4-hour urine collection
Plasma fluoride		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	A bone scan will be performed in participants with plasma fluoride >4.0 µmol/L (>0.076 mg/L) who also experience an AE of bone pain (see Section 8.3.7).
Serum PTH		X						X		X										
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period:	**Screen**	**Part 1 Double-blind Dose-Ranging`**									**Part 2 Selected Dose Open-label[b]**				**Part 3 ISL + MK-8507 Open-Label**					**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]	13[b]	14[b,c]	15	16	17	18	19	
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 2	Week 4 (Fasting)	Week 8	Week 12	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 100	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Each visit should be calculated from date of Day 1. A visiting nurse may be used for visits after randomization per Section 8.11.2.2. Week 100 is only for participants in Group 4.
Visit Window	≤45 days[a]	NA	± 5 days							± 7 days					± 7 days					
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics																				
Blood (Plasma) for ISL and MK-8507 PK		X		X	X	X		X		X		X		X					X	The sample at Day 1, Week 72, Week 96, & Week 144 will be taken predose. A predose & postdose sample will be taken at Weeks 4, 24, & 48. A single sample will be collected at any time at Weeks 8 and 12.
Blood (Plasma) for Investigational PK			X				X		X		X		X				X			Samples will be stored and used if needed.
CCI [redacted]																				
Biomarkers																				
Blood for Genetic Analysis		X																		See Section 8.8

Study Period:	**Screen**	**Part 1 Double-blind Dose-Ranging`**									**Part 2 Selected Dose Open-label[b]**				**Part 3 ISL + MK-8507 Open-Label**					**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]	13[b]	14[b,c]	15	16	17	18	19	
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 2	Week 4 (Fasting)	Week 8	Week 12	Week 16	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72 (Fasting)	Week 84	Week 96 (Fasting)	Week 100	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Each visit should be calculated from date of Day 1. A visiting nurse may be used for visits after randomization per Section 8.11.2.2. Week 100 is only for participants in Group 4.
Visit Window	≤45 days[a]	NA	± 5 days							± 7 days					± 7 days					
Whole Blood for Future Biomedical Research		X						X		X				X					X	Optional participation; requires FBR consent
DEXA Scan (Only Where Permitted by Local Law)		X								X				X					X	Perform after <u>all</u> eligibility criteria are confirmed & within 14 days after Day 1. At Weeks 48, 96, & 144, scans may be performed ± 14 days of the scheduled visit. May require additional planning/scheduling.
Waist and Hip Measurements		X								X				X					X	

AE=adverse event; anti-HBc=Hepatitis B core antibody; bp=blood pressure; CD4+=CD4-positive; DEXA=Dual X-ray Absorptiometry; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FBR=future biomedical research; HAT-QoL=HIV/AIDS-Targeted Quality of Life; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus Type 1; HIV-2=human immunodeficiency virus Type 2; HIVTSQs=HIV Treatment Satisfaction Questionnaire, status version; INR=international normalized ratio; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetics; PT=prothrombin time; PTH=parathyroid hormone; RNA=ribonucleic acid; rr=respiratory rate; TBNK=T- and B- Lymphocyte and Natural Killer Cell; temp=body temperature; WOCBP=a woman/women of childbearing potential.

a. A screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.
b. Part 2 will begin after the MK-8507 dose is confirmed based on the Week 48 data from all participants. Once Part 2 is initiated, participants will begin open-label study intervention at their next study visit. Participants who reach their next study visit (eg, Week 60, Week 72, etc.) before Part 2 initiates will continue taking blinded study intervention until their next visit after Part 2 initiation.
c. Week 96 is the end of Part 2 and the start of Part 3.

1.3.2 Schedule of Activities – Viremia Confirmation, Skeletal Fluorosis, and End of Treatment

Note: As of Amendment 013-02, all participants should follow the SoA in Section 1.3.3 and Section 1.3.4.

Study Period	**Viremia Confirmation**	**Skeletal Fluorosis Evaluation[a]**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Skeletal Fluorosis Evaluation	Early Discontinuation of Treatment	End of Treatment Follow-up	The End of Treatment Follow-up visit should also be performed for participants who will not continue study intervention after Week 144.
Visit Window	Within 2 to 4 Weeks of HIV-1 Viremia (≥50 copies/mL)	NA	NA	42 (+ 7) days after the end of treatment	
Administrative Procedures					
Prior and Concomitant Medications Review	X	X	X	X	
Register Study Visit in IRT	X	X	X		
Study Intervention Compliance Review	X	X	X		Reconcile doses and study intervention compliance.
Administration of HIVTSQs, HAT-QoL, and Treatment Preference Questionnaires			X		Administered prior to being seen by investigator & discussions about medical conditions or test results. Administered to participants who received ≥4 weeks of open-label study intervention
Efficacy Procedures					
Plasma HIV-1 RNA Quantification (Real Time PCR)	X		X	X	
CD4+ T-cell Count/TBNK Panel			X	X	

Study Period	**Viremia Confirmation**	**Skeletal Fluorosis Evaluation[a]**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Skeletal Fluorosis Evaluation	Early Discontinuation of Treatment	End of Treatment Follow-up	The End of Treatment Follow-up visit should also be performed for participants who will not continue study intervention after Week 144.
Visit Window	Within 2 to 4 Weeks of HIV-1 Viremia (≥50 copies/mL)	NA	NA	42 (+ 7) days after the end of treatment	
Plasma for HIV Viral Drug Resistance Testing	X		X	X	If HIV drug resistance sample is collected at Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit. Analysis of samples collected at Early Discontinuation of Treatment or End of Treatment Follow-up visits triggered by Sponsor as needed.
Safety Procedures					
Full Physical Examination		X	X	X	
Vital Signs		X	X	X	Includes weight, pulse, bp, temp, and rr.
Contraceptive Use Confirmation (WOCBP Only)	X	X	X	X	
Serum Pregnancy Test (WOCBP Only)			X	X	
Chemistry			X	X	
Hematology			X	X	
Plasma fluoride		X	X		
Bone Scan		X			See Section 8.3.7
Urinalysis			X	X	
Review of Adverse Events	X	X	X	X	

Study Period	**Viremia Confirmation**	**Skeletal Fluorosis Evaluation[a]**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Skeletal Fluorosis Evaluation	Early Discontinuation of Treatment	End of Treatment Follow-up	The End of Treatment Follow-up visit should also be performed for participants who will not continue study intervention after Week 144.
Visit Window	Within 2 to 4 Weeks of HIV-1 Viremia (≥50 copies/mL)	NA	NA	42 (+ 7) days after the end of treatment	
Pharmacokinetics					
Blood (Plasma) for Investigational PK	X	X	X	X	Samples will be stored and used if needed
Biomarkers					
Whole Blood for Future Biomedical Research	X		X		If FBR sample was collected at Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit.

AE=adverse event; bp=blood pressure; CD4+=CD4-positive; FBR=future biomedical research; HAT-QoL=HIV/AIDS-Targeted Quality of Life; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus Type 1; HIVTSQs=HIV Treatment Satisfaction Questionnaire, status version; IRT=Interactive Response Technology; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; rr=respiratory rate; TBNK=T- and B- Lymphocyte and Natural Killer Cell; temp=body temperature; WOCBP=a woman/women of childbearing potential.

a. Skeletal Fluorosis Evaluation visit to be completed only if participant experiences an AE of bone pain **and** has elevated plasma fluoride >4.0 µmol/L (>0.076 mg/L) (See Section 8.11.5).

1.3.3 Schedule of Activities – Unblinded Safety Monitoring

Study Period	Early Discon of Tx[a]	**Unblinded Safety Monitoring (Groups 1, 2, and 3 Only)[a, b]**													End of Tx Telephone Contact[c] (42 days after last dose)	**Notes**: Each visit should be calculated from date of Day 1[b]. For Groups 1-3, Unblinded Safety Monitoring should continue for ≥6 months after switch to non-study ART or until lab results recover[a].
Visit Number		**7**	**8**	**UNS**		**9**	**UNS**		**10**	**UNS**		**11**	**12**	**13**		
Scheduled Day/Week		WK 20	WK 24	WK 28	WK 32	WK 36	WK 40	WK 44	WK 48	WK 52	WK 56	WK 60	WK 72	WK 84		
Visit Window (Days)[d]	±7 days														+7	
Administrative Procedures																
Informed Consent for Amendment		<----------												---------->		
Study Intervention Compliance Review	X															
Initiate Non-study ART	X															ART recorded on CM eCRF
Register Study Visit in IRT	X															
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Procedures																
Plasma HIV-1 RNA Quantification (RT PCR)	X					X			X			X				
CD4+ T-cell Count/TBNK Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Safety Procedures																
Vital Signs	X															Includes pulse, bp, temp, & rr
Weight	X															
Directed Physical Examination	X					X			X			X		X		Full examination as needed
Chemistry	X					X			X			X		X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X															
HBsAg	X															Only if anti-HBc positive at screening
HBV DNA	X															
Contraceptive Use Confirm (WOCBP only)	X															
Urine Pregnancy Test (WOCBP only)	X					X			X			X		X		If urine +, confirm with serum
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics																
Blood (Plasma) for ISL and MK-8507 PK	X[d]	X	X	X	X	X	X	X	X							Groups 1, 2, & 3 only
CCI [redacted]	X[d]															

ART=anti-retroviral therapy; bp=blood pressure; CM=concomitant medication; DNA=deoxyribonucleic acid; eCRF=electronic case report form; HBc=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV=human immunodeficiency virus; IRT=interactive response technology; ISL=islatravir; PK=pharmacokinetics; RNA=ribonucleic acid; rr=respiratory rate; RT PCR=real time polymerase chain reaction; TBNK=T- and B- Lymphocyte and Natural Killer Cell; temp=body temperature; Tx=treatment; UNS=unscheduled; WK=Week; WOCBP=women of child bearing potential.

Study Period	Early Discon of Tx[a]	**Unblinded Safety Monitoring (Groups 1, 2, and 3 Only)[a, b]**												End of Tx Telephone Contact[c] (42 days after last dose)	**Notes**: Each visit should be calculated from date of Day 1[b]. For Groups 1-3, Unblinded Safety Monitoring should continue for ≥6 months after switch to non-study ART or until lab results recover[a].
Visit Number		**7**	**8**	**UNS**		**9**	**UNS**		**10**	**UNS**		**11**	**12**	**13**	
Scheduled Day/Week		WK 20	WK 24	WK 28	WK 32	WK 36	WK 40	WK 44	WK 48	WK 52	WK 56	WK 60	WK 72	WK 84	
Visit Window (Days)[d]	±7 days														+7

a. As of Amendment 013-02, all participants have been unblinded and brought to the clinic for an Early Discontinuation of Treatment visit so that non-study ART could be initiated. Subsequently, participants in Group 4 will undergo an End of Treatment Telephone Contact 42 days after last dose, whereas participants in Groups 1-3 will undergo at least 6 months of Unblinded Safety Monitoring. Participants in Groups 1-3 are considered to have completed the study if, at or after the 6-month Unblinding Safety Monitoring, the participant has 2 total lymphocyte and 2 CD4+ T-cell counts that have recovered to within 10% of baseline (average between screening and Day 1) that were assessed approximately 12 weeks apart with no more than 1 intervening value that is outside of the 10% margin. Participants who have not met these criteria at 6 months should continue the Unblinded Safety Monitoring follow-up every 12 weeks for total lymphocyte and CD4+ T-cell monitoring.

b. If during the Unblinded Safety Monitoring period, if a participant has a visit within 2 weeks of another visit, it will be at the discretion of the investigator, taking into consideration the current laboratory results, whether the participant should return in 2 weeks or 6 weeks.

c. The End of Treatment Telephone Contact 42 days after last dose is applicable to ALL participants in Group 4, and participants in Groups 1-3 if they have less than 42-days of Unblinded Safety Monitoring.

d. Plasma PK and CCI [redacted] collection should only be performed in participants in Groups 1-3.

1.3.4 Schedule of Activities – Long-term Unblinded Safety Monitoring

Study Period	**Long-term Unblinded Safety Monitoring (Groups 1, 2, and 3 Only)[a]**	**Notes**: Each visit should be calculated from date of Day 1. For Groups 1-3, long-term Unblinded Safety Monitoring should continue every 12 weeks until total lymphocyte and CD4+ T-cell lab results recover[a].
Visit Number	Unscheduled	
Scheduled Day/Week	Every 12 weeks[a]	
Visit Window (Days)	±7 days	
Administrative Procedures		
Concomitant Medication Review	X	
Efficacy Procedures		
CD4+ T-cell Count/TBNK Panel	X	
Safety Procedures		
Directed Physical Examination	X	Full examination as needed
Chemistry	X	
Hematology	X	
Urine Pregnancy Test (WOCBP only)[b]	X[b]	If urine positive, confirm with serum
Review of Adverse Events	X	See Section 8.4 for reportable events during follow-up

TBNK=T- and B- Lymphocyte and Natural Killer Cell; WOCBP=women of childbearing potential.

a. Long-term Unblinded Safety Monitoring is required for participants in Groups 1-3 of whom total lymphocyte and CD4+ T-cell counts have not recovered within 10% of baseline during the initial 12-months of follow-up as outlined in Section 1.3.3. Participants in Groups 1-3 will continue to be followed up every 12 weeks ±7 days until total lymphocyte and CD4+ T-cell criteria for recovery are met which is defined as having 2 values approximately 12 weeks apart within 10% of the baseline with no more than 1 intervening value that is outside of the 10% margin. The baseline value for total lymphocyte and CD4+ T-cell safety monitoring is defined as the average value between Visit 1 Screening and Visit 2 Day 1.

b. Urine pregnancy testing should be performed only if locally required.

2 INTRODUCTION

ISL (also known as MK-8591) is a first-in-class investigational NRTTI. MK-8507 is a potent novel NNRTI. The combination of ISL and MK-8507 is being developed for QW treatment of HIV-1 infection in adults.

2.1 Study Rationale

Rationale for Amendment 013-02:

Downward trends of total lymphocytes and CD4+ T-cell counts were observed which triggered ad hoc eDMC recommendations to immediately discontinue study intervention administration for all participants and to initiate an Unblinded Safety Monitoring of participants who were randomized to ISL + MK-8507.

Original Study Rationale:

As treatment regimens have improved, HIV-1 infection has become a chronic, manageable condition, and those receiving effective ART regimens can expect to live near-normal lifespans [Trickey, A., et al 2017]. With anticipation of life-long treatment, long-term tolerability and safety of antiretrovirals as well as patient adherence and preference have become increasingly important considerations. Furthermore, as the population living with HIV ages, there is also increasing concern for the risks of long-term toxicity and DDIs with respect to comorbid conditions (ie, neuropsychiatric, cardiovascular).

The current standard-of-care for the treatment of HIV-1 is a combination of 2 NRTIs with a third agent (eg, InSTI, NNRTI, or PI) taken daily [AIDS info 2017] [European AIDS Clinical Society 2016] [World Health Organization 2016]. Although such regimens have become increasingly well tolerated and highly efficacious, the current paradigm of life-long treatment is associated with a need for simpler and safer regimens, with reduced long-term drug exposure. There is accumulating evidence that simplified 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens, better tolerability, and improved quality of life, which can help to sustain virologic suppression [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. The viability of 2-drug regimens depends on both components having distinct mechanisms of action with at least 1 of the components having a relatively high barrier to resistance.

A well-tolerated, effective extended duration regimen may provide additional convenience advantages for life-long treatment, such as ease of administration, improved adherence, treatment anonymity, and long-term patient acceptance as compared with traditional QD regimens. This has the potential to decrease pill burden and daily dosing frequency; factors that have been identified as barriers to adherence. Poor adherence is a predictor of virologic failure, development of resistance, and increased mortality among people living with HIV-1 [Lima, V. D., et al 2009] [Genberg, B. L., et al 2012] [von Wyl, V., et al 2013].

Extended duration parenteral regimens are currently in development [Orkin, C., et al 2020]. However, most parenteral options use an extended-release formulation. Limitations of these

regimens may include potential local tolerability issues, the requirement for an oral lead-in, and the potential for late-onset toxicity or AEs, which may be difficult to manage without a removable formulation [Gulick, R. M. 2019]. Additionally, not all patients will prefer an injectable formulation. Therefore, there remains a need for extended duration oral treatment regimens.

The combination of ISL and MK-8507 is a novel 2-drug regimen for the treatment of HIV-1 infection due to its potent antiretroviral activity in vitro (including activity against common NRTI- and NNRTI-resistant variants) by multiple mechanisms of action, lack of food requirements, PK profiles consistent with oral QW administration, and favorable safety and DDI profiles observed to-date.

2.2 Background

Refer to the IBs for detailed background information on ISL and MK-8507.

2.2.1 ISL (MK-8591)

Note: As of Amendment 013-02, this section is no longer applicable.

ISL is the first member of a new class of antiretroviral agents, known as NRTTIs, that block HIV-1 reverse transcriptase by novel mechanisms of action. It is an inactive nucleoside analogue 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 differentiated from other HIV-1 antiretrovirals by its high potency, long half-life (ISL-TP, 79 to 214 hours), and favorable drug resistance profile. At concentrations equivalent to or above the trough levels of the proposed dose of 20 mg QW, ISL exhibits potent antiviral activity against wild-type HIV-1 and variants bearing the most prevalent NRTI resistance-associated mutations, including M184V in vitro, and as part of a QW regimen should provide durable efficacy.

ISL has been extensively evaluated in preclinical safety studies, including genetic toxicity assays and repeat-dose oral toxicity studies. ISL monotherapy safety studies did not reveal any specific cause of concern at acceptable exposure margins. The preclinical toxicity profile of ISL administered orally supports the continued development in participants with or without HIV-1.

ISL administered at a daily dose of 0.75 mg in combination with DOR is being evaluated in ongoing Phase 2 and 3 studies. In the Phase 2 study MK-8591 Protocol 011, all ISL QD doses (0.25 to 2.25 mg) administered in combination with DOR+3TC for 24 weeks and then with DOR alone, demonstrated potent antiretroviral activity comparable to DOR/3TC/TDF as assessed by the percentage of participants with HIV-1 RNA <50 copies/mL through Week 96. DOR + ISL, administered with 3TC or alone, had a favorable safety and tolerability profile through Week 96, comparable to that of DOR/3TC/TDF.

The safety and PK of ISL QW was characterized in 18 healthy adult participants in a Phase 1 double-blind, randomized, placebo-controlled study (MK-8591 Protocol 002). Weekly oral doses of ISL (10 mg, 30 mg, and 100 mg) or placebo were administered for 3 weeks. All doses of ISL were generally well tolerated with no SAEs or discontinuations due to an AE. ISL plasma exposure and ISL-TP levels increased in an approximately dose-proportional manner over the entire dose range.

2.2.2 MK-8507

Note: As of Amendment 013-02, this section is no longer applicable.

MK-8507 is a novel NNRTI that blocks HIV-1 reverse transcriptase by binding to the classic NNRTI binding pocket. It has potent in vitro activity against wild-type HIV-1 virus and variants bearing the most common NNRTI resistance-associated mutations. Unlike currently approved NNRTI agents, which require QD or BID regimens, CCI [redacted]

The results of completed preclinical toxicity studies in rodents and dogs support the evaluation of MK-8507 in Phase 2. CCI [redacted]

In Phase 1 clinical studies, MK-8507 demonstrated favorable clinical safety, tolerability, PK, and PD profiles when evaluated in 64 adult participants, with or without HIV-1. Based on a Phase 1 clinical study CCI [redacted]

In a Phase 1b study in treatment-naïve adult participants with HIV-1 (MK-8507 Protocol 003), single doses of MK-8507 from 40 mg to 600 mg achieved robust viral load declines by 7-days postdose, comparable to those observed with daily administration of other NNRTIs (ie, >1 log10 drop in viral load) (see Section 4.3).

2.2.3 Information on Other Study-related Therapy

Note: As of Amendment 013-02, this section is no longer applicable.

BIC/FTC/TAF was first approved in 2018 for the treatment of HIV-1 infection and will be administered at the approved marketed dose. Refer to approved labeling for detailed information on BIC/FTC/TAF.

2.3 Benefit/Risk Assessment

Note: As of Amendment 013-02, this section is no longer applicable.

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and efficacy of an investigational medicine. Safety of the combination of ISL + MK-8507 in humans has not been studied. However, based on available data from preclinical and clinical studies, both ISL and MK-8507 have the potential to be highly potent and effective ART agents with favorable safety and tolerability profiles and PK properties that support QW administration. Switching to a QW oral regimen that is as efficacious and safe as a QD oral regimen has the potential to reduce pill/treatment fatigue, HIV stigma and desire for anonymity, and ultimately improve treatment adherence and outcomes. The comprehensive preclinical safety evaluations of ISL and MK-8507, as single entity or in combination, have not revealed toxicities of concern at acceptable exposure margins and support the clinical evaluation of these 2 compounds.

Across the ISL clinical development program, as of 14-JAN-2020, approximately 300 participants with or without HIV-1 received oral ISL in Phase 1 and 2 clinical studies. Overall, ISL was generally well-tolerated with no dose-dependent increases in AEs and no drug-related SAEs or deaths reported. The combination of DOR and ISL QD has demonstrated effective antiretroviral activity through Week 96 in approximately 90 treatment-naïve participants with HIV-1 in the ongoing Phase 2 clinical study (MK-8591 Protocol 011).

MK-8507 has been evaluated in 4 Phase 1 studies involving 46 healthy adult participants and 18 adult participants with HIV-1. A single oral dose (up to 1200 mg) or multiple doses (up to 800 mg, QW, × 3 doses) of MK-8507 has been generally well-tolerated with no treatment-related SAEs, no AEs causing discontinuation of study intervention, and no deaths reported.

CCI [redacted]. Increased urinary fluoride excretion was also observed in a Phase 1 study with MK-8507 (MK-8507 Protocol 005). A potential concern with excess fluoride intake is the development of skeletal fluorosis characterized by bone pain and radiologic evidence of periostitis [Tan, I., et al 2019]. However, the amount of fluoride estimated to be released at the 400 mg weekly dose of MK-8507 (1.2 mg/day of fluoride) is expected to be well below the US EPA RfD. Even when typical daily fluoride intake from other sources (~2.9 mg/day) is considered, the total daily fluoride intake would be expected to be ~4.1 mg, which is 15% below the US EPA RfD (4.8 mg/day)

[Health and Ecological Criteria Division, et al 2010]and 42% below the EU Scientific Committee on Health and Environmental Risks upper limit (7.0 mg/day) [Scientific Committee on Health and Environmental Risks 2011]. Although elevated plasma fluoride levels are not expected at the doses of MK-8507 in this study, participants will have plasma fluoride concentrations measured throughout the study. If a participant experiences an AE of bone pain and his or her plasma fluoride concentration exceeds 4.0 µmol/L (>0.076 mg/L), a bone scan will be performed to diagnose periostitis (see Section 8.3.7).

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Note: As of Amendment 013-02, formal comparisons between study treatment arms will no longer be conducted; therefore, evaluation of the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 will no longer be considered a primary endpoint. Imaging, PROs, and biomarkers are no longer being collected. The only study objective is to evaluate the safety and tolerability of ISL + MK 8507 once-weekly as assessed by review of the accumulated safety data. Updated analyses are described in Section 9.

In participants ≥18 years of age with HIV-1 who have been virologically suppressed for ≥6 months on BIC/FTC/TAF:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of ISL + MK-8507 once-weekly as assessed by review of the accumulated safety data.	• Adverse events • Adverse events leading to discontinuation of study intervention
• [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral activity of ISL administered with different doses of MK-8507 once-weekly after switching from BIC/FTC/TAF compared to continued treatment with BIC/FTC/TAF once-daily as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48.	• HIV-1 RNA

Objectives	Endpoints
Secondary	
• [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral activity following switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 48: HIV-1 RNA <50 copies/mL HIV-1 RNA <40 copies/mL	• HIV-1 RNA
• [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral activity following switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 24: HIV-1 RNA ≥50 copies/mL HIV-1 RNA <50 copies/mL HIV-1 RNA <40 copies/mL	• HIV-1 RNA
• [No longer an objective as of Amendment 013-02] To evaluate the sustained antiretroviral suppression in participants who switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 96: HIV-1 RNA ≥50 copies/mL HIV-1 RNA <50 copies/mL HIV-1 RNA <40 copies/mL	• HIV-1 RNA

Objectives	Endpoints
• [No longer an objective as of Amendment 013-02] To evaluate the immunologic effect of switching to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as measured by change from baseline in CD4+ T-cell count at Weeks 24, 48, and 96.	• CD4+ T-cell count
• [No longer an objective as of Amendment 013-02] To evaluate the antiretroviral suppression and immunologic effect of ISL + MK-8507 as assessed by the following at Week 144: Percentage of participants with HIV-1 RNA ≥50 copies/mL Change from baseline in CD4+ T-cell count	• HIV-1 RNA • CD4+ T-cell count
• [No longer an objective as of Amendment 013-02] To evaluate the development of viral drug resistance to any study intervention in participants who switch to ISL + MK-8507 and in participants who continue treatment with BIC/FTC/TAF.	• Viral resistance-associated substitutions
Tertiary/Exploratory	
• [No longer an objective as of Amendment 013-02] To evaluate the effect of MK-8507 on urinary fluoride excretion as measured by levels of urine fluoride at baseline and Week 4.	• Urinary fluoride levels

Objectives	Endpoints
• [No longer an objective as of Amendment 013-02] To evaluate the effect on fasting lipid and metabolic profiles, and body composition following switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF as measured by the mean change in laboratory and radiological markers from baseline at Weeks 48 and 96.	• Laboratory and radiological markers
• [No longer an objective as of Amendment 013-02] To evaluate the pharmacokinetics of ISL + MK-8507 when administered in combination.	• Pharmacokinetic parameters, such as AUC, C_{max}, and C_{168}
• [No longer an objective as of Amendment 013-02] To describe the following PRO concepts: Change from baseline to Week 96 and Week 144 in treatment satisfaction, life satisfaction, disclosure worries, and medication concerns. Stigma at baseline. Treatment preference at Week 96 (participants in Groups 1-3) and at Week 144 (all participants).	• HIVTSQs • Shortened HAT-QoL • HIV Stigma Scale • Treatment preference
• [No longer an objective as of Amendment 013-02] To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

Amendment 013-02

As of Amendment 013-02, all participants have been unblinded and brought to the clinic for an Early Discontinuation of Treatment visit so that non-study ART could be initiated. Subsequently, participants in Group 4 will undergo an End of Treatment Safety Telephone Contact, whereas participants in Groups 1-3 should undergo monthly safety follow-up visits for a duration of at least 6 months. Participants in Groups 1-3 are considered to have completed the study if, at or after the 6-month Unblinding Safety Monitoring, the participant has 2 total lymphocyte and 2 CD4+ T-cell counts that have recovered to within 10% of baseline that were assessed approximately 12 weeks apart with no more than 1 intervening value that is outside of this margin. The baseline value for total lymphocyte and CD4+ T-cell counts is defined as the average value between screening (within 45 days before the first dose of study medication) and Day 1. Participants in Group 1-3 who have not met these criteria at 6 months should continue the Unblinded Safety Monitoring every 12 weeks for total lymphocyte and CD4+ T-cell monitoring until the criteria to complete the study outlined above are met. Participants who no longer want to undergo monthly monitoring should be advised to follow up with their HIV care provider.

Original Design:

This is a 3-part dose-ranging, randomized, active-controlled study to evaluate a switch from BIC/FTC/TAF QD to ISL + MK-8507 QW in participants with HIV-1 who have been virologically suppressed on BIC/FTC/TAF for ≥6 months.

Part 1 (Double-blind Dose-ranging Treatment Period)
Part 1 is a double-blind, double-dummy treatment period in which approximately 140 participants will be randomized in a 1:1:1:1 ratio into 1 of the following 4 blinded treatment groups (Figure 1):

- **Group 1** (n~35): ISL (20 mg) + MK-8507 (100 mg) QW
- **Group 2** (n~35): ISL (20 mg) + MK-8507 (200 mg) QW
- **Group 3** (n~35): ISL (20 mg) + MK-8507 (400 mg) QW
- **Group 4** (n~35): BIC/FTC/TAF QD

After all participants have completed Week 24 visit assessments, an interim analysis will be conducted on safety and efficacy data through Week 24 to select a preliminary dose of MK-8507 for Part 2 (Section 9.7). After all participants have completed Week 48 visit assessments, the preliminary dose of MK-8507 will be confirmed by analysis of safety and efficacy data through Week 48 (Section 9.7). Since the Week 48 interim analysis is not conducted until all participants complete their Week 48 visit, participants who enroll earlier

into the study may continue in Part 1 on blinded study intervention beyond Week 60 until the MK-8507 dose is selected and communicated to sites.

Part 2 (Selected-dose Open-label Treatment Period)
Part 2 of the study will be initiated once sites have been notified of the selected dose of MK-8507. Participants will receive open-label study intervention starting at their next scheduled study visit as follows (Figure 1):

- **Groups 1, 2, and 3**: ISL + MK-8507 QW (at the selected dose)
- **Group 4**: BIC/FTC/TAF QD

Each participant will continue in Part 2 through their Week 96 visit.

Part 3 (ISL+MK-8507 Open-label Treatment Period)
In Part 3, all participants will receive open-label ISL + MK-8507 QW (at the selected dose) from Week 96 through Week 144. Participants randomized to Group 4, who received open-label BIC/FTC/TAF QD in Part 2, will switch to receive open-label ISL + MK-8507 QW beginning at their Week 96 visit to allow for all participants in the study to experience the QW dosing regimen.

Clinical site personnel and participants will remain blinded through Part 1. To allow timely completion of dose response and population PK modeling, select Sponsor personnel (not affiliated with the study team) will be unblinded for the Week 24 interim analysis. No Sponsor personnel directly associated with study conduct will be unblinded to participant treatment assignments before Week 48 (see Section 6.3.3). Participant safety will be monitored by an independent eDMC through periodic review of safety and efficacy data (received from an unblinded statistician) (Appendix 1).

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. At any point in the study, participants with confirmed viremia, as described in Section 4.2.1.1.2, will be assessed for development of viral drug resistance and potential discontinuation from study intervention. Viral resistance data will remain masked for each participant until he/she switches to open-label therapy.

4.2 Scientific Rationale for Study Design

Amendments 013-02 and 013-03

Based on the recommendation of the eDMC to stop study intervention administration in this study, Amendments 013-02 and 013-03 are designed to allow for the discontinuation of study intervention for all participants, the safety follow-up of participants who were randomized to Groups 1-3, and the discontinuation from the study for participants who were randomized to Group 4.

Original rationale:

This randomized blinded active-controlled Phase 2 study design is considered appropriate to support MK-8507 dose selection in combination with ISL 20 mg QW for further evaluation in Phase 3. Part 1 of the study is blinded and will provide 48 weeks of efficacy, safety, and PK data of ISL 20 mg + MK-8507 (dose-ranged) QW compared with BIC/FTC/TAF to support MK-8507 dose selection. Part 2 and Part 3 of the study are open-label and will provide longer term efficacy and safety data and allow for assessment of participants' adherence to a QW regimen without daily BIC/FTC/TAF placebos.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Note: As of Amendment 013-02, HIV-1 RNA measurements will be collected periodically but will not be considered efficacy endpoints. Management of viremia will be at the discretion of the investigator outside of the study.

4.2.1.1.1 HIV-1 RNA Measurements

The primary efficacy endpoint in this study is plasma HIV-1 RNA ≥50 copies/mL. Eligible participants in the switch population being studied are virologically suppressed, with HIV-1 RNA <50 copies/mL at baseline. The assessment of interest is the percentage of participants who are unable to maintain virologic suppression after switching to a new antiretroviral regimen [Food and Drug Administration (CDER) 2015].

Clinical studies of antiretroviral agents in multiple drug classes have shown that virologic suppression of HIV-1 RNA to <50 copies/mL reflects a clinically-relevant standard used across development programs for antiretroviral therapies and in clinical practice [Vandenhende, M. A., et al 2015]. Suppressing HIV-1 RNA to <50 copies/mL preserves the immune system and minimizes the risk of opportunistic infections and disease progression.

The efficacy endpoint of plasma HIV-1 RNA <40 copies/mL corresponds to the LLOQ of the assay being used in this study.

4.2.1.1.2 Definition of Clinically-significant Confirmed Viremia

For the purpose of managing participants in this study, clinically-significant confirmed viremia is defined as:

- **Virologic Rebound**: Two consecutive (2 to 4 weeks apart) occurrences of HIV-1 RNA ≥200 copies/mL at any time during the study.

There is currently no global standard for definition of patients with low-level viremia (viral load ≥50 and <200 copies/mL), and the predictive implication of such low-level viremia is uncertain [Vandenhende, M. A., et al 2015] [Charpentier, C., et al 2014]. The US Department of Health and Human Services guidelines currently define virologic failure as confirmed HIV RNA ≥200 copies/mL and do not recommend that low-level viremia (detectable HIV RNA

<200 copies/mL) automatically result in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. Participants with HIV-1 RNA between 50 and 200 copies/mL have a lower risk of developing resistance compared to those with HIV-1 RNA >200 copies/mL and should continue on their current regimen, with HIV-1 RNA levels monitored as outlined in Section 8.2.2.

An HIV-1 RNA level of ≥50 copies/mL must be confirmed and requires further management as described in Section 8.2.2.

4.2.1.2 Safety Endpoints

Note: As of Amendment 013-02, study intervention administration has been stopped but the study will continue so that participants who received ISL + MK-8507 can be followed for at least 6 months. Participants in Groups 1-3 are considered to have completed the study if, at or after the 6-month Unblinding Safety Monitoring follow-up, the participant has 2 total lymphocyte and 2 CD4+ T-cell counts that have recovered to within 10% of baseline (average between screening and Day 1) that were assessed approximately 12 weeks apart with no more than 1 intervening value that is outside of this margin. Participants who have not met these criteria at 6 months should continue the Unblinded Safety Monitoring every 12 weeks for total lymphocyte and CD4+ T-cell monitoring until the criteria for completion of the study have been met.

Safety evaluations will include physical examinations (including vital signs) and laboratory tests (hematology, chemistry, and urinalysis) performed per the SoA to provide an overall assessment of the safety and tolerability of ISL + MK-8507 administered QW. 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.

4.2.1.2.1 CCI [redacted]

CCI [redacted]

In CCI [redacted] Phase 1 clinical study (MK-8507 Protocol 005), MK-8507 has been shown to release fluoride (see Section 2.2.2). Therefore, this study will include the following assessments to monitor fluoride and serum PTH levels in all participants:

- 4-hour urine collection at Day 1 (baseline) and Week 4 (steady-state accumulation)
- Plasma fluoride levels at Day 1, Weeks 8, 16, 24, and every 12-weeks thereafter
- Serum PTH at Day 1, Week 24, and Week 48

The selected 4-hour duration to assess urinary fluoride excretion levels was based on the correlation data collected in MK-8507 Protocol 005.

In addition, to further evaluate the potential impact of elevated fluoride levels, the following assessments will be conducted in participants with plasma fluoride levels >4.0 µmol/L (>0.076 mg/L):

- Association between serum alkaline phosphatase levels and plasma fluoride levels
- Association between relevant AEs and plasma fluoride levels
- Analysis of the potential fluorosis-related AEs stratified by baseline fluoride levels
- If participant is also experiencing an AE of bone pain: Bone scan (or other imaging method per local standard-of-care) (see Sections 8.3.7 and 8.11.5)

To monitor for potential signs of fluorosis, AEs of periostitis, fracture, and bone pain will be listed as events of clinical interest.

4.2.1.3 Laboratory and Radiological Markers

Note: As of Amendment 013-02, lipid and radiological markers will no longer be collected.

The study will evaluate changes in laboratory and radiological markers from baseline to Weeks 48 and 96 following the switch to ISL + MK-8507 compared to continued treatment with BIC/FTC/TAF.

Fasting Lipids

Some antiretrovirals have been associated with lipid abnormalities [U.S. Prescribing Information 2017]; thus, key indicators of fasting lipid profiles will be measured (Section 8.8.2).

Body Composition

Decreases in BMD and lipodystrophy (peripheral and central fat redistribution) have been reported in patients with HIV-1 receiving ART [AIDS info 2017], particularly with the use of certain NRTIs. Key indicators of body composition (including DEXA assessments) will be measured (Section 8.8.4).

4.2.1.4 Pharmacokinetic Endpoints

Note: As of Amendment 013-02, sparse plasma PK will be collected, as described in the SoA (Section 1.3.3), and the CCI [redacted]**.**

The sparse PK data (collected as described in the SoA and Section 8.6.1.) will be used for updating the population PK model for ISL and MK-8507.

Venous blood samples will be collected for measurement of ISL and MK-8507 plasma concentrations.

CCI

[redacted]

4.2.1.5 Patient-reported Outcomes

Note: As of Amendment 013-02, PROs will no longer be collected.

While current HIV ARTs have conferred high efficacy and good tolerability overall, the focus has shifted to treatment satisfaction and improvement in quality of life. A treatment modality that minimally interferes with a patients' lifestyle, helps maintain HIV-status anonymity, reduces stigma, and/or facilitates adherence may be the preferred treatment choice by patients living with HIV. Because the HIV treatment experience is largely subjective, PRO instruments are important in the evaluation and differentiation of treatment strategies.

This study will include 4 self-administered PRO questionnaires:

- The HIVTSQs is a validated 10-item instrument used to measure satisfaction with medications for people with HIV infection and covers 3 domains (convenience, ease of use, and flexibility).

- The HAT-QoL is a validated 34-item instrument used for the measurement of quality of life in participants with HIV/AIDS and covers 9 domains. The version of this questionnaire used for this study will include 3 domains hypothesized to be most impacted by the study design (disclosure worries, life satisfaction, and medication concerns).

- A novel, 5-item treatment preference questionnaire developed specifically for this study will be administered to participants treated with ISL + MK-8507 to assess preference between weekly and daily dosing of ART.

- The 12-item HIV Stigma Scale is a validated, shortened version of the frequently used 40-item HIV Stigma Scale with 3 questions from each of the 4 stigma subscales/domains (personalized stigma, disclosure concerns, concerns with public attitudes, and negative self-image).

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

Note: As of Amendment 013-02, samples for FBR will no longer be collected.

The Sponsor will conduct future biomedical research on specimens for which consent 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

Note: As of Amendment 013-02, all study intervention administration has been stopped.

The approved 3-drug regimen of BIC/FTC/TAF will be the comparator in this study. BIC/FTC/TAF has been approved by the EMA and the FDA for both treatment-naïve and switch patients and is a recommended initial regimen for most people living with HIV-1

[Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. Although some previous switch studies have been conducted within-class (eg, from one NNRTI to another), this study is designed to compare switching to ISL + MK-8507 from an InSTI-containing regimen. The InSTI-containing regimen was chosen as the comparator because the InSTI class is recommended by both the US Department of Health and Human Services [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018] and the European AIDS Clinical Society[European AIDS Clinical Society 2018] as part of all first-line, standard-of-care treatment regimens. However, emerging data suggest that some InSTIs may have tolerability issues including possible weight gain and CNS side effects. Furthermore, long-term renal and bone defects have been associated with the use of TAF [U.S. Prescribing Information 2016]. Thus, some patients may want to switch from the combination of BIC/FTC/TAF [Norwood, J., et al 2017] [Hoffmann, C., et al 2017].

Matching placebo will be used to provide a robust evaluation of the safety and tolerability profile of ISL + MK-8507 by maintaining double-blind, double-dummy study intervention in Part 1.

4.2.3 Rationale for the Study Population

Patients who have achieved virologic suppression for ≥6 months on an oral 3-drug QD regimen have already demonstrated the ability to be adherent to ART but the high dosing frequency of the QD regimen may result in pill fatigue. An oral 2-drug QW regimen provides convenience advantages and also reduces exposure to the number of ARV medications, which can lower the potential for DDIs with concomitant medications. By decreasing the dosing frequency, an extended duration oral QW regimen may lead to better life-long adherence to ART and offer greater treatment anonymity.

It is anticipated that the extended duration regimen of ISL + MK-8507 QW will be used most often in this patient population looking to switch from their QD regimens after achieving and maintaining virologic suppression. Clinicians will have an understanding of their patients' abilities to adhere to their QD regimens and can evaluate their potential for success on a less frequent, QW regimen.

4.2.4 Rationale for Collecting Specific Data

- **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, collecting race and ethnicity data is important in order to understand any potential differential effects 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 to other groups, and the factors contributing to this remain to be elucidated

[Weintrob, A. C., et al 2009] [Ribaudo, H. J., et al 2013]. Thus, subgroup analyses on race and ethnicity will be performed to better understand how these parameters may influence clinical outcome and toxicity.

- **Gender Identity Data**: Transgender people, defined as those whose gender identities and/or expressions differ from the sex assigned to them at birth, have a high prevalence and incidence of HIV infection globally [Poteat, T., et al 2016]. Specifically, transgender women have an increased risk of HIV infection attributed to challenges associated with coping with psychosocial issues such as discrimination, stigmatization, and marginalization [Centers for Disease Control and Prevention 2019] [Department of HIV/AIDS 2015]. When considering HIV treatment, the WHO considers transgender people to be a separate key population because of their specific health needs and high vulnerability [Department of HIV/AIDS 2015]. Data will be collected in this study to assess clinical outcomes in the transgender population.

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

4.3 Justification for Dose

Note: As of Amendment 013-02, study intervention administration has been stopped.

The doses of ISL + MK-8507 selected for this study were based on the following rationale.

ISL 20 mg QW

A single dose of ISL 20 mg QW CCI [redacted]

CCI

MK-8507 100 to 400 mg QW

- **MK-8507 100 mg:** CCI

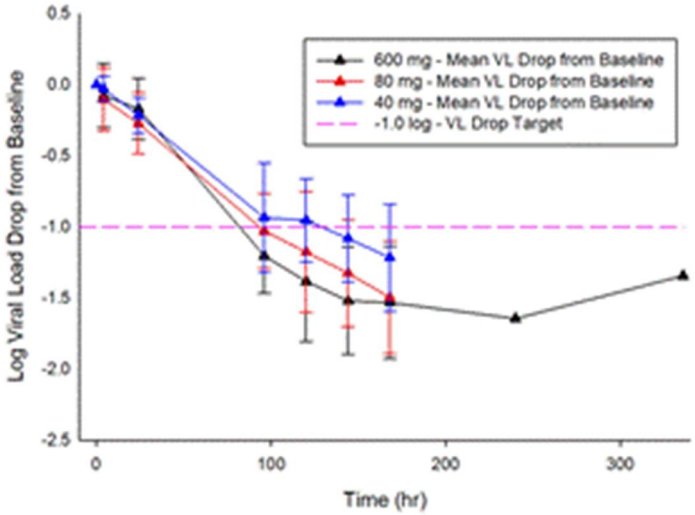
CCI

- **MK-8507 200 mg**: This dose was selected to be bracketed by the 100 mg and 400 mg doses to account for the potential impact of intrinsic or extrinsic factors on MK-8507 PK.

- **MK-8507 400 mg**: This dose level was selected to establish safety of the regimen over a range of exposures (ie, from 100 mg to 400 mg QW). Preclinical and clinical data indicate that MK-8507 undergoes metabolic defluorination. Data from a Phase 1 pilot fluoride study and MK-8507 Protocol 005 provide estimates of daily fluoride release across a range of MK-8507 doses, enabling a selection of doses that when combined with the average total daily fluoride intake would remain below the EPA reference dose of 4.8 mg/day [Health and Ecological Criteria Division, et al 2010]. This level is likely to be without an appreciable risk of deleterious effects during a lifetime, such as severe fluorosis of primary teeth, skeletal fluorosis, and increased risk of bone fracture in adults. The average adult daily intake of fluoride in the US is approximately 2.9 mg/day, with a range of 1.4 to 3.4 mg/day in people from the US and Canada. The proposed highest MK-8507 dose of 400 mg QW is estimated to release an average of 1.24 mg/day of fluoride across the 7-day dosing interval. At the upper end of the range of daily fluoride intake in US adults (3.4 mg), the 400 mg QW dose of MK-8507 would result in a combined average daily intake of 4.64 mg/day, which is below the EPA reference dose [Health and Ecological Criteria Division, et al 2010].

- **Viral load decline**: In the Phase 1b, proof-of-concept, open-label study in treatment-naïve adult participants with HIV-1 (MK-8507 Protocol 003), 3 panels of 6 participants each were administered single doses of 600 mg, 80 mg, and 40 mg of MK-8507. These single doses resulted in HIV-1 plasma viral load declines of >1.0 log10 copies/mL from baseline at Day 7 at all dose levels (Figure 5).

Figure 5 Log10 Viral Load Change from Baseline as a Function of Time Following Single Oral Doses of MK-8507 to Treatment-naïve Adults with HIV-1 (N=6/dose level)



ISL 20 mg QW + MK-8507 ≤400 mg QW

CCI

[redacted]

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

Early study termination will be the result of the following specified criteria:

1. The eDMC recommends termination of the study and the Executive Oversight Committee agrees per Appendix 1, or as stated in the eDMC charter.

2. The extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the overall study population is unacceptable.

3. Plans to modify or discontinue the development of ISL and/or MK-8507.

In addition, further recruitment in the study or at a particular study site may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or excessive discontinuations for administrative reasons.

4.4.2 Clinical Criteria for Closing a Treatment Group

CCI

[redacted]

5 STUDY POPULATION

Participants ≥18 years of age with HIV-1 who have been virologically suppressed for ≥6 months on BIC/FTC/TAF 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 HIV-1 positive with plasma HIV-1 RNA <50 copies/mL at screening.

   Note: A single repeat of the plasma HIV-1 RNA screening test will be allowed, provided results are available within the 45-day screening window.

2. Has a screening CD4+ T-cell count ≥200 cells/mm^3 (completed by the central laboratory).

   Note: A single repeat of the CD4+ T-cell count screening test will be allowed, provided results are available within the 45-day screening window.

3. Has been receiving BIC/FTC/TAF therapy with documented viral suppression (HIV-1 RNA <50 copies/mL) for ≥6 months prior to signing informed consent and has no history of prior virologic treatment failure on any past or current regimen.

   Note: A nonclinically-significant HIV-1 RNA result above the limit of quantification (ie, transient detectable viremia) during the 6 months prior to screening is acceptable.

   Note: Previous regimen switches for tolerability, side effects, dosing convenience, or cost are permitted if they occurred >6 months prior to signing informed consent.

Demographics

4. Is male or female, at least 18 years of age, at the time of signing the informed consent.

Contraception/Pregnancy

Female Participants

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

   - Is not a WOCBP

     OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 6 weeks, corresponding to the time needed to eliminate any study intervention(s) (eg, 5 terminal half-lives) after the last dose of study intervention. The investigator should evaluate the potential for

contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

6. The participant (or legally acceptable representative if applicable) provides written 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.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has HIV-2 infection.

2. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.

3. Has active HCV coinfection (defined as detectable HCV RNA) or HBV coinfection (defined as HBsAg-positive or HBV DNA positive) (completed by the central laboratory).

   Note: Participants with prior/inactive HCV infection (defined as undetectable HCV RNA) or past HBV infection (defined as HBsAg-negative and positive for antibody against HBsAg) may be enrolled.

4. Has a current (active) diagnosis of acute hepatitis due to any cause.

5. Has a history of malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or cutaneous Kaposi's sarcoma.

6. Has a history or current evidence of any condition (including active tuberculosis infection), therapy, laboratory abnormality or other circumstance (including drug or alcohol use or dependence) that might, in the opinion of the investigator, confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate.

Prior/Concomitant Therapy

7. Is taking or is anticipated to require systemic immunosuppressive therapy, immune modulators, or any prohibited therapies outlined in Section 6.5 from 45 days prior to Day 1 through the study treatment period.
   Note: Time-limited courses of corticosteroids (eg, for asthma exacerbation) will be allowed.

Prior/Concurrent Clinical Study Experience

8. Is currently participating in or has participated in a clinical study with an investigational compound or device from 45 days prior to Day 1 through the study treatment period.
   Note: BIC/FTC/TAF is not considered as investigational in countries where it has received health authority approvals, regardless of commercial availability.
   Note: Concurrent participation in observational or noninterventional studies may be permitted and should be discussed with the Sponsor prior to enrollment and through study duration.

Diagnostic Assessments

9. Has a documented or known virologic resistance to:
   - CCI [redacted]
   - CCI [redacted]

   Note: Prior resistance testing results are not required for enrollment.

10. Has exclusionary laboratory values (completed by the central laboratory) 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 based on documented prior laboratory results, but the repeat test results must be available within the 45-day screening window.

Table 1 Laboratory Exclusion Criteria

Laboratory Assessment	**Exclusionary Values**
Alkaline Phosphatase	≥1.5 × ULN
ALT and AST	≥1.5 × ULN
Hemoglobin	<9.0 g/dL (female) or <10.0 g/dL (male)
INR	>1.2
Urine protein	Outside of normal limits (more than trace protein by urine dipstick)
Absolute neutrophil count	<1000/mm^3
Platelet count	<100,000/mm^3
Total serum bilirubin	>ULN
Calculated Cr_{cl}	≤30 mL/min based on the Cockcroft-Gault equation (Appendix 8).
ALT=alanine aminotransferase; AST=aspartate aminotransferase; Cr_{cl}=creatinine clearance; INR=International Normalized Ratio; ULN=upper limit of normal.	

Other Exclusions

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

    Note: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study intervention. Consistent with the recommendations for contraceptive use, it is recommended that all female participants refrain from egg donation for 6 weeks following their last dose of study intervention.
    Note: Donation of sperm should follow local guidelines for individuals who are HIV-positive.

5.3 Lifestyle Considerations

There are no lifestyle restrictions in this study.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

Note: As of Amendment 013-02, study intervention administration has been stopped and all participants will be switched to non-study ART.

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 (ISL, MK-8507, BIC/FTC/TAF, and placebos for each study intervention) 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	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP/ NIMP	Sourcing
Group 1	Experi mental	ISL	Drug	Capsule	20 mg	20 mg QW	Oral	Parts 1, 2[a], and 3	Experi mental	IMP	Central
Group 1	Experi mental	MK-8507	Drug	Tablet	100 mg	100 mg QW	Oral	Part 1	Experi mental	IMP	Central
Group 1	Experi mental	Placebo to MK-8507	Drug	Tablet	0 mg	0 mg QW	Oral	Part 1	Placebo	IMP	Central
Group 1	Experi mental	Placebo to BIC/FTC/ TAF	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1	Placebo	IMP	Central
Group2	Experi mental	ISL	Drug	Capsule	20 mg	20 mg QW	Oral	Parts 1, 2[a], and 3	Experi mental	IMP	Central
Group 2	Experi mental	MK-8507	Drug	Tablet	100 mg	200 mg QW	Oral	Part 1	Experi mental	IMP	Central
Group 2	Experi mental	Placebo to MK-8507	Drug	Tablet	0 mg	0 mg QW	Oral	Part 1	Placebo	IMP	Central
Group 2	Experi mental	Placebo to BIC/FTC/ TAF	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1	Placebo	IMP	Central
Group3	Experi mental	ISL	Drug	Capsule	20 mg	20 mg QW	Oral	Parts 1, 2[a], and 3	Experi mental	IMP	Central
Group 3	Experi mental	MK-8507	Drug	Tablet	100 mg	400 mg QW	Oral	Part 1	Experi mental	IMP	Central
Group 3	Experi mental	Placebo to BIC/FTC/ TAF	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1	Placebo	IMP	Central

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP/ NIMP	Sourcing
Group 4	Active Comparator	Placebo to ISL	Drug	Capsule	0 mg	0 mg QW	Oral	Part 1	Placebo	IMP	Central
Group 4	Active Comparator	Placebo to MK-8507	Drug	Tablet	0 mg	0 mg QW	Oral	Part 1	Placebo	IMP	Central
Group 4	Active Comparator	BIC/FTC/TAF	Drug	Tablet	50/200/25 mg	50/200/25 mg QD	Oral	Parts 1 and 2[a]	Experimental	IMP	Central
Group 4	Active Comparator	ISL	Drug	Capsule	20 mg	20 mg QW	Oral	Part 3	Experimental	IMP	Central
Group 4	Active Comparator	MK-8507	Drug	Tablet	100 mg	100, 200, or 400 mg QW	Oral	Part 3	Experimental	IMP	Central
Groups 1,2, and 3	Experimental	MK-8507	Drug	Tablet	100 mg	100, 200, or 400 mg QW	Oral	Parts 2[a] and 3	Experimental	IMP	Central

BIC=bictegravir; FTC=emtricitabine; ISL=islatravir; QD=once daily; QW=once weekly; TAF=tenofovir alafenamide.

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

a. Part 2 will begin after the MK-8507 dose is confirmed based on the Week 48 data from all participants. Once Part 2 is initiated, participants will begin open-label study intervention at their next study visit. Participants who reach their next study visit (eg, Week 60, Week 72, etc.) before Part 2 initiates will continue taking blinded study intervention until their next visit after Part 2 initiation.

All supplies indicated in Table 2 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

Note: As of Amendment 013-02, study intervention administration has been stopped and all participants will be switched to non-study ART.

Intervention randomization will occur centrally using an IRT system. There are 4 study intervention arms. Participants will be assigned randomly in a 1:1:1:1 ratio to 1 of 3 doses of MK-8507 administered QW with ISL and placebo to BIC/FTC/TAF QD (Groups 1-3) or BIC/FTC/TAF QD and placebos to MK-8507 and ISL QW (Group 4).

6.3.2 Stratification

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

6.3.3 Blinding

Note: As of Amendment 013-02, all participants have been unblinded, study intervention administration has been stopped, and all participants will be switched to non-study ART.

In Part 1 of the study, a double-blinding technique with in-house blinding will be used. MK-8507, ISL, and BIC/FTC/TAF will be packaged identically relative to their matching placebos so that the 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.

Clinical site personnel and participants will remain blinded through Part 1 (see Section 4.1). To allow timely completion of dose response and population PK modeling, select Sponsor personnel (not affiliated with the study team) will be unblinded for the Week 24 interim analysis. No Sponsor personnel directly associated with study conduct will be unblinded to participant treatment assignments before the Week 48 (ie, when the last participant completes their Week 48 visit) interim analysis database lock. However, some Sponsor personnel, including some study team members, will have access to the treatment-group level summaries from the Week 24 interim analyses (including dose response and population PK modeling and efficacy and safety summaries) to support a preliminary dose selection. Before granting access to select personnel to unblinded data at the individual participant level, an official memo detailing the unblinding procedures and listing the personnel who will have access (before the Week 24 interim analysis) to the unblinded data will be generated per Sponsor SOP.

Part 2 and Part 3 of this study are conducted as open label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Two methods to determine compliance with study intervention will be used based on the study intervention packaging:

- Electronic tracking for ISL and MK-8507 in blister packs
- Pill count for BIC/FTC/TAF in bottles

Participants should be instructed to bring the study intervention blister packs and bottles (empty, partially empty, or full) to each visit.

CCI

[redacted]

BIC/FTC/TAF (Bottles)

At each visit, the number of tablets remaining in the bottles will be counted and reviewed; the results will be used to assess participant compliance. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant and the explanation must be documented.

Decisions to temporarily withhold study intervention because of an AE or other reason(s) will be reviewed on a case-by-case basis by the investigator. Interruptions from the protocol-specified treatment plan that are expected to be ≥14 consecutive days for QW administration or ≥7 consecutive days for QD administration 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 or capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance 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.

6.5 Concomitant Therapy

Note: As of Amendment 013-02, there are no study defined prohibited medications. The local label for the non-study ART should be consulted for potential drug interactions.

Medications specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol. 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.

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

Prior and concomitant therapies listed in Table 3 are not permitted from 45 days prior to Day 1 through the study treatment period. The therapies listed in Table 3 are only prohibited based on the part of the study a participant is in and, once in the open-label parts of the study, the treatment group assigned. Table 3 is not comprehensive, and the investigator should use his/her medical judgment when assessing a participant's prior and concomitant therapy(ies). The Sponsor's Clinical Director or designee should be contacted if there are any questions about a therapy not listed or regarding potential DDIs with a specific treatment that the participant may plan to receive.

ISL

ISL metabolism occurs primarily via adenosine deaminase, a non–CYP-mediated process. Given the very low propensity for patients with HIV-1 to require an adenosine deaminase inhibitor (eg, pentostatin), the likelihood of ISL being a victim of DDI is low. ISL is not metabolized by CYP enzymes and therefore is not expected to be a victim of CYP-mediated drug interactions.

MK-8507

CCI [redacted]

BIC/FTC/TAF

Refer to the local product circular for BIC/FTC/TAF for information regarding metabolism and potential drug interactions.

For participants taking metformin, close monitoring is recommended (BIC/FTC/TAF may increase metformin levels). Sucralfate and inhibitors of P-gp and/or BCRP should be used with caution.

For participants taking medications or oral supplements containing polyvalent cations (eg Mg, Al, Ca, Fe), BIC/FTC/TAF (or its placebo) should be taken either 2 hours before or 6 hours after taking any polyvalent cation-containing medicine.

In instances where the local product circular for BIC/FTC/TAF is more restrictive with regard to prohibited (ie, contraindicated or not recommended) therapy(ies), the local product circular supersedes this section.

Table 3 Prohibited Therapies

Parts 1, 2, and 3			
Nonstudy ART	All nonstudy antiretrovirals		
Immunosuppressive or immunomodulating therapies	Immune therapy agents, immune modulators or other systemic immunosuppressive therapy, including interferon-based treatment for hepatitis *Time-limited courses of corticosteroids (eg, for asthma exacerbation) are permitted.*		
Investigational agents	All nonstudy investigational agents including devices		
Part 1	**Part 2**		**Part 3**
All participants	**Groups 1-3**	**Group 4**	**All participants**
CCI [redacted]			

ART=antiretroviral therapy; CYP3A=cytochrome P450 3A; ISL=islatravir.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

No dose modification of ISL, MK-8507, or BIC/FTC/TAF is allowed during the study with the exception of participants who will switch to the selected dose of MK-8507 in Part 2 of the study.

6.7 Intervention After the End of the Study

Note: As of Amendment 013-02, study intervention administration has been stopped so the section is no longer applicable.

Provided development of ISL and MK-8507 continues, there will be a mechanism for all eligible participants to continue receiving study intervention without interruption until it becomes commercially available. Eligible participants are those who have completed the last scheduled study visit and are considered by the investigator to derive clinical benefit from continued administration of their current regimen.

6.8 Clinical Supplies Disclosure

Note: As of Amendment 013-02, this section is no longer applicable.

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity during Part 1 of this study. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Clinical site personnel and participants will remain blinded through Part 1 while Sponsor personnel will remain blinded through the Week 48 interim analysis database lock.

Part 2 and Part 3 of the study will be open-label.

6.9 Standard Policies

Note: As of Amendment 013-02, this section is no longer applicable.

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the comparator 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 BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) as much as possible.

You did not receive the active drug/vaccine BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) as manufactured by Gilead Sciences Inc."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Note: As of Amendment 013-02, study intervention administration has been stopped so the section is no longer applicable.

Discontinuation of study intervention does not represent immediate 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 8.11.3.

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 a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has confirmed HIV-1 virologic rebound as defined in Section 4.2.1.1.2.
- The participant has a positive serum pregnancy test.
- The participant has a Cr_{cl} of <30 mL/min based on the Cockcroft-Gault equation.
  Note: Creatinine clearance should be confirmed by repeat analysis prior to discontinuing study intervention.

- The participant has an SAE or Grade 4 laboratory AE assessed by the investigator to be related to study intervention AND is life-threatening or results in prolonged hospitalization.

- The participant becomes HBsAg or HBV DNA positive.

- CCI [redacted]

For country-specific study intervention discontinuation requirements, see Appendix 7 (Section 10.7.1).

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study is presented in Appendix 2.

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 consent from each potential participant or each participant's legally acceptable representative prior to participating in a 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The

participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

Note: As of Amendment 013-02, collection of specimens for FBR will no longer be done so this section is not applicable.

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

8.1.1.3

8.1.1.4 Consent for Infant Safety Follow-up

Depending on applicable laws and regulations, a separate informed consent may be required for participation in the infant safety follow-up period (Section 8.3.10). If a separate consent is required, the investigator or medically qualified designee will explain the infant safety follow-up consent to the participant, answer all questions, and obtain written informed consent before collecting any data related to the infant follow-up. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history should include information pertaining to the diagnosis of HIV-1 and AIDS (if applicable) and year diagnosed. If the participant has been previously diagnosed with any AIDS-defining conditions or CD4+ T-cell count <200 cells/mm3, the condition as well as a corresponding medical history of AIDS must be reported. In addition, participants' history of tobacco use and alcohol consumption should be obtained and recorded on the appropriate eCRF.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 45 days before the first dose of study intervention.

All prior ARTs taken by the participant from the initiation of treatment (if available) will be recorded before the first dose of study intervention.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Note: As of Amendment 013-02, study intervention administration has been stopped so the section is no longer applicable.

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

Study intervention should begin on the day of randomization.

8.1.8.1 Timing of Dose Administration

Note: As of Amendment 013-02, study intervention administration has been stopped so the section is no longer applicable.

Study intervention will be taken without regard to food. If more than 1 bottle of BIC/FTC/TAF or matching placebo is dispensed, the participant is instructed to use all of the medication in 1 bottle before opening another bottle. Study intervention should be taken at approximately the same time each dosing day.

Part 1

All participants will take the following:

- 1 capsule of ISL or matching placebo and 4 tablets of MK-8507 or matching placebo once-weekly from a single blister pack.
- 1 tablet of BIC/FTC/TAF or matching placebo once-daily from a bottle.

Part 2

Participants in Groups 1 to 3 will take 1 capsule of ISL and MK-8507 (number of tablets to be determined based on selected dose) once-weekly from a single blister pack.

Participants in Group 4 will take 1 tablet of BIC/FTC/TAF once-daily from a bottle.

Part 3

All participants will take 1 capsule of ISL and MK-8507 (number of tablets to be determined based on selected dose) once-weekly from a single blister pack.

8.1.8.1.1 Missed Dose(s)

Note: As of Amendment 013-02, study intervention administration has been stopped so the section is no longer applicable.

ISL and MK-8507

ISL (or matching placebo) and MK-8507 (or matching placebo) should be dosed once-weekly, on the same day of each week (scheduled day of dosing). If a participant misses a dose of ISL (or matching placebo) or MK-8507 (or matching placebo) on the scheduled day of dosing, the missed dose should be taken as soon as the participant remembers. The missed dose can be taken at any day of the 7-day dosing period up to the day before the next scheduled dose. The day of the week of the scheduled dosing should not change as a result of the missed dose. For example, if a participant has a scheduled day of dosing each Monday, the participant can take a missed dose up until Sunday. The next scheduled dose is still taken on Monday, even if the missed dose was taken the day before (Sunday).

If a participant misses a dose of ISL (or matching placebo) or MK-8507 (or matching placebo) for more than 1 consecutive week, only the missed dose for the last week should be taken before the next scheduled dose.

BIC/FTC/TAF

If a participant misses a dose of BIC/FTC/TAF or matching placebo, the following guidance should be followed:

- If ≤12 hours from the missed dose, the missed dose should be taken, and the normal dosing schedule resumed.
- If >12 hours from the missed dose, the missed dose should be skipped, and the normal dosing schedule resumed. The participant should not double the next dose to compensate for what has been missed.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should have an Early Discontinuation visit performed per SoA (Section 1.3) and be encouraged to continue to be followed as outlined in Section 8.11.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Early Discontinuation visit should be performed (at the time of

withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

Note: As of Amendment 013-02, the study has been unblinded so this section is no longer applicable.

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

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

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

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. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

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 Administration of Participant Questionnaires

Note: As of Amendment 013-02, participant questionnaires will no longer be administered so the section is no longer applicable.

Participants will complete 4 PRO questionnaires during the study:

- HIVTSQs and HAT-QoL at Day 1, Week 96, Week 144 and/or the Early Discontinuation Visit
- Treatment Preference at Week 96 (Groups 1-3 only), Week 144, and/or the Early Discontinuation Visit
- HIV Stigma Scale Questionnaire at Day 1

Only participants who have received ≥4 weeks of open-label study intervention will complete PRO questionnaires at the Early Discontinuation visit.

Participants are to complete the questionnaires on their own at the site on paper during the appropriate study visit (see SoA) prior to being seen by the investigator, discussing any medical conditions with the study personnel, or receiving any medical results. The questionnaires will not be administered to participants if native language translations are not available for all questionnaires.

The participant responses to questionnaires will be entered in the appropriate eCRF by site staff according to data entry guidelines.

8.2 Efficacy Assessments

8.2.1 HIV-1 RNA

Note: As of Amendment 013-02, HIV-1 RNA collection is according to the schedule in the SoA (Section 1.3.3).

Plasma HIV-1 RNA quantification will be performed at the central laboratory using a real time PCR assay with a lower limit of detection of 40 copies/mL.

8.2.2 Management of Study Participants With Viremia

Note: As of Amendment 013-02, management of participants with viremia will be at the discretion of the investigator outside of the study.

When viremia (HIV-1 RNA ≥50 copies/mL) is detected (Section 4.2.1.1.2), the investigator should query the participant regarding adherence to study intervention, intercurrent illness, or recent immunization. All cases of viremia must be confirmed, and **the participant should continue to take the full assigned dosage of study intervention while awaiting confirmation.**

8.2.2.1 Viremia Confirmation

Confirmation of viremia requires 2 consecutive plasma HIV-1 RNA results of ≥50 copies/mL (Section 4.2.1.1.2) with the second sample collected at a "Viremia Confirmation" visit at least 2 weeks but not more than 4 weeks from the date of the initial sample. This timeframe may be extended if study intervention is interrupted for 1 of the following circumstances:

- **Intercurrent illness**: redraw 2 to 4 weeks following resolution of the illness, during which time the participant should continue to receive the assigned dosage of study intervention(s) without interruption;
- **Immunization**: redraw at least 4 weeks following any immunization, during which time the participant should continue to receive the assigned dosage of study intervention(s) without interruption;
- **Toxicity management, noncompliance, or other reason**: redraw 2 to 4 weeks following resuming the assigned dosage of study intervention(s).

8.2.2.2 Participants With Clinically-significant Viremia (≥200 copies/mL)

Study participants with confirmed HIV-1 RNA of ≥200 copies/mL will be assessed for development of viral drug resistance (Section 8.2.2.4) and discontinuation from study intervention (Section 7.1). Once it is determined that study intervention discontinuation is appropriate, Early Discontinuation and End of Treatment visit procedures should be

completed (Sections 1.3.2 and 8.11.3) and the participant managed by the investigator per local standard-of-care.

8.2.2.3 Participants With Low-level Viremia (≥50 and <200 copies/mL)

Study participants with confirmed HIV-1 RNA of ≥50 and <200 copies/mL should continue study intervention and all regularly-scheduled study visits during which HIV-1 RNA levels will be monitored per SoA (approximately every 3 months). Additional visits may be conducted to monitor HIV-1 RNA levels more frequently than every 3 months, if appropriate, after discussion with the Sponsor. Participants with confirmed low-level viremia at Week 48 will not be automatically discontinued from study intervention but will be included in the virologic failure rate calculated for the purposes of the primary analyses (Section 9.6.1).

Investigators should use their clinical judgment regarding the most appropriate clinical management of participants, if more stringent local guidelines apply, and may contact the Sponsor's Clinical Director to discuss questions on clinical management of individual participants.

8.2.2.4 Viral Drug Resistance Testing

Participants with HIV-1 RNA ≥200 copies/mL at any time during the study will be assessed for development of viral drug resistance. Genotypic and phenotypic resistance will be assessed at Monogram Biosciences using the commercially available GenoSure PRIme® and PhenoSense assays®, respectively.

Samples will be collected for genotypic and phenotypic HIV-1 drug resistance testing per SoA (Section 1.3) and used to assess resistance-associated substitutions as applicable during the study.

8.2.3 T- and B- Lymphocyte and Natural Killer Cell Panel Including CD4+ T-cell Counts

A TBNK panel, including CD4+ T-cell count, will be performed at the central laboratory (see Table 17 in Appendix 2). A subset of the TBNK panel results will be added on previously collected and tested samples.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Table 18, Table 19, and Table 20 in Appendix 2.

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

8.3.1 Physical Examinations

Note: As of Amendment 013-02, height and full physical examinations are no longer performed. Only directed physical examinations and weight will be performed according to the SoA (Section 1.3.3 and Section 1.3.4).

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at the visits specified in the SoA (Section 1.3.1). The full 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 will also be measured and recorded at the visits specified in the SoA (Section 1.3.1). Height measurements should be taken using a stadiometer (recommended but not required). Participants should remove their shoes and stand as tall and straight as possible.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the visits specified in the SoA (Section 1.3.1). This examination will be sign- and symptom-directed and based on the participant's condition and circumstances. The investigator should note any changes in the participant's condition (body systems) since the last examination, not precluding examination of any body system(s) as clinically indicated.

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

8.3.1.1 Weight

Weight will be measured and recorded at the visits specified in the SoA (Section 1.3.1). Participants should remove their shoes and wear a single layer of clothing at each measurement.

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 are preferred but not required.

8.3.3 Electrocardiograms

Note: As of Amendment 013-02, ECGs will no longer be collected so the section is no longer applicable.

A local 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) within 7 days prior to the Day 1 visit and prior to the first dose of study intervention as indicated in the SoA. Results must be available prior

to randomization. Sites are to use an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Clinically-significant findings must be documented in the source documents and captured in the appropriate eCRF.

If an ECG is performed for any medical reason while the participant is on study intervention or during the follow-up period, any clinically-significant changes compared with the baseline ECG must be captured as AEs.

8.3.4 Confirmation of Contraception and Pregnancy Testing

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

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

Urine pregnancy test kits will be provided by the central laboratory, and routine testing will be performed by the site or local laboratory. In the event of a positive urine pregnancy test result, serum pregnancy testing must be performed by the central laboratory. If a participant becomes pregnant, refer to Section 7.1.

8.3.5 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 42 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6 CCI [redacted]

CCI [redacted]

8.3.6.1 CCI [redacted]

CCI [redacted]

[redacted]

8.3.6.2 CCI [redacted]

CCI [redacted]

8.3.6.3 CCI [redacted]

CCI [redacted]

8.3.7 CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

8.3.8 HBV Assessments

Note: As of Amendment 013-02, HBV monitoring will not be performed after the Early Discontinuation of Treatment visit.

All eligible participants must be HBsAg-negative at screening. Participants who are anti-HBc positive and HBV DNA positive at screening are excluded. Participants who are anti-HBc positive but HBV DNA negative at screening are eligible to enroll. For the duration of the study, participants positive for anti-HBc should be monitored for possible HBV reactivation. Samples will be taken to monitor HBsAg and HBV DNA per the SoA (Section 1.3). Investigators should also pay close attention to changes from baseline in ALT, AST, bilirubin, and alkaline phosphatase (included in chemistry laboratory assessments).

8.3.9 Tobacco and Alcohol Assessments

Note: As of Amendment 013-02, tobacco and alcohol assessments will not be conducted so the section is no longer applicable.

Participants' use of tobacco and alcohol will be obtained and recorded at Weeks 48, 96, and 144.

8.3.10 Infant Safety Follow-up Assessments

Infants, born to participants who become pregnant while receiving study intervention (which would include the protocol-specified follow-up period) and consent to infant follow-up, will have safety follow-up through approximately 1 year of age as outlined in Table 4. This infant safety follow-up data may be collected by phone call or in person. Length, weight, and head circumference measurements will be collected at birth and at 1 year of age. Infant SAEs, including congenital anomalies identifiable on physical examination at birth or shortly after birth, will be collected as per Section 8.4.1 and should be reviewed at the participant's scheduled study visits that occur during this time.

Table 4 Infant Safety Follow-up: Data Collection Through 1 Year of Age

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

Study Period	**Infant Safety Follow-up**	
Scheduled Day	At Birth	1 Year After Birth[a]
Data Collection Window	+90 days	+90 days

SAE=serious adverse event.
[a] If a participant withdraws from the study, data from 1 year after birth should be collected at the time of withdrawal.
[b] Depending on applicable laws and regulations, a separate informed consent may be required (Section 8.1.1.4).
[c] Collect and report pregnancy outcome (health of infant) per Section 8.4.5.
[d] Collect SAEs, including any congenital anomalies, per Section 8.4.1 and review at participant's regularly scheduled study visits.

8.4 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 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 consent form is signed but before intervention randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through study duration, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

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

For infants born to participants who become pregnant while receiving study intervention and consent to infant follow-up, SAEs occurring (in these infants) from the time of birth through

1 year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
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

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

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

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

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

This section is not applicable to the study.

8.4.7 Events of Clinical Interest

Note: as of Amendment 013-02, ECIs will be reported through 42 days after the last dose of study intervention.

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. CCI [redacted]

8.5 Treatment of Overdose

In this study, an overdose of study intervention is defined as:

- QW Regimen: >3 doses within 14 calendar days
- QD Regimen: >1 dose in a single calendar day

No specific information is available on the treatment of overdose.

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

8.6.1 Blood Collection for ISL and MK-8507 Pharmacokinetics

8.6.1.1 Venous Blood (Plasma) PK Sampling

Note: As of Amendment 013-02, plasma PK sample collection was revised and investigational PK sample collection has been removed, as outlined in the SoA (Section 1.3.3).

Venous blood samples will be collected for measurement of ISL and MK-8507. Sample collection, storage, and shipment instructions for plasma samples will be provided in the laboratory manual. Investigational PK samples will be collected from all participants as outlined in the SoA (Section 1.3). Analysis of these samples will be triggered by the Sponsor as needed.

PK samples will be collected from all participants as outlined in Table 6.

Table 6 Collection of PK Samples

Study Visit	Time Relative to Dose (ISL + MK-8507)
Day 1	Predose
Week 4[a]	Samples to be collected predose and within 0.5 to 4 hours postdose
Week 8	One sample to be collected at any time during the visit
Week 12	One sample to be collected at any time during the visit
Week 24[a]	Samples to be collected predose and within 0.5 to 4 hours postdose
Week 48[a]	Samples to be collected predose and within 0.5 to 4 hours postdose

Study Visit	Time Relative to Dose (ISL + MK-8507)
Week 72[a]	One sample to be collected predose
Week 96[a]	One sample to be collected predose
Week 144[a]	One sample to be collected predose

ISL=islatravir; PK=pharmacokinetic.
a. For participants who have taken ISL + MK-8507 (or matching placebos) prior to coming to the clinic during Weeks 4, 24, 48, 72, 96, and 144, one sample will be collected at any time during the visit.

8.6.1.2 CCI

CCI

CCI

CCI

[redacted]

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Note: As of Amendment 013-02, samples for biomarker research will no longer be collected so the section is no longer applicable.

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

- Blood for Genetic Analysis
- Blood for fasting lipids and metabolic profile

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 signs

the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

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

8.8.2 Fasting Lipids

Note: As of Amendment 013-02, samples for analysis of fasting lipids will no longer be collected so the section is no longer applicable.

Participants will be asked to fast for at least 8 hours prior to visits where blood will be taken to measure HDL-C, LDL-C, TGs, TC, and non-HDL-C.

8.8.3 Waist and Hip Measurements

Note: As of Amendment 013-02, waist and hip measurements will no longer be collected so the section is no longer applicable.

Participants should be asked to stand erect, relaxed and should not hold in their stomach during measurements. Waist circumference will be measured midway between the iliac crest and the lower rib margin. Hip circumference will be measured at the intertrochanteric level. Measurements should be taken with a stretch-resistant measuring tape held parallel to the floor. Waist-to-hip ratios will be calculated as waist (cm)/hip (cm) circumferences.

BMI will be calculated using weight and height measurements taken as specified in the SoA (Section 1.3).

8.8.4 DEXA Assessments

Note: As of Amendment 013-02, DEXA assessments will no longer be conducted so the section is no longer applicable.

DEXA images to monitor fat distribution and BMD should be collected from all participants/sites willing and able to have the test performed and according to country law (Section 1.3). These participants will undergo total body DEXA scans for BMD of the spine and hip as well as peripheral and trunk fat. Participants will not be excluded from participation in the study if unwilling/unable to have DEXA images performed.

Only those participants who are confirmed eligible to be randomized will undergo DEXA images for BMD of the spine and hip as well as peripheral and trunk fat. For Day 1 (baseline), DEXA images should be performed after eligibility is confirmed and may be performed up to 14 days after randomization. The DEXA images at subsequent visits should be performed ± 14 days of the scheduled visit. Only participants with valid baseline DEXA images should have DEXA images performed at subsequent visits as indicated in the SoA (Section 1.3).

DEXA images will be evaluated by a central imaging reader; these analyses are not performed in real-time and will not be provided to the site/participant. For clinical management of the participant, the DEXA images should be reviewed and interpreted locally by a qualified individual. Clinically-significant findings noted in the local interpretation of the baseline DEXA images should be recorded in the participant's medical history. Clinically-significant findings noted in the local interpretation of the DEXA images during the treatment period should be recorded appropriately. Refer to the Site Imaging Manual for additional details regarding DEXA procedures including participant preparation instructions to be considered before DEXA imaging.

8.9 Future Biomedical Research Sample Collection

Note: As of Amendment 013-02, this section is no longer applicable.

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover extracted DNA for future research
- Leftover main study plasma from HIV-1 RNA quantification
- Leftover main study plasma from HIV drug resistance samples
- Whole blood for future biomedical research

Sample collection, storage, and shipment instruction for whole blood future biomedical research samples will be provided in the laboratory manual. Refer to the SoA (Section 1.3) for timing of sample collection.

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

Note: As of Amendment 013-02, this section is no longer applicable.

Screening

Prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. A screening period of up to 45 days is allowed but participants are expected to enroll as soon as possible after eligibility is confirmed.

Rescreening

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

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

- Vital signs, weight, and directed physical examination
- Review medical history and prior/concomitant medications for new information
- All laboratory assessments (includes serum hCG pregnancy testing for WOCBP)
- Review of AEs

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

If a participant had a Day 1 ECG during the original screening period, it should be repeated (at the Day 1 visit or within 7 days prior).

If a participant had a baseline Day 1 DEXA scan during the original screening period, and >30 days have elapsed, the Day 1 DEXA should be repeated. If <30 days have elapsed since the DEXA it is not necessary to repeat the Day 1 DEXA scan during rescreening.

Participants who were previously considered screen failures because the duration of baseline ART was <6 months are allowed to rescreen if they have continued to receive BIC/FTC/TAF therapy with documented viral suppression (HIV-1 RNA <50 copies/mL) for ≥6 months before the rescreening visit and have no history of prior virologic treatment failure on any past or current regimen.

8.11.2 Treatment Period

All procedures and their timing should be completed as per SoA (Section 1.3).

8.11.2.1 Fasting

Note: As of Amendment 013-02, this section is no longer applicable.

Visits at Day 1, Week 4, Week 24, Week 48, Week 72, Week 96, Week 120, and Week 144 require that participants fast (ie, do not consume any food or beverages except water) for at least 8 hours prior to the visit. The investigator/study coordinator are responsible to remind participants to fast prior to these visits and to confirm with participants their fasting status in the appropriate source documentation.

8.11.2.2 Optional Nurse Visits and Telephone Visits

Note: As of Amendment 013-02, this section is no longer applicable.

A visiting nurse service may be used (if locally available and approved for use) at any visit after a participant is randomized. If a visiting nurse service is used for any visit, the investigator should contact the participant by phone on the same day as the nurse visit, or as soon as possible to perform an investigator AE assessment. Refer to the nursing manual for additional details.

For visits conducted by the visiting nurse, whole blood for FBR samples will not be collected by the visiting nurse. Participants should be instructed to return to the site within 2 to 4 weeks from the scheduled visit for collection of whole blood for FBR, when possible. If an unscheduled visit for collection of whole blood for FBR is not possible, the sample should be drawn at the next scheduled visit at the site.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Note: As of Amendment 013-02, this section is no longer applicable.

A participant must be discontinued from study intervention for any of the reasons listed in Section 7.1.

For all discontinuations which are not related to pregnancy, when it is determined that discontinuation from study intervention is appropriate, the participant should have both an Early Discontinuation of Treatment visit (Section 8.11.3.2) and an End of Treatment Follow-up visit (Section 8.11.3.3) conducted. After the visit procedures are completed, the participant will be withdrawn from the study and managed by the investigator per local standard-of-care.

8.11.3.1 Participants Who Become Pregnant

If a participant becomes pregnant during the study (has a positive serum pregnancy test), study intervention should be discontinued, and the participant may be unblinded to be managed by the investigator per local standard-of-care, as appropriate.

The participant should not be withdrawn from the study but should have an Early Discontinuation of Treatment visit (Section 8.11.3.2). If the pregnancy is reported at a scheduled study visit, the assessments for the Early Discontinuation of Treatment visit should be conducted at that time. The participant will then continue with the protocol-specified visits for the duration of their pregnancy per the regular schedule in the SoA for the duration of their pregnancy (Section 1.3.1). At these visits (in-person or via telephone), concomitant medications will be reviewed, and safety assessments will be completed.

All reported pregnancies occurring during the study must be followed to the completion/termination of the pregnancy (Section 8.4.5). The participant will be asked to join a pregnancy registry, which collects information about the outcome of the pregnancy. Infants

born to participants who become pregnant while receiving study intervention and consent to infant follow-up, will have safety follow-up through approximately 1 year of age (Section 8.3.10).

8.11.3.2 Early Discontinuation of Treatment

Participants who discontinue treatment early for any reason should have an Early Discontinuation of Treatment visit as outlined in Section 1.3.2. If early discontinuation occurs during the timeframe of a scheduled study visit, the assessments for the Early Discontinuation of Treatment visit should be conducted.

8.11.3.3 End of Treatment Follow-up Visit

Participants who discontinue study intervention at any time (including at the Week 144 visit) for any reason(s) not related to pregnancy will have a safety follow-up visit in-clinic approximately 42 days after the last dose of study intervention. Assessments for this visit are outlined in Section 1.3.2.

8.11.4 Viremia Confirmation

Note: As of Amendment 013-02, this section is no longer applicable.

If a participant has a viral load of ≥50 copies/mL at any time during the study, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (Sections 1.3.2 and 4.2.1.1). If a scheduled visit is to occur within the timeframe that a participant would return for a viremia confirmation visit, the assessments for the scheduled visit should be conducted, and the HIV viral drug resistance sample must be collected.

8.11.5 CCI

CCI

[redacted]

CCI

[redacted]

9 STATISTICAL ANALYSIS PLAN

Note: As of Amendment 013-02, overall Section 9 is no longer applicable unless otherwise specified here or in each specific subsection, including Sections 9.4.1, 9.4.2, 9.5, 9.6, 9.6.1.2, 9.6.2, 9.11, and 9.12. Efficacy and safety data will be summarized for available data from Part 1 and from the Unblinded Safety Monitoring period separately. Safety data will be evaluated for the following periods:

- **From Day 1 through on-treatment before Unblinded Safety Monitoring period**
- **Unblinded Safety Monitoring period**

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

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below.

Study Design Overview	A Phase 2b, Randomized, Active-Controlled, Double-Blind, Dose-Ranging Clinical Study to Evaluate a Switch to ISL + MK-8507 QW in Adults with HIV-1 Virologically Suppressed on BIC/FTC/TAF QD
Treatment Assignment	Part 1 (Double-blind Dose Ranging Treatment Period): ~140 participants will be randomized in a 1:1:1:1 ratio to receive 1 of the 4 following study interventions: • Group 1: ISL 20 mg QW + MK-8507 100 mg QW (n=35) • Group 2: ISL 20 mg QW + MK-8507 200 mg QW (n=35) • Group 3: ISL 20 mg QW + MK-8507 400 mg QW (n=35) • Group 4: BIC/FTC/TAF QD (n=35) All participants will remain in Part 1 and receive assigned study intervention until the MK-8507 dose is confirmed for Part 2 based on Week 48 results. Part 2 (Selected-dose Open-label Treatment Period): Once the MK-8507 dose is confirmed and communicated to sites, participants will receive the following open-label study intervention through Week 96: • Groups 1, 2, and 3: ISL 20 mg QW + MK-8507 QW (at the selected dose) • Group 4: BIC/FTC/TAF QD Part 3 (ISL + MK-8507 Open-label Treatment Period): All participants will receive ISL 20 mg QW + MK-8507 QW (at the selected dose) from Week 96 through Week 144.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)

Primary Endpoint(s)	Efficacy: [No longer an endpoint as of Amendment 013-02] Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 Safety: 1. Percentage of participants experiencing AEs 2. Percentage of participants experiencing AEs leading to discontinuation of study intervention
Statistical Methods for Efficacy and Safety Analyses	The primary efficacy and safety objectives will be assessed using 2-sided 95% CIs for the treatment difference in the primary efficacy and safety endpoints between each of treatment Groups 1-3 and active control Group 4. The CIs will be based on unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Multiplicity	Since there are no formal hypothesis tests, no multiplicity adjustment is needed in this study.
Interim Analysis	After all participants have reached Week 24, an interim analysis will be conducted to assess the safety, efficacy, and PK objectives and to support a preliminary dose selection for MK-8507. Select Sponsor personnel (not affiliated with the study team) will be unblinded for the Week 24 interim analysis to support dose response and population PK modeling. The external unblinded statistician will conduct the efficacy and safety analyses associated with the Week 24 interim analysis. Site personnel, study participants, and Sponsor study-team personnel will remain blinded to participant treatment assignments, although the Sponsor study-team will have access to treatment-level summaries presented in the interim analysis report and the preliminary dose selection at the Week 24 interim analysis. After all participants have reached Week 48, the Sponsor study-team will be unblinded and safety and efficacy data through Week 48 will be analyzed to support final dose selection for Part 2. Periodic safety and efficacy reviews by an eDMC will be performed as specified in the eDMC charter.
Sample Size	The planned sample size is 140 participants to be randomized in a 1:1:1:1 ratio to Groups 1-4 (35 participants per treatment group). With 35 participants in each treatment group, there is approximately 80% probability to obtain a 2-sided 95% CI for the treatment difference in the proportions of participants with HIV-1 RNA ≥50 copies/mL that would exclude a ≥22.2% treatment difference when the true proportions are, in fact, equal to 2% in both treatment groups. This statement applies to the 3 treatment differences corresponding to the difference between each specific ISL + MK-8507 treatment group and the active control group, for each applicable time point. Detailed information is in Section 9.9.1.

9.2 Responsibility for Analyses/In-house Blinding

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

Part 1 is double-blinded with in-house blinding through Week 48 (eg, the participant, the investigator, and Sponsor personnel are unaware of the intervention assignments). Clinical site personnel and participants will remain blinded in Part 1 (through at least Week 48). To support the Week 24 interim analysis, select sponsor personnel (not affiliated with the study team) will be unblinded to participant treatment assignments to support the dose response

and population PK modeling. The external unblinded statistician will conduct the efficacy and safety analyses associated with the Week 24 interim analysis. Sponsor study-team personnel will remain blinded to participant treatment assignments until the unblinding to support the Week 48 interim analysis; however, they will have access to treatment-group summaries presented in the Week 24 interim analysis report as well as knowledge of the preliminary dose selection.

Part 2 and Part 3 of this study are conducted as open label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

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

9.3 Hypotheses/Estimation

There are no hypotheses to be tested in this study. The study objectives are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints for the study, which will be evaluated for within-and/or between-treatment differences, are listed below, followed by the descriptions of the derivations of selected endpoints. These endpoints will be evaluated by treatment group according to study part.

9.4.1 Efficacy Endpoints

Note: As of Amendment 013-02, this section is no longer applicable except CD4+ T-cell counts will continue to be monitored through the Unblinded Safety Monitoring period, according to Section 1.3.3 and Section 1.3.4.

Unless otherwise specified, the efficacy endpoints will be evaluated by the Part 1 treatment group for Part 1 summaries. In Part 2, the efficacy endpoints will be evaluated by treatment group in Part 1 and by treatment group in Part 2 (ie, participants from Group 4 will remain in Group 4 as an active control and participants from Groups 1-3 will be in a combined group). In Part 3, the efficacy endpoints will be evaluated by Part 2 treatment group (Groups 1-3 combined and Group 4 presented separately).

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

Percentage of Participants with Predefined HIV-1 RNA Levels

The Abbott Real Time PCR assay with a reliable LLOQ of 40 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The following efficacy endpoints associated with HIV-1 RNA will be derived based on HIV-1 RNA test results and reconfirmed results, if applicable.

Primary Efficacy Endpoints

- Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48

Secondary Efficacy Endpoints

- Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 24
- Percentage of participants with HIV-1 RNA <50 copies/mL at Week 24
- Percentage of participants with HIV-1 RNA <40 copies/mL at Week 24
- Percentage of participants with HIV-1 RNA <50 copies/mL at Week 48
- Percentage of participants with HIV-1 RNA <40 copies/mL at Week 48
- Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96
- Percentage of participants with HIV-1 RNA <50 copies/mL at Week 96
- Percentage of participants with HIV-1 RNA <40 copies/mL at Week 96
- Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 144

Change from Baseline in CD4+ T-cell Count

Results of CD4+ T-cell counts from the central laboratory will be used to evaluate the immunologic effect. Changes in CD4+ T-cell count will be estimated at each applicable timepoint. Specific secondary efficacy endpoints include the following:

- Change from baseline in CD4+ T-cell count at Week 24
- Change from baseline in CD4+ T-cell count at Week 48
- Change from baseline in CD4+ T-cell count at Week 96
- Change from baseline in CD4+ T-cell count at Week 144

For analyses of change from baseline, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline. For assessments of change from baseline in Group 4 at Week 144, baseline will be the Week 96 measurement (or the last measurement prior to the switch to ISL + MK-8507 QW).

Clinically-significant Confirmed Viremia

Participants with confirmed virologic rebound as defined in Section 4.2.1.1.2 will be identified.

Viral Resistance-associated Substitutions

Participants who meet the definition of confirmed virologic rebound (Section 4.2.1.1.2), or who discontinue study intervention for another reason and have HIV-1 RNA ≥200 copies/mL at the time of discontinuation, will be assessed for development of viral drug resistance. Among such participants, those with HIV-1 RNA ≥400 copies/mL or anyone for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load, will be included for resistance analyses. The resistance analysis will count the number of participants who have evidence of resistance associated with each study intervention and will be summarized through study duration, with primary interest at Weeks 48 and 96.

9.4.2 Safety Endpoints

Note: As of Amendment 013-02, this section is no longer applicable except AEs, DILI laboratory criteria, PDLC, and selected laboratory parameters will continue to be monitored through the Unblinded Safety Monitoring period, according to Section 1.3.3 and Section 1.3.4.

Unless otherwise specified, the safety endpoints will be evaluated for the following periods:

- Day 1 through Week 48
- Day 1 through Week 96
- Day 1 through Week 144 for Groups 1-3
- Week 96 through Week 144 for Group 4

Unless otherwise indicated, safety summaries will be presented by Part 1 treatment group, and by combining Groups 1-3 where appropriate. Further details on the safety comparisons and treatment group pooling strategy for each study part will be provided in the sSAP.

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

Adverse Events

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed.

CCI

The percentage of participants falling into the following clinical AE categories will be summarized as Tier 2 endpoints: 1) at least 1 AE; 2) at least 1 drug-related AE; 3) at least 1

SAE; 4) at least 1 serious and drug-related AE; 5) AEs leading to discontinuation of study intervention; and 6) AE(s) leading to death.

Events of Clinical Interest (ECI)

Specific ECIs, including events meeting DILI lab criteria [redacted] (predefined in Section 8.4.7), will be summarized.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a baseline and postrandomization on-treatment measurement to be included. 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, July 2017, Version 2.1 (Appendix 3). A listing of the participants who meet the criteria will also be provided.

Selected Laboratory Parameters

The mean change from baseline to Weeks 48, 96, and 144 in select laboratory parameters will be summarized.

For analyses of change from baseline, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline. For assessments of change from baseline in Group 4 at Week 144, baseline will be the Week 96 measurement (or the last measurement prior to the switch to ISL + MK-8507 QW).

9.4.3 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoA and Section 8.6.1 will be used for updating the population PK model for ISL and MK-8507, and as appropriate, evaluate the PK-efficacy, and PK-AE relationships of ISL and MK-8507.

9.4.4 Patient-reported Outcome Endpoints

An initial description of patient-reported outcome measures is provided in Section 4.2.1.5. HIVTSQs and shortened HAT-QOL at Day 1 and Weeks 96 and 144 will be summarized for each treatment group. Participants who do not experience a minimum of 4 weeks of open-label study intervention in Part 2 will be excluded from the Week 96 analysis. HIV stigma scale results at Day 1 will be summarized for each treatment group. Results from the preference questionnaire will be summarized for participants in Groups 1-3 at Week 96 and for all participants at Week 144.

9.5 Analysis Populations

Note: As of Amendment 013-02, this section is no longer applicable except FAS and APaT populations for summaries associated with available data of Part 1. The Unblinded Non-study ART Treated population is defined as participants who were in Groups 1, 2, and 3 and were to switch to non-study ART treatment.

9.5.1 Efficacy Analysis Populations

9.5.1.1 Full Analysis Set

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who:

- Received at least 1 dose of study treatment, and
- Have baseline data for those analyses that require baseline data.

Participants will be included in the treatment group to which they are randomized for the analyses of efficacy data using the FAS population.

9.5.1.2 Resistance Analysis Subset

The resistance analysis subset will include all participants in the FAS with confirmed HIV-1 RNA ≥400 copies/mL and any participants for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received. Participants in Group 4 who receive at least 1 dose of weekly study intervention (ISL + MK-8507) in Part 3 will be included in summaries and analyses from Week 96 through Week 144.

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

9.6 Statistical Methods

Note: As of Amendment 013-02, this section is no longer applicable. Efficacy data will be summarized separately for available data observed from Part 1 and the Unblinded Safety Monitoring period.

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 Quantitative Pharmacology and Pharmacometrics. Methods related to exploratory objectives will be described in the sSAP.

Unless otherwise specified, efficacy and safety data will be summarized and analyzed separately according to study part. Additional pooled or sliced analyses may be provided in sSAP.

9.6.1 Statistical Methods for Efficacy Analyses

Percentage of Participants with Predefined HIV-1 RNA Levels

For Part 1, the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 will be summarized by treatment group. The treatment difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL between each of Groups 1-3 and Group 4 at Week 48 and the associated 95% CIs will be calculated using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The same efficacy analysis approach will be performed for the secondary efficacy endpoints (as specified in Section 9.4.1) at Week 24, Week 48, and Week 96 according to study part.

For the efficacy endpoints at Week 144, summary statistics will be provided.

The missing data will be handled based on the approaches defined in Section 9.6.1.1. The primary missing data approach for primary efficacy analysis is based on FDA Snapshot approach. The rest of missing data approaches are supportive for sensitivity analyses.

For the primary efficacy endpoints, the following categorization of virologic outcome at a timepoint by the snapshot approach will further be summarized by treatment group: 1) HIV-1 RNA <50 copies/mL, 2) HIV-1 RNA ≥50 copies/mL, and 3) no virologic data in window for reasons of a) discontinued study due to an AE/death, b) discontinued study for other reasons (includes withdrawal of consent, loss to follow-up, move, etc.), or c) on study but missing data in window.

Change from Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be summarized at each time point, with particular interest in Weeks 24, 48, 96, and 144 as specified in Section 9.4.1. For Week 144, the change from baseline will be based on the Week 96 baseline for Group 4.

The treatment difference in change from baseline in CD4+ T-cell count at Weeks 24, 48, and 96 will be estimated using an ANCOVA model adjusted by baseline CD4+ T-cell count and

treatment group and will be based on study part. The DAO approach will be used to handle missing data for these analyses. Under the DAO approach, participants must have both a baseline measurement and at least 1 postbaseline measurement within the analysis window specified in Table 10 in Section 9.6.1.2 for the time point of interest to be included in the analyses of the mean change from baseline in CD4+ T-cell count by time point. Supportive analyses will also be provided using the LOCF method to account for missing data.

Clinically-significant Confirmed Viremia

The number of participants with confirmed virologic rebound, as defined in Section 4.2.1.1.2, will be summarized according to study part through Week 144.

Viral Resistance-associated Substitutions

The number of participants in the resistance analysis subset with genotypic and/or phenotypic resistance to each study intervention will be summarized according to study part with primary interest at Weeks 48 and 96.

Table 9 summarizes the key efficacy analyses of the study.

Table 9 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Primary vs Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Efficacy Endpoints				
Percentages of participants with HIV-1 RNA ≥50 copies/mL at Week 48	P	M&N	FAS	Snapshot
	S	M&N	FAS	OF
Secondary Efficacy Endpoints				
Percentages of participants with HIV-1 RNA <50 copies/mL and <40 copies/mL at Weeks 24, 48, and 96	P	M&N	FAS	Snapshot
	S	M&N	FAS	OF
Percentages of participants with HIV-1 RNA ≥50 copies/mL at Weeks 24 and 96	P	M&N	FAS	Snapshot
Percentages of participants with HIV-1 RNA ≥50 copies/mL at Week 144	P	Descriptive Statistics	FAS	Snapshot
Change from baseline to Weeks 24, 48, and 96 in CD4+ T-cell count	P	ANCOVA	FAS	DAO
	S	ANCOVA	FAS	LOCF
Change from baseline to Week 144 in CD4+ T-cell count	P	Descriptive Statistics	FAS	DAO
	S	Descriptive Statistics	FAS	LOCF

ANCOVA=analysis of covariance; DAO=Data-As-Observed; FAS=Full Analysis Set; HIV-1=human immunodeficiency virus type 1; LOCF=Last Observation Carried Forward; M&N=Miettinen and Nurminen; OF=Observed Failure; P=Primary approach; RNA=ribonucleic acid; S=Supportive approach; vs=versus.

9.6.1.1 Missing Data Approaches

There are 3 types of missing values:

- intermittent missing values due to a missed or skipped visit or due to an inadequate sample;
- nonintermittent missing values due to premature discontinuations because of treatment-related reasons such as, "adverse event" (regardless of relationship to study intervention) and "withdrew based on HIV-1 RNA results";
- nonintermittent missing values due to premature discontinuations because of other reasons which are not related to study intervention such as loss to follow-up, protocol violation, participant withdrew consent, etc.

Two approaches will be used to handle missing values: 1) FDA "snapshot" approach; and 2) the OF approach.

FDA Snapshot Approach

The primary approach for analysis of the percentage of participants with HIV-1 RNA ≥50 copies/mL is the FDA "snapshot" approach [Food and Drug Administration (CDER) 2015]. Virologic outcome will be defined according to the following categories:

- **HIV-1 RNA <50 copies/mL**: participants who have the last available on-treatment HIV-1 RNA measurement <50 copies/mL at the timepoint of interest within the time window specified in Table 10 in Section 9.6.1.2.
- **HIV-1 RNA ≥50 copies/mL**: this includes participants

  1) Who have the last available on-treatment HIV-1 RNA measurement ≥50 copies/mL at the timepoint of interest within the time window specified in Table 10 in Section 9.6.1.2.

  2) Who do not have on-treatment HIV-1 RNA data in timepoint of interest analysis window and

     a) Who discontinue study intervention prior to or in the timepoint of interest analysis window due to lack of efficacy, or

     b) Who discontinue study intervention prior to or in the point of interest analysis window due to reasons other than lack of efficacy and whose last available on-treatment HIV-1 RNA measurement is ≥50 copies/mL.

- **No Virologic Data in Specified Analysis Time Window**: this includes participants who do not have on-treatment HIV-1 RNA data in the timepoint of interest analysis window because of the following:

    1) Discontinued study intervention due to AE or death: this includes participants who discontinued because of an AE or death at any timepoint from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL.

    2) Discontinued study intervention for other reasons: this includes participants who discontinued study intervention prior to or in the timepoint of interest analysis window due to reasons other than lack of efficacy or AE/death (ie, lost to follow-up, noncompliance with study intervention, physician decision, protocol deviation, withdrawal by participant, etc.) and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL.

    3) On study but missing data in window: only data in the predefined analysis window can be used for participants remaining on study intervention. Participants should be classified as on study but missing data in window regardless of the HIV-1 RNA results outside of the timepoint of interest analysis window.

For primary and secondary efficacy endpoints associated with predefined HIV-1 RNA level, the numerators will be evaluated according to the FDA snapshot algorithm for missing data, divided by the number of participants in the FAS population, and multiplied by 100.

Observed Failure Approach

A second approach, the OF approach will also be performed as a sensitivity analysis for the HIV-1 RNA measurement <50 copies/mL endpoint. Under this approach, participants with nonintermittent missing data who prematurely discontinue study intervention due to lack of efficacy or who discontinue study intervention for other reasons and are virologic failures (HIV-1 RNA ≥50 copies/mL) at the time of study intervention discontinuation are considered as failures at timepoints thereafter. Participants who discontinue study intervention for reasons other than lack of efficacy and who are not failures at the time of study intervention discontinuation will be excluded from the analyses at subsequent timepoints. Participants with intermittent missing data will be considered as successes (HIV-1 RNA <50 copies/mL) if both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements are <50 copies/mL; all other intermittent missing results will be imputed as failures.

The same sensitivity analyses based on the OF approach will also be performed on primary and secondary efficacy endpoints related to percentage of participants achieving HIV-1 RNA <40 copies/mL.

9.6.1.2 Definition of Time Points (or Analysis Visit)

Note: As of Amendment 013-02, the definition of time points after Week 24 associated with Parts 1, 2, and 3 in this section is no longer applicable. The definition of time windows for Unblinded Safety Monitoring period (in Section 1.3.3 and Section 1.3.4) is presented in Table 10.

Table 10 lists the definition of timepoint by time windows (day-ranges) that will be used for the purposes of the statistical analyses and the target relative day for the scheduled visits in the study which will be used for all analyses by timepoint. The last available on-treatment measurement within a window will be used for analyses at a specific timepoint, unless otherwise specified. Results from additional timepoints beyond Week 144 may be summarized, and day-range rules for determining the analysis time windows will follow the same pattern where the ranges start and end at the midpoints between target days.

Assignment of a particular analysis visit to Part 1 or Part 2 will depend on the timing of communication of the selected dose of MK-8507 and the introduction of open-label study intervention. It is likely that Part 2 will not begin until at least Week 60 for all participants, and depending on the duration of enrollment, may not begin until Week 72 or later for at least some participants.

Table 10 Definition of Time Points (or Analysis Visit)

Treatment Phase	Treatment Period	Analysis Visit	Day-Range Rules	Target Day[a]
Pretreatment	Baseline	Day 1	≤1	1
Treatment	Double-blind Dose-ranging Treatment Period (Part 1) or Selected-dose Open-label Treatment Period (Part 2)[b]	Week 2	≥2 and ≤21	15
		Week 4	≥22 and ≤42	29
		Week 8	≥43 and ≤70	57
		Week 12	≥71 and ≤98	85
		Week 16	≥99 and ≤126	113
		Week 24	≥127 and ≤210	169
		Week 36	≥211 and ≤294	253
		Week 48	≥295 and ≤378	337
		Week 60	≥379 and ≤462	421
		Week 72	≥463 and ≤546	505
		Week 84	≥547 and ≤630	589
		Week 96	≥631 and ≤714	673
	ISL + MK-8507 Open-label Treatment Period (Part 3)	Week 100	≥687 and ≤728	701
		Week 108	≥729 and ≤798	757
		Week 120	≥799 and ≤882	841
		Week 132	≥883 and ≤966	925
		Week 144	≥967 and ≤1022	1009

Treatment Phase	Treatment Period	Analysis Visit	Day-Range Rules	Target Day[a]
Non-study ART Treatment	Unblinded Safety Monitoring Period	Follow-up Through Day 42	Within 42 days after the last dose	NA
		Follow-up Week 8	Between 43 and 56 days after the last dose	NA
		For visits beyond Follow-up Week 8 until 60 weeks after last dose, analysis visits will be performed every 4 weeks	Between the upper limit of last follow-up window +1 and the upper limit of last follow-up window +29 after the last dose	NA
	Long-term Unblinded Safety Monitoring	For visits beyond 60 weeks after last dose, analysis visits will be performed every 12 weeks	Between the upper limit of last follow-up window +1 and the upper limit of last follow-up window +85 after the last dose	NA

ISL=islatravir. NA=not applicable

[a] Relative days and target days are computed from the first day of study intervention.

[b] All participants will remain in Part 1 and continue to receive double-blind study intervention until the dose selection decision is confirmed to switch to the selected dose for Part 2.

9.6.2 Statistical Methods for Safety Analyses

Note: As of Amendment 013-02, only descriptive statistics based on available data for Part 1 and Unblinded Safety Monitoring period is applicable for this section. Events that are described below as either Tier 1, 2, or 3 events will now all be summarized descriptively.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. The analysis of safety results will follow a tiered approach by study part (Table 11). The tiers differ with respect to the analyses that will be performed. Adverse events of special interest that are predefined in Section 9.4.2 constitute "Tier 1" safety endpoints. Other safety parameters will be considered as Tier 2 or Tier 3.

Tier 1 and Tier 2 parameters will be assessed via point estimates and 95% CIs provided for between-treatment differences in the percentage of participants with Tier 1 and Tier 2 events according to study part. While there is no inferential testing planned for Tier 1, p-Values will be presented and 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 comparisons. These analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. Change from baseline analyses for appropriate Tier 1 and Tier 2 endpoints will be assessed by ANCOVA models, adjusted by the baseline value.

AEs (specific terms as well as system organ class terms), predefined limits of change in laboratory parameters, and vital signs that are not prespecified as Tier 1 endpoints will be

classified as belonging to “Tier 2” or “Tier 3”, based on the number of participants who exhibit the event. Membership in Tier 2 requires that at least 4 participants in each treatment group exhibit the event during the period under evaluation.

The threshold of at least 4 participants was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 participants that exhibit the event and would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should also 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 laboratory parameters that meet predefined limits of change.

Safety endpoints that are not Tier 2 events are considered Tier 3 events. Only point estimates will be provided by treatment group for Tier 3 safety parameters.

The rest of continuous measures such as change from baseline in laboratory and vital signs parameters that are not prespecified as Tier 2 endpoints, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group according to study part in table format.

Missing safety parameters, unless otherwise specified, will be handled using the DAO approach, that is, any participant with a missing value will be excluded from the analysis. 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 11 summarizes the key safety analyses of the study.

Table 11 Analysis Strategy for Key Safety Endpoints

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Difference	Descriptive Statistics
Tier 1	CCI [redacted]	X	X	X
Tier 2	• The percentage of participants with an AE in each of the following categories: 1 or more AE(s); drug-related AE(s), serious AE(s), AE(s) which are both drug-related and serious, AE(s) [drug-related and nondrug-related] leading to discontinuation of study intervention, and AE(s) leading to death • Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence ≥4 participants in at least 1 treatment group • Change from baseline in select laboratory parameters		X	X
Tier 3	• Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence <4 participants in all treatment groups • Change from baseline in laboratory measurements and vital signs • ECIs			X

AE=adverse event; CI=confidence interval; ECIs=events of clinical interest; PDLC=predefined limit of change; SOC=System Organ Class.

[a] Adverse Experience references refer to both Clinical and Laboratory AEs.

[b] Includes AEs predefined in Section 9.4.2.

CCI [redacted]

- CCI [redacted]

More details of these analyses will be provided in the sSAP.

9.7 Interim Analyses

In addition to routine safety and efficacy monitoring by an eDMC, 2 formal interim analyses will be conducted at Week 24 and Week 48 to aid in dose selection. Although the eDMC may make recommendations regarding the dose selection, the final dose selection will be made by the Sponsor.

Interim Analysis at Week 24

Note: As of Amendment 013-02, interim analysis at Week 24 will no longer be conducted.

Efficacy and safety summaries in support of the Week 24 interim analysis will be conducted by an external unblinded statistician. In addition, select Sponsor personnel (not affiliated with the study team) will be unblinded to support the PK objectives and additional dose selection analyses, including dose response and population PK modeling. The Sponsor study team will remain blinded to participant treatment assignments through the Week 48 interim analysis, although the study team will have access to the treatment-level summaries presented in the Week 24 interim analysis report and will be aware of the preliminary dose selection.

The Week 24 interim analysis report will summarize safety and key secondary efficacy endpoints at Week 24 as well as summarize all accumulated efficacy and safety data received at the time of data cutoff.

Interim Analysis at Week 48

Note: As of Amendment 013-02, interim analysis at Week 48 will no longer be conducted.

When all participants have either reached Week 48 (or discontinued prior), safety and efficacy results through Week 48 will be assessed to support confirmation of MK-8507 dose selection for Part 2. The Sponsor study-team will be unblinded at this time and will prepare the efficacy and safety summaries in support of this interim analysis.

The Week 48 interim analysis report will summarize the primary and secondary efficacy and safety endpoints at Week 48 as well as summarize all accumulated efficacy and safety data received at the time of data cutoff.

Periodic Safety and Efficacy Assessments

Periodic safety and efficacy reviews by an eDMC will be performed regularly as specified in the eDMC charter. The analyses and summaries in support of these reviews will be performed by the external unblinded statistician.

If any of the safety and efficacy criteria defined in Section 4.4.2 are met, the external unblinded statistician will report it to the eDMC who may recommend closing a treatment group on the basis of those criteria. The AEs related to fluorosis and lack of efficacy due to viremia are defined in Sections 9.4.2 and 4.2.1.1.2, respectively.

9.8 Multiplicity

Since there are no formal hypothesis tests, no multiplicity adjustment is planned in this study.

9.9 Sample Size and Power Calculations

Note: As of Amendment 013-02, no between group comparisons will be conducted and power calculations are no longer applicable.

9.9.1 Sample Size and Power for Efficacy Analyses

This study will include approximately 140 participants randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups (35 participants per treatment group). The sample size of the study was not based on formal statistical criteria but there is interest in quantifying the magnitude of treatment differences that can be detected with reasonable certainty. Table 12 displays the treatment differences (ISL + MK-8507 treatment group [either Groups 1-3] minus BIC/FTC/TAF active control group [Group 4]) in event rates (the percentage of participants with HIV-1 RNA ≥50 copies/mL) associated with 80% probability and 35 participants per treatment group. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. and Manning, G. 1990].

Table 12 Treatment Differences in Efficacy Event Rate Associated with 80% Probability (N=35 vs 35)

Hypothetical True Control Event Rate (≥50 copies/mL) in Group 4 (BIC/FTC/TAF)	Hypothetical True Treatment Event Rate (≥50 copies/mL) in ISL + MK-8507	Treatment Difference (ISL + MK-8507 minus BIC/FTC/TAF)
1%	22.0%	21.0%
2%	24.2%	22.2%
3%	26.3%	23.3%
4%	28.2%	24.2%
5%	30.0%	25.0%

Hypothetical True Control Event Rate (≥50 copies/mL) in Group 4 (BIC/FTC/TAF)	Hypothetical True Treatment Event Rate (≥50 copies/mL) in ISL + MK-8507	Treatment Difference (ISL + MK-8507 minus BIC/FTC/TAF)
6%	31.8%	25.8%
7%	33.5%	26.5%
8%	35.1%	27.1%
9%	36.6%	27.6%
10%	38.2%	28.2%

BIC=bictegravir; FTC=emtricabine; ISL=islatravir; TAF=tenofovir disoproxil fumarate.
Calculated using SAS v9.4.

For example, with 35 participants per treatment group, there is approximately 80% probability of obtaining a 2-sided 95% CI for the treatment difference in the proportions of participants with HIV-1 RNA ≥50 copies/mL that would exclude a ≥22.2% treatment difference (in both directions) when the true proportions are, in fact, equal to 2% in both of the treatment groups. This probability statement applies to the 3 treatment differences corresponding to the difference between each specific ISL + MK-8507 treatment group and the active control group, for each applicable time point.

Table 13 provides a selection of observed minimum treatment differences associated with 95% CIs that exclude 0 to give examples of treatment effect sizes that can be detected in a study of this size. This table presents these possible outcomes for a variety of potential observed event rates in the control group (Group 4).

Table 13 Minimum Treatment Difference with the Lower Bound of 95% CI that Excludes 0 (N=35 vs 35)

Minimum Treatment Difference with 95% CI that Excludes 0					
Group 4 (N=35)		Either Groups 1-3 (N=35)		Treatment Difference (Either Groups 1-3 – Group 4) (Percentage Points)	95% CI
Observed Number ≥50 copies/mL	Observed Event Rate ≥50 copies/mL	Observed Number ≥50 copies/mL	Observed Event Rate ≥50 copies/mL		
0	0.0%	4	11.4%	11.4	(0.8, 26.1)
1	2.9%	6	17.1%	14.3	(0.2, 30.5)
2	5.7%	8	22.9%	17.1	(0.7, 34.5)
3	8.6%	10	28.6%	20.0	(1.8, 38.2)
4	11.4%	11	31.4%	20.0	(0.7, 38.8)

Minimum Treatment Difference with 95% CI that Excludes 0					
Group 4 (N=35)		Either Groups 1-3 (N=35)		Treatment Difference (Either Groups 1-3 – Group 4) (Percentage Points)	95% CI
Observed Number ≥50 copies/mL	Observed Event Rate ≥50 copies/mL	Observed Number ≥50 copies/mL	Observed Event Rate ≥50 copies/mL		
5	14.3%	13	37.1%	22.9	(2.3, 42.2)
6	17.1%	14	40.0%	22.9	(1.6, 42.6)
7	20.0%	15	42.9%	22.9	(1.0, 43.0)
8	22.9%	16	45.7%	22.9	(0.5, 43.3)
9	25.7%	17	48.6%	22.9	(0.1, 43.5)
10	28.6%	19	54.3%	25.7	(2.5, 46.4)
CI=confidence interval. Calculated using SAS v9.4.					

For example, with 35 participants per treatment group and an observed event rate of 2.9% in Group 4 (1 out of 35 participants with HIV-1 RNA ≥50 copies/mL), the minimum treatment difference that results in a 95% CI whose lower bound is >0 is 14.3 percentage points, which corresponds to an observed event rate (percentage of participants with HIV-1 RNA ≥50 copies/mL) of 17.1% in either Groups 1-3.

9.9.2 Sample Size and Power for Safety Analyses

Adverse Events

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 incidence of a particular AE is 1%, there is a 29.7% chance of observing at least 1 AE among 35 participants in a treatment group. If no AE of that type is observed among the participants, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <10.0% for a treatment group.

The estimate of, and the upper bound of the 95% CI for, the underlying percentage of participants with an AE given various hypothetical observed number of participants with the AE within each treatment group and active control group are provided in Table 14. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 14 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Number of Participants with AEs

Sample Size	Hypothetical Number of Participants With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
35	0	0.0%	10.0%
35	1	2.9%	14.9%
35	2	5.7%	19.2%
35	5	14.3%	30.3%
35	7	20.0%	36.9%
35	10	28.6%	46.3%

[a] Based on the 2-tailed exact confidence interval of a binomial proportion [Clopper, C. J. and Pearson, E. S. 1934].

Table 15 gives the difference in the incidence of an AE (either Groups 1-3 minus Group 4) that can be ruled out with different probability levels and 95% confidence when there are 35 participants in each treatment group. The underlying incidence of the AE is assumed to be the same for a treatment and active control groups. For example, for a reasonably common AE, which occurs in 20% of participants in both groups, the study has 80% probability to declare with 95% confidence that the true difference between the treatment groups is no more than 31.6 percentage points. The calculations are based on an asymptotic method proposed by Farrington and Manning [Farrington, C. P. and Manning, G. 1990].

Table 15 Difference in Incidence of AEs (either Groups 1-3 minus Group 4) That Can Be Ruled Out (N=35 vs 35)

Target Probability	Underlying AE Incidence Rate						
	1%	5%	10%	20%	30%	40%	50%
80%	21.0	25.0	28.2	31.6	32.8	32.7	31.3
85%	23.3	27.3	30.4	33.8	35.0	34.7	33.1
90%	26.2	30.1	33.2	36.6	37.6	37.1	35.2
95%	30.5	34.3	37.4	40.5	41.3	40.5	38.2

AE=adverse event; CI=confidence interval.

Note: The upper bound of the 2-sided 95% CI (Farrington and Manning [Farrington, C. P. and Manning, G. 1990]) for the difference in AE incidences (either Groups 1-3 minus Group 4).

CCI

[redacted]

CCI [redacted]

9.10 Subgroup Analyses

Note: As of Amendment 013-02, subgroups analyses will no longer be conducted.

The estimate of the between-group treatment effect for the primary efficacy endpoints will be assessed and plotted within each category of the following classification variables:

- Age category (<50, ≥50)
- Sex (female, male)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- CCI [redacted]

The OF approach will be used to handle missing values in these subgroup analyses. No stratification will be used for these analyses. Nominal 2-sided 95% CIs will be calculated for subgroups with at least 10% (4 or more) of participants in both treatment groups of a comparison.

9.11 Compliance (Medication Adherence)

Note: As of Amendment 013-02, summaries associated with Part 1 are applicable and summaries associated with Parts 2 and 3 are no longer applicable for this section.

Compliance will be summarized separately for Part 1 (double-blind period) and Parts 2 and 3 (open-label periods). In addition, compliance will be presented separately for weekly treatments (ISL and its placebo, MK-8507 and its placebo, ISL, and MK-8507) from daily treatments (BIC/FTC/TAF and its placebo).

Daily Compliance:

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

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

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

Summary statistics will be provided on percent compliance for daily treatments by treatment group according to study part for the FAS population. There will be no daily treatments for Groups 1-3 in Part 2 and Part 3 by design.

Weekly Compliance:

For a participant who is followed for the entire period, the "Number of Weeks Should be on Therapy" is the total number of complete weeks from the first dose day to the last scheduled day for treatment administration for that participant per period. For a participant who discontinued from the study permanently, the "Number of Weeks Should be on Therapy" is the total number of complete weeks from the first dose day to the date of the last dose of study medication. A participant must take all required study intervention during a week to be counted in the numerator for a given week.

$$\text{Percent Compliance} = \frac{\text{Number of Complete Weeks on Therapy}}{\text{Number of Complete Weeks Should be on Therapy}} \text{ X } 100$$

Summary statistics will be provided on percent compliance for weekly treatments by treatment group according to the study part for the FAS population. There will be no weekly treatments for Group 4 in Part 2 by design.

Because this assessment does not account for when these weekly treatments are taken relative to the target/scheduled day, additional summaries (including graphical presentations) will be made looking at when doses were taken over time and how dosing deviates from scheduled dosing days.

9.12 Extent of Exposure

Note: As of Amendment 013-02, the summary associated with Part 1 is applicable and summaries associated with Parts 2 and 3 are no longer applicable for this section.

The extent of exposure to study therapy for all randomized and treated participants will be summarized. The number of participants exposed to various doses (actual total daily dose) for defined periods of time will be listed, along with a summary of the mean (range) duration participants were exposed to various doses.

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/subinvaestigator(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

Note: As of Amendment 013-02, administration of study intervention for all treatment groups has been stopped based on Sponsor acceptance of the eDMC recommendation; therefore, there is no longer a need to convene these committees.

10.1.4.1 Executive Oversight Committee

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

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 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.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator

will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including signed ICF, 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 17 will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

- Pregnancy testing:

    - Pregnancy testing requirements for study inclusion are described in Section 5.1.

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

Table 17 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCH concentration RDW	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
CD4+ T-cell Count/TBNK Panel	CD4/CD8 ratio CD3+CD4+% and absolute CD3+CD8+% and absolute CD3+ CD4+ CD8+ % and absolute CD3- CD19+ % and absolute CD3+ CD45+ % and absolute CD16+ CD56+ % and absolute			
Coagulation	PT/INR			
Chemistry	BUN	Potassium	AST	Total bilirubin • Direct bilirubin • Indirect bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT	Total Protein
	Glucose, nonfasting	Calcium	Alkaline phosphatase	Creatinine Clearance
	Creatine kinase	Lipase	Amylase	Magnesium
Additional chemistry at fasting visits (fasting for at least 8h)	Glucose (fasting) HDL-C LDL-C TGs TC Non-HDL-C			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes			
Fluorosis monitoring	Plasma fluoride Urine fluoride PTH			
Pregnancy testing	Serum and urine hCG pregnancy test (for WOCBP)			
Hepatitis screening and monitoring[a]	HBsAg Hepatitis B surface antibody Anti-HBc HBV DNA Hepatitis C antibody (if positive perform plasma hepatitis C virus quantitative test) (at screening only)			
HIV-1 serology	HIV 1/2 antibody test			
Virology	HIV-1 viral RNA quantification (Real Time PCR)			
Pharmacokinetics	Plasma ISL PK Plasma MK-8507 PK CCI [redacted]			

Laboratory Assessments	Parameters
ALT=alanine aminotransferase; anti-HBc=Hepatitis B core antibody; AST=aspartate aminotransferase; BUN=blood urea nitrogen; DNA=deoxyribonucleic acid; HBV=Hepatitis B virus; HBsAg=Hepatitis B surface antigen; hCG=human chorionic gonadotropin; HDL-C=high-density lipoprotein cholesterol; HIV-1=human immunodeficiency virus, Type 1; INR=international normalized ratio; ISL=islatravir; LDL-C=low density lipoprotein cholesterol; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; non-HDL-C=non-high density lipoprotein cholesterol; PCR=polymerase chain reaction; PK=pharmacokinetics; PT=prothrombin time; PTH=parathyroid hormone; RBC=red blood cell; RDW=red cell distribution width; RNA=ribonucleic acid; TBNK=T- and B- Lymphocyte and Natural Killer Cell; TC=total cholesterol; TGs=triglycerides; WBC=white blood cell; WOCBP=a woman/women of childbearing potential. [a] All participants will be screened for HBsAg, Hepatitis B surface antibody, anti-HBc, and HBV DNA. Participants that are anti-HBc positive but HBV DNA negative will have HBsAg and HBV DNA monitored for the duration of the study.	

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

Note: As of Amendment 013-02, Table 20 outlines the blood volume collection for the remainder of the study per the SoA in Section 1.3.3. Table 18 and Table 19 are no longer applicable.

Table 18 Blood Volumes – Screening and Parts 1, 2, and 3

Study Period	**Screening**	**Intervention**																	
Scheduled Day/Week	Screening	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 100[c]	Week 108	Week 120	Week 132	Week 144
Blood Parameter	**Approximate Blood Volume (mL)**																		
Plasma HIV-1 RNA Quantification (Real Time PCR)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
CD4+ T-cell Count/TBNK Panel	6	6				6		6	6	6		6		6			6		6
Plasma for HIV Viral Drug Resistance Testing		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
HIV-1 & 2 and Hepatitis[a] Serology	6																		
HIV-1 confirmation (Geenius)	1																		
HBsAg[a,b]		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
HBV DNA[a]	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Chemistry (Includes Serum Pregnancy at Screening)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Hematology	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Fasting Lipids		2		2				2		2		2		2			2		2
PT/INR	2.7																		
Plasma fluoride		4			4		4	4	4	4	4	4	4	4	4	4	4	4	4
Serum PTH		2						2		2									
Blood (Plasma) for ISL and MK-8507 PK		4		8	4	4		8		8		4		4					4

Study Period	**Screening**	**Intervention**																
Scheduled Day/Week	Screening	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 100[c]	Week 108	Week 120	Week 132	Week 144
Blood Parameter	**Approximate Blood Volume (mL)**																	
Blood (Plasma) for Investigational PK			4				4		4		4		4				4		
CCI																			
Blood for Genetic Analysis		8.5																	
Whole Blood for FBR		8						8		8				8					8
Total Blood Volume per Visit (mL)	36	69	38	44	42	44	42	64	48	64	42	50	42	58	38	38	50	38	58

anti-HBc=Hepatitis B core antibody; CD4+=CD4-positive; DNA=deoxyribonucleic acid; FBR=future biomedical research; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus, Type 1; INR=international normalized ratio; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic(s); PT=prothrombin time; PTH; parathyroid hormone; RNA=ribonucleic acid; TBNK=T- and B- Lymphocyte and Natural Killer Cell.

a. All participants will be screened for HBsAg, Hepatitis B surface antibody, anti-HBc, and HBV DNA. Participants that are anti-HBc positive, but HBV DNA negative, will have HBsAg and HBV DNA monitored for the duration of the study.

b. HBsAg is tested as part of the HIV-1 & 2 and Hepatitis Serology sample at Screening.

c. Week 100 is only for participants in Group 4.

Note: Approximately 1025 mL of blood will be collected during the study.

Table 19 Blood Volumes – Unscheduled Visits

Study Period	Viremia Confirmation	Skeletal Fluorosis Evaluation	Early Discontinuation of Treatment	End of Treatment Follow-Up
Scheduled Day/Week	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**			
Plasma HIV-1 RNA Quantification (Real Time PCR)	6		6	6
CD4+ T-cell Count/TBNK Panel			6	6
Plasma for HIV Viral Drug Resistance Testing	12[a]		12[a]	12
Chemistry (Includes Serum Pregnancy at Early Discontinuation of Treatment and End of Treatment Follow-up visits)			6	6
Hematology			2	2
Plasma fluoride		4	4	
Blood (Plasma) for Investigational PK	4	4	4	4
Whole Blood for FBR	8		8	
Total Blood Volume per Visit (mL)	30	8	48	36

CD4+=CD4-positive; FBR=future biomedical research; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus Type 1; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; TBNK=T- and B- Lymphocyte and Natural Killer Cell.
a. If HIV drug resistance sample is collected at Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit.
Note: Approximately 1025 mL of blood will be collected during the study.

Note: As of Amendment 013-02, Table 20 outlines the blood volume collection for the remainder of the study per the SoA in Section 1.3.3. Table 18 and Table 19 are no longer applicable.

Table 20 Blood Volumes – Amendment 02

Study Period	Early Discontinuation of Treatment	**Unblinded Safety Monitoring (Groups 1, 2, and 3 Only)**													End of Treatment Telephone Contact (42 days after last dose)
Scheduled Day/Week		Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 72	Week 84	
Blood Parameter	**Approximate Blood Volume (mL)**														
Plasma HIV-1 RNA Quantification	6					6			6			6			
CD4+ T-cell Count/TBNK Panel	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
HBsAg	2														
HBV DNA	6														
Chemistry	6					6			6			6		6	
Hematology	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
Blood ISL & MK-8507 Plasma PK	4	4	4	4	4	4	4	4	4	4	4	4			
CCI [redacted]	0.12														
Total Blood Volume per Visit (mL)	**32.1**	**12**	**12**	**12**	**12**	**24**	**12**	**12**	**24**	**12**	**12**	**24**	**8**	**14**	**0**

CD4+=CD4-positive; DNA=deoxyribonucleic acid; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; HIV-1=human immunodeficiency virus, Type 1; ISL=islatravir; PK=pharmacokinetic(s); RNA=ribonucleic acid; TBNK=T- and B- Lymphocyte and Natural Killer Cell.

Note: For participants in Groups 1-3, approximately 222.1 mL of blood will be collected during the remainder of the study (Early Discontinuation of Treatment visit and Unblinded Safety Monitoring period). For participants in Group 4, approximately 32.1 mL of blood will be collected during the remainder of the study (Early Discontinuation of Treatment visit and End of Treatment Telephone Contact).

Note: As of Amendment 013-03, Table 21 outlines the blood volume collection for the Long-term Unblinded Safety Monitoring of the study per the SoA in Section 1.3.4.

Table 21 Blood Volumes – Amendment 03

Study Period	**Long-term Unblinded Safety Monitoring: (Groups 1, 2, and 3 Only) [a]**
Scheduled Day/Week	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**
CD4+ T-cell Count/TBNK Panel	6
Chemistry	6
Hematology	2
Total Blood Volume per Visit (mL)	**14**

CD4+=CD4-positive; TBNK=T- and B- Lymphocyte and Natural Killer Cell.

a. Long-term Unblinded Safety Monitoring as outlined in Section 1.3.4 is required for participants in Groups 1-3 of whom total lymphocyte and CD4+ T-cell counts have not recovered within 10% of baseline during the initial 12-months of follow-up. Participants in Groups 1-3 will continue to be followed up every 12 weeks ±7 days until total lymphocyte and CD4+ T-cell criteria for recovery are met.

b. Approximately 14 mL of blood will be collected at each visit every 12 weeks ±7 days during the long-term Unblinded Safety Monitoring period of the study until total lymphocyte and CD4+ T-cell criteria for recovery are met. The total volume of blood collected during the long-term safety monitoring period will vary depending on the number of visits required to meet the recovery criteria for total lymphocyte and CD4+ T-cell counts.

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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.

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

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

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

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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE 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.

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman (including a transgender male who is assigned female sex at birth) is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

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

Women in the following categories are not considered WOCBP:

- Transgender Women (assigned male sex at birth)
- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to

continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

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

10.5.2 Contraception Requirements

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

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link 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

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

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@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

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

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-Specific Requirement for France

CCI [redacted]

- CCI [redacted]

10.8 Appendix 8: Calculation of Creatinine Clearance

Cockcroft-Gault equations:

- If male:

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

- If female:

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

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ANCOVA	analysis of covariance
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	anti-retroviral therapy
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
hCG	human chorionic gonadotropin
BIC	bictegravir
BID	twice daily
BMI	body mass index
BP	blood pressure
C_{168}	Concentration at 168 hours postdose
CAC	Clinical Adjudication Committee
CD4+	CD4-positive
CG	Cockcroft-Gault
CI	confidence interval
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CL	clearance
C_{max}	maximum (peak) observed drug concentration
Cr_{Cl}	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
DAIDS	Division of AIDS
DAO	data-as-observed
DDIs	drug-drug interactions
DEXA	Dual X-ray Absorptiometry
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravirine
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
ECOG	Eastern Cooperative Oncology Group
eDMC	external Data Monitoring Committee
EFV	efavirenz
eGFR	estimated glomerular filtration rate

Abbreviation	Expanded Term
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FBR	future biomedical research
FSH	follicle stimulating hormone
FTC	Emtricitabine
GCP	Good Clinical Practice
GI	Gastrointestinal
HAT-QoL	HIV/AIDS-Targeted Quality of Life
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVTSQs	HIV Treatment Satisfaction Questionnaire, status version
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals of Human Use
iCRO	imaging CRO
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ISL	Islatravir (MK-8591)
ISL-TP	triphosphate form of islatravir
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCS	not clinically significant
NDA	New Drug Application
NK	Natural killer

Abbreviation	Expanded Term
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OF	observed failure
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PI	protease inhibitor
PK	pharmacokinetic
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
QD	Once daily
QW	Once weekly
QOL	quality of life
QP2	department of quantitative pharmacology and pharmacometrics
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TBNK	T- and B- Lymphocyte and Natural Killer Cell
TDF	tenofovir disoproxil fumarate
US	United States
VDM	viral dynamics model
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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