

Official Protocol Title:	A Phase 3, Randomized, Active-Controlled, Open-Label Clinical Study to Evaluate a Switch to Doravirine/ Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Antiretroviral Therapy
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TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Active-Controlled, Open-Label Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Antiretroviral Therapy

Protocol Number: 051-04

Compound Number: MK-8591A

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

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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 4	07-MAR-2025	To add ECIs requiring expedited reporting to the Sponsor at the request of a health authority.
Amendment 3	08-AUG-2024	To extend the study from Week 96 to Week 144 (base study) to provide additional safety and efficacy data, and to add an optional study extension with access to DOR/ISL up to Week 240 or until commercially accessible (whichever comes first).
Amendment 2	27-OCT-2023	To provide for increased HIV-1 RNA monitoring during pregnancy (if recommended in local guidelines), to clarify the management of participants with decreases in total lymphocyte and in CD4+ T-cell counts and the management of participants with HIV-1 viremia.
Amendment 1	17-FEB-2023	This protocol amendment is applicable only to South Africa and participants entering study MK-8591A-051 from study MK-8591A-020 on BIC/FTC/TAF as their ART regimen. Because BIC/FTC/TAF is registered but not commercially available in South Africa, participants in South Africa randomized to Group 2 in study MK-8591A-051 will continue to receive MSD-supplied BIC/FTC/TAF as their ART regimen.
Original Protocol	18-OCT-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

To add ECIs requiring expedited reporting to the Sponsor at the request of a health authority.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 8.4.7 Events of Clinical Interest	Added 2 study-specific ECIs for elevated liver-related laboratory values for Group 2 participants during the first 48 weeks of DOR/ISL treatment that are to be reported to the Sponsor within 24 hours of learning of the event.	Health authority/agency feedback requiring these changes.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Table 5: Updated table to reflect that potential or confirmed DILI would be reported as SAE with OME criteria in the absence of other serious criteria.	To maintain continued regulatory reporting compliance in alignment with new Health Authority DILI reporting requirements
Section 8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information	Specified that reportable safety events include potential DILI or confirmed DILI.	See rationale for Section 8.4.1.
Section 8.4.7 Events of Clinical Interest	Initial ECI updated to potential DILI or confirmed DILI events, with associated reporting requirements.	See rationale for Section 8.4.1.
Section 10.1.6 Compliance with Study Registration and Results Posting Requirements	Added statement that a summary of the study results will be submitted.	For compliance with the EU Clinical Trials Regulation 536/2014.
Section 10.3.3 Definition of SAE	Added potential DILI or confirmed DILI to the definition of SAE with OME criteria in the absence of other serious criteria.	See rationale for Section 8.4.1.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Active-Controlled, Open-Label Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Antiretroviral Therapy

Short Title: DOR/ISL 100 mg/0.25 mg QD Open-Label Switch

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in participants ≥ 18 years of age with HIV-1 who have been virologically suppressed (ie, HIV-1 RNA < 50 copies/mL) for ≥ 3 consecutive months on a stable oral 2- or 3-drug combination (\pm PK booster) ART.

Primary Objective	Primary Endpoint
To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued baseline ART, as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 Hypothesis (H1): DOR/ISL is non-inferior to continued baseline ART, as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48. A margin of 4 percentage points is used to define non-inferiority.	HIV-1 RNA
To evaluate the safety and tolerability of a switch to DOR/ISL compared with continued baseline ART, as assessed by review of the safety data accumulated through Week 48	Adverse events Adverse events leading to discontinuation of study intervention

Secondary Objectives	Secondary Endpoints
<p>To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued baseline ART, as assessed by the percentage of participants with the following at Week 48:</p> <ul style="list-style-type: none"> • HIV-1 RNA <200 copies/mL • HIV-1 RNA <50 copies/mL 	HIV-1 RNA
<p>To evaluate the antiretroviral activity of a switch to DOR/ISL in participants who switched from baseline ART to DOR/ISL on Day 1, as assessed by the percentage of participants with the following at Week 96 and Week 144:</p> <ul style="list-style-type: none"> • HIV-1 RNA \geq50 copies/mL • HIV-1 RNA <200 copies/mL • HIV-1 RNA <50 copies/mL 	HIV-1 RNA
<p>To evaluate the antiretroviral activity of a switch to DOR/ISL in participants who continued baseline ART and switched to DOR/ISL at Week 48, as assessed by the percentage of participants with the following at Week 96 and Week 144:</p> <ul style="list-style-type: none"> • HIV-1 RNA \geq50 copies/mL • HIV-1 RNA <200 copies/mL • HIV-1 RNA <50 copies/mL 	HIV-1 RNA
<p>To evaluate the immunologic effect of a switch to DOR/ISL compared with continued baseline ART, as assessed by the mean change from baseline in CD4+ T-cell count at Week 48</p>	CD4+ T-cell count

<p>To evaluate the immunologic effect of a switch to DOR/ISL, as assessed by the mean change in CD4+ T-cell count:</p> <ul style="list-style-type: none"> • From baseline (Day 1) to Week 96 and from Week 48 to Week 96 in participants who switched from baseline ART to DOR/ISL on Day 1 • From baseline (Day 1) to Week 144 and from Week 48 to Week 144 in participants who switched from baseline ART to DOR/ISL on Day 1 • From Week 48 to Week 96 in participants who continued baseline ART and switched to DOR/ISL at Week 48 • From Week 48 to Week 144 in participants who continued baseline ART and switched to DOR/ISL at Week 48 	<p>CD4+ T-cell count</p>
<p>To evaluate the development of viral drug resistance to any study intervention at Week 48, Week 96, and Week 144</p>	<p>Viral resistance-associated substitutions</p>
<p>To evaluate the effect on fasting LDL-C and non-HDL-C of a switch to DOR/ISL compared with continued baseline ART by baseline ART class (PI- containing regimens [including PI- + InSTI-containing regimens], InSTI-containing regimens [non-PI-containing regimens], and non-PI- and non-InSTI-containing regimens), as assessed by the mean change in fasting LDL-C and non-HDL-C from baseline to Week 48</p> <p>If non-inferiority of DOR/ISL to continued baseline ART at Week 48 (H1) is met, the following hypothesis will be tested for each parameter within each stratum:</p>	<p>Fasting LDL-C and non-HDL-C</p>

<p>Hypothesis (H2): DOR/ISL is superior to continued baseline ART in each baseline ART stratum (in the order of: PI-containing regimens [including PI- + InSTI-containing regimens], non-PI- and non-InSTI-containing regimens, and InSTI-containing regimens [non-PI-containing regimens]), as assessed by the mean change from baseline in fasting LDL-C and non-HDL-C at Week 48.</p>	
<p>To evaluate the safety and tolerability of a switch to DOR/ISL compared with continued baseline ART, as assessed by review of the safety data accumulated through Week 144:</p> <ul style="list-style-type: none"> • From baseline (Day 1) through Week 96 and from Week 48 through Week 96 in participants who switched from baseline ART to DOR/ISL on Day 1 • From baseline (Day 1) through Week 144 and from Week 48 through Week 144 in participants who switched from baseline ART to DOR/ISL on Day 1 • From Week 48 through Week 96 in participants who continued baseline ART and switched to DOR/ISL at Week 48 • From Week 48 through Week 144 in participants who continued baseline ART and switched to DOR/ISL at Week 48 	<p>Adverse events</p> <p>Adverse events leading to discontinuation of study intervention</p>

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	HIV infection
Population	Participants ≥ 18 years of age with HIV-1 who have been virologically suppressed for ≥ 3 consecutive months on a stable oral 2-drug or 3-drug combination (\pm PK booster) ART
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 501 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Group 1	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Day 1 to Week 144	Test Product
Group1	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product
Group 2	Baseline antiretroviral therapy regimen	Per Approved Product Label	Per Approved Product Label	Oral	Day 1 to Week 48	Comparator
Group 2	Baseline antiretroviral therapy regimen (bictegravir/ emtricitabine/ tenofovir alafenamide only)	Per Approved Product Label	Per Approved Product Label	Oral	Day 1 to Week 48	Comparator
Group 2	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 48 to Week 144	Test Product
Group 2	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product

QD=once-daily

Note: Applicable only to South Africa. The Sponsor will centrally supply bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as active comparator for participants in South Africa to continue receiving BIC/FTC/TAF as their ART regimen (ie, participants receiving BIC/FTC/TAF in study MK-8591A-020 who enroll in study MK-8591A-051 and are randomized to Group 2).

Allowed drug classes for baseline ART regimen include NRTIs, NNRTIs, PIs, InSTIs, and PK boosters.

The Sponsor will not provide baseline ART medications for participants continuing their baseline ART regimens. Participants will provide their own ART medications, in accordance with local regulations. Country-specific requirements are noted in Appendix 7.

Study intervention will be extended for participants who become pregnant on-treatment and provide documented informed consent to continue their assigned study intervention (DOR/ISL or baseline ART), as specified in Sections 1.3.4 and 8.11.6.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the base study for approximately 3 years from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 45 days, each participant will receive assigned open-label study intervention for approximately 48 weeks. After 48 weeks of the assigned therapy, all participants will receive open-label DOR/ISL through Week 144. After Week 144, participants will be given the option to continue in an optional study extension and receive DOR/ISL for up to an additional 96 weeks or until DOR/ISL is commercially accessible (whichever comes first). Participants who discontinue study intervention or who become pregnant will be followed as described in the protocol.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

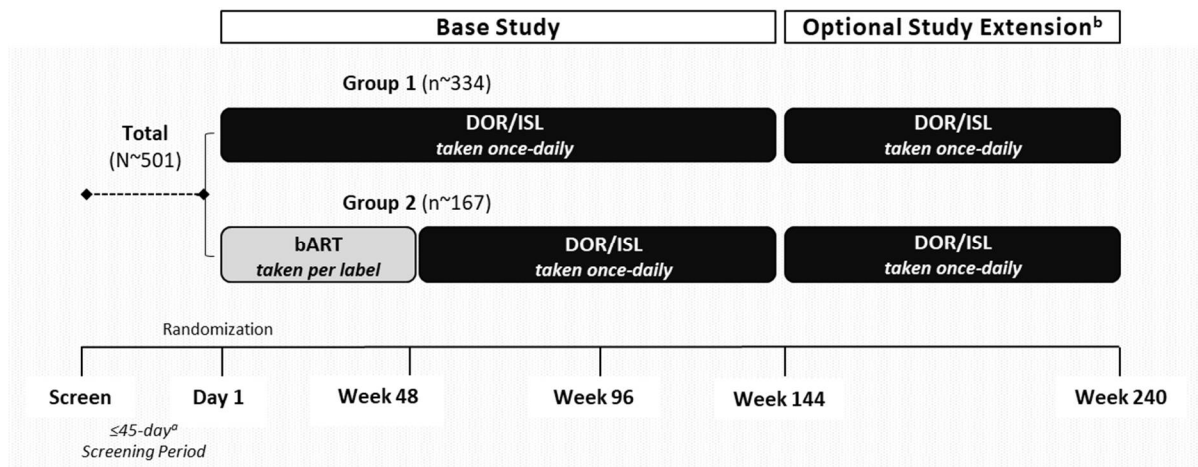
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in [Figure 1](#).

Figure 1 Study Schema and Treatment Plan



bART=baseline antiretroviral therapy; DOR=doravirine; ISL=islatravir; N=total number of participants in the study; n=number of participants in the intervention group.

- ^a Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed.
- ^b For participants who continue optional study extension, study visits will occur every 24 weeks.

1.3 Schedule of Activities

1.3.1 Schedule of Activities – Screening Through Week 144 – Open-Label Intervention (Base Study)

This SoA applies to all participants in the base study. Manage pregnant participants per Section 8.11.6. For the optional study extension, see Sections 8.11.2.4 and Section 1.3.5 (SoA).

- The Early Discontinuation of Treatment Visit applies to any participant who discontinues study intervention prior to Week 144 (Section 8.11.3).
- Manage participants with viremia per Section 8.11.4 and Section 1.3.2 (SoA).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 and Section 1.3.3 (SoA).

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes			
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled					
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)				
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment					
							Administrative Procedures															
Informed Consent	X																					
Informed Consent for Future	X																					

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Biomedical Research																			
Post-Base Study Disposition Planning														X	X	X			Proactively discuss prior to the Week 144 visit (see Section 8.11.2.2)
Informed Consent for Optional Study Extension																X			Obtain prior to dispensing study intervention at Week 144.
Informed Consent for DOR/ISL During Pregnancy			<-----X----->																Obtain upon confirmation of pregnancy. See Section 8.1.1.3.
Collect and Enter Data From Prenatal Care Provider			<-----X----->																See Section 8.11.6 for prenatal safety monitoring.
Informed Consent for Infant Data Safety Collection			<-----X----->																Obtain after confirmation of continuing pregnancy. See Sections 8.1.1.4 and 8.11.6.4.

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Administration of EQ-5D-5L, HIVTSQ, and HIV-SI/SDM Patient Questionnaires		X	X	X			X					X					(X)		Administer in the order listed, before the participant is seen by the investigator and before discussing medical conditions or test results. (Do not administer after the Week 96 visit).
Inclusion/Exclusion Criteria	X	X																	Review prior to randomization on Day 1 to confirm eligibility.
Participant Identification Card	X	X																	Site personnel will add treatment/randomization number.
Medical History	X																		
Tobacco and Alcohol Assessments	X						X					X				X			

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Prior and Concomitant Medications Review	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		
Intervention Randomization		X																	All pretreatment procedures should be completed prior to randomization on Day 1.
Dispense DOR/ISL Using IRT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)			(Dispense at Week 144 for eligible participants entering the optional study extension and if needed for those whose pregnancy or Postpartum visit(s) extends past Week 144.)

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Study Intervention Compliance Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		For participants whose pregnancy or Postpartum visit(s) extends past Week 144, see Section 1.3.4.
Efficacy Procedures																			
Plasma HIV-1 RNA Quantification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.1. See Section 8.11.6.1 for testing in participants who become pregnant.
Blood (Plasma) for HIV-1 Drug Resistance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
Whole Blood for HIV-1 Viral Drug Resistance Testing		X																	Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Safety Procedures																			
Full Physical Examination	X																X		
Height		X																	
Weight	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	
Local 12-lead ECG		X																	Perform up to 7 days prior to Day 1 and after all other eligibility criteria are confirmed.
Contraceptive Use Confirmation (POCBP Only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Contraception is required for 42 days after the last dose of study intervention (see Section 8.3.4).
Serum Pregnancy Test (hCG) (POCBP Only)	X																		A highly sensitive urine pregnancy test may be performed instead of serum. See Section 5.1.

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Urine Pregnancy Test (hCG) (POCBP Only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Pregnancy must be excluded on Day 1 before randomization. Confirm positive or indeterminant urine test with serum.
HIV-1 and HIV-2 Serology	X																		
Hepatitis B Serology and HBV DNA	X						X					X					X		Repeat serology and HBV DNA testing at Weeks 48, 96, and 144. Encourage HBV vaccination to participants who are not immune to HBV.
HBsAg and HBV DNA (Group 1)		(X)	(X)	(X)	(X)	(X)	(X)		(X)	(X)	(X)	(X)		(X)		(X)			(Only anti-HBc-positive participants at each visit. See Section 8.3.6.)

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
HBsAg and HBV DNA (Group 2)						(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)		(X)			(Only anti-HBc-positive participants at each visit [starting at Week 36 for Group 2]).
Hepatitis B Serology and HBV DNA in Pregnant Participants (DOR/ISL only)		<------(X)----->																Collect once after pregnancy is confirmed or report local laboratory results. See Section 8.11.6.1.	
Hepatitis C Serology	X																		See Section 8.3.7. Repeat screening if indicated per local standard of care.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Fasting required at Day 1 and Weeks 24, 48, 96, and 144 (see Section 8.3.9.1 and Appendix 2). Pregnant participants should not fast.

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Manage participants who meet the discontinuation criteria for total lymphocyte count (Table 4) per Sections 1.3.3 and 8.11.5
PT/INR	X																		
Urinalysis		X			X		X			X		X		X		X	X		
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics																			
Blood (Plasma) for ISL PK		X	X	X	X		X												For Group 1 only. At Week 4, if daytime dosing, obtain pre- and postdose or, if evening dosing, collect only 1 sample irrespective of time of last dose. See Section 8.6.1 (Table 6).

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Blood (Plasma) for Investigational ISL PK (Group 1)						X			X	X	X	X							See Section 8.6.1.
Blood (Plasma) for Investigational ISL PK (Group 2)								X	X	X	X	X							See Section 8.6.1.
Blood (Plasma) for DOR and ISL PK in Pregnant Participants (DOR/ISL only)			<-----X----->														X		Collect during the 1st, 2nd, and 3rd trimesters and postpartum. See Section 8.11.6.1 (Table 7).
Exploratory Clinical Markers																			
Waist and Hip Measurements		X					X					X				X			Not applicable to pregnant participants.
Blood and Urine for Renal Markers		X			X		X					X				X			
Blood for Energy and Metabolism Markers		X			X		X					X				X			Do not collect during pregnancy.

Study Period	Screening ^a	DOR/ISL or Baseline ART Regimen (Base Study)					DOR/ISL (Base Study)										End of Treatment		Notes
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unscheduled		
Scheduled Day/Week	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment ^b	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 days	NA	±7 days (Calculate each visit from date of Day 1)														NA	42 (+7) days after end of treatment	
Biomarkers																			
Blood for Genetic Analysis ^c		X																	Collect predose. See Section 8.8.1.
Whole Blood for FBR		X			X		X			X		X				X	X		Optional participation; requires FBR consent. Collect Day 1 sample predose; remaining samples may be collected at any time irrespective of last dose.

AE=adverse event; anti-HBc=hepatitis B core antibody; ART=antiretroviral therapy; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; INR=international normalized ratio; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; SAE=serious adverse event; TBNK=T and B Lymphocyte and Natural Killer Cell.

^a Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed.

^b Participants discontinued at a Scheduled Visit, should complete the assessments for the Scheduled Visit as well as for the Early Discontinuation of Treatment Visit. Collection of laboratory samples should not be duplicated.

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

1.3.2 Schedule of Activities – Viremia Confirmation and End of Treatment for Participants With Viremia (Except Those With Specified Decreases in Total Lymphocyte Count and/or CD4+ T-cell Count)

This SoA only applies to participants requiring viremia confirmation in the base study and/or optional study extension.

- Clinically significant confirmed viremia requires discontinuation (Sections 8.2.2.1.1 and 8.11.4).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 and Section 1.3.3 (SoA).

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	NA	42 (+7) days after the end of treatment	
Administrative Procedures						
Prior and Concomitant Medications Review	X	X	X	X	X	
Register Study Visit in IRT	X	X		X		
Study Intervention Compliance Review	X	X				

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	NA	42 (+7) days after the end of treatment	
Administration of EQ-5D-5L, HIVTSQ, and HIV-SI/SDM Patient Questionnaires		(X)				Administer in the order listed, before participant is seen by the investigator and before discussing medical conditions or test results. (Do not administer after Week 96 visit.)
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X	X	See Section 8.2.1.
Plasma for HIV-1 Drug Resistance	X	(X)		(X)		(Do not collect at Discontinuation of Treatment visit if collected at the Viremia Confirmation visit.) Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
TBNK Panel/CD4+ T-cell Count		X		X		
Safety Procedures						
Full Physical Examination		X				

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	NA	42 (+7) days after the end of treatment	
Directed Physical Examination			X	X	X	
Weight		X	X			
Vital Signs		X	X			
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	Contraception is required 42 days after the last dose of study intervention (Section 8.3.4).
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	Confirm positive or indeterminant urine test with serum. If positive, manage participant per Section 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Chemistry		X				
Hematology		X		X		
Urinalysis		X				
AE/SAE Review	X	X	X	X	X	
Pharmacokinetics						
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK	X	X				Do not collect during pregnancy. Analysis performed by Sponsor as needed. See Section 8.6.1.

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	NA	42 (+7) days after the end of treatment	
Blood (Plasma) for DOR and ISL PK	X	X		X		Only for pregnant participants on DOR/ISL. Collect irrespective of time of last dose and record time of last dose of study intervention in appropriate source documentation.
Biomarkers						
Whole Blood for FBR	X	(X)				Optional participation; requires FBR consent. Collect irrespective of time of last dose. (If collected at preceding Viremia Confirmation visit, do not collect at Early Discontinuation of Treatment visit.)
AE=adverse event; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; RNA=ribonucleic acid; SAE=serious adverse event; TBNK=T and B Lymphocyte and Natural Killer Cell. ^a Participants who discontinue at a Scheduled Visit, should complete the assessments for the Scheduled Visit as well as for the Early Discontinuation of Treatment Visit. Collection of laboratory samples should not be duplicated.						

1.3.3 Schedule of Activities for Participants Who Meet the Discontinuation Criteria for Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count

This SoA only applies to participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts in the base study and/or optional study extension.

- Manage participants with Viremia per Sections 8.2.2, Section 8.11.4 and Section 1.3.2 (SoA).

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Administrative Procedures							
Prior and Concomitant Medications Review	X	X	X	X	X	X	
Register Study Visit in IRT	X	X		X		X	

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Study Intervention Compliance Review	X	X					
Administration of EQ-5D-5L, HIVTSQ, and HIV-SI/SDM Patient Questionnaires		(X)					Administer in the order listed, before the participant is seen by the investigator and before discussing medical conditions or test results. (Do not administer after the Week 96 visit.)

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Efficacy Procedures							
Plasma HIV-1 RNA Quantification		X	X	X	X		See Section 8.2.1.
Plasma for HIV-1 Drug Resistance		X		X			Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X	
Safety Procedures							
Full Physical Examination		X					

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Directed Physical Examination			X	X	X		
Weight		X	X				
Vital Signs		X	X				
Contraceptive Use Confirmation (POCBP Only)		X	X	X	X		Contraception is required for 42 days after the last dose of study intervention.

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Urine Pregnancy Test (hCG) (POCBP Only)		X	X	X	X		Confirm positive or indeterminant urine test with serum. If positive, manage participant per Section 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Chemistry		X					
Hematology	X	X	X	X	X	X	
Urinalysis		X					
AE/SAE Review	X	X	X	X	X	X	

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Pharmacokinetics							
Blood (Plasma) for Investigational ISL PK	X	X					Do not collect during pregnancy. Analysis performed by Sponsor as needed. See Section 8.6.1.

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Biomarkers							
Whole Blood for FBR		(X)					Optional participation; requires FBR consent. Collect irrespective of time of last dose. (If collected at preceding CD4/Lymph Confirmation visit, do not collect at Early Discontinuation of Treatment visit.)

Study Period	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	End of Treatment (Base Study)		End of Treatment (Optional Study Extension)		Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)	Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study) ^a	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease (or at next scheduled visit)	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
AE=adverse event; DOR=doravirine; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential RNA=ribonucleic acid; SAE=serious adverse event; TBNK=T and B Lymphocyte and Natural Killer Cell.							
^a Participant discontinued at a Scheduled Visit, should complete the assessments for the Scheduled Visit as well as the Early Discontinuation of Treatment Visit. Collection of laboratory samples should not be duplicated.							

1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 144

This SoA only applies to eligible participants who are pregnant at Week 144 or who become pregnant in the optional study extension and consent to continue study intervention during pregnancy. Participants will have visits every 12 weeks during the pregnancy and once postpartum. If delivery is premature or the 1st trimester visit is missed, the participant may have ≤ 3 visits before delivery plus the postpartum visit. See Section 8.11.6.

- Manage participants with viremia per Sections 8.2.2, Section 8.11.4 and Section 1.3.2 (SoA).
- Participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 and Section 1.3.3 (SoA).

Study Period	Pregnancy			Postpartum	End of Treatment ^a	Notes
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days				42 (+7) days after the end of treatment	
Administrative Procedures						
Collect and Enter Data From Prenatal Care Provider	<-----X----->					Obtain relevant prenatal clinical and laboratory data to monitor the safety of the mother and fetus per Section 8.11.6.
Register Study Visit in IRT	X	X	X	X		
Dispense DOR/ISL Using IRT	X	X	X	X		See Section 1.3.1 or 1.3.5 as applicable.
Study Intervention Compliance Review	X	X	X	X		
Prior and Concomitant Medications Review	X	X	X	X	X	
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X	X	See Section 8.2.1. Manage participants with viremia per Sections 1.3.2 and 8.2.2.

Study Period	Pregnancy			Postpartum	End of Treatment ^a	Notes
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days				42 (+7) days after the end of treatment	
Plasma for HIV-1 Drug Resistance	X	X	X	X	X	Analysis performed by Sponsor if indicated per Section 8.2.2.1.2
TBNK Panel/CD4+ T- cell Count	X	X	X	X	X	
Safety Procedures						
Weight	X	X	X	X	X	
Directed Physical Examination	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Hepatitis B Serology and HBV DNA (DOR/ISL only)	<-----X----->					Collect once after pregnancy is confirmed or report local laboratory results. See Section 8.11.6.1.
Chemistry	X	X	X	X	X	
Hematology	X	X	X	X	X	
Urinalysis	X	X	X	X	X	
AE/SAE Review	X	X	X	X	X	
Pharmacokinetics						
Blood (Plasma) for DOR and ISL PK	X	X	X	X	X	Collect only for participants on DOR/ISL during the 1 st , 2 nd , and 3 rd trimesters and postpartum per Section 8.11.6.1 (Table 7).
AE=adverse event; ART=antiretroviral therapy; DNA=deoxyribonucleic acid; DOR=doravirine; FBR=future biomedical research; HBV=hepatitis B virus; HIV-1= human immunodeficiency virus type 1; IRT=Interactive Response Technology; ISL=islatravir; PK=pharmacokinetic(s); RNA=ribonucleic acid; SAE=serious adverse event; TBNK=T and B Lymphocyte and Natural Killer Cell. ^a The procedures in this End of Treatment Follow-up visit should be followed for those participants not continuing in the optional study extension.						

1.3.5 Schedule of Activities –Week 144 Through Week 240 (Optional Study Extension)

This SoA only applies to participants who enter the optional study extension at Week 144. Duration of participation in the optional study extension is dependent on when DOR/ISL becomes commercially accessible, with a maximum treatment duration of 96 weeks (ie, total study intervention duration of up to 240 weeks).

- Manage participants with viremia per Section 8.11.4 and Section 1.3.2 (SoA).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 and Section 1.3.3 (SoA).
- Manage pregnant participants per Section 8.11.6 and Section 1.3.4 (SoA).

Study Period	Optional Study Extension				End of Treatment		Notes
Visit Number	17	18	19	20	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (Optional Study Extension) ^a	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	±14 days (Calculate each visit from date of Day 1)				NA	42 (+7) days after end of treatment	
Evaluate Local Accessibility of DOR/ISL	X	X	X	X			Once DOR/ISL is commercially accessible, participants should return to the study site for the Discontinue of Treatment visit and transition to the local supply.
Prior and Concomitant Medication Review	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X		
Dispense Study Intervention Using IRT	X	X	X	(X)			(Dispense at Week 240 if needed for pregnant participants, see Section 1.3.4).
Study Intervention Compliance Review	X	X	X	X	X		

Study Period	Optional Study Extension				End of Treatment		Notes
Visit Number	17	18	19	20	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (Optional Study Extension) ^a	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	±14 days (Calculate each visit from date of Day 1)				NA	42 (+7) days after end of treatment	
Plasma HIV-1 RNA Quantification	X	X	X	X	X		See Section 8.2.1
TBNK Panel/CD4+ T- cell Count	X	X	X	X	X		
Blood (Plasma) for HIV- 1 Drug Resistance	X	X	X	X	X		Analysis will be performed by Sponsor if indicated per Section 8.2.2.1.2.
Hepatitis B Serology and HBV DNA		X		X			Encourage HBV vaccination to participants who are not immune to HBV.
HBsAg and HBV DNA	(X)	(X)	(X)	(X)			(Only anti-HBc-positive participants, at each visit.) See Section 8.3.6.
Hematology	X	X	X	X	X		Manage participants who meet the discontinuation criteria for total lymphocyte count per Sections 1.3.3 and 8.11.5.
Directed Physical Examination	X	X	X	X	X	X	
AE/SAE Review	X	X	X	X	X	X	
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	X	Contraception is required 42 days after the last dose of study intervention.
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	X	Manage participants who have a positive or indeterminant urine test per Sections 1.3.4 and 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Informed Consent for Study Intervention During Pregnancy	<-----X----->						Obtain upon confirmation of pregnancy. See Sections 1.3.4 and 8.1.1.3.

Study Period	Optional Study Extension				End of Treatment		Notes
Visit Number	17	18	19	20	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (Optional Study Extension) ^a	End of Treatment Follow-up (Optional Study Extension)	
Visit Window	±14 days (Calculate each visit from date of Day 1)				NA	42 (+7) days after end of treatment	

AE=adverse event; anti-HBc=hepatitis B core antibody ; IC=bictegravir; BP=blood pressure; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; ; FBR=future biomedical research; FTC=emtricitabine; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/symptom distress module; INR=international normalized ratio; IRT=interactive response technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cells; temp=body temperature.

^a If discontinuation occurs at a Scheduled Visit, perform Discontinuation of Treatment (optional study extension) visit assessments.

2 INTRODUCTION

DOR/ISL (also known as MK-8591A) is a novel 2-drug FDC of DOR (100 mg) (an approved NNRTI) and ISL (0.25 mg) (an investigational NRTTI). DOR/ISL is being developed for QD treatment of HIV-1 infection.

2.1 Study Rationale

As treatment regimens have improved, HIV-1 infection has become a chronic, manageable condition, and PLWH receiving effective ART regimens can expect to live near-normal lifespans. Anticipating that individuals can receive decades of treatment during their lifetime, long-term tolerability and safety of antiretrovirals have become increasingly important considerations.

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) [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022] [European AIDS Clinical Society 2021] [World Health Organization 2021]. Although these 3-drug regimens are well tolerated and highly efficacious, the current paradigm of lifelong daily treatment is associated with a need for simpler and safer regimens that reduce overall drug exposure [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. As this population ages, there is increasing concern about polypharmacy, long-term toxicity, and DDIs related to comorbidity and multimorbidity and risks associated with the emergence of HIV-1 variants resistant to InSTI, NRTI, and NNRTI treatments.

There is evidence that 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens, better tolerability, and improve quality of life; all of which can support adherence and help to sustain virologic suppression [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. The effectiveness 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.

DOR/ISL has the potential to be an effective and well tolerated 2-drug regimen for the treatment of HIV-1 infection in the switch setting due to its potent antiretroviral activity (including activity against common NRTI- and NNRTI-resistant variants), multiple mechanisms of action, lack of food requirements, and favorable DDI profiles observed to date (see Section 2.2.3).

2.2 Background

Refer to the approved local labeling for DOR and to the IB for ISL for detailed background information.

2.2.1 Islatravir

ISL is a novel and potent NRTTI that blocks HIV-1 reverse transcriptase by novel mechanisms of action. It is a nucleoside analog that is converted to the pharmacologically active triphosphate (ISL-TP) form via endogenous intracellular kinases. It acts through

multiple mechanisms, including immediate chain termination by blocking translocation and delayed chain termination by preventing nucleotide excision [Michailidis E 2014].

ISL is differentiated from other HIV-1 antiretrovirals by its high potency, long half-life, and favorable drug resistance profile. At the proposed dose of 0.25 mg QD, ISL achieves higher steady-state IQs (the ratio of drug exposure to viral susceptibility [$C_{\text{trough}}/IC_{50}$]) against wild-type HIV-1 than any NRTI currently approved for treatment. It also exhibits potent activity against the most prevalent NRTI resistance mutations, including M184V.

2.2.2 Doravirine

DOR, a potent NNRTI with demonstrated efficacy and good tolerability, was first approved for the treatment of HIV-1 infection by the FDA and EMA in 2018. It is differentiated from other NNRTIs by its distinct resistance profile, low likelihood of selection for viral resistance in vivo, and low potential for DDIs. It exhibits potent activity against both wild-type HIV-1 virus and frequently transmitted NNRTI-resistant variants (eg, K103N, Y181C, G190A, and E138K) in vitro. The efficacy and safety profiles of DOR have been well characterized in Phase 3 studies conducted in treatment-naïve adult participants [Orkin, C., et al 2019] [Molina, J. M., et al 2018] and in virologically suppressed adult participants switching from a stable antiretroviral regimen [Johnson, M., et al 2019].

2.2.3 Doravirine/Islatravir

DOR/ISL is an FDC containing DOR (100 mg) and ISL (0.25 mg), administered as a single-tablet QD. DOR and ISL represent 2 distinct antiretroviral agents that inhibit reverse transcription by different mechanisms. Based on the profile of each and data available to date, the combination DOR/ISL is expected to be well tolerated and highly efficacious, with a high barrier to resistance. The combination has demonstrated additive antiretroviral activity, with complementary resistance profiles, and suppressed the emergence of resistance in vitro at clinically relevant concentrations.

DOR/ISL (100 mg/0.75 mg) has demonstrated antiretroviral activity in Phase 3 studies in virologically suppressed (MK-8591A-017 and MK-8591A-018) and TN adults (MK-8591A-020) with HIV-1. Additional details are available in the IB.

In MK-8591-011 (Phase 2, dose-ranging study) ISL doses of 0.25, 0.75, and 2.25 mg were administered to treatment-naïve adults initially in 3-drug regimens (ISL+DOR+3TC) until virologic suppression (HIV-1 RNA <50 copies/mL) was achieved, at which point the regimen was simplified to a 2-drug regimen (ISL+DOR) for maintenance of suppression. The DOR+ISL regimens achieved efficacy (HIV-1 RNA <50 copies/mL) comparable with the FDC comparator (DOR/3TC/TDF) used in MK-8591-011. No participant met criteria for clinically significant confirmed viremia (HIV-1 RNA \geq 200 copies/mL) through Week 144. The overall AE profile for ISL+DOR (\pm 3TC) was similar for each dose of ISL and generally comparable with DOR/3TC/TDF through Week 144. Differences in changes from baseline in total lymphocyte and CD4+ T-cell counts were observed for the different ISL dose groups (see Section 2.3).

In MK-8591A-020, DOR/ISL (100 mg/0.75 mg) was noninferior to BIC/FTC/TAF, as assessed by the percentage of participants achieving virologic suppression (HIV-1 RNA <50 copies/mL) at Week 48 (88.9% vs 88.3%, respectively). Treatment-emergent resistance has been observed for 2 participants in the study (DOR/ISL group), which was considered in both to be due to nonadherence to treatment as the participants' ISL levels were BLOQ at the time of viremia.

2.2.4 Information on Other Study-related Therapy

For participants in Group 2, refer to local labeling for detailed information for their continued baseline ART.

2.3 Benefit/Risk Assessment

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 effectiveness of an investigational medicine.

The totality of available nonclinical and clinical data supports continued evaluation of DOR/ISL 100 mg/0.25 mg FDC in Phase 3 studies.

There remains significant unmet need for novel ART as an alternative option for HIV-1 treatment that is suitable across the population of PLWH, including the elderly and those with multiple comorbidities. High in vitro potency against wild-type HIV-1 virus and a high barrier to resistance make DOR and ISL suitable candidates for treatment of HIV-1 infection. Administration of ISL in doses of 0.25, 0.75, and 2.25 mg with DOR 100 mg and 3TC 300 mg in MK-8591-011 achieved virological suppression in >90% of treatment-naïve participants by Week 24, which was maintained after switching from the 3-drug regimen (ISL+DOR+3TC) to the 2-drug regimen (ISL+DOR) through Week 144. The antiviral efficacy and overall AE profile through Week 72 (the dose-ranging part of MK-8591-011) were not distinguishable among the 3 ISL dose groups (0.25, 0.75, and 2.25 mg).

DOR/ISL (100 mg/0.75 mg QD) was highly efficacious in maintaining virologic suppression (>95% and >93% of participants had HIV-1 RNA <50 copies/mL at Week 48) in participants who switched from various baseline ARTs, including BIC/FTC/TAF, in 2 Phase 3 studies (MK-8591A-017 and MK-8591A-018, respectively). To date, viral resistance was observed for 2 participants receiving DOR/ISL across the Phase 2 (MK-8591-011) and the Phase 3 (MK-8591A-017, MK-8591A-018, and MK-8591A-020) program, in which 1693 TN and virologically suppressed participants with HIV-1 infection received DOR/ISL. These participants were enrolled in the MK-8591A-020 study. Across the ISL clinical development program involving approximately 2300 participants enrolled in Phase 2 and Phase 3 studies, there was a low incidence of drug-related AEs, SAEs, and deaths with ISL when administered alone or with DOR; decreases in lymphocyte counts were observed.

Comprehensive nonclinical safety evaluation of DOR and ISL as mono-entities has not revealed toxicities of concern. Nonclinical developmental and reproductive toxicity studies did not identify any clinically relevant concerns that would preclude continued dosing of

DOR/ISL in participants who become pregnant during the study. Both DOR and ISL may be administered without regard to food and have a low potential for DDIs, a favorable attribute for those who have multiple chronic comorbidities.

Decreases in total lymphocyte and lymphocyte subset (including CD4+ T-cell counts) have been observed in Phase 2 and Phase 3 studies with ISL given QM (60 and 120 mg), QW (20 mg in combination with MK-8507, an NNRTI), and QD (0.75 mg in combination with DOR 100 mg). As a result, dosing was stopped in December 2021 for ISL 60 mg QM for HIV-1 PrEP, ISL QW 20 mg (with MK-8507) for HIV-1 treatment, and DOR/ISL (100 mg/0.75 mg) QD for HIV-1 treatment in pediatric participants.

The Sponsor has conducted a comprehensive investigation into ISL-related decreases in lymphocyte counts to identify possible mechanism(s) of action and to assess the timing and extent of lymphocyte decreases while on-treatment with ISL and the recovery of lymphocyte counts when off-treatment with ISL.

Investigations of possible mechanisms for the lymphocyte decreases support the conclusion that the preferential accumulation of ISL-TP in lymphocytes can lead to inhibition of cell growth and apoptosis at high ISL-TP concentrations. Toxicity due to high TP levels is a common mechanism among HIV nucleoside analog drugs. Mitochondrial toxicity is not a contributing mechanism to the decrease in lymphocytes.

An overall summary of the comprehensive investigation into ISL-related decreases in lymphocyte counts is as follows:

- No changes in general hematology parameters (including hemoglobin, basophils, eosinophils, monocytes, leukocytes, neutrophils, platelets) were observed for participants receiving ISL alone or in combination with other ART in any study.
- ISL dose-dependent decreases from baseline were observed in mean total lymphocyte counts and lymphocyte subset (CD4+ T-cell, CD8+ T-cell, B-cell) counts, with greater decreases observed at the higher ISL doses administered QW (20 mg) and QM (60 mg) compared with QD (0.75 mg) administration.
 - In VS participants in MK-8591A-017 and MK-8591A-018 receiving DOR/ISL 100 mg/0.75 mg QD, mean percent changes from baseline were observed in total lymphocyte (-10.6% and -8.4%, respectively), CD4+ T-cell (-0.68% and +0.87%, respectively), CD8+ T-cell (-8.2% and -7.4%, respectively) and B-cell (-4.4% and -8.6%, respectively) counts at Week 48.
 - In VS participants in MK-8591-013 receiving ISL 20 mg + MK-8507 100 to 400 mg QW, mean percent changes from baseline were observed in total lymphocyte (-15.1% to -30.9%), CD4+ T-cell (-7.6% to -28.1%), CD8+ T-cell (-18.1% to -32.8%), and B-cell (-36.8% to -46.3%) counts at Week 24.
 - In participants with low risk of HIV-1 infection receiving ISL 60 or 120 mg QM for PrEP, the on-treatment mean decreases from baseline in total lymphocyte count were -21.3% and -35.6% at Week 24, respectively.

- Stabilization of the decreases from baseline in mean total lymphocyte count and lymphocyte subset counts observed for the DOR/ISL 100 mg/0.75 mg QD program occurred between Weeks 48 and 72, depending on the lymphocyte subset.
- Decreases from baseline in mean total lymphocyte count and lymphocyte subset counts were not associated with increased incidence of infection.
- A return toward baseline in lymphocyte and lymphocyte subset counts has been observed across the ISL clinical development program. However, a full recovery was not observed by 24 weeks after stopping ISL. The most robust data on recovery of the lymphocyte counts available at this point was from the studies involving administration of ISL QW (20 mg) and QM (60-120 mg), as detailed below. Data on recovery to baseline following discontinuation of DOR/ISL 100 mg/0.75 mg QD in VS adults (MK-8591A-017 and MK-8591A-018) is not yet available.
 - Approximately 6 months after discontinuation of ISL 20 mg QW in adult VS participants (MK-8591-013), among those with $\geq 30\%$ decrease in total lymphocyte or CD4+ T-cell counts at their last on-treatment measurement and at least 1 follow-up result, 10/40 (25%) and 15/32 (47%) participants demonstrated an increase in total lymphocyte and CD4+ T-cell counts, respectively, to within 10% of baseline.
 - Approximately 5 months after discontinuation of ISL 60 mg QM in adults at risk of HIV-1 infection, 43 (29.9%) of the 144 participants in MK-8591-022 and MK-8591-024 with a $\geq 30\%$ decrease in total lymphocyte count at the last on-treatment visit demonstrated an increase in total lymphocyte counts to within 10% of baseline.

Overall, the evaluation of data from across the ISL clinical programs to date suggests that the decrease in mean total lymphocyte and lymphocyte subset counts is ISL dose-dependent, with lower doses less likely to cause decreases. A new FDC of DOR/ISL containing a 0.25 mg dose of ISL will be evaluated in the current study. In the dose-ranging phase of MK-8591-011 (Part 1 and Part 2 through Week 72), participants who received ISL 0.25 mg QD had changes in total lymphocyte and CD4+ T-cell counts comparable to those observed for participants in the DOR/3TC/TDF comparator group. The results of modeling analyses of ISL exposure-effect predict no meaningful decreases in total lymphocyte or CD4+ T-cell counts with the 0.25 mg daily dose (see Section 4.3). To mitigate any risk, close monitoring and discontinuation criteria (Sections 1.3.3, 7.1, and 8.11.5) for individuals who experience significant decreases in lymphocytes are included in this protocol.

Additional details regarding DOR can be found in the local product label. Details regarding ISL and DOR/ISL can be found in the accompanying IB.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in participants ≥ 18 years of age with HIV-1 who have been virologically suppressed (ie, HIV-1 RNA < 50 copies/mL) for ≥ 3 consecutive months on a stable oral 2- or 3-drug combination (\pm PK booster) ART.

Primary Objective	Primary Endpoint
<p>To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued baseline ART, as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48</p> <p>Hypothesis (H1): DOR/ISL is non-inferior to continued baseline ART, as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48. A margin of 4 percentage points is used to define non-inferiority.</p>	HIV-1 RNA
<p>To evaluate the safety and tolerability of a switch to DOR/ISL compared with continued baseline ART, as assessed by review of the safety data accumulated through Week 48</p>	<p>Adverse events</p> <p>Adverse events leading to discontinuation of study intervention</p>
Secondary Objectives	Secondary Endpoints
<p>To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued baseline ART, as assessed by the percentage of participants with the following at Week 48:</p> <ul style="list-style-type: none"> HIV-1 RNA < 200 copies/mL HIV-1 RNA < 50 copies/mL 	HIV-1 RNA

<p>To evaluate the antiretroviral activity of a switch to DOR/ISL in participants who switched from baseline ART to DOR/ISL on Day 1, as assessed by the percentage of participants with the following at Week 96 and Week 144:</p> <ul style="list-style-type: none"> • HIV-1 RNA ≥ 50 copies/mL • HIV-1 RNA < 200 copies/mL • HIV-1 RNA < 50 copies/mL 	HIV-1 RNA
<p>To evaluate the antiretroviral activity of a switch to DOR/ISL in participants who continued baseline ART and switched to DOR/ISL at Week 48, as assessed by the percentage of participants with the following at Week 96 and Week 144:</p> <ul style="list-style-type: none"> • HIV-1 RNA ≥ 50 copies/mL • HIV-1 RNA < 200 copies/mL • HIV-1 RNA < 50 copies/mL 	HIV-1 RNA
<p>To evaluate the immunologic effect of a switch to DOR/ISL compared with continued baseline ART, as assessed by the mean change from baseline in CD4+ T-cell count at Week 48</p>	CD4+ T-cell count
<p>To evaluate the immunologic effect of a switch to DOR/ISL, as assessed by the mean change in CD4+ T-cell count:</p> <ul style="list-style-type: none"> • From baseline (Day 1) to Week 96 and from Week 48 to Week 96 in participants who switched from baseline ART to DOR/ISL on Day 1 • From baseline (Day 1) to Week 144 and from Week 48 to Week 144 in participants who switched from baseline ART to DOR/ISL on Day 1 	CD4+ T-cell count

<ul style="list-style-type: none"> • From Week 48 to Week 96 in participants who continued baseline ART and switched to DOR/ISL at Week 48 • From Week 48 to Week 144 in participants who continued baseline ART and switched to DOR/ISL at Week 48 	
<p>To evaluate the development of viral drug resistance to any study intervention at Week 48, Week 96, and Week 144</p>	<p>Viral resistance-associated substitutions</p>
<p>To evaluate the effect on fasting LDL-C and non-HDL-C of a switch to DOR/ISL compared with continued baseline ART by baseline ART class (PI- containing regimens [including PI- + InSTI-containing regimens], InSTI-containing regimens [non-PI-containing regimens], and non-PI- and non-InSTI-containing regimens), as assessed by the mean change in fasting LDL-C and non-HDL-C from baseline to Week 48</p> <p>If non-inferiority of DOR/ISL to continued baseline ART at Week 48 (H1) is met, the following hypothesis will be tested for each parameter within each stratum:</p> <p>Hypothesis (H2): DOR/ISL is superior to continued baseline ART in each baseline ART stratum (in the order of: PI-containing regimens [including PI- + InSTI-containing regimens], non-PI- and non-InSTI-containing regimens, and InSTI-containing regimens [non-PI-containing regimens]), as assessed by the mean change from baseline in fasting LDL-C and non-HDL-C at Week 48.</p>	<p>Fasting LDL-C and non-HDL-C</p>

<p>To evaluate the safety and tolerability of a switch to DOR/ISL compared with continued baseline ART, as assessed by review of the safety data accumulated through Week 144:</p> <ul style="list-style-type: none"> • From baseline (Day 1) through Week 96 and from Week 48 through Week 96 in participants who switched from baseline ART to DOR/ISL on Day 1 • From baseline (Day 1) through Week 144 and from Week 48 through Week 144 in participants who switched from baseline ART to DOR/ISL on Day 1 • From Week 48 through Week 96 in participants who continued baseline ART and switched to DOR/ISL at Week 48 • From Week 48 through Week 144 in participants who continued baseline ART and switched to DOR/ISL at Week 48 	<p>Adverse events</p> <p>Adverse events leading to discontinuation of study intervention</p>
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
<p>To evaluate the effects on weight, fasting lipid and metabolic profiles, and renal function of a switch from baseline ART to DOR/ISL on Day 1 compared with continued baseline ART, as assessed by the mean change from baseline in these parameters at Week 48</p>	<p>Weight and laboratory markers</p>
<p>To evaluate the effects on weight, fasting lipid and metabolic profiles, and renal function of a switch from baseline ART to DOR/ISL on Day 1 compared with continued baseline ART and a switch to DOR/ISL at Week 48, as assessed by the mean change in these parameters at Week 96 and Week 144:</p>	<p>Weight and laboratory markers</p>

<ul style="list-style-type: none"> • From baseline (Day 1) to Week 96 and from Week 48 to Week 96 in participants who switched to DOR/ISL on Day 1 • From baseline (Day 1) to Week 144 and from Week 48 to Week 144 in participants who switched to DOR/ISL on Day 1 • From Week 48 to Week 96 in participants who continued baseline ART and switched to DOR/ISL at Week 48 • From Week 48 to Week 144 in participants who continued baseline ART and switched to DOR/ISL at Week 48 	
<p>To evaluate the effects of DOR/ISL on total lymphocyte count at Weeks 48, 96, and 144</p>	<p>Total lymphocyte count</p>
<p>To evaluate the pharmacokinetics of ISL when administered as a component of DOR/ISL</p>	<p>Pharmacokinetic values including AUC, C_{max}, and C₂₄</p>
<p>To describe PROs (HRQoL, HIV treatment satisfaction, and HIV symptoms) after a switch to DOR/ISL compared with continued baseline ART at Week 48 and Week 96</p>	<p>EQ-5D-5L, HIVTSQ, and HIV-SI/SDM</p>
<p>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 this study</p>	<p>Germline genetic variation and association to clinical data collected in this study</p>

<p>To evaluate the long-term antiretroviral activity of DOR/ISL in participants in Group 1 and the antiretroviral activity of a switch to DOR/ISL in participants in Group 2, as assessed by the percentage of participants in those enrolled in the optional study extension:</p> <ul style="list-style-type: none"> • HIV-1 RNA ≥ 50 copies/mL • HIV-1 RNA < 50 copies/mL • HIV-1 RNA < 200 copies/mL 	HIV-1 RNA
To evaluate the long-term immunologic effect of DOR/ISL, as assessed by mean changes in CD4+ T-cell count over time in participants enrolled in the optional study extension	CD4+ T-cell count
To evaluate the long-term effects of DOR/ISL on total lymphocyte count in participants enrolled in the optional study extension	Total lymphocyte count
To evaluate the development of viral drug resistance to DOR/ISL in the optional study extension	Viral resistance-associated substitutions
To evaluate the long-term safety and tolerability of DOR/ISL, as assessed by review of the safety data accumulated in participants enrolled in the optional study extension	<p>Adverse events</p> <p>Adverse events leading to discontinuation of study intervention</p>

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, multisite, open-label study to evaluate a switch from any stable oral 2-drug or 3-drug combination (\pm PK booster) ART regimen to DOR/ISL (100 mg/0.25 mg QD) in participants with HIV-1 who have been virologically suppressed for ≥ 3 consecutive months with no history of virologic treatment failure.

The study consists of a screening period of up to 45 days, a 144-week base study, followed by an optional study extension period up to Week 240 (Figure 1).

Base Study

A total of approximately 501 participants will be randomized, stratified by baseline ART regimen (PI-containing [including PI- + InSTI-containing] regimens, InSTI-containing [non-PI-containing] regimens, and non-PI- and non-InSTI-containing regimens) in a 2:1 ratio into 1 of 2 treatment groups (Figure 1):

- Group 1 (n=approximately 334): Switch from baseline ART to DOR/ISL (100 mg/0.25 mg QD) on Day 1 and continue DOR/ISL QD through Week 144
- Group 2 (n=approximately 167): Continue baseline ART until Week 48 and switch to DOR/ISL (100 mg/0.25 mg QD) from Week 48 through Week 144

After 48 weeks of assigned therapy, all participants will receive DOR/ISL (100 mg/0.25 mg QD) through Week 144. Participants who complete the last visit will be given an option to continue receiving open-label DOR/ISL up to Week 240, or until it is commercially accessible (whichever comes first) (Section 6.7). Study intervention will be extended for participants who become pregnant on-treatment and provide documented informed consent to continue their study intervention (DOR/ISL or baseline ART), as specified in Sections 1.3.4 and 8.11.6.

Baseline ART regimen allowed drug classes for this study include NRTIs, NNRTIs, PIs, InSTIs, and PK boosters. The Sponsor will not provide baseline ART regimens. Participants will provide their own ART medications, in accordance with local regulations. Country-specific requirements for baseline ART categorization in this study are in Appendix 7.

Any participants with clinically significant confirmed viremia (Section 4.2.1.1.2) will be assessed for development of viral drug resistance and discontinuation from study intervention per the SoA (Section 1.3.2) and Section 7.1.

Participant safety will be monitored by an independent eDMC through periodic review of efficacy and safety data throughout the study per the timing specified in the eDMC charter (Appendix 1). Additionally, the following IA is planned (see Section 9.7).

- Week 24 IA: An IA to assess fertility will be performed by the external independent statistician when approximately 30% of the total target enrollment has completed the Week 24 visit assessments. The nonbinding fertility criterion is described in Section 9.7.

Optional Study Extension

At Week 144, participants who meet eligibility criteria and consent to enter the optional study extension will continue with DOR/ISL up to Week 240 or until it is commercially accessible (whichever comes first). Procedures to be followed upon exiting the study extension are outlined in Section 6.7.

Consistent with global HIV-1 treatment guidelines [Food and Drug Administration (CDER) 2015] [European AIDS Clinical Society 2021] the optional study extension consists of in-clinic visits every 6 months to assess maintenance of virologic suppression, CD4+ T-cell and total lymphocyte counts, and tolerability. To gain additional data on the effect of long-term ISL exposure on lymphocytes, the total lymphocyte count and lymphocyte subsets will also be assessed at these visits. Where local treatment guidelines require study visits more frequently than every 6 months, these are permitted and should be conducted by the primary investigator and/or the treating physician.

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

4.2 Scientific Rationale for Study Design

Base Study

The randomized, active-controlled, non-inferiority study design is consistent with the FDA CDER 2015 Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment [Food and Drug Administration (CDER) 2015] and is considered appropriate for a treatment-experienced study population that is switching from another stable ART regimen with HIV RNA <50 copies/mL. Small differences in virologic efficacy, emergence of resistance, and loss of tolerability or safety may be detected prior to 48 weeks of treatment, particularly for therapies with largely comparable characteristics. Thus, an efficacy and safety outcome through 48 weeks is aligned with current regulatory guidance [Food and Drug Administration (CDER) 2015], and the primary efficacy and safety analyses will occur after 48 weeks of treatment with DOR/ISL or continued baseline ART regimens. A 2:1 randomization ratio optimizes collection of efficacy and safety data on the DOR/ISL investigational product relative to the approved baseline ART regimens taken by the Group 2 participants in this study.

The open-label design allows a broader comparator treatment population to be evaluated in this study. All 2- and 3-drug regimens can be included as continued baseline regimens, allowing for comparison and analysis closer to what is observed in a real-world population.

It is anticipated that the baseline ART regimens will be heterogeneous and, in some cases, may be associated with considerable pill burden. Therefore, after collecting 48 weeks of data, switching participants who are on continued baseline ART regimen to DOR/ISL at Week 48 may simplify regimens for some participants, potentially optimizing the study, including improving study retention.

Optional Study Extension

The optional study extension provides access to DOR/ISL until it is commercially accessible. Participation in the study extension is optional and allows eligible participants who are deriving benefit from DOR/ISL to continue DOR/ISL and avoid interruption of treatment. The study extension will also allow for long-term efficacy and safety data collection for DOR/ISL.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

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 screening. The assessment of interest is the percentage of participants who are unable to maintain virologic suppression after switching to a new antiretroviral regimen.

Clinical studies of antiretroviral agents in multiple drug classes have demonstrated 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 secondary efficacy endpoint of plasma HIV-1 RNA < 200 copies/mL corresponds to the clinically relevant threshold. With values ≥ 200 copies/mL, there is an increased risk of development of resistance.

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:

- Two consecutive occurrences 4 weeks (± 1 week) apart of HIV-1 RNA ≥ 200 copies/mL at any time during the study.

There is currently no global standard for the definition of low-level viremia 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 results in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. PLWH with HIV-1 RNA ≥ 50 and < 200 copies/mL have a lower risk of developing resistance compared with those with HIV-1 RNA ≥ 200 copies/mL. Therefore, study participants with HIV-1 RNA ≥ 50 and < 200 copies/mL should continue their current regimen, with HIV-1 RNA levels monitored as outlined in Section 8.2.2.

If a participant has an HIV-1 RNA value ≥ 50 copies/mL, a reflex HIV-1 RNA test will be conducted by the central laboratory on the same plasma sample obtained at that visit, if available. For management of participants see Section 8.2.2.

4.2.1.2 Safety Endpoints

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

Due to decreases in total lymphocyte counts observed in clinical studies with DOR/ISL 100 mg/0.75 mg, these parameters will be evaluated at Weeks 48, 96, 144, and in the optional study extension.

4.2.1.3 Weight and Laboratory Markers

The study will evaluate changes from baseline at Week 48, Week 96, and Week 144 in weight, and laboratory markers in the treatment groups to evaluate the impact of DOR/ISL on the following outcomes per the SoA (Section 1.3):

Weight

Increases in body weight have been reported in PLWH on long-term ART and have long been considered a return-to-health phenomenon. However, evidence suggests that excess weight gain may be associated with certain ARV agents, which may have long-term health effects [Bailin, S. S., et al 2020] [Shah, S., et al 2021] [Buzon-Martin, L. 2020] [Wood, B. R. 2021]. In contrast, other ARV drugs, such as TDF and EFV, may have an antiobesogenic effect [Hill, A., et al 2019]. The mean change in weight will be compared between participants who switch to DOR/ISL and participants who continue taking their baseline ART (Sections 8.3.1 and 8.3.9.3). In addition to weight, fat distribution will be measured by waist:hip ratio.

Fasting Lipid and Metabolic Profiles

Some antiretrovirals have been associated with lipid abnormalities [U.S. Prescribing Information 2017]; thus, key indicators of fasting lipid profiles will be measured (Section 8.3.9.1).

Insulin resistance has been reported with certain antiretroviral therapies [Carr, A., et al 1998]. It is associated with metabolic complications including diabetes, cardiovascular disease, fatty liver, and weight gain [Vazquez-Carrera, M. 2016]. Fasting insulin and glucose will be measured to calculate HOMA-IR, and HbA1c (fasting or nonfasting) will be measured to evaluate glycemic control over time.

The adipokines, leptin and adiponectin, will be measured as exploratory assessments of metabolic function and predictors of weight gain [Taylor, E. B. 2021]. These are established markers for lipid metabolism and energy utilization to be explored against the various baseline ART regimens, particularly as more data emerge about the metabolic effects of InSTIs.

Renal Function

Decreases in renal function have been noted with the use of certain NRTIs [U.S. Prescribing Information 2019]; thus, key indicators of renal function will be measured (Section 8.3.9.2).

4.2.1.4 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoAs (Section 1.3) and Section 8.6 will be used to evaluate PK concentrations of ISL, and as appropriate, PK-efficacy, PK-pharmacodynamic, and PK-AE relationships of ISL. PK values including AUC, C_{max} , and C_{24} will be explored.

4.2.1.5 Patient-reported Outcomes

PROs can provide unique information on the impact of HIV infection and its treatment from the patient's perspective as some domains are difficult to observe or are subjective and best collected through patient report. HIV infection and its treatment can impair HRQoL. Symptom burden associated with HIV treatment has decreased with improvements in ART regimens but persists despite viral suppression and immunologic recovery. In conjunction with efficacy and safety, PRO data may help clinicians and patients in making informed decisions on appropriate ART regimens. HTA authorities in many countries recommend patient perspectives data and HRQoL measurement as part of their drug benefit evaluations. HRQoL data are used to estimate health utility scores, which inform cost-effectiveness model analysis.

This study will include 3 self-administered PRO questionnaires (Sections 1.3 SoA, 8.3.10, and 9.4.3). The EQ-5D-5L, a generic HRQoL questionnaire, will provide a simple descriptive profile and index value for health status used to compute health utilities for health economic analyses. The HIVTSQ is a 10-item instrument used to measure satisfaction with medications for people with HIV infection. The status version (HIVTSQs) will be used to evaluate treatment satisfaction over time. The HIV-SI (also known as the HIV-SDM) is a 20-item HIV disease-specific questionnaire designed to assess the prevalence and burden of adverse effects associated with ART regimens. The PRO questionnaires will be completed up to Week 96 at the time points specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3.).

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

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR 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 FBR.

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

4.2.2 Rationale for the Use of Comparator

This study will evaluate switching from various baseline ART regimens to reflect the diverse regimens that are currently used and from which patients might be switched in practice. Participants' baseline antiretroviral combinations have likely been chosen on a case-by-case basis, for side effect profile, schedule, pill burden, or any number of other reasons. Allowed ART regimens will include stable oral 2-drug or 3-drug combinations (\pm PK booster) (provided a participant meets all other inclusion requirements and does not meet any exclusionary criterion). This allows better representation of the real-world use of antiretroviral agents and current HIV-1 treatment guidelines. This study will be open-label, because blinding of all potential baseline regimens is considered infeasible, not only because of the anticipated diversity of the baseline regimens, but also because it could result in a large

pill burden for the participants who are not on single-tablet regimens QD at baseline. Furthermore, the primary efficacy endpoint is based on HIV-1 RNA results, an objective laboratory value, which is less susceptible to unblinding bias.

4.2.3 Rationale for the Selected Participant Population

The rationale for the participant population selected for this study is as follows:

- **Participants Switching ART Regimens:** Many ART regimens are associated with a high likelihood of achieving and maintaining undetectable HIV-1 RNA levels. Although 70% of all PLWH globally know their HIV status, only 44% are virologically suppressed [Joint United Nations Programme on HIV/AIDS 2017]. Drug-associated adverse effects and toxicities, food requirements, high pill burdens, frequent dosing, and DDIs with concomitant medications are among the reasons that may contribute to lack of adherence to prescribed ART regimens. These are the same motivators for patients and prescribers to consider switching components of an ART regimen, even in the setting of viral suppression before failure can occur.

Furthermore, as the population ages, it is anticipated that switches will become even more common in the setting of increasing concern about polypharmacy, long-term toxicity, and DDIs related to co- and multimorbidity and risks associated with the emergence of HIV-1 variants that are resistant to InSTI, NRTI, and NNRTI treatments.

Life expectancy for PLWH receiving suppressive ART is generally similar to people without HIV infection [Farahani, M., et al 2017] [Wandeler, G., et al 2016]. The leading cause of mortality in PLWH is no longer attributed to HIV-related complications, but rather to comorbid conditions commonly associated with an aging population (eg, diabetes, cardiovascular disease, renal disease, cancer).

Participants With Virological Suppression for ≥ 3 Months: With increasing prevalence of early treatment initiation, increasing life expectancy for those who are infected with HIV-1, and decreasing incidence rates of new HIV-1 infections in many parts of the world, an important population in need of improved treatment regimens is those who are already virologically suppressed. Data from the Phase 2 study (MK-8591-011) demonstrate that after receiving at least 3 consecutive months of the 3-drug regimen, ISL+DOR+3TC, almost all participants with HIV-1 RNA <50 copies/mL maintained virologic suppression on a 2-drug regimen, ISL+DOR, through an additional 24 weeks. Based on the results of MK-8591-011, enrollment in this study will be open to those who have demonstrated stable suppression with HIV-1 RNA <50 copies/mL for ≥ 3 consecutive months.

4.2.4 Rationale for Collecting Race and Ethnicity Data

The differential effect on efficacy and safety based on any demographic parameter, including race or ethnicity, cannot be predicted when evaluating a new investigational drug. Therefore, it is important to collect race and ethnicity data to ensure that there is not a differential effect based on these parameters and to gain assurance the results observed in the clinical study will be representative of the drug's use in a broader population. As an example, non-Caucasian patients were found to have higher plasma concentrations of EFV (an NNRTI) than their

Caucasian counterparts, indicating an increased risk of EFV-induced toxicity in non-Caucasian persons [Burger, D., et al 2005]. As another example, among PLWH in the US, those of African heritage have been found to be less likely to maintain virologic suppression compared with other groups, and the factors contributing to this remain to be elucidated [Weintrob, A. C., et al 2009] [Ribaud, 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.

4.2.5 Rationale for Collecting Gender Identity Data

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

4.2.6 Rationale for Infant Safety Data Collection

Follow-up through 1 year of age for infants born to participants who become pregnant while receiving DOR/ISL 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.

4.2.7 Rationale for Continuing Study Intervention During Pregnancy

The US Department of Health and Human Services guidelines currently advise that persons who become pregnant while receiving ART for HIV infection should continue their regimen provided it is safe, well tolerated, and effective at virologic suppression, because altering the regimen could cause an increase in viral load [Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]. Nonclinical developmental and reproductive toxicology studies did not identify any teratogenicity or other clinically relevant concerns that would preclude continued dosing of DOR/ISL in participants who become pregnant and provide documented informed consent to continue study intervention (where allowed by local regulations, health authorities, and ethics committees and as appropriate based on available data/local standard of care guidelines) (Sections 8.1.1.4 and 8.1.1.6). For those participants continuing on their baseline ART regimens who become pregnant and provide documented informed consent to continue study intervention, investigators will need to follow local circulars/guidelines for the baseline ART regimen.

There are no clinical data currently available to support breastfeeding by participants who are receiving DOR/ISL.

4.2.8 Rationale for Collecting Alcohol and Tobacco Use

Both alcohol use and tobacco use are associated with poor health outcomes. A significant number of PLWH across the world die from cardiovascular disease, non-AIDS malignancies, and liver disease, which are associated with alcohol and tobacco use [Farahani, M., et al 2017]. New or worsening existing clinical signs/symptoms, including abnormal laboratory results, can be influenced by alcohol and/or tobacco use. The prospective collection of these data, occurring once prior to randomization and annually thereafter, is intended to assist in the medical management of study participants to help better understand comorbid disease outcomes as well as the primary investigators' determination of the likelihood that the study intervention may have caused a potential AE (ie, causality assessment). With smoking and alcohol use as known risk factors for cardiovascular disease and liver disease, collection of data to monitor these risks among participants is essential to comprehensive safety monitoring and better understanding of the safety profile of the IMP(s) against the background of comorbid conditions.

4.3 Justification for Dose

IQ ($C_{\text{trough}}/IC_{50}$) is the ratio of drug exposure to viral susceptibility. In a Phase 1b proof-of-concept study (MK-8591-003), single doses as low as 0.5 mg ISL showed robust antiretroviral activity at 7 days postdose; this low single-dose provided an IQ threshold of 5 for wild-type HIV-1 virus. Simulations suggest the ISL-TP trough concentrations achieved 24 hours after a single-dose of 0.25 mg ISL provide IQs of ~11 for wild-type virus and ~2 for M184V virus. After 3 daily doses of 0.25 mg ISL, IQs increase to ~29 for wild-type virus and ~6 for M184V/I virus. Steady-state concentrations at later time points will produce even higher IQs, as ISL-TP reaches steady-state at ~28 days. These simulations support the selection of 0.25 mg ISL in combination with 100 mg DOR to maintain virologic suppression in participants who switch from a stable ART regimen at baseline.

In the Phase 2 clinical study (MK-8591-011), 3 daily doses of ISL (0.25, 0.75, and 2.25 mg) were evaluated in combination with DOR (100 mg) + 3TC for 24 weeks and subsequently with DOR alone through Week 48. All 3 doses of ISL with DOR ± 3TC demonstrated potent antiretroviral activity comparable with the comparator (DOR/3TC/TDF) at Week 24 (as a 3-drug regimen, ISL+DOR+3TC) and at Week 48 (as a 2-drug regimen, ISL+DOR). Overall, no ISL dose-response for efficacy was observed. Graphical analysis of steady-state ISL-TP trough concentrations and response at Week 48 from MK-8591-011 showed no trends in exposure-response. The totality of these efficacy data supports the conclusion that the dose range studied (0.25 to 2.25 mg daily) is on the plateau of the dose-response curve. MK-8591-011 also demonstrated that all doses of ISL studied, when administered with DOR + 3TC or DOR alone, had a favorable AE and tolerability profile through Week 144, comparable with that of DOR/3TC/TDF. In the dose-ranging phase of MK-8591-011 (Part 1 and Part 2 through Week 72), participants who received ISL 0.25 mg QD had similar changes in total lymphocyte count and comparable increases in CD4+ T-cell count to those in the DOR/3TC/TDF group. See Section 2.2.3 for additional DOR/ISL background information.

DOR will be administered at the approved dose of 100 mg. This dose has been studied in Phase 1 to Phase 3 studies in treatment-naïve and virologically suppressed participants with HIV-1 and was selected based upon favorable efficacy, safety, tolerability, and metabolic profiles, as confirmed in Phase 3 studies [Orkin, C., et al 2019] [Molina, J. M., et al 2018] [Johnson, M., et al 2019]. Of note, in MK-1439A-024 and MK-1439A-030 [Johnson, M., et al 2019] [Wong, A., et al 2019], among 32 participants infected with HIV-1 harboring the NNRTI resistance mutations K103N, Y181C, and/or G190A at study entry, all achieved virologic suppression following 48 weeks of treatment with DOR/3TC/TDF (24 of 32 participants had been virologically suppressed on PI or InSTI regimens and 8 had been treatment-naïve). Across the Phase 2 and Phase 3 DOR/ISL program, viral resistance was observed for 2 TN participants who had received DOR/ISL in study MK-8591A-020.

In summary, a 0.25 mg dose of ISL in combination with 100 mg DOR is predicted to have an acceptable safety profile and provide concentrations that will demonstrate potent antiretroviral activity against both wild-type virus and most common NRTI- and NNRTI-resistant variants.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Early study termination may also be considered if the futility criterion is met at the Week 24 IA (Section 9.7).

5 STUDY POPULATION

Participants ≥ 18 years of age with HIV-1 who have been virologically suppressed for ≥ 3 consecutive months on a stable oral 2-drug or 3-drug combination (\pm PK booster) ART will be enrolled in this study.

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

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Is 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 been receiving continuous, stable oral 2-drug or 3-drug combination (\pm PK booster) ART with documented viral suppression (HIV-1 RNA < 50 copies/mL) for ≥ 3 consecutive months prior to providing documented informed consent and has no history of prior virologic treatment failure on any past or current regimen.

Notes:

An HIV-1 RNA result above the lower level of detection (ie, transient detectable viremia) that is not clinically significant during the 3 months prior to providing documented informed consent is acceptable.

Previous regimen switches for tolerability, side effects, dosing convenience, or cost are permitted if they occurred > 3 months prior to providing documented informed consent.

Demographics

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

Participants Assigned Female Sex at Birth

4. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:
 - Is not a POCBP
OR
 - Is a POCBP and:
 - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 42 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
 - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4 and Appendix 2.
 - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has 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 a diagnosis of an active AIDS-defining opportunistic infection within 30 days prior to screening.
4. Has active HBV infection (defined as HBsAg-positive or HBV DNA-positive).

Note: Past HBV infection or previous HBV vaccination (defined as HBsAg-negative and anti-HBs-positive) is not an exclusion criterion.

5. Has chronic HCV infection (detectable HCV RNA) with laboratory values consistent with cirrhosis (serum albumin <2.8 g/dL or INR >1.7 or platelets <100 × 10⁹ cells/L in the absence of another explanation for the abnormal laboratory values).

Note: Treatment with direct-acting antiviral therapies is not exclusionary.

6. Has a history of malignancy ≤5 years prior to providing documented informed consent except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or cutaneous Kaposi's sarcoma.
7. Has a history or current evidence of any condition (including active tuberculosis), 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

8. Is taking or is anticipated to require systemic immunosuppressive therapy, immune modulators, or strong and moderate CYP3A inducers (or any other 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) are allowed.

9. Has taken long-acting HIV therapy at any time (eg, cabotegravir, lenacapavir).

Prior/Concurrent Clinical Study Experience

10. Is currently participating in or has participated in a clinical study and received (or is receiving) an investigational compound or device from 45 days prior to Day 1 through the study treatment period.

Notes:

Participants who have had prior exposure to ISL (any duration any time prior to Day 1) are excluded.

Baseline ART is not considered investigational in countries where it has received health authority approvals, regardless of commercial availability.

Participants completing other clinical studies who are receiving placebo or approved therapy may be eligible to enroll without waiting 45 days with approval from the Sponsor.

Concurrent participation in observational or noninterventional studies may be permitted and must be discussed with the Sponsor prior to enrollment and through study duration.

Diagnostic Assessments

11. Has a documented or known virologic resistance to DOR, as demonstrated by any of the following DOR resistance substitutions in reverse transcriptase: V106A/M, V108I, Y188L, H221Y, P225H, F227C/L/V, M230I/L, L234I, P236L, or Y318F.

Notes:

Participants who do not have documentation of resistance testing may enroll.

This exclusionary list is for the purpose of this study and includes major (or primary) DOR resistance substitutions, but not substitutions that are minor and found as naturally occurring polymorphisms.

12. 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
ALP	$>3 \times \text{ULN}$
AST	$>5 \times \text{ULN}$
ALT	$>5 \times \text{ULN}$
Calculated CrCl	$\leq 30 \text{ mL/min}$ based on the Cockcroft-Gault equation (Appendix 8)
CD4+ T-cell Count	$< 50 \text{ cells/mm}^3$
Hemoglobin	$< 9.0 \text{ g/dL}$ (female) or $< 10.0 \text{ g/dL}$ (male)
Total Lymphocyte Count	$< 0.650 \times 10^9 \text{ cells/L}$ (Grade 1 DAIDS criteria)
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; DAIDS=Division of AIDS; ULN=upper limit of normal.	

Other Exclusions

None

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Day 1 to Week 144	Test Product	IMP	Provided centrally by the Sponsor
Group 1	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product	IMP	Provided centrally by the Sponsor
Group 2	Active Comparator	Baseline antiretroviral therapy regimen	Drug	Unassigned	Per Approved Product Label	Per Approved Product Label	Oral	Day 1 to Week 48	Comparator	IMP	Local country-level sourcing
Group 2	Active Comparator	Baseline antiretroviral therapy regimen (bictegravir/ emtricitabine/ tenofovir alafenamide only)	Drug	Tablet	Per Approved Product Label	Per Approved Product Label	Oral	Day 1 to Week 48	Comparator	IMP	Provided centrally by the Sponsor ^a
Group 2	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 48 to Week 144	Test Product	IMP	Provided centrally by the Sponsor
Group 2	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product	IMP	Provided centrally by Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once-daily.

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

Note: Applicable only to South Africa. The Sponsor will centrally supply bictegrovir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as active comparator for participants in South Africa to continue receiving BIC/FTC/TAF as their ART regimen (ie, participants receiving BIC/FTC/TAF in study MK-8591A-020 who enroll in study MK-8591A-051 and are randomized to Group 2).

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

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

Study intervention will be extended for participants who become pregnant on-treatment and provide documented informed consent to continue their assigned study intervention (DOR/ISL or baseline ART), as specified in Sections 1.3.4 and 8.11.6.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to Group 1 or Group 2, respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factor:

1. Baseline ART Regimen (PI-containing regimens [including PI- + InSTI-containing regimens], InSTI-containing regimens [non-PI-containing regimens], and non-PI- and non-InSTI-containing regimens)

The stratification factor helps to ensure that the treatment arms will be well balanced and the study results will not be confounded by the participants' baseline ART regimens.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Participants should be instructed to bring the study intervention bottles, whether clinical supplies provided by the Sponsor or ART provided by study participants, to their visits. At each visit, the number of tablets remaining in the study packaging will be counted, reviewed, and recorded. 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. All participants should be reminded of the importance of taking their study intervention as instructed for the entire duration of the study.

Decisions to temporarily withhold study intervention 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 ≥ 7 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc, during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

- A record of the number of DOR/ISL tablets 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 will also be recorded in the CRF.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations 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 or vaccination 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 or vaccine (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

The Sponsor Clinical Director should be contacted if there are any questions regarding prior or concomitant therapy.

Prior and concomitant therapies listed in [Table 3](#) are not permitted from 45 days prior to Day 1 through the study treatment period. [Table 3](#) is not comprehensive, and the investigator should use their medical judgment when assessing a participant's prior and concomitant therapy(ies). The Sponsor Clinical Director or designee should be contacted if there are any questions about a therapy not on the list below or regarding potential DDIs with a specific treatment that the participant may plan to receive.

In instances where the local product information for DOR or baseline ART regimen is more restrictive with regard to prohibited (ie, contraindicated or not recommended) therapy(ies), the local product information supersedes this section.

Table 3 Prohibited Therapies

Therapy Type	Prohibited Therapy(ies)
Strong and moderate CYP3A inducers	<u>Including but not limited to:</u> Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Enzalutamide Rifabutin Rifampin Rifapentine Mitotane St. John's Wort Herbal remedies (only those that are strong or moderate CYP3A inducers) Modafinil Bosentan Nafcillin Lumacaftor Metamizole
Nonstudy ART	All nonstudy antiretrovirals (with the exception of baseline ART during the screening period and intrapartum treatment [eg, IV AZT] in the case of pregnancy) including treatments for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1 <i>Entecavir therapy for HBV infection is permitted.</i> Long-acting HIV therapy (eg, cabotegravir, lenacapavir) is not permitted at any time. <i>Time-limited course of ritonavir as a pharmacokinetic enhancer is permissible (eg, nirmatrelvir/ritonavir for the treatment of COVID-19).</i>
Immunosuppressive therapies	Immune therapy agents, immune modulators, or other systemic immunosuppressive therapy, including interferon-based treatment for hepatitis <i>Time-limited courses of corticosteroids (eg, for asthma exacerbation) are permitted.</i>
Investigational agents	All nonstudy investigational agents including devices <i>Any agents (eg, vaccine or therapy for COVID-19) approved locally for Emergency Authorized Use, or equivalent, that do not have a known or anticipated DDI with study intervention, are permitted.</i>
Additional prohibited therapies based on baseline ART	Refer to the approved local label
Additional prohibited therapies based on ISL	Pentostatin
ART=antiretroviral therapy; AZT=zidovudine; COVID-19=coronavirus disease caused by severe acute respiratory syndrome coronavirus 2; CYP3A=cytochrome P450 3A; DDI=drug-drug interaction; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; IV=intravenous.	

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

Dose modification of DOR/ISL is not permitted during the study (see Section 4.3 for dose justification).

Modifications and/or regimen changes of baseline ART (Group 2) may be permissible, but require Sponsor approval (ie, FTC and 3TC substitutions, PI dose escalation during pregnancy).

6.7 Intervention After the End of the Study

If DOR/ISL is commercially accessible, participants in both groups who complete the Week 144 visit should follow the end of treatment procedures outlined in Section 1.3.1 and transition to commercially accessible DOR/ISL or local standard of care, as clinically appropriate.

If DOR/ISL is not commercially accessible, participants in both groups who complete the Week 144 visit will be provided the option to receive DOR/ISL in an optional study extension until Week 240 or until DOR/ISL becomes commercially accessible (whichever comes first). Participants who do not enter the optional study extension should follow Section 1.3.1 and transition to local standard of care as clinically appropriate.

If DOR/ISL is not commercially accessible when the optional study extension ends at Week 240, and provided DOR/ISL clinical development continues, a mechanism will be put in place (eg, pre-license patient access program) for participants to continue receiving DOR/ISL beyond the end of the study until it becomes commercially accessible. The details of this mechanism will vary per local regulations.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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.

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

Participants who discontinue study intervention before completion of the protocol-specified treatment period may continue to be monitored in the study as specified in Section 8.11.3, unless the participant has withdrawn from the study (see Section 7.2).

A participant must be discontinued from study intervention for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- After prolonged study intervention interruption that prohibits restarting study intervention (per Section 6.4).
- The participant has a medical condition or personal circumstance (for pregnancy, see Section 8.11.6) which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant chooses to breastfeed.
Note: Study intervention can continue until breastfeeding is initiated.
- The participant has clinically significant confirmed viremia as defined in Section 4.2.1.1.2. Do not discontinue prior to consultation with the Sponsor when feasible.
- The participant has a new AIDS-defining opportunistic infection as listed in Appendix 9, ie, a Category C condition according to the CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults [Centers for Disease Control (CDC) 1992].
- The participant has an SAE or Grade 4 laboratory AE assessed by the investigator to be related to study intervention AND that is life-threatening or results in prolonged hospitalization.
- A participant must be discontinued from study intervention and managed per Section 8.11.5 if any of the criteria in [Table 4](#) are confirmed. If the investigator believes there is an alternative explanation for the result (eg, COVID-19), consultation between the investigator and Sponsor is required when evaluating the participant for discontinuation.

Table 4 Discontinuation Criteria for Specified Decreases in Total Lymphocyte Counts or CD4+ T-cell Counts

Laboratory Test	Criterion ^a		Confirmation ^{b,c}
Total lymphocyte count	A new on-treatment value $<1.0 \times 10^9$ cells/L with a $\geq 30\%$ decline from baseline ^a		Repeat measurement 10 to 14 weeks later (or at the next scheduled study visit)
CD4+ T-cell count	If at baseline ^a :	And on-treatment:	Repeat measurement 10 to 14 weeks later (or at the next scheduled study visit)
	≥ 500 cells/mm ³	<350 cells/mm ³	
	≥ 350 to ≤ 499 cells/mm ³	$\geq 30\%$ decline from baseline and <350 cells/mm ³	
	≥ 200 to ≤ 349 cells/mm ³	$\geq 30\%$ decline from baseline and <200 cells/mm ³	
	≤ 199 cells/mm ³	$\geq 30\%$ decline from baseline	

CD4+=cluster of differentiation 4-positive; DOR=doravirine; ISL=islatravir; SoA=Schedule of Activities.

^a Baseline is at Day 1 for participants in Group 1. Baseline is at Week 48 for participants in Group 2. Baseline in the optional study extension is at Week 144 for all participants who continue in the extension.

^b If the on-treatment measurement meets the specified discontinuation criteria, a consecutive, confirmatory measurement within 10 to 14 weeks is required. Confirmatory laboratory measurements can be conducted at the next clinic visit if the next scheduled visit occurs within the interval required for repeat testing. Note: If repeat testing at the next scheduled visit occurs sooner than 10 weeks and shows resolution, the results may be used to confirm the resolution, and testing should be resumed per the routine SoA. If repeat testing at the next scheduled visit occurs sooner than 10 weeks and does not show resolution, discontinuation is not required. Testing is still required in the timeframe of 10 to 14 weeks to confirm discontinuation.

^c The time frame for confirmation of decreases in total lymphocyte count or CD4+ T-cell count may be extended in the setting of intercurrent illness, immunization, or treatment nonadherence or other treatment interruption. Allow approximately 4 weeks following resolution of illness, immunization, or treatment nonadherence or other treatment interruption before collecting the confirmation sample.

In addition to this list of discontinuation criteria, Country-specific criteria are in Appendix 7.

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 FBR, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- 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 amount of blood collected from each participant over the duration of the study is provided 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 informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy

Upon confirming that a participant is pregnant (Section 8.3.4), the investigator or medically qualified designee and the participant will discuss the potential benefits and risks of continuing (or discontinuing) study intervention (Section 8.11.6). A separate consent is required to continue study intervention in participants who become pregnant (Section 8.11.6.1). Study intervention (DOR/ISL or baseline ART, depending on study intervention assignment at the time of the confirmatory pregnancy test) will be provided for participants who consent to continue study intervention during pregnancy. Note, participants who become pregnant are not allowed to switch study intervention at any time during the pregnancy. The investigator or medically qualified designee will explain the consent to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before continuing study intervention. A copy of the informed consent will be given to the participant.

8.1.1.4 Consent for Postnatal Infant Safety Data Collection Through One Year of Age

Once a pregnancy is confirmed to be continuing, the investigator or medically qualified designee will explain the consent for infant safety data collection to the participant, or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent to collecting any data related to infant safety. A copy of the informed consent will be given to the participant.

8.1.1.5 Consent for Optional Study Extension

The investigator or medically qualified designee will explain the consent for the optional study extension to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to the optional study extension. A copy of the informed consent will be given to the participant. The participant must be informed that once DOR/ISL becomes commercially accessible they will discontinue from the study.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. 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 recorded. In addition, participants' history of smoking and alcohol consumption should be obtained and recorded on the appropriate eCRF. For participants assigned female sex at birth, childbearing potential should be assessed. Menstrual history, contraceptive use, and recent sexual activity should be reviewed for POCBP to exclude potential or early, undiagnosed pregnancy prior to and on Day 1.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication(s) 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 their therapy (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 before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

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

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

DOR/ISL will be provided per [Table 2](#) and dispensed through the IRT system at visits indicated in the SoA (Sections 1.3.1, 1.3.4, and 1.3.5).

The Sponsor will not provide baseline ART regimens. Participants will provide their own ART medications, in accordance with local regulations ([Table 2](#)). Country-specific requirements are noted in Appendix 7.

Study intervention should begin within 24 hours of randomization (ie, on the day of randomization after all pretreatment assessments, as specified in the SoA, are performed or as soon as possible after randomization).

8.1.8.1 Timing of Dose Administration

Group 1

From Day 1 to Week 144, participants in Group 1 will take 1 tablet of DOR/ISL at approximately the same time each day without regard to food. If more than 1 bottle is dispensed, the participant is instructed to use all of the medication in the 1 bottle before opening another bottle.

Group 2

- Day 1 to Week 48: Participants will take baseline ART as per approved label.
- After Week 48 and up to Week 144: Participants will take 1 tablet of DOR/ISL (unsupervised at their home) at approximately the same time each day without regard to food. If more than 1 bottle is dispensed, the participant is instructed to use all of the medication in the 1 bottle before opening another bottle.

Note: Those participants in Group 2 who become pregnant prior to Week 48 and consent to continue baseline ART will not switch to DOR/ISL and will discontinue from the study (Section 8.11.6).

From Week 144 to 240, all participants will take 1 tablet of study intervention (DOR/ISL) QD at the same time each day.

If a participant misses a dose of DOR/ISL, 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.

If a participant misses a dose of baseline ART, guidance in the approved label should be followed.

For participants who become pregnant and consent to continue DOR/ISL, see Section 8.11.6.1.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the base study should have an Early Discontinuation visit performed per SoA (Section 1.3.1) and should be encouraged to continue to be followed as outlined in the SoA and Section 8.11.3.1.

Participants who end study intervention while in the optional study extension (after Week 144 and prior to Week 240) should have a Discontinuation of Study Treatment

(optional study extension) visit performed per the SoA (Section 1.3.5) and should be followed as outlined in the SoA and Section 8.11.3.2.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Early Discontinuation visit 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.

Participants who discontinue study intervention due to specified decreases in total lymphocyte count or CD4+ T-cell count (Table 4) should be managed per Section 8.11.5 until their counts recover. Participants who become pregnant and discontinue study intervention should be managed per Section 8.11.6.2.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 HIV-1 RNA

Plasma HIV-1 RNA quantification will be performed at the central laboratory using a PCR assay with a lower limit of detection of <50 copies/mL.

8.2.2 Management of Participants With Viremia

When viremia (HIV-1 RNA \geq 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.

If a participant has an on-treatment HIV-1 RNA value \geq 50 copies/mL, a reflex HIV-1 RNA test will be conducted by the central laboratory on the same plasma sample obtained at that visit, if available. Management of participants should be based on reflex HIV-1 RNA results if available.

- If the reflex HIV-1 RNA result is <50 copies/mL, no further action is required.
- If the reflex HIV-1 RNA result is \geq 50 copies/mL or there is insufficient sample available for reflex testing, the participant will be asked to return to the clinic in 4 weeks (\pm 1 week) for Viremia Confirmation (see Section 8.2.2.1 and the SoA in Section 1.3.2).

8.2.2.1 Viremia Confirmation

At the Viremia Confirmation visit:

- If the HIV-1 RNA value is \geq 50 copies/mL, a reflex HIV-1 RNA test will be conducted by the central laboratory on the same plasma sample obtained at that visit, if available.
- If the reflex HIV-1 RNA result is <50 copies/mL, no further action is required.
- If HIV-1 RNA result is \geq 200 copies/mL (on both primary and reflex tests, if available) on consecutive visits 4 weeks (\pm 1 week) apart, then clinically significant viremia is confirmed, and the participants will be assessed for potential discontinuation from study intervention (Sections 7.1. and 8.2.2.1.1).

Allow approximately 4 weeks after resolution of illness, immunization, or treatment nonadherence or other treatment interruption for drawing these confirmation samples.

8.2.2.1.1 Participants With Clinically Significant Confirmed Viremia (\geq 200 Copies/mL)

Participants with confirmed HIV-1 RNA of \geq 200 copies/mL (per Section 4.2.1.1.2) will be assessed for development of viral drug resistance (Section 8.2.2.1.2) and discontinuation from study intervention (Section 7.1).

If it is determined that study intervention discontinuation is appropriate, Early Discontinuation of Treatment and End of Treatment Follow-up 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.

8.2.2.1.2 HIV-1 Viral Drug Resistance Testing

Participants with confirmed HIV-1 RNA ≥ 200 copies/mL at any time during the study will be assessed for development of viral drug resistance.

Samples will be collected for genotypic and phenotypic HIV-1 viral drug resistance testing per the SoA (Section 1.3) and used to assess resistance-associated substitutions and viral susceptibility as applicable during the study. If clinically significant viremia is confirmed, the plasma sample from the Viremia Confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing.

8.2.2.1.3 Participants With Low-level Viremia (≥ 50 and < 200 Copies/mL)

Participants with confirmed HIV-1 RNA ≥ 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 the 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.

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.

8.2.3 T and B Lymphocyte and Natural Killer Cell (TBNK) Profile

A TBNK panel, including CD4+ T-cell count (Table 18), will be performed as specified in Appendix 2. Refer to Section 8.11.5 for guidance on management of participants with decreased total lymphocyte count or decreased CD4+ T-cell count. TBNK panel assessments that are considered exploratory do not need to be evaluated by the investigator.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Table 19, Table 20, Table 21, and Table 22 in Appendix 2.

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

8.3.1 Physical Examinations

A complete 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). 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 and weight will also be measured and recorded at the visits specified in the SoA (Section 1.3.1 for Height and Section 1.3 for Weight). 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. Weight measurements should be taken per Section 8.3.1.1.

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). 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). 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 rest and will include pulse, systolic and diastolic BP, body temperature, and RR.

Note: Oral temperatures are preferred but not required.

8.3.3 Electrocardiograms

A local 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA. Results must be available prior to randomization. Sites are to use an ECG machine that automatically calculates the HR 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 appropriately reported as per requirements of safety reporting.

8.3.4 Confirmation of Contraception and Pregnancy Testing

POCBP are required to confirm heterosexual abstinence or use of contraception to prevent pregnancy during the base study, optional study extension, and for 42 days after the last dose of study intervention (base study or optional study extension). POCPBP will be tested for pregnancy at each visit as outlined in Sections 1.3 and 5.1 and Appendix 5.

Participants who are POCPBP should be asked at study visits per the SoA to verbally confirm heterosexual abstinence or 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 to perform locally at each visit. In the event of a positive urine or indeterminate pregnancy test result, serum pregnancy testing for confirmation of the pregnancy must be performed by the central laboratory. A duplicate serum pregnancy test may be sent to a local laboratory to expedite results per investigator discretion. Positive urine pregnancy tests (except those from the Screening Visit) which have been confirmed by serum testing must be reported to the Sponsor using the appropriate eCRF within 24 hours of learning of the event. If a participant becomes pregnant, refer to Section 8.11.6.

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 participation in the study.

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 [Table 18](#) 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 until a new baseline is established as determined by the investigator.

- If laboratory values indicate specified decreases in total lymphocyte count or CD4+ T-cell count (Table 4), participants must be managed per Section 8.11.5. TBNK panel assessments that are considered exploratory do not need to be evaluated by the investigator (Section 8.2.3 and Table 18).

8.3.6 HBV Assessments

Participants coinfecting with HIV-1 and HBV who discontinue an antiretroviral medication that also has activity against HBV (3TC, FTC, TAF, or TDF) may experience an acute exacerbation of HBV. Therefore, participants who have evidence of past HBV exposure (anti-HBc-positive) and who meet enrollment criteria will be closely monitored during the study.

All eligible participants must be HBsAg-negative and HBV DNA-negative at screening. Individuals who are anti-HBc-positive and HBV DNA-positive at screening are excluded. Individuals who are anti-HBc-positive but HBV DNA-negative at screening are eligible to enroll. All participants will have repeat hepatitis B serology and HBV DNA testing at Weeks 48, 96, and 144 during the base study (per the SoA Section 1.3.1) and at Week 192 during the optional study extension (per the SoA Section 1.3.5).

For the duration of the study (base study and optional study extension), participants who are anti-HBc-positive should be monitored for possible HBV reactivation. Samples will be taken to monitor for 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.

Participants in Group 1 will be monitored for possible HBV reactivation for the duration of the study.

Group 2 participants who were anti-HBc-positive, but HBV DNA-negative at baseline and remain so, may continue in the study and switch study intervention at Week 48. Group 2 participants will be monitored for possible HBV reactivation beginning at Week 36.

Participants in either treatment group who are confirmed to be HBsAg-positive or have confirmed quantifiable HBV DNA after randomization will be managed by the investigator per local standard of care and/or referred for management of their HBV infection.

Participants may be allowed to continue study intervention if deemed medically appropriate upon consultation with the Sponsor. After Week 144 while in the optional study extension, participants who are confirmed to be HBsAg-positive or have confirmed quantifiable HBV DNA will be managed by the investigator per local standard of care and/or referred for management of their HBV infection. See Appendix 7 for Country-specific requirements.

Therapies indicated for HBV that also have potent activity against HIV (eg, adefovir, TDF, TAF, FTC, or 3TC) are prohibited (Section 6.5). Entecavir therapy for HBV infection is allowed.

8.3.7 HCV Assessment

HCV serology will be performed at screening and if the individual is HCV antibody positive, reflex testing will be performed for HCV RNA to assess study eligibility. Repeat screening if indicated per local standard of care.

8.3.8 Tobacco and Alcohol Assessments

Participants' use of tobacco/vaping and alcohol will be obtained and recorded as specified in the SoA (Section 1.3.1).

8.3.9 Exploratory Clinical Marker Assessments

The following samples will be collected and assessments performed as specified in the SoA (Section 1.3.1) and Appendix 2 ([Table 18](#)) for exploratory evaluation of markers of energy and metabolism, renal function, and body composition:

- Blood for fasting lipid and metabolic profiles (Section 8.3.9.1)
- Blood for renal function markers (Section 8.3.9.2)
- Urine for renal function markers (Section 8.3.9.2)
- Waist and hip measurements (Section 8.3.9.3)

8.3.9.1 Fasting Lipid and Metabolic Profiles

Participants will be asked to fast for at least 8 hours prior to visits where blood will be taken to measure insulin, glucose, HDL-C, LDL-C, TG, TC, and non-HDL-C as specified in the SoA (Section 1.3.1). HOMA-IR will be calculated.

Note: Participants with type 1 diabetes mellitus should not fast and should not have insulin levels tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing.

HbA1c should be collected for all nonpregnant participants irrespective of fasting or nonfasting status; HgbA1c should not be collected in pregnant participants.

Blood to evaluate energy and metabolism, as measured by the adipokines, leptin and adiponectin, will be collected as indicated in the SoA (Section 1.3.1).

8.3.9.2 Renal Function

Urine and blood samples will be collected to evaluate renal function as measured by key indicators, such as the following potential analytes and calculations, as indicated in the SoA (Section 1.3.1) and Appendix 2 (Table 18):

- Urine: albumin/Cr, eGFR, protein, B-2M/Cr, and RBP/Cr
- Serum: cystatin-C and Cr

Equations for CrCl and eGFR calculation (Cockcroft-Gault and MDRD equations, respectively) are in Appendix 8.

8.3.9.3 Waist and Hip Measurements

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. Waist-to-hip ratios will be calculated as waist (cm)/hip (cm) by the Sponsor circumferences.

BMI will be calculated by the Sponsor using weight and height measurements taken as specified in the SoA (Section 1.3) and Section 8.3.1.

8.3.10 Administration of Patient Questionnaires

Participants will complete 3 PRO questionnaires to be administered in the following order: EQ-5D-5L, HIVTSQ, and HIV-SI/SDM, as specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). 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 should not be administered to participants who are unable to complete questionnaires unassisted or for whom native language translations of the questionnaires are unavailable.

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

PROs are not administered after Week 96.

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

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

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

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

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

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

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

For infants born to participants who become pregnant and consent to infant safety data collection, SAEs (including perinatal HIV-1 infection) occurring through 1 year of age must be reported by the investigator to the Sponsor within 24 hours of learning of the event.

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

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

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

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

Type of Event	<u>Reporting Period:</u> Consent to Randomization/ Allocation	<u>Reporting Period:</u> Randomization/ Allocation Through Protocol-specified AE Collection Period	<u>Reporting Period:</u> After the Protocol-specified AE Collection Period	Time Frame to Report Events and Follow-up Information to Sponsor
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Potential or confirmed DILI events (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI/confirmed DILI – to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event

Type of Event	<u>Reporting Period:</u> Consent to Randomization/ Allocation	<u>Reporting Period:</u> Randomization/ Allocation Through Protocol-specified AE Collection Period	<u>Reporting Period:</u> After the Protocol- specified AE Collection Period	Time Frame to Report Events and Follow-up Information to Sponsor
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report if: - requiring regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
Potential DILI/DILI=drug-induced liver injury; ECI= event of clinical interest; NSAE=nonserious adverse event; OME=Other Important Medical 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. SAEs and other reportable safety events, including potential or confirmed DILI events, 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). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy.

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

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

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

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

This section is not applicable to this study.

8.4.7 Events of Clinical Interest

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

ECIs for this study include:

All potential or confirmed DILI events will be reported to the Sponsor as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential or confirmed DILI events defined as:

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

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

CCI

CCI

8.5 Treatment of Overdose

In this study, an overdose of DOR/ISL is any dose higher than twice the prescribed dose of study intervention (3 or more tablets of DOR/ISL) in a day.

No specific information is available on the treatment of DOR/ISL overdose.

If a participant experiences an overdose of baseline ART, guidance in the approved label should be followed.

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 Plasma ISL

Venous blood samples will be collected for measurement of ISL. The Sponsor may assess these samples for DOR as needed. Samples will be collected only from participants in Group 1. Sample collection, storage, and shipment instructions for plasma samples will be provided in the Operations/Laboratory Manual.

Investigational PK samples will be collected (except during pregnancy) for participants in Group 1 at Week 36 and in Group 1 and Group 2 after Week 48 as outlined in the SoA (Section 1.3). Investigational ISL PK samples will be collected irrespective of time of last dose. The time of last dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation. Analysis of these samples will be performed by the Sponsor as needed.

Population PK samples will be collected from all participants in Group 1 as outlined in [Table 6](#). The time of dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

At the Week 4 visit, participants who routinely take their study intervention during the day will have a predose and postdose sample collected per [Table 6](#). Participants who routinely take their study intervention in the evening should continue to do so, and will have only 1 sample collected at the Week 4 visit, irrespective of the time of the last dose.

For participants who become pregnant and consent to continue DOR/ISL (base study or optional study extension) (Section 8.11.6.1), PK samples will be collected to evaluate DOR and ISL concentration levels per [Table 7](#) in Section 8.11.6.1.

Table 6 Collection of Population PK Samples

Study Visit	Sample Time Relative to Dose of Study Intervention ^a
Day 1	Predose
Week 4	Daytime dosing: Predose AND within 0.5 to 2 hours postdose OR Evening dosing: Only 1 sample, irrespective of time of last dose
Week 12	Irrespective of time of last dose
Week 24	Irrespective of time of last dose
Week 48	Irrespective of time of last dose
PK=pharmacokinetic(s).	
^a Time of last dose and time of PK sample collection must be documented for all samples.	

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant has provided documented informed consent for FBR, FBR-specific specimen collections, including leftover specimens, will be obtained. The following specimens will be included for FBR:

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

8.10 Health Economics and Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening/Rescreening

8.11.1.1 Screening

Before randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed.

8.11.1.2 Rescreening

If the screening window has been exceeded, participants are allowed to rescreen one 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 and/or urine hCG pregnancy testing for POCBP)
- Review of AEs

If the informed consent form has been updated, participants should be reconsented before rescreening. If no updates have been made, documented informed consent 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).

Participants, who were previously considered screen failures because the duration of baseline ART was < 3 consecutive months, are allowed to rescreen if they have continued to receive a stable oral 2-drug or 3-drug combination (\pm PK booster) with documented viral suppression (HIV-1 RNA < 50 copies/mL) for ≥ 3 consecutive 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 per the SoA (Section 1.3).

8.11.2.1 Fasting

Visits at Day 1, Weeks 24, 48, 96, and 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 must remind participants to fast prior to these visits and must confirm with participants their fasting status and record in the appropriate source documentation and laboratory requisition(s).

Note: Participants with type 1 diabetes mellitus and participants who are pregnant should not fast and should not have insulin levels or lipids tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing.

8.11.2.2 Switch

At the Week 48 visit, participants in Group 2 will begin receiving DOR/ISL.

Participants in Group 2 who switch to DOR/ISL will have their baseline values for total lymphocyte count and CD4+ T-cell count defined as the last nonmissing value at or before Week 48. This new baseline will serve as the new baseline for discontinuation criteria (Table 4) and participant management per Section 8.11.5.

Those participants in Group 2 who become pregnant prior to Week 48 and consent to continue baseline ART will not switch to DOR/ISL and will discontinue from the study (Section 8.11.6.1).

8.11.2.3 End-of-Base Study Week 144 Visit

Week 144 represents the end of the base study. Prior to the end of the base study/Week 144 visit, site staff should proactively discuss the potential plan for treatment to facilitate either a transition to locally available ART or DOR/ISL in the optional study extension. For participants who are enrolling in the optional study extension, the Week 144 visit serves as the start of the study extension, and DOR/ISL will be dispensed, and participants will follow procedures outlined in SoA (Section 1.3.5).

Participants who complete Week 144 should follow End of Treatment Follow-Up visit assessments per the Week 144 SoA (Section 1.3.1).

Participants who are pregnant at Week 144 will be managed per Section 8.11.6 and SoA (Section 1.3.4).

Participants who have laboratory values at the Week 144 visit that meet any of the discontinuation criteria for specified decreases in total lymphocyte count or CD4+ T-cell count (Section 7.1 and Table 4) must be managed per Section 8.11.5.

8.11.2.4 Optional Study Extension (Week 144 up to Week 240)

If DOR/ISL is not commercially accessible by Week 144, participants will be provided the option to enroll in an optional study extension to continue to receive open-label DOR/ISL up to Week 240 or until DOR/ISL becomes commercially accessible (whichever comes first) per the SoA (Section 1.3.5).

A participant entering the optional study extension must meet all of the following criteria:

- Is considered, in the opinion of the investigator, to benefit from continued study participation.
- Understands the procedures in study extension and provides documented informed consent to enter the study extension.
- Does not meet any of the discontinuation criteria (See Section 7.1).

Once DOR/ISL becomes commercially accessible, participants should be contacted and informed that they will complete the Discontinuation of Treatment (optional study extension) visit and transition to DOR/ISL or other commercially accessible ART at their next study visit (or sooner at the PI's discretion). In rare circumstances and with permission of the Sponsor, study participation may be extended for a limited amount of time to ensure all participants are able to secure continued treatment access in the commercial market before exiting the study.

The Week 240 Visit represents the end of the optional study extension and the end of the study.

Manage participants with viremia per Section 8.11.4 and SoA (Sections 1.3.2). Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 and SoA (Section 1.3.3). Manage participants who are pregnant per Section 8.11.6 and SoA Section 1.3.4).

8.11.3 Participants Who Discontinue Study Intervention

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

When it is determined that discontinuation from study intervention is appropriate, the participant should have both an Early Discontinuation of Treatment visit (Section 8.11.3.1) and an End of Treatment Follow-up visit (Section 8.11.3.2) conducted. After the visit procedures are completed, the participant will be withdrawn from the study and managed for treatment of their HIV-1 infection per local standard of care.

Participants who discontinue study intervention due to confirmed specified decreases in total lymphocyte counts or CD4+ T-cell counts ([Table 4](#)) must be managed per Section 8.11.5.

Participants who discontinue study intervention due to other reasons, but have laboratory values at the Early Discontinuation of Treatment visit that meet any of the discontinuation criteria for specified decreases in total lymphocyte count or CD4+ T-cell count ([Table 4](#)) must be managed per Section 8.11.5.

8.11.3.1 Discontinuation of Treatment

Participants who discontinue study intervention due to specified decreases in total lymphocyte counts or CD4+ T-cell counts (per Section 7.1) will be managed per Section 8.11.5.

Early Discontinuation (Base Study)

Participants who discontinue study intervention prior to Week 144 for any reason(s) should have an Early Discontinuation of Treatment visit as outlined in the SoA (Sections 1.3.1, 1.3.2, or 1.3.3). If discontinuation occurs during the time frame of a scheduled study visit, the assessments for the scheduled visit as well as the Early Discontinuation of Treatment visit should be conducted, however, collection of laboratory samples should not be duplicated.

Discontinuation (Optional Study Extension)

Participants in the optional study extension who discontinue DOR/ISL prior to Week 240 for any reason(s) should have a Discontinuation of Treatment (optional study extension) visit as outlined in the SoA (Sections 1.3.2, 1.3.3, or 1.3.5). Participants who complete Week 240 should follow assessments per the Week 240 SoA (Section 1.3.5).

8.11.3.2 End of Treatment Follow-up

Participants who discontinue study intervention for any reason(s) will have an End of Treatment Follow-up visit 42 days (+7 days) after the last dose of study intervention. Assessments for this visit are outlined in Sections 1.3.1, 1.3.2, 1.3.3, and 1.3.5, as applicable.

8.11.4 Viremia Confirmation

If a participant has a viral load of ≥ 50 copies/mL (confirmed as described in Sections 4.2.1.1.2 and 8.2.2.1) at any time during the study, a Viremia Confirmation visit must be conducted within 4 weeks (± 1 week) after the initial HIV-1 viremia, as specified in the SoA (Section 1.3.2). If a scheduled visit is to occur within the time frame that a participant would return for a Viremia Confirmation visit, the assessments for the scheduled visit should be conducted, and the HIV-1 viral drug resistance sample must be collected. PK will be assessed for both DOR and ISL (from same sample) at the time of viremia confirmation.

8.11.5 Management of Participants With Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count

To meet the protocol-defined discontinuation criteria in the base study or the optional study extension, participants must have a confirmed total lymphocyte count or CD4+ T-cell count that indicates a specified decrease ([Table 4](#)) on 2 consecutive measurements 10 to 14 weeks apart. A minimum interval of 10 weeks between consecutive tests is required to meet discontinuation criteria. The confirmation visit must occur within 10 to 14 weeks after the initial decrease (or at the next scheduled visit), as specified in the SoA (Section 1.3.3) and [Table 4](#).

Management of Participants who Discontinue due to Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count

Participants discontinued from study intervention due to specified decreases in total lymphocyte count or CD4+ T-cell count (Section 7.1 and Table 4) should undergo assessments for the Discontinuation of Treatment visit and the End of Treatment Follow-up visit (regardless of treatment assignment) as specified in the SoA (Sections 1.3.3, 1.3.5). After discontinuation from study intervention, participants will be managed for treatment of their HIV-1 infection per local standard of care but will continue to be followed in the study. Consult with Sponsor prior to discontinuation if the investigator believes there is an alternative explanation for the result (eg, COVID-19).

Monitoring for Participants Receiving DOR/ISL

After completion of the Discontinuation of Treatment visit (base study or optional study extension) and the End of Treatment Follow-up visit, participants who discontinued for confirmed decreases in CD4+ T-cell or lymphocyte counts (per Table 4) should have monitoring visits every 10 to 14 weeks (Section 1.3.3). Participants should be monitored until the total lymphocyte counts or CD4+ T-cell counts no longer meet the criteria in Section 7.1 Table 4 at 2 consecutive visits. If conditions that impact lymphocytes arise during the follow-up monitoring period and are expected to persist, monitoring may be stopped.

Management of Participants Receiving DOR/ISL Who Discontinue Study Intervention Due to Reasons Other Than Decreases in Total Lymphocyte Count or CD4+ T-cell Count

Participants noted to have their first decrease in total lymphocyte count or CD4+ T-cell count that meets the criteria for Table 4 at the Discontinuation of Treatment visit (base study or optional study extension) or at the Week 144 visit only require monitoring as described above if the count declines are confirmed by the End of Treatment Follow-up visit.

8.11.6 Clinical Management of Participants Who Become Pregnant

If a participant becomes pregnant (confirmed by a positive serum pregnancy test), the investigator should refer the participant to a local provider for obstetric (prenatal) care per local standard of care. The provider should be informed of the participant's study participation by site personnel.

All pregnancies must be followed to completion or termination of the pregnancy by the investigator per Section 8.4.5. Severity assessment of AEs that are pregnancy-related complications should follow guidance provided as part of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3) "Addendum 1: Female Genital Grading Table for Use in Microbicide Studies," particularly the section "Complications of Pregnancy" [National Institute of Allergy and Infectious Diseases 2017].

Upon confirmation of pregnancy by serum testing, the investigator or appropriate designee should discuss the following with the participant:

- The appropriateness of continuing study intervention based on available data and local standard-of care guidelines (where allowed by local regulations, health authorities, and ethics committees). For participants receiving baseline ART, the investigator should refer to the local product circular(s) and local guidelines to determine if treatment may be continued. **Documented informed consent must be obtained to continue study intervention regardless of treatment assignment** (Section 8.1.1.3)
- Joining a pregnancy registry (the Antiretroviral Pregnancy Registry), which collects information about the outcome of the pregnancy, if applicable

Upon confirming that the pregnancy is continuing, the site will discuss with the participant (per timing at the discretion of the Principal Investigator):

- Intentions for breastfeeding (Section 8.11.6.3)
- Consenting to infant safety data collection per Sections 8.1.1.3 and 8.11.6.4

8.11.6.1 Continuing Study Intervention in Pregnancy

Participants who become pregnant and consent to continue their assigned study intervention (DOR/ISL or baseline ART) should complete all remaining protocol-specified visits and procedures per the regular schedule in the applicable SoA (Section 1.3.5), with the following exceptions:

- Only participants in Group 1 will have PK samples collected (per the timing in [Table 7](#)). Participants in Group 2 will not have PK collection.
- Participants on DOR/ISL who are pregnant at Week 144 will have the opportunity to continue into the optional study extension.

Pregnancy visits are to occur at least every 12 weeks (~1 during each trimester and a postpartum visit ≤ 8 weeks after delivery) in both the base study and the optional study extension (Sections 1.3.1 and 1.3.4, as applicable). This applies to participants whose pregnancy extends beyond Week 240 (Section 1.3.4). More frequent HIV-1 RNA testing should be performed per local guidelines or as determined by the investigator. If HIV-1 RNA testing is performed in a local laboratory with an approved assay (Appendix 10), the results must be promptly recorded in the appropriate CRF.

For participants receiving baseline ART, the investigator should refer to local product circulars and local guidelines to determine if study intervention can be continued or must be modified during pregnancy. Modifications (eg, dose adjustment) and/or regimen changes may be permitted, but require Sponsor approval (Section 6.6). Those participants in Group 2 who become pregnant prior to Week 48 and consent to continue baseline ART will not switch to DOR/ISL and will discontinue from the study. The participant will continue with

the protocol-specified visits (with the exception of PK collection) per the schedules in the SoA (Section 1.3) for the duration of their pregnancy.

For participants receiving study intervention and continuing their pregnancy, prenatal care should be coordinated between the investigator and the local obstetric care provider. The investigator (or designee) is responsible for reviewing records from prenatal care at each study visit and obtaining relevant clinical and laboratory data from the obstetric care provider to monitor the safety and well-being of the mother and fetus. Relevant data obtained by the site should be entered into the appropriate CRF and source documentation.

The participant's medical records will be collected and reviewed by the study site for:

- Clinical safety laboratory assessments
- Pregnancy screening laboratory assessments (for participants on DOR/ISL only) for hepatitis B serology and HBV DNA; if local laboratory test results are unavailable, collect central laboratory sample
- Plasma HIV-1 RNA level
- Results of 2nd trimester ultrasound(s) providing gestational age and anatomic survey
- Any complications associated with the pregnancy
- Outcome of pregnancy
- Information that could indicate congenital abnormalities

For participants who are pregnant at the last regularly scheduled study visit (Week 144 [base study] or Week 240 [optional study extension]), their visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum and, as applicable, a 42-day follow-up period with an End of Treatment Follow-up visit (Section 1.3.4). After completion of the pregnancy, the participant will have completed the study after completing either the postpartum visit (if the participant chooses to breastfeed) or the End of Treatment Follow-up visit (if the participant does not choose to breastfeed and completed the 42-day follow-up period) (Section 1.3.4). Participants on DOR/ISL at the completion of the pregnancy will have continued access to DOR/ISL through the optional study extension, until DOR/ISL becomes commercially accessible per Section 6.7. The time of last dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

8.11.6.1.1 Collection of Population PK Samples During Pregnancy and Postpartum (Participants Continuing DOR/ISL Only)

For participants who continue DOR/ISL, PK samples will be collected at their scheduled visit/pregnancy visit during the 1st, 2nd, and 3rd trimesters and postpartum to evaluate DOR and ISL concentration levels per [Table 7](#). These samples will be used to characterize the PK profile of DOR/ISL during pregnancy. Participants who do not learn of their pregnancy until the 2nd trimester may not have had a PK sample collection during the 1st trimester.

Participants who routinely take their DOR/ISL during the day will have a predose and 2 postdose samples collected per Table 7. Participants who routinely take their DOR/ISL in the evening should continue to do so and will have only 1 sample collected at the 2nd trimester, 3rd trimester, and postpartum visits, irrespective of time of the last dose. Time of last dose and time of PK sample collection must be documented for all samples.

Table 7 Collection of Population PK Samples During Pregnancy and Postpartum

Study Visit	Sample Time Relative to Dose of DOR/ISL ^a
1st Trimester ^b	Daytime dosing: Predose OR Evening dosing: Irrespective of time of last dose
2nd Trimester	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
3rd Trimester	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
Postpartum ^c	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
DOR=doravirine; ISL=islatravir; PK=pharmacokinetic(s). ^a Time of last dose and time of PK sample collection must be documented for all samples. ^b Collect at the scheduled 1st Trimester visit after a participant reports gravid status. (May not be collected if participant does not learn of their pregnancy until after the first trimester.) ^c Postpartum visit ≤8 weeks after delivery.	

8.11.6.2 Discontinuing Study Intervention for Pregnancy

Participants who become pregnant and discontinue study intervention should have a Discontinuation of Treatment visit (base study or optional study extension) per the SoA (Section 1.3.1 or 1.3.5, as applicable). If the decision to discontinue study intervention occurs during the time frame of a scheduled study visit, the assessments for the Scheduled Visit as well as for the Discontinuation of Treatment Visit should be completed. Collection of laboratory samples should not be duplicated. In addition, these participants will have an End of Treatment Follow-up visit 42 days (+7) days after the last dose of study intervention.

The investigator (or local HIV care provider, if not the study site) should develop a new treatment plan per local standard of care before discontinuing study intervention to minimize the risk of a gap in ART.

8.11.6.3 Participants Who Choose to Breastfeed

A participant who chooses to breastfeed must discontinue study intervention before initiating breastfeeding (Section 7.1) and be followed in the study per Section 8.11.6.2. The investigator (or local HIV care provider, if not the study site) should make every effort to develop a new treatment plan (per local standard of care) within sufficient time prior to delivery to minimize the likelihood of a gap in ART.

8.11.6.4 Infant Safety Data Collection

For participants who become pregnant while receiving study intervention, or within 42 days after the last dose of study intervention, the data in Section 8.11.6.4.1 should be obtained by the site and entered into the appropriate CRF and source documentation.

Infant SAEs, including perinatal HIV-1 infection, 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. Infant safety data collection will be captured if exposure to study intervention occurs during pregnancy.

8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection

Time Point	At Birth ^a	1 Year After Birth ^{a,b}
Visit Name	NA	Infant Follow-up-1
Administrative and Safety Procedures		
Infant Informed Consent		X ^c
Gestational Age at Birth	X	
Apgar Score	X	
Length	X	X
Weight	X	X
Head Circumference	X	X
Directed Pediatric Examination	X	
Concomitant Medications Review ^d	X	X
Review Infant SAEs ^e	-----X-----	
HIV=human immunodeficiency virus; NA=Not applicable; SAE=serious adverse event.		
^a Data to be collected and entered at the site within 12 weeks of each time point.		
^b If a participant withdraws from the study, data from 1 year after birth should be collected at the time of withdrawal.		
^c Consent for infant safety data collection can be obtained from the mother at any time following confirmation of pregnancy.		
^d Concomitant medications taken by the infant (for SAEs or HIV postpartum prophylaxis).		
^e Collect SAEs, including any congenital anomalies and HIV infection in the infant, per Section 8.4.1 and review at participant’s regularly scheduled study visits.		

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an sSAP and referenced in the CSR for the study. Posthoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (eg, those specific to the analyses of PK data, PROs, and FBR) will be documented in separate analysis plans. Data collected from the optional study extension for those participants who consent to enter the optional study extension, will be summarized separately using only descriptive statistics.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Randomized, Active-Controlled, Open-Label Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Virologically Suppressed on Antiretroviral Therapy
Treatment Assignment	Approximately 501 participants will be randomly assigned in a 2:1 ratio to either switch to DOR/ISL on Day 1 (Group 1) or continue baseline ART from Day 1 to Week 48 with delayed switch to DOR/ISL at Week 48 (Group 2). Randomization will be stratified by baseline ART regimen (PI-containing regimens [including PI- + InSTI-containing regimens], InSTI-containing regimens [non-PI-containing regimens], and non-PI- and non-InSTI-containing regimens).
Analysis Populations	Efficacy: FAS, PP, FAS-E, and Resistance Analysis Subset Safety: APaT and APaT-E
Primary Endpoints	<ol style="list-style-type: none"> 1. Percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 2. Percentage of participants who experience AEs and percentage of participants who discontinue study intervention due to AEs through Week 48
Secondary Endpoints	<ol style="list-style-type: none"> 1. Percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 96 and Week 144 2. Percentage of participants with HIV-1 RNA < 50 and < 200 copies/mL at Week 48, Week 96, and Week 144. 3. Mean change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144. 4. Mean change from baseline in fasting LDL-C and non-HDL-C at Week 24 and Week 48 5. Viral resistance-associated substitutions 6. General safety and tolerability through Week 144.

Statistical Methods for Key Efficacy Analyses	For the primary hypothesis (H1), DOR/ISL will be considered non-inferior to continued baseline ART if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the between-treatment difference in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 (DOR/ISL minus continued baseline ART) is less than 4 percentage points (non-inferiority margin). The CI will be based on the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with Cochran-Mantel-Haenszel weights. The FDA snapshot algorithm [Food and Drug Administration (CDER) 2015] will be used to handle missing data for the analysis of the primary efficacy hypothesis.
Statistical Methods for Key Safety Analyses	For overall safety endpoints, specific AEs, and safety topics of special interest that meet predefined threshold rules, point estimates and 2-sided nominal 95% CIs for the differences between treatment groups (DOR/ISL minus continued baseline ART) in the percentages of participants with events will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Inferential analyses with 2-sided multiplicity-adjusted CIs and p-values obtained using ANCOVA models will be provided for the differences between groups (DOR/ISL minus continued baseline ART) in the mean change from baseline in fasting LDL-C and non-HDL-C at Week 48.
IAs	<p>An IA will be performed when approximately 30% of participants have completed the Week 24 visit assessments. Results will be reviewed by an eDMC. All available efficacy and safety data for participants enrolled at the time of the Week 24 IA will be reviewed, and the data from the first 30% of participants who reach Week 24 will be included in the futility assessment. The nonbinding futility criterion is if the upper bound of the 2-sided 95% CI for the treatment difference (DOR/ISL minus continued baseline ART) in the percentage of participants with Week 24 HIV-1 RNA ≥ 200 copies/mL is greater than 8 percentage points, consideration may be given to stop the study. Additional details are provided in Section 9.7.</p> <p>In addition, the eDMC will periodically review efficacy and safety data (per the timelines specified in the eDMC charter).</p>
Multiplicity	<p>The Type 1 error rate over the multiple hypothesis tests will be controlled by a sequential testing procedure. A formal futility analysis at Week 24 is planned as described in section 9.7, a small amount of alpha ($\alpha=0.00001$) will be allocated for this IA, purely for statistical rigor. The trial will not be stopped early for positive efficacy at the IA. The following hypotheses will be tested sequentially at a 1-sided 2.499% Type 1 error rate in the following order:</p> <ol style="list-style-type: none"> 1. Primary efficacy hypothesis (H1) testing non-inferiority of DOR/ISL to continued baseline ART, as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 2. Secondary safety hypothesis (H2) testing superiority of DOR/ISL to continued baseline ART, as assessed by the mean change from baseline in fasting LDL-C and non-HDL-C at Week 48 <p>If the first hypothesis test fails to reach statistical significance, the second hypothesis test would not be considered for statistical significance. In this way, the overall 1-sided 2.5% Type 1 error rate in testing these hypotheses is strongly controlled. Additional details are provided in Section 9.8.</p>

Sample Size and Power	The planned sample size is 501 participants (334 in the DOR/ISL group and 167 in the continued baseline ART group). For the primary efficacy endpoint of the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48, the study has 93.3% power to demonstrate that DOR/ISL is non-inferior to continued baseline ART at a 1-sided 2.5% alpha-level if the true rate of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 is 1.5% in both treatment groups. This power calculation does not account for the futility assessment at Week 24.
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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.

This study is being conducted as a randomized, open-label study; ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

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

The planned IAs are described in Section 9.7.

9.3 Hypotheses/Estimation

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

Success of this study is predicated only on establishing non-inferiority of DOR/ISL to continued baseline ART, as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 (ie, establishing statistical significance of H1).

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.4.1 Efficacy/Pharmacokinetics Endpoints

9.4.1.1 Efficacy Endpoints

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

Percentage of Participants With HIV-1 RNA ≥ 50 Copies/mL

A PCR assay with a lower level of detection of < 50 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The primary objective will be assessed based on the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48. A secondary objective will assess the sustained antiretroviral suppression of

DOR/ISL after 96 weeks of treatment in Group 1 and after 48 weeks of treatment in Group 2 by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 96 and Week 144.

The percentage of participants with HIV-1 RNA ≥ 50 copies/mL will be summarized over time for participants who consent to the optional study extension.

Percentage of Participants With HIV-1 RNA <200 Copies/mL and Percentage of Participants With HIV-1 RNA <50 Copies/mL

A secondary objective addressing the antiretroviral activity following a switch to DOR/ISL will be assessed based upon the percentage of participants with HIV-1 RNA <200 copies/mL at Week 48, as well as the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48.

At Weeks 96 and 144, a secondary objective addressing the antiretroviral activity of DOR/ISL after 96 weeks and 144 weeks of treatment in Group 1 and after 48 weeks and 96 weeks of treatment in Group 2 will be assessed based on the percentage of participants with HIV-1 RNA <200 copies/mL and the percentage of participants with HIV-1 RNA <50 copies/mL.

The percentage of participants with HIV-1 RNA <50 copies/mL and <200 copies/mL will be summarized over time for participants who consent to the optional study extension.

In addition, HIV-1 RNA will be summarized using the following bands: <20 copies/mL (the LLOQ of the assay), 20 to <50, 50 to <100, 100 to <200, 200 to <400 and ≥ 400 copies/mL to further characterize efficacy response over time through the end of the study.

Change From Baseline in CD4+ T-cell Count

The mean change from baseline in CD4+ T-cell count will be estimated at each time point at which CD4+ T-cell count is collected. A secondary objective will compare the mean change from baseline in CD4+ T-cell count between treatment groups at Week 48. In addition, change from baseline in the absolute CD4+ T-cell count and change from baseline in CD4+ T-cell/lymphocyte ratio will be summarized at each timepoint.

At Week 96, the immunologic effect of DOR/ISL will be assessed via the mean change from baseline (Day 1) to Week 96 in CD4+ T-cell count after 96 weeks of treatment in Group 1, the mean change from Week 48 to Week 96 in CD4+ T-cell count after an additional 48 weeks of treatment in Group 1, and the mean change from Week 48 to Week 96 in CD4+ T-cell count after 48 weeks of treatment in Group 2.

At Week 144, the immunologic effect of DOR/ISL will be assessed via the mean change from baseline (Day 1) to Week 144 in CD4+ T-cell count after 144 weeks of treatment in Group 1, the mean change from Week 48 to Week 144 in CD4+ T-cell count after an additional 96 weeks of treatment in Group 1, and the mean change from Week 48 to Week 144 in CD4+ T-cell count after 96 weeks of treatment in Group 2.

For analyses of the mean change from baseline in CD4+ T-cell count, 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, when available. For the analyses of the mean change from Week 48 in CD4+ T-cell count, for Group 1, baseline measurements are defined as the last nonmissing value obtained at or prior to the Week 48 visit; for Group 2, baseline measurements are defined as the last nonmissing value obtained prior to the switch to DOR/ISL.

The change from baseline in CD4+ T-cell count during the optional study extension will be analyzed over time for participants who consent to the optional extension.

Clinically Significant Confirmed Viremia

Participants with clinically significant confirmed viremia as defined in Section 4.2.1.1.2 will be identified.

Viral Resistance-associated Substitutions

Participants who meet the definition of clinically significant confirmed viremia (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 will be included in the resistance analyses. In addition, anyone for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load, will also be included in the resistance analyses. The resistance analyses will count the number of participants in each treatment group who have evidence of resistance-associated substitutions. The data will be summarized with primary interest at Weeks 48, 96, 144, and during the optional study extension.

9.4.1.2 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoA (Section 1.3) and Section 8.6 will be used to evaluate PK concentrations of ISL, and as appropriate, PK-efficacy, PK-pharmacodynamic, and PK-AE relationships of ISL.

9.4.2 Safety Endpoints

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

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test values, and vital signs.

Adverse Events

The following clinical and laboratory AEs will be summarized: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 Grade 3 or 4 AE; 5) participants with at least 1 serious and drug-related AE; 6) participants with at least 1 AE which is both Grade 3 or 4 and

drug-related; 7) participants who discontinued study intervention due to an AE;
8) participants who discontinued study intervention due to a drug-related AE; and
9) participants with an AE leading to death.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory test results, participants must have both a baseline and a post-randomization, on-treatment measurement to be included. Participants' laboratory test 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 the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3) [National Institute of Allergy and Infectious Diseases 2017].

Weight and Laboratory Markers

The mean change from baseline to Weeks 48, 96, and 144 in select weight and laboratory markers of fasting lipid and metabolic profiles and renal function will be summarized.

Change From Baseline in Fasting Lipids

The mean change from baseline in fasting lipids (LDL-C, non-HDL-C, TC, HDL-C, TGs, and TC/HDL ratio) will be analyzed with primary interest in LDL-C and non-HDL-C at Week 48.

Total Lymphocyte Counts

The mean change from baseline in total lymphocyte count will be calculated at each time point at which lymphocytes are assessed. The comparison of mean change from baseline in total lymphocyte count between treatment groups will be conducted at Weeks 48. The mean change from Week 48 in total lymphocyte count will be calculated at each time point beyond Week 48 at which lymphocytes are assessed.

For analyses of the mean change from baseline in lymphocyte, 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, when available. For the analyses of the mean change from Week 48 in lymphocyte, for Group 1, baseline measurements are defined as the last nonmissing value obtained at or prior to the Week 48 visit; for Group 2, baseline measurements are defined as the last nonmissing value obtained prior to the switch to DOR/ISL.

The change from baseline in lymphocytes during the optional study extension period will be analyzed over time for participants who consent to the optional extension.

Definition of Baseline Measurements for Safety Analyses

For analyses of changes from baseline in safety parameters (eg, weight, vital signs, and laboratory parameters), 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, when available. For analyses of changes from Week 48, for Group 1, baseline measurements are defined as the last nonmissing value obtained at or prior to the Week 48 visit; for Group 2, baseline measurements are defined as the last nonmissing value obtained prior to the switch to DOR/ISL.

The change from baseline in safety parameters during the optional study extension period will be analyzed over time for participants who consent to the optional study extension.

9.4.3 Patient-reported Outcome Endpoints

An initial description of patient-reported outcome measures is provided in Section 4.2.1.5.

PROs from each questionnaire at Day 1 and Weeks 4, 12, 48, and 96 will be summarized for each treatment group.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

FAS

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

- Receive at least 1 dose of study intervention
- Have baseline data for those analyses that require baseline data

Note that the number of participants included in the FAS population may vary across endpoints due to the applicability of exclusion criteria to each endpoint (eg, the need for baseline data only applies to those endpoints that are derived relative to baseline). Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using FAS population.

PP Analysis Population

The secondary analysis set for the efficacy analyses is defined as the PP analysis population, which will exclude participants in the FAS population who had at least one major deviation that may substantially affect the results of the efficacy endpoints. Potential deviations that may result in the exclusion of a participant from the Per-Protocol population include:

- Receipt of any ongoing prohibited therapies listed in [Table 3](#)
- Nonadherence to study intervention: <95% drug compliance rate
- Pregnancy

The PP analysis will be performed for the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 48, 96, and 144, the percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 48, 96, and 144, and the percentage of participants with HIV-1 RNA <200 copies/mL at Weeks 48, 96, and 144 (see [Table 9](#))

The final determination of major protocol deviations, and thereby the composition of the Per-Protocol population, will be made prior to the Week 48 database lock and will be documented. A participant who deviates from the protocol at randomization (eg, violation of certain inclusion or exclusion criteria, such as the use of a prohibited prior treatment) will be excluded from the Per-Protocol population. For participants who have major deviations from the protocol during the study (eg, taking a prohibited concomitant medication), data obtained after the deviation will be excluded from analysis. As such, the composition of the Per-Protocol population may vary by the analysis time point, based on the number of participants who satisfy the Per-Protocol criteria at that time point.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the Per-Protocol population.

FAS for the Optional Study Extension (FAS-E)

The FAS-E population will be used to analyze efficacy data in the optional study extension. It consists of all FAS participants in the base study who entered the optional study extension and received at least 1 dose of study intervention during the extension.

Resistance Analysis Subset

The resistance analysis subset will include all participants in the FAS with 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 Populations

APaT

The APaT population will be used for the analysis of safety data in the base study. The APaT population consists of all randomized participants who receive 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 2 who switch to DOR/ISL at Week 48 and subsequently receive at least 1 dose of DOR/ISL will be included in summaries and analyses from Week 48 through Week 144.

At least 1 laboratory or vital sign measurement obtained subsequent to 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. The composition of the APaT population may vary based on the availability of baseline measurements for the relevant safety parameters of interest.

APaT-E

The APaT-E population will be used to analyze safety data from the optional study extension period. It consists of all APaT participants in the base study who entered the optional study extension and received at least 1 dose of study intervention during the extension.

9.6 Statistical Methods

The statistical methods used to evaluate the primary and secondary objectives are described below. Methods related to evaluation of exploratory objectives will be described in the sSAP.

Participants in Group 1 will receive DOR/ISL from Day 1 through end of study. Participants in Group 2 will continue their baseline regimen from Day 1 through Week 48 and then receive DOR/ISL from Week 48 through end of study. Between-treatment comparisons that address key efficacy and safety objectives will be limited to data before the switch. Efficacy and safety data from Week 48 through Week 144 will be summarized separately. For Group 2, to evaluate the effects of switching from baseline ART to DOR/ISL on safety data, within participant mean changes in safety parameters from Week 48 to Week 144 will be analyzed. The safety data from Day 1 through Week 144 for participants in Group 1 will also be summarized. Safety data for participants who consent to continue the treatment in the optional study extension (from Week 144 to Week 240) will be summarized separately.

Definition of On-treatment Measurements for Efficacy Analyses

For participants who have either discontinued or completed study intervention, all measurements within 1 day following the last dose of study intervention will be considered to be on-treatment measurements. For participants who are on study intervention (ie, have not discontinued or completed study intervention), all measurements will be considered to be on-treatment measurements.

Definition of On-treatment Measurements for Safety Analyses

For participants who have either discontinued or completed study intervention, all measurements within 42 days following the last dose of study intervention will be considered to be on-treatment measurements; the 42-day window was selected to account for the half-life of ISL. For participants who are on study intervention (ie, have not discontinued or completed study intervention), all measurements will be considered to be on-treatment measurements.

9.6.1 Statistical Methods for Efficacy Analyses

Time Windows

Definitions of time windows (day-ranges) and target days for the scheduled study visits, which will be used for all statistical analyses by time point, are shown in [Table 8](#). The last available on-treatment measurement within a window will be used for analyses at a specific time point, unless otherwise specified. Results from additional time points beyond Week 96 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.

Table 8 Definitions of Study Time Points

Treatment Phase	Treatment Period	Visit	Day-Range ^a	Target Day ^a	
Pretreatment	Baseline	Day 1	≤1	1	
Treatment	DOR/ISL or Baseline ART Regimen	Week 4	≥2 and ≤56	29	
		Week 12	≥57 and ≤126	85	
		Week 24	≥127 and ≤210	169	
		Week 36	≥211 and ≤294	253	
		Week 48	Group 1: ≥295 and ≤378 Group 2: ≥295 and ≤last baseline ART dose day + 1	Group 1 and Group 2: 337	
	DOR/ISL	Week 52 ^b	Group 1: NA Group 2: >last baseline ART dose day+1 and ≤392	Group 1: NA Group 2: 365	
		Week 60	Group 1: ≥379 and ≤462 Group 2: ≥393 and ≤462	Group 1 and Group 2: 421	
		Week 72	≥463 and ≤546	505	
		Week 84	≥547 and ≤630	589	
		Week 96	≥631 and ≤714	673	
		Week 108	≥715 and ≤798	757	
		Week 120	≥799 and ≤882	841	
		Week 132	≥883 and ≤966	925	
		Week 144	≥967 and ≤1091	1009	
		Treatment Extension ^c	DOR/ISL	Week 168	≥1092 and ≤1260
	Week 192			1261≥ and ≤1428	1345
	Week 216			1429≥ and ≤1596	1513
	Week 240			1597≥ and ≤1764	1681

ART=antiretroviral therapy; DOR=doravirine; ISL=islatravir; min=minimum; NA=not applicable.

^a Day-ranges and target days are computed relative to the first day of study intervention.

^b The Week 52 visit applies only to participants in Group 2.

^c The treatment extension phase visits apply only to participants who consent to the optional study extension.

Missing Data Approaches

Three approaches will be used to handle missing HIV-1 RNA values. The primary approach for analysis of the percentage of participants with HIV-1 RNA ≥ 50 copies/mL is the FDA “snapshot” algorithm [Food and Drug Administration (CDER) 2015]. Using this approach, for data collected in a given analysis window (see [Table 8](#)), the last available measurement while the participant is on-treatment is used to define the virologic outcome. Virologic outcome is 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 within the time point of interest analysis window specified in [Table 8](#).
- **HIV-1 RNA ≥ 50 copies/mL:** this includes participants:
 - Who have the last available on-treatment HIV-1 RNA measurement ≥ 50 copies/mL within the time point of interest analysis window specified in [Table 8](#).
 - Who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window and:
 - Who discontinue study intervention prior to or in the time point of interest analysis window due to lack of efficacy, or
 - Who discontinue study intervention prior to or in the time point of interest analysis window due to reasons other than lack of efficacy and have the last available on-treatment HIV-1 RNA measurement ≥ 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 time point of interest analysis window specified in [Table 8](#) because of the following:
 - Discontinued study intervention due to AE or death: This includes participants who discontinued study intervention because of an AE or death at any time point from Day 1 through the analysis window if this resulted in no on-treatment HIV-1 RNA measurements during the specified window and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL. In addition, this category will include participants who discontinued study intervention because of an AE or death and had no on-treatment HIV-1 RNA measurements during the entirety of the study.
 - Discontinued study intervention for other reasons: This includes participants who discontinued study intervention prior to or in the time point of interest analysis window due to reasons other than lack of efficacy and 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. In addition, this category will include participants who discontinued study intervention due to reasons other than lack of efficacy and AE/death and had no on-treatment HIV-1 RNA measurements during the entirety of the study.

- On study intervention but missing data in window: Only data in the predefined analysis window can be used for the statistical analysis at a given time point for participants remaining on study intervention. Participants with HIV-1 RNA results outside this window will be classified as “on study intervention but missing data in window” regardless of the out of window HIV-1 RNA results.

For the primary evaluation of non-inferiority as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL, the parameter for evaluation is the number of participants classified as “HIV-1 RNA ≥ 50 copies/mL” according to the FDA snapshot algorithm defined above, divided by the number of participants in the FAS. For the secondary endpoint involving those with HIV-1 RNA < 50 copies/mL, the parameter for evaluation is the number of participants classified as “HIV-1 RNA < 50 copies/mL” according to the FDA snapshot algorithm, divided by the number of participants in the FAS. Similar logic will also be used to define the percentage of participants with HIV-1 RNA < 200 copies/mL in accordance with the relevant secondary endpoints.

A second approach, the M=F approach, will be performed as a sensitivity analysis for the percentage of participants with HIV-1 RNA < 50 copies/mL. Under this approach, participants who 1) have the last available on-treatment measurement within the time point of interest analysis window specified in Table 8 < 50 copies/mL, OR 2) are on study intervention and have no HIV-1 RNA measurements within the time point of interest analysis window specified in Table 8 and have both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements < 50 copies/mL, will be classified as a virologic success (ie, HIV-1 RNA < 50 copies/mL) at the time point of interest. Participants with other reasons for missing data will be classified as a virologic failure (ie, HIV-1 RNA ≥ 50 copies/mL) at the time point of interest.

A third approach, the OF approach, will also be performed as a sensitivity analysis for the percentage of participants with HIV-1 RNA ≥ 50 copies/mL and for the percentage of participants with HIV-1 RNA < 50 copies/mL. Under this approach, participants with nonintermittent missing data who discontinue study intervention early due to lack of efficacy or who discontinue study intervention for other reasons and are failures (HIV-1 RNA ≥ 50 copies/mL) at the time of study intervention discontinuation are considered to be failures at time points 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 time points. Participants with intermittent missing data will be considered to be successes (HIV-1 RNA < 50 copies/mL) if both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA values are < 50 copies/mL; all other intermittent missing results will be imputed as failures.

The same supportive approaches as described above will similarly be used for the analysis of the percentage of participants with HIV-1 RNA < 200 copies/mL.

Percentage of Participants With HIV-1 RNA ≥ 50 Copies/mL

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA ≥ 50 copies/mL in the base study.

Non-inferiority of a switch to DOR/ISL on Day 1 (Group 1) to continued baseline ART from Day 1 to Week 48 (Group 2) with respect to the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 will be evaluated using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with Cochran-Mantel-Haenszel weights (stratified by baseline ART regimen: PI-containing regimens [including PI- + InSTI-containing regimens], InSTI-containing regimens [non-PI-containing regimens], and all other [non-PI- and non-InSTI-containing] regimens). For the evaluation of the primary efficacy hypothesis, a margin of 4 percentage points is used to define the non-inferiority of a switch to DOR/ISL on Day 1 to the continuation of baseline ART for 48 weeks; non-inferiority will be concluded if the upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL (Group 1 minus Group 2) is less than 4 percentage points. The choice of non-inferiority margin is based on the amount of virologic failure that is clinically acceptable; with an anticipated virologic failure rate of approximately 2%, a stringent margin of 4 percentage points is clinically acceptable.

To summarize virologic response over time, the difference in percentages between treatment groups at each time point through Week 48 will be estimated and the associated 2-sided 95% CI will be derived in a similar fashion to that described for the primary efficacy analysis.

In addition, for participants who become pregnant and consent to continue their assigned study intervention (Section 8.11.6.1), a listing of HIV-1 RNA values over time at the scheduled visits will be provided.

In the optional study extension, the percentage of participants with HIV-1 RNA ≥ 50 copies/mL will be summarized at the scheduled visits using the DAO approach. This analysis will be summarized based on number of participants who have reached the timepoint of interest.

Percentage of Participants With HIV-1 RNA < 200 Copies/mL and Percentage of Participants With HIV-1 RNA < 50 Copies/mL

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA < 200 copies/mL and the percentage of participants with HIV-1 RNA < 50 copies/mL in the base study. These endpoints will be summarized by treatment group at each time point, with primary interest at Week 48 by comparing Group 1 and Group 2. For this time point of interest, the difference in percentages between treatment groups (Group 1 minus Group 2) and the associated 2-sided 95% CI will be calculated using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with Cochran-Mantel-Haenszel weights (stratified by baseline ART regimen). A summary of virologic response over time for Group 1 from Day 1 through Week 144 and for Group 2 from Week 48 through Week 144 will be provided separately.

Supportive analyses using the M=F and OF approaches (as defined above) will also be presented.

In the optional study extension, the percentage of participants with HIV-1 RNA <50 and <200 copies/mL will be summarized in a similar manner as for those with HIV-1 RNA \geq 50 copies/mL.

The percentages of participants with HIV 1 RNA <20 copies/mL (the LLOQ of the assay), 20 to <50, 50 to <100, 100 to <200, 200 to <400 and \geq 400 copies/mL will be summarized by treatment groups at all scheduled study visit timepoints.

Change From Baseline in CD4+ T-cell Count

The mean change from baseline in CD4+ T-cell count will be summarized by treatment group at each time point at which CD4+ T-cell count is scheduled to be collected in the base study. To estimate the treatment difference (Group 1 minus Group 2), and corresponding 2-sided 95% CI, in mean changes from baseline to Week 48 and from baseline to Week 96 (where the data collected from Week 48 to Week 144, is temporally compared between treatment groups) in CD4+ T-cell count at each time point, a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of the baseline value and the values observed at each post-baseline time point. The analysis model will adjust for treatment group, time, stratum (at the time of randomization), the interaction of time-by-treatment group, and the interaction of time-by-stratum. This model will allow for different baseline means for each stratum, but restrict the baseline mean within each stratum to be the same for both treatment groups. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment [Kenward, M. G. and Roger, J. H. 1997] will be used with restricted (or residual) maximum likelihood to make proper statistical inference.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups. Of note, if there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Moreover, this model allows the inclusion of participants who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

The cLDA method assumes that data are MAR. In this study, it is expected that MAR/MCAR mechanisms will underlie most of the missingness, and the proportion of data MNAR, driven solely by unobserved values of the study endpoints, will be small. Reasons for discontinuation from the study may include lack of efficacy, death, withdrawal of

consent, protocol deviations, lost to follow-up (eg, relocation), etc. Missing data caused by a participant's relocation are likely to be MCAR. Missing data caused by discontinuations due to lack of efficacy may belong to MAR because this type of discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If the assigned study intervention in large part determines the loss of data for these other reasons, the mechanism may be close to MAR, because the intervention assignment is an observed variable and included in the analysis model.

To estimate the treatment difference (Group 1 minus Group 2), and corresponding 2-sided 95% CI, in mean changes from baseline to Week 48 in Group 1 and from Week 48 to Week 96 in Group 2 (where the data reflects the first 48 weeks of treatment with DOR/ISL in each treatment group) in CD4+ T-cell count at each time point, a similar longitudinal model as described above will be used. However, because the baseline value in Group 1 (ie, the Day 1 value) and the baseline value in Group 2 (ie, the Week 48 value) will likely have different distributions (since participants in Group 2 will have had an additional 48 weeks of baseline ART experience relative to participants at baseline in Group 1), the constraint of equal baseline means across treatment groups will not be imposed. That is, an LDA model, rather than a cLDA model, will be used. Other model specifications will be consistent with those specified above. The estimates of the between-group differences in the mean change from baseline in CD4+ T-cell count will not be subject to an absolute criterion for similarity as the clinical interpretation of treatment difference is dependent upon the absolute values at baseline and the magnitude and direction of the CD4+ T-cell count changes observed in each treatment arm.

In addition to CD4+ T-cell count, the observed mean CD4+ T-cell percentage will also be summarized by study intervention groups at each timepoint at which the TBNK panel/CD4+ T-cell count is scheduled to be collected.

During the optional study extension, the change from baseline in CD4+ T-cell count will be summarized separately using descriptive statistics based on the DAO approach. For assessments of change from baseline in Group 2 during the optional study extension, the baseline measurement will be taken as the Week 48 measurement (or, if the Week 48 measurement is not available, the last measurement before the switch to DOR/ISL)

Clinically Significant Confirmed Viremia

The number of participants with clinically significant confirmed viremia, as defined in Section 4.2.1.1.2, will be summarized for each treatment group.

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 for each treatment group with primary interest at Weeks 48, 96, 144, and timepoints of interest during the optional study extension.

HBV Acute Infection/Reactivation

If the clinical management of HBV acute infection/reactivation requires the addition of a concomitant therapy that is also active against HIV-1, efficacy assessments in these participants from that point forward will be handled in a similar manner as the FDA snapshot algorithm classification rules for participants with missing data due to discontinuation of study intervention in the base study. During the optional study extension, efficacy assessments from that point forward in these participants will be reported separately.

Participants Who Discontinue Due to Pregnancy or Breastfeeding

For participants who become pregnant and choose to discontinue study intervention, or participants who choose to breastfeed and must discontinue study intervention in the base study, efficacy assessments from that point forward will be handled in a similar manner as the FDA snapshot algorithm classification rules for participants with missing data due to discontinuation of study intervention. Results for participants who become pregnant during the study will be reported separately.

Participants in Group 2 who become pregnant prior to the Week 48 visit are not eligible for a switch to DOR/ISL, but may consent to remain in the study on their baseline ART (Section 8.11.6.1). For such participants, efficacy assessments from that point forward will be handled in a similar manner as the FDA snapshot algorithm classification rules for participants with missing data due to discontinuation of study intervention.

[Table 9](#) summarizes the key efficacy analyses of the base study.

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple endpoints, multiple time points, and/or IAs is described in Sections 9.7 and 9.8.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach ^a	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis H1				
Percentage of participants with HIV-1 RNA \geq 50 copies/mL at Week 48	P	M&N with CMH weights ^b	FAS	Snapshot
	S	M&N with CMH weights ^b	PP	OF
Secondary Endpoints				
Percentage of participants with HIV-1 RNA <200 and <50 copies/mL at Weeks 48, 96, and 144	P	M&N with CMH weights ^b	FAS	Snapshot
	S	M&N with CMH weights ^b	FAS	M=F
	S	M&N with CMH weights ^b	PP	OF
Mean change from baseline in CD4+ T-cell count at Weeks 48, 96, and 144	P	cLDA ^c	FAS	Model-based
cLDA=constrained longitudinal data analysis; CMH=Cochran-Mantel-Haenszel; FAS=Full Analysis Set; HIV-1=human immunodeficiency virus type 1; InSTI=integrase strand transfer inhibitor; M=F=missing equal to failure; M&N=Miettinen and Nurminen; OF=Observed Failure; PI=protease inhibitor; PP=Per-Protocol; RNA=ribonucleic acid. ^a P=primary approach; S=supportive approach. ^b The M&N method with CMH weights will be stratified by baseline ART regimen: PI-containing regimens (including PI- + InSTI-containing regimens), InSTI-containing regimens (non-PI-containing regimens), and non-PI- and non-InSTI-containing regimens [Miettinen, O. and Nurminen, M. 1985]. ^c The cLDA model will include terms for treatment group, time, stratum, the interaction of time-by-treatment group, and the interaction of time-by-stratum.				

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results and vital signs. For analyses of safety by time point, the same analysis windows as specified in [Table 8](#) will be used, unless otherwise specified.

Safety summaries will be presented by treatment arm for data collected up to Week 48 (ie, data collected from Day 1 to prior to the switch to DOR/ISL in Group 2). The post-Week 48 safety data (ie, data collected from Week 48 through Week 144) in both treatment arms will be summarized. In addition, for Group 1, the safety data from Day 1 through Week 144 will be summarized. All between-group comparisons of safety endpoints will only be conducted up to Week 48 (prior to the switch to DOR/ISL in Group 2).

9.6.2.1 Overall Safety Assessment

The overall safety evaluation in the base study will include a summary by treatment group of the number and percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 or 4 AE, with an AE that is both serious and drug-related, with an AE that is both Grade 3 or 4 and drug-related, who discontinued study intervention due to an AE, who discontinued study intervention due to a drug-related AE, and with an AE resulting in death. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with the event will be provided.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 2-sided 95% CIs for the differences between treatment groups in the percentages of participants with specific AEs will be provided for AEs that occur in at least 8 participants in the DOR/ISL treatment group or at least 2 participants in the baseline ART group. These thresholds for the numbers of events were chosen because the 95% CI for the between-group difference in percent incidence will always include 0 when fewer participants per group have events and thus would add little to the interpretation of potentially meaningful differences.

CIs for between-treatment group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. CIs that are not adjusted for multiplicity should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Point estimates and 2-sided 95% CIs for the differences between treatment groups in the percentages of participants with safety parameters that meet predefined limits of change will be provided based on the same criteria used above for specific AEs.

For continuous safety measures, such as change from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group. For participants who become pregnant during the study, measurements collected after the estimated date of conception will be excluded from the analyses. Missing data will not be imputed.

To evaluate the effect on weight of a switch to DOR/ISL at Day 1 compared with continued baseline ART, the treatment difference (Group 1 minus Group 2) and corresponding 2-sided 95% CI for the mean change from baseline to Week 48 in weight will be estimated using an ANCOVA model adjusted by baseline weight, sex at birth, race, stratum, presence of EFV or TDF in the baseline ART regimen, and treatment group. Presence of EFV or TDF in the baseline ART regimen will be adjusted for in the ANCOVA models as these are antiobesogenic ARTs. Additional ANCOVA models may be run within each stratum to

estimate the treatment difference among participants with PI-containing baseline ART regimens (including PI- + InSTI-containing regimens), among participants with InSTI-containing baseline ART regimens (non-PI-containing regimens), and among participants with non-PI- and non-InSTI-containing baseline ART regimens; therefore, these ANCOVA models will not adjust for stratum.

For the mean change from baseline to Week 48 in lymphocyte, the treatment difference (Group 1 minus Group 2) and corresponding 2-sided 95% CI will be estimated using ANCOVA models adjusted by baseline value and treatment group.

Safety data for participants who consent to continue the treatment in the optional study extension (from Week 144 to Week 240) will be summarized separately. Additional details are provided in the sSAP.

9.6.2.2 Assessment of Safety Topics of Special Interest

Opportunistic infections and lipid profiles are considered safety topics of special interest in the base study.

The number and percentage of participants with any opportunistic infection will be summarized by treatment group. The point estimate and 2-sided 95% CI for the difference between treatment groups (Group 1 minus Group 2) in the percentage of participants with any opportunistic infection will be provided. The number and percentage of participants with specific opportunistic infections will also be summarized by treatment group. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with these events will be provided based on the criteria described above for specific AEs. CIs for between-treatment group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Opportunistic infections will be identified through SMQs using the MedDRA dictionary. SMQs on both broad and narrow PTs will be performed and will be summarized separately.

The effect on LDL-C and non-HDL-C at Week 48 of a switch to DOR/ISL on Day 1 compared with the continuation of baseline ART for each baseline ART class will be evaluated. Of particular interest is assessing the superiority of a switch to DOR/ISL on Day 1 compared with the continuation of baseline ART for those in each stratum at Week 48.

For the evaluation of the secondary objective to assess the effect on lipid profiles of a switch to DOR/ISL at Day 1 compared with continued baseline ART, the treatment difference (Group 1 minus Group 2) and 2-sided 95% CI for all lipid parameters will be estimated using ANCOVA models adjusted by baseline lipid level and treatment group. Separate ANCOVA models will be constructed for each baseline ART stratum. Participants who receive lipid-lowering therapy at baseline will be excluded from the lipid-related analyses. For participants who initiate lipid-lowering therapy during the study, the last lipid measurement before initiating the lipid-lowering therapy will be carried forward. For participants who become pregnant, lipid data collected after the estimated date of conception will be excluded. Missing lipid data will not be imputed; as such, any participant with a missing value will be

excluded from the analyses. The percentages of participants who initiate or modify lipid-lowering therapy prior to Week 48 will be summarized by treatment group. Additional details will be provided in the sSAP.

The same ANCOVA models used to estimate the between-group differences in lipid profiles for each stratum will be used to evaluate the secondary composite hypothesis regarding the effect on LDL-C and non-HDL-C of a switch to DOR/ISL at Day 1 compared with the continuation of baseline ART for each stratum at Week 48. In accordance with the multiplicity strategy (Section 9.8), the hypothesis will be tested for each stratum sequentially (ie, statistical significance for the first stratum must be established before testing the next stratum, and so forth) in the order of PI-containing regimens (including PI- + InSTI-containing regimens), non-PI- and non-InSTI-containing regimens, and InSTI-containing regimens (non-PI-containing regimens). The superiority of a switch to DOR/ISL on Day 1 compared with continuation of baseline ART as assessed by having a lower mean increase from baseline in LDL-C and/or non-HDL-C at Week 48 will be concluded if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the estimate of the between-group difference (Group 1 minus Group 2) is less than 0. P-values for the comparisons will also be provided.

9.6.2.3 Handling of Missing Data and Pregnancies in Safety Analyses

Missing safety parameters, unless otherwise specified, will not be imputed; as such, any participant with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. 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, when available. If no baseline result is available for a given analysis, that participant will not be included in the analysis. Safety data for participants who consent to enter the optional study extension at Week 144 will be summarized from Week 144 to Week 240.

For participants who become pregnant during the study, all safety data collected on or after the estimated date of conception will be summarized separately from the primary and secondary safety analyses. Data collected for participants whose pregnancy or Postpartum visit(s) extends beyond Week 144 will be reported separately. Infant safety data will also be reported separately.

[Table 10](#) summarizes the analysis strategy for safety endpoints in the base study.

Table 10 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI	Inferential Analysis
Overall Safety Assessment	Any AE	X	X	
	Any drug-related AE	X	X	
	Any SAE	X	X	
	Any Grade 3 or 4 AE	X	X	
	Any serious drug-related AE	X	X	
	Any Grade 3 or 4 drug-related AE	X	X	
	Discontinued study intervention due to an AE	X	X	
	Discontinued study intervention due to a drug-related AE	X	X	
	AE resulting in death	X	X	
	Specific AEs	X	X ^a	
	SOCs, PDLCS	X	X ^a	
	Mean Change from Baseline (Laboratory, Vital Signs Parameters, and Lymphocyte Parameters)	X	X	
Assessment of Safety Topics of Special Interest	Any Opportunistic Infection	X	X	
	Specific Opportunistic Infections and Corresponding SOC	X	X ^a	
	Lipid Profiles (Mean Change from Baseline in LDL-C, non-HDL-C, TC, HDL-C, TGs, and TC/HDL-C Ratio)	X	X	X ^b
AE=adverse event; CI=confidence interval; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; non-HDL-C=non-high-density lipoprotein cholesterol; PDLCS=predefined limit of change; SAE=serious adverse event; SOC=system organ class; TC=total cholesterol; TG=triglyceride. ^a The between-group 95% CI will only be provided for events that occur in at least 8 participants in Group 1 or at least 2 participants in Group 2. ^b Inferential analysis will only be performed for the mean change from baseline in the LDL-C and non-HDL-C lipid parameters at Week 48 in accordance with the relevant secondary hypothesis, H2. P-values will be provided for the mean change from baseline in LDL-C and non-HDL-C at Week 48.				

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, region, etc), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Study enrollment is likely to be ongoing at the time of the IA. The IA results will not be shared with the investigators prior to the completion of the study.

An eDMC will serve as the primary reviewer of the interim efficacy and safety review results and may make recommendations for discontinuation of the study or for protocol modifications to an executive committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) will review results at the treatment-level to act on these recommendations. Additional logistical details will be provided in the DMC charter.

Once approximately 30% of target enrollment (n=150 participants) have completed the Week 24 visit assessments, the Week 24 IA will be conducted by the external statistician to assess futility. This analysis will be reviewed by the eDMC. All available efficacy and safety data for all participants enrolled at the time of the Week 24 IA will be reviewed. The futility analysis will include the first approximately 30% of study participants who complete the Week 24 visit assessments. The nonbinding futility criterion is as follows:

Nonbinding Futility Criterion: If the upper bound of the 2-sided 95% CI for the between-group difference (Group 1 minus Group 2) in the percentage of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 is greater than 8 percentage points, consideration may be given to stop the study. The CI will be based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

For the purpose of the futility assessment, those classified as HIV-1 RNA ≥ 200 copies/mL will include participants:

- Who have the last available on-treatment HIV-1 RNA measurement within the Week 24 analysis visit window specified in [Table 8](#) ≥ 200 copies/mL.

Note: For such participants, if the HIV-1 RNA value of ≥ 200 copies/mL is not confirmed at the subsequent assessment (ie, the participant does not meet the criteria for clinically significant confirmed viremia [Section 4.2.1.1.2]), their virologic outcome will be reassessed for the primary efficacy analysis (Section 9.6.1).

- Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis visit window specified in Table 8 and
 - Discontinued study intervention prior to or in the Week 24 analysis visit window due to lack of efficacy or clinically significant confirmed viremia (Section 4.2.1.1.2), or
 - Discontinued study intervention prior to or in the Week 24 analysis visit window due to reasons other than lack of efficacy/clinically significant confirmed viremia and have their last on-treatment HIV-1 RNA measurement ≥ 50 copies/mL.

Note: Such participants will be classified as virologic failures (ie, HIV-1 RNA ≥ 50 copies/mL) in the primary efficacy analysis (Section 9.6.1) in accordance with the FDA snapshot approach.

The endpoint of HIV-1 RNA ≥ 200 copies/mL for the futility assessment is clinically meaningful as it is a threshold associated with increased likelihood of development of viral drug resistance and subsequently a potential need to switch to a new regimen, while values < 200 copies/mL do not necessarily indicate the need for a change in therapy. Furthermore, use of this endpoint protects against over-interpretation of transient viremia (ie, an HIV-1 RNA measurement ≥ 50 copies/mL in a previously suppressed person that quickly resolves to < 50 copies/mL); a single value of HIV-1 RNA ≥ 200 copies/mL is more likely to indicate a true treatment failure than a single value ≥ 50 copies/mL and is thus a useful measure for assessing futility at the Week 24 IA.

Given the anticipated small number of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 and the expected sample sizes of 100 participants in Group 1 and 50 participants in Group 2 included in the futility assessment, the specified futility criterion is sensitive to imbalances in the number of failures (ie, HIV-1 RNA ≥ 200 copies/mL) between the treatment groups. For example, if there are 2 failures out of 100 participants in Group 1 and 0 failures out of 50 participants in Group 2, the estimated treatment difference is 2% and the upper bound of the between-group 95% CI is 7.03, which would not meet the futility criterion. However, if there are 3 failures in Group 1 and 0 failures in Group 2, then the treatment difference is 3% and the upper bound of the between-group 95% CI is 8.48, thus meeting the futility criterion and leading to consideration to stop the study. If there are 3 failures in Group 1 and 1 failure in Group 2, then the treatment difference is 1% and the upper bound of the between-group 95% CI is 6.84, which would not meet the futility criterion. However, with 4 failures in Group 1 and 1 failure in Group 2, the treatment difference is 2% and the upper bound of the between-group 95% CI is 8.25, which meets the futility criterion. Additional details on the operational characteristics of the futility criterion are provided in Section 9.9.1.

The eDMC will review accumulating efficacy and safety data at regular intervals throughout the study duration, or at modified intervals based on the recommendation of the eDMC. The

eDMC will recommend steps to ensure the safety of study participants and the integrity of the study as needed.

An analysis will be conducted to test the primary non-inferiority efficacy hypothesis once all participants have completed the Week 48 visit assessments. This will be the formal evaluation of the primary non-inferiority efficacy hypothesis. All available efficacy and safety data will be reviewed at this interim time point. Treatment-level results from this analysis will be provided to the eDMC.

Since the hypotheses listed in Section 3 will be tested only at Week 48 (and not at the Week 24 IA nor any periodic review of data by the eDMC) and as there is no plan to stop the study early for a positive efficacy finding, testing of H1 and H2 will not be adjusted for multiplicity on account of any eDMC reviews. The multiplicity strategy for hypothesis testing is described in Section 9.8.

At least until the Week 48 database lock, treatment-level results from all IAs will be provided to the eDMC by the external statistician. The external statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

If the study is stopped early, the CSR will include all available data up to and including the close-out visits. This approach to include all available information is in line with the ICH-E9 guideline.

9.8 Multiplicity

As noted in Section 9.7, an eDMC will convene at routine intervals to monitor efficacy and safety. A formal futility analysis at Week 24 is planned as described in Section 9.7; a small amount of alpha ($\alpha=0.00001$) will be allocated for this IA, purely for statistical rigor. The trial will not be stopped early for positive efficacy at the IA.

In order to have strong control of the overall Type I error rate across the primary and secondary hypotheses, the following hypotheses will be tested sequentially at a 1-sided 2.499% Type 1 error rate in the following order:

1. Primary efficacy hypothesis (H1) testing non-inferiority of Group 1 to Group 2 as assessed by the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48.
2. Secondary safety hypothesis (H2) testing superiority of Group 1 to Group 2 as assessed by the mean change from baseline in LDL-C and non-HDL-C at Week 48. It is noted that H2 is really a composite hypothesis involving 6 statistical tests (2 cholesterol parameters and 3 randomization strata). These 6 tests will be evaluated following the graphical approach of Maurer and Bretz [Maurer, W., et al 2011] to strongly control the overall 1-sided Type 1 error rate at 2.499%.

Figure 2 shows the hierarchical testing procedure in H2 between LDL-C and non-HDL-C endpoints in the 3 strata. In each stratum, testing will stop with the first of these tests failing to reach statistical significance. The testing in a given stratum is considered a success if superiority is established for both the hypotheses in that stratum. The weight ω is defined

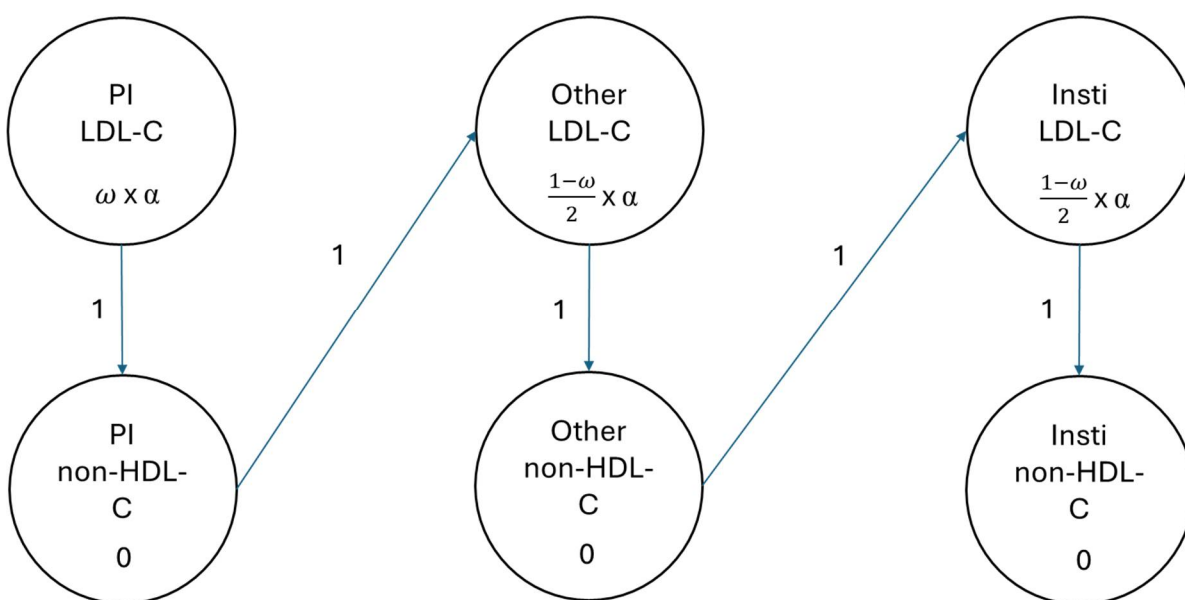
based on the sample size of the PI stratum. Here, “a” denotes the sample size of the PI stratum and “N” denotes the total sample size. The assumptions on “a” and weight ω , as described below, are based on clinical judgment from historical data and the prevalence of the ARTs from the PI stratum and also from observed data at Week 48 in the MK-8591A-017 study. Specifically, from historical data, the PI stratum is most likely to show a significant treatment difference but the sample size in this stratum is uncertain as PI use is diminishing in some regions. Therefore, contingent on a sufficient sample size, a large fraction of alpha (α) is initially allocated to the PI stratum with the rest distributed equally to the other 2 strata.

$$\text{If } a \geq 130 \text{ then } \omega = \text{maximum}\left(\frac{a}{N}, 1 - \frac{a}{N}\right)$$

$$\text{If } 70 < a < 130 \text{ then } \omega = \frac{1}{2}$$

$$\text{If } a \leq 70 \text{ then } \omega = 0.01$$

Figure 2 Multiplicity Graph for Type I Error Control of the Secondary Hypothesis



Insti=integrase strand transfer inhibitor; LDL-C=low-density lipoprotein cholesterol;
 non-HDL-C=non-high-density lipoprotein cholesterol; PI= protease inhibitor; ω =weight

Table 11 illustrates the initial Type 1 error (α) allocation to all the hypotheses in the 3 strata for different hypothetical sample sizes observed in the PI stratum.

Table 11 Initial Alpha Allocation Based on PI Stratum Sample Size

PI Sample Size	ω	PI - LDL-C	PI - Non-HDL-C	Other - LDL-C	Other - Non-HDL-C	InSTI - LDL-C	InSTI - Non-HDL-C	Total Type I Error (α)
200	0.60079	0.01501	0	0.00499	0	0.00499	0	0.02499
180	0.64072	0.01601	0	0.00449	0	0.00449	0	0.02499
130	0.74052	0.01815	0	0.00324	0	0.00324	0	0.02499
100	0.5	0.01249	0	0.00625	0	0.00625	0	0.02499
70	0.01	0.000249	0	0.01237	0	0.01237	0	0.02499
50	0.01	0.000249	0	0.01237	0	0.01237	0	0.02499
InSTI=integrase strand transfer inhibitor; LDL-C=low-density lipoprotein cholesterol; non-HDL-C=non-high-density lipoprotein cholesterol; PI=protease inhibitor; ω =weight.								

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

9.9.1.1 Evaluation of the Primary Hypothesis

This section presents power calculations for the primary efficacy analysis of demonstrating non-inferiority of a switch to DOR/ISL on Day 1 to continued baseline ART at Week 48. The power calculations provided in this section do not account for the futility assessment at the Week 24 IA or the sequential testing strategy described in Section 9.8.

For efficacy analyses using the FDA snapshot algorithm, missing data (eg, due to study intervention discontinuation) are classified as either HIV-1 RNA ≥ 50 copies/mL (which will contribute to both the numerator and denominator in the calculation of the percentage of participants with HIV-1 RNA ≥ 50 copies/mL) or as No Virologic Data in Specified Analysis Time Window (which will contribute only to the denominator in the calculation of the percentage of participants with HIV-1 RNA ≥ 50 copies/mL). Therefore, the impact of missing data on study power is subsumed within the rates of HIV-1 RNA ≥ 50 copies/mL assumed in the power calculations throughout Section 9.9.1.

Non-inferiority will be concluded if the upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 (Group 1 minus Group 2) is less than 4 percentage points. The choice of non-inferiority margin is based on the amount of virologic failure that is clinically acceptable; with an anticipated virologic failure rate of approximately 1.5% to 2%, a stringent margin of 4 percentage points is clinically acceptable. The observed percentages of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 are based on experience with MK-8591A-017 and MK-8591A-018. They are 0.0% in DOR/ISL group and 1.5% in Baseline ART group in MK-8591A-017 and 0.6% in DOR/ISL group and 0.3% in BIC/FTC/TAF group in MK-8591A-018.

Table 12 summarizes the power to declare a switch to DOR/ISL on Day 1 non-inferior to continued baseline ART at Week 48 under various assumptions for the response rate (ie, the percentage of participants with HIV-1 RNA ≥ 50 copies/mL) in Group 2 and the underlying between-group difference in response rates. For example, if the true rate of participants with HIV-1 RNA ≥ 50 copies/mL is 1.5% in both groups, this study has approximately 93.3% power to demonstrate non-inferiority. If the true rates are 2.0% in both groups, this study has approximately 87.0% power to demonstrate non-inferiority.

Table 12 Power (%) to Establish Non-inferiority at Week 48 Under Various Response Rate Assumptions

True Response Rate in Group 2	True Difference in Response Rates (Group 1 Minus Group 2)				
	-1.0 Percentage Points	-0.5 Percentage Points	0.0 Percentage Points	0.5 Percentage Points	1.0 Percentage Points
0.5%	NA	100	99.9	96.9	83.8
0.75%	NA	100	99.4	93.5	77.7
1.0%	100	100	98.2	89.4	72.1
1.25%	100	99.7	96.1	84.9	67.2
1.5%	100	99.0	93.3	80.6	63.1
1.75%	99.8	97.7	90.2	76.6	59.5
2.0%	99.4	95.9	87.0	72.9	56.3
2.25%	98.7	93.8	83.8	69.5	53.3
2.5%	97.5	91.5	80.7	66.3	50.5
2.75%	96.2	89.1	77.6	63.2	48.0
3.0%	94.6	86.6	74.6	60.3	45.6

CI=confidence interval; HIV-1=human immunodeficiency virus type 1; NA=not applicable; PASS=power analysis and sample size; RNA=ribonucleic acid.
 334 participants in Group 1 and 167 participants in Group 2
 The response rate is the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48.
 The non-inferiority margin is 4 percentage points. To establish non-inferiority, the upper bound of the 2-sided 95% CI for the difference between groups (Group 1 minus Group 2) in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL must be <4 percentage points. The 95% CI is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.02499. Calculations were performed using PASS 16.
 The observed percentages of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 are based on experience with MK-8591A-017 and MK-8591A-018. They are 0.0% in DOR/ISL group and 1.5% in Baseline ART group in MK-8591A-017 and 0.6% in DOR/ISL group and 0.3% in BIC/FTC/TAF group in MK-8591A-018.

9.9.1.2 Evaluation of the Futility Criterion and Non-inferiority at Week 48

The futility assessment will be conducted on the first approximately 30% of the total planned study enrollment (approximately 100 participants in Group 1 and 50 participants in Group 2) who complete the Week 24 visit assessments. The study may be stopped if the upper bound of the 2-sided 95% CI for the difference in the percentage of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 (Group 1 minus Group 2) is greater than 8 percentage points.

Table 13 summarizes the probability of not meeting the futility criterion at Week 24 under various assumptions for the response rate (ie, the percentage of participants with HIV-1 RNA ≥ 200 copies/mL) in Group 2 and the underlying between-group difference in response rates. For example, if the true rate of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 among 100 participants in Group 1 and 50 participants in Group 2 is 0.75% in both groups, then the probability of not meeting the futility criterion is 0.971. If the true rates are 1.0% in both groups, then the probability of not meeting the futility criterion is 0.946. If the true rate in Group 1 is 2.0% and the true rate in Group 2 is 1.0%, then the probability of not meeting the futility criterion is 0.757.

Table 13 Probability of Not Meeting the Futility Criterion at the Week 24 Interim Analysis

True Response Rate in Group 2	True Difference in Response Rates (Group 1 Minus Group 2)				
	-1.0 Percentage Points	-0.5 Percentage Points	0.0 Percentage Points	0.5 Percentage Points	1.0 Percentage Points
0.50%	NA	1.000	0.989	0.935	0.839
0.75%	NA	0.999	0.971	0.900	0.797
1.0%	1	0.991	0.946	0.864	0.757
1.25%	0.999	0.976	0.917	0.827	0.720
1.5%	0.993	0.956	0.885	0.791	0.684
1.75%	0.981	0.931	0.853	0.756	0.652
2.0%	0.964	0.904	0.820	0.723	0.622
2.25%	0.943	0.875	0.789	0.692	0.595
2.5%	0.919	0.846	0.758	0.664	0.570
2.75%	0.894	0.817	0.730	0.638	0.549
3.0%	0.868	0.790	0.704	0.615	0.529
CI=confidence interval; HIV-1=human immunodeficiency virus type 1; NA=not applicable; PASS=power analysis and sample size; RNA=ribonucleic acid. 100 participants in Group 1 and 50 participants in Group 2 The response rate is the percentage of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24. Futility Criterion: Upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 (Group 1 minus Group 2) is greater than 8 percentage points. The 95% CI is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.02499. Calculations were performed using PASS 16.					

The probability of not meeting the futility criterion at the Week 24 IA and the power to demonstrate non-inferiority at Week 48 under a variety of assumptions is presented in [Table 14](#).

The power calculations shown in [Table 14](#) incorporate the futility assessment stopping rules. Of interest is the likelihood that the study would not meet the futility criterion at Week 24 for a variety of assumed Week 24 response rates and also whether the non-inferiority criterion at Week 48 would be subsequently met (ie, the conditional power of declaring DOR/ISL non-inferior to baseline ART at Week 48).

For example, if the true rate of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 is 0.5% in both groups, the rate of HIV-1 RNA ≥ 50 copies/mL at Week 48 among participants who had HIV-1 RNA ≥ 200 copies/mL at Week 24 is 95% in both groups, and the rate of HIV-1 RNA ≥ 50 copies/mL at Week 48 among participants who had HIV-1 RNA < 200 copies/mL at Week 24 is 1% in both groups, then the probability of not meeting the futility criterion at the Week 24 IA is 98.9% and the subsequent power to declare non-inferiority of DOR/ISL to baseline ART at Week 48 is 93.8%.

Additional power calculations are provided in the sSAP.

Table 14 Probability of Not Meeting the Futility Criterion at the Week 24 Interim Analysis and the Conditional Power to Declare Non-inferiority at Week 48 for Various Underlying True Response Rates

Parameter	Base Case		More Conservative Base Case		Most Conservative Base Case		Low Efficacy for DOR/ISL; Low Efficacy for Baseline ART		Low Efficacy for DOR/ISL; High Efficacy for Baseline ART		High Efficacy for DOR/ISL; Low Efficacy for Baseline ART		High Efficacy for DOR/ISL; High Efficacy for Baseline ART		Lowest Efficacy for DOR/ISL; High Efficacy for Baseline ART	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Assumptions ^a																
% with Week 24 HIV-1 RNA ≥200 copies/mL	0.5%	0.5%	0.75%	0.75%	1.0%	1.0%	1.5%	1.0%	1.5%	0%	0%	1.0%	0%	0%	3%	0%
% with Week 48 HIV-1 RNA ≥50 copies/mL if Week 24 HIV-1 RNA ≥200 copies/mL	95%	95%	100%	100%	100%	100%	100%	100%	100%	92%	92%	100%	92%	92%	100%	92%
% with Week 48 HIV-1 RNA ≥50 copies/mL if Week 24 HIV-1 RNA <200 copies/mL	1%	1%	1.25%	1.25%	1.5%	1.5%	3%	2%	3%	0.5%	0.5%	2%	0.5%	0.5%	3%	0.5%
% with Week 48 HIV-1 RNA ≥50 copies/mL	1.5%	1.5%	2.0%	2.0%	2.5%	2.5%	4.5%	3.0%	4.5%	0.5%	0.5%	3.0%	0.5%	0.5%	5.9%	0.5%
Study Power																
Probability of Not Meeting the Futility Criterion ^b	98.9%		97.0%		94.7%		86.5%		81.1%		~100%		~100%		42.4%	
Conditional Power to Establish Non-inferiority at Week 48 ^c	93.8%		87.8%		82.4%		35.9%		2.4%		~100%		99.9%		0.2%	
ART=antiretroviral therapy; BIC=bictegravir; CI=confidence interval; COVID-19=coronavirus disease 2019; DOR=doravirine; FTC=emtricitabine; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; RNA=ribonucleic acid; TAF=tenofovir alafenamide.																
The calculations assume 100 participants in Group 1 and 50 participants in Group 2 for the assessment of futility at Week 24 and 334 participants in Group 1 and 167 participants in Group 2 for the assessment of non-inferiority at Week 48.																

Parameter	Base Case		More Conservative Base Case		Most Conservative Base Case		Low Efficacy for DOR/ISL; Low Efficacy for Baseline ART		Low Efficacy for DOR/ISL; High Efficacy for Baseline ART		High Efficacy for DOR/ISL; Low Efficacy for Baseline ART		High Efficacy for DOR/ISL; High Efficacy for Baseline ART		Lowest Efficacy for DOR/ISL; High Efficacy for Baseline ART	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
<p>^a The assumptions for calculating power are based on observed rates in the MK-8591A-017 and MK-8591A-018 switch studies. Specifically, MK-8591A-017 showed a rate ≥ 50 copies/mL at Week 48 of 0.0% in the DOR/ISL arm and 1.5% in the continued baseline ART arm; MK-8591A-018 showed a rate ≥ 50 copies/mL at Week 48 of 0.6% in the DOR/ISL arm and 0.3% in the BIC/FTC/TAF arm. For the 3 base cases, the assumed percentages of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 are generally higher than the rates observed across the MK-8591A-017 and MK-8591A-018 study arms and, therefore, are considered to be conservative. The conservative rates were selected in recognition that MK-8591A-017 and MK-8591A-018 were conducted during the global COVID-19 pandemic, during which time participants may have been restricted to home stay or limited travel, potentially leading to higher adherence to study intervention and subsequently lower rates of virologic failure than would be otherwise expected.</p> <p>^b Futility Criterion: Upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥ 200 copies/mL at Week 24 (Group 1 minus Group 2) is greater than 8 percentage points. Values for the probability of not meeting the futility criterion were calculated via simulation.</p> <p>^c Each value was calculated via 10,000 simulations to evaluate first whether the futility criterion was met and if not, evaluate non-inferiority between groups using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The non-inferiority margin is 4 percentage points and the Type 1 error is 0.0249 (1-sided). Calculations were performed in R 3.5.0.</p>																

9.9.2 Sample Size and Power for Safety Analyses

9.9.2.1 Evaluation of 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 96.5% chance of observing at least 1 AE among 334 participants in a treatment group and an 81.3% chance of observing at least 1 AE among 167 participants in a treatment group. If no AE of that type is observed among 334 participants in a treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <1.10% (1 in every 91 participants) in the treatment group; if no AE of that type is observed among 167 participants in a treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <2.18% (1 in every 45 participants) in the treatment group.

The point estimate and the upper bound of the corresponding 2-sided 95% CI for the underlying percentage of participants with an AE given various hypothetical observed numbers of participants with the AE within each treatment group are provided in [Table 15](#). These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 15 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants With AEs

Number of Participants in the Treatment Group	Number of Participants With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound ^a
334	0	0%	0.9%
167	0	0%	1.8%
334	1	0.3%	1.7%
167	1	0.6%	3.3%
334	2	0.6%	2.1%
167	2	1.2%	4.3%
334	5	1.5%	3.5%
167	5	3.0%	6.8%
334	10	3.0%	5.4%
167	10	6.0%	10.7%
334	15	4.5%	7.3%
167	15	9.0%	14.4%
334	20	6.0%	9.1%
167	20	12.0%	17.9%
334	25	7.5%	10.9%
167	25	15.0%	21.3%
334	30	9.0%	12.6%
167	30	18.0%	24.6%
AE=adverse event; CI=confidence interval.			
^a Based on the 2-sided exact 95% CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. and Pearson, E. S. 1934]). In the 0-event case, the CI is 1-sided ($\alpha=0.05$ all in the upper tail).			

Table 16 gives the difference in the incidence of an AE (Group 1 minus Group 2) that can be ruled out with different power levels and 95% confidence when there are 334 participants in Group 1 and 167 participants in Group 2. The underlying incidence of the AE is assumed to be the same for the 2 treatment groups. For example, for a reasonably common AE which occurs in 20% of participants in both groups, the study has 80% power to declare with 95% confidence that the true difference between the treatment groups is no more than 11.7 percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 16 Difference in Incidence (Percentage Points) of AEs (Group 1 Minus Group 2) That Can Be Ruled Out With 334 Participants in Group 1 and 167 Participants in Group 2

Target Power	Underlying AE Incidence Rate						
	1%	5%	10%	20%	30%	40%	50%
80%	5.1	7.7	9.6	11.7	12.8	13.2	13.1
85%	5.5	8.3	10.3	12.5	13.7	14.1	14.0
90%	6.1	9.1	11.2	13.6	14.8	15.3	15.1
95%	7.1	10.3	12.6	15.2	16.5	17.0	16.7

AE=adverse event; CI=confidence interval.
 Values represent the upper bound of the 2-sided 95% CI (unstratified Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]) for the difference in AE incidences (Group 1 minus Group 2) assuming the incidences are the same.

9.9.2.2 Evaluation of Change from Baseline in Lipid Profiles

Because it is unknown in advance how many participants will be enrolled into each baseline ART stratum, and among those, how many will be on lipid-lowering therapy at baseline or initiate lipid-lowering therapy prior to Week 48 and thus be excluded from the lipid-related analyses, it is unknown how many participants will be available for the evaluation of the lipid-related hypothesis. As such, [Table 17](#) summarizes the power to declare Group 1 superior to Group 2 in the PI stratum as assessed by the mean change from baseline in LDL-C and non-HDL-C at Week 48 under various assumed treatment differences, standard deviations, and numbers of participants in each treatment group. The graphical approach will be used to test the LDL-C and non-HDL-C parameters within the PI stratum; the PI stratum sample sizes and corresponding 1-sided Type 1 error is used in [Table 17](#) for illustrative purposes.

For example, if the between-treatment difference (Group 1 minus Group 2) in the mean change in fasting LDL-C/non-HDL-C is 10 mg/dL with a standard deviation of 15 mg/dL in both treatment groups, 80 participants in Group 1 and 40 participants in Group 2 in the PI stratum, and a 1-sided Type 1 error of 0.0125 for that stratum, then this study has approximately 87.8% power to demonstrate that Group 1 is superior to Group 2 with respect to having a lower mean increase from baseline in LDL-C/non-HDL-C at Week 48.

Table 17 Power to Establish Superiority of Group 1 to Group 2 as Assessed by the Mean Change from Baseline in LDL-C/non-HDL-C at Week 48 Under Various Assumed Treatment Differences, Standard Deviations, and Numbers of Participants in Each Treatment Group

Number of Participants in Group 1	Number of Participants in Group 2	Type I Error (α)	Standard Deviation of Mean Change from Baseline			
			15 mg/dL	17 mg/dL	20 mg/dL	25 mg/dL
Assumed Between-group Difference in the Mean Change from Baseline=10 mg/dL						
46	24	0.00025	17.1%	10.6%	5.7%	2.5%
60	30	0.0125	75.7%	63.7%	48.5%	31.6%
80	40	0.0125	87.8%	77.8%	62.3%	42.2%
100	50	0.0125	94.2%	87.0%	73.3%	51.9%
120	60	0.016	98.0%	94.0%	84.1%	64.4%
Assumed Between-group Difference in the Mean Change from Baseline=13 mg/dL						
46	24	0.00025	42.4%	28.2%	15.6%	6.6%
60	30	0.0125	94.3%	87.1%	73.4%	52.0%
80	40	0.0125	98.6%	95.2%	86.0%	66.1%
100	50	0.0125	99.7%	98.4%	93.0%	76.9%
120	60	0.016	~100%	99.6%	97.4%	86.9%
Assumed Between-group Difference in the Mean Change from Baseline=16 mg/dL						
46	24	0.00025	71.4%	53.6%	32.8%	14.7%
60	30	0.0125	99.3%	97.2%	90.1%	71.9%
80	40	0.0125	99.9%	99.5%	96.8%	84.8%
100	50	0.0125	~100%	99.9%	99.0%	92.3%
120	60	0.016	~100%	~100%	99.8%	97.0%
LDL-C=low-density lipoprotein cholesterol; non-HDL-C=non-high-density lipoprotein cholesterol; PASS=power analysis and sample size. Power was calculated for each scenario using the 2-sample t-test assuming equal variance. Calculations were performed using PASS 16. Observations from MK-8591A-017 Week 48 data: Sample Size in PI Stratum: 29 in Group 1, 35 in Group 2. Difference in the Mean Change from Baseline in PI Stratum (Group 1 – Group 2)=-14.12 mg/dL. Pooled SD=24.56 mg/dL						

9.10 Subgroup Analyses

To assess whether the treatment effect with respect to the primary efficacy endpoint of the percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 and the secondary efficacy endpoint of the percentage of participants with HIV-1 RNA < 50 copies/mL at Week 48 is consistent across various subgroups of the study population, the between-treatment group effect (with a nominal 95% CI based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]) will be estimated within each subgroup of the following classification variables:

- Age category (< 50 years of age, ≥ 50 years of age)
- Sex at birth (female, male)
- Gender identity (boy/man, girl/woman, transgender boy/man, transgender girl/woman, genderqueer/non-binary/gender non-conforming, other)
- Region (North America, South America, Europe, Asia, Africa, etc)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Chronic hepatitis C status (HCV-infected, HCV-uninfected)
- Baseline NRTI backbone (TAF, TDF, Other)
- ART class used in the baseline regimen (PI-containing regimens [including PI- + InSTI-containing regimens], InSTI-containing regimens [non-PI-containing regimens], non-PI- and non-InSTI-containing regimens)
- Duration of baseline ART therapy prior to enrollment (≥ 1 year, < 1 year)

The snapshot approach will be used to handle missing values in these subgroup analyses.

9.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study intervention taken by each participant, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate participant compliance.

A day within the study will be considered an “On Therapy” day if the participant takes at least 1 tablet from any bottle provided for this study.

In the base study, the “Number of Days Should be On Therapy” is the total number of days from Day 1 to the date of the last dose of study intervention for each participant. As such, the “Number of Days Should be On Therapy” will be the number of days from Day 1 to the time point of interest (ie, Weeks 48, 96, or 144) for those participants who are on study intervention for the entire study period of interest. For participants who discontinue study intervention prior to or within the study period of interest, the “Number of Days Should be

On Therapy” will be the number of days from Day 1 to the date of discontinuation of study intervention.

For each participant and each study period of interest, percent compliance will be calculated using the following formula:

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

Summary statistics will be provided for percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

The extent of exposure to study intervention for all randomized and treated participants will be summarized for participants in Group 1 only in the base study. The number of participants exposed to various doses (actual total daily dose) for defined periods of time will be tabulated, 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 Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the 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 an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include 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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, www.clinicaltrialsregister.eu, <https://euclinicaltrials.eu>, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

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

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

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

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

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

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 18](#) will be performed by a central laboratory.
Note: In rare instances, if central laboratory use is not feasible, local laboratory tests may be used at scheduled study visits after consultation with the Sponsor. Plasma HIV-1 RNA quantification requires use of a validated PCR assay with a lower limit of detection of <50 copies/mL (see Appendix 10).
- Unscheduled 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, if feasible. 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.
- The amount of blood collected from each participant over the duration of the study is provided in [Table 19](#), [Table 20](#), [Table 21](#), and [Table 22](#). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 18 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH MCH Concentration RDW		WBC count with Differential ^a : Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
TBNK Panel/ CD4+ T-cell Count	TBNK Cell profile includes the following assessments: CD3+CD4+ Percent CD3+CD4+ Value/Absolute Count CD3+CD8+ Percent CD3+CD8+ Value/Absolute Count CD4/CD8 Ratio and the following exploratory assessments (which do not need to be evaluated by the investigator): CD3+ Percent CD3+ Value/Absolute Count CD3-CD19+ Percent CD3-CD19+ Value/Absolute Count CD16+CD56+ Percent CD16+CD56+ Value/Absolute Count CD3+CD4+CD8+ Percent CD3+CD4+CD8+ Value/Absolute Count			
Coagulation	PT/INR			
Chemistry (nonfasting)	BUN	Potassium	AST/SGOT	Total bilirubin Direct bilirubin Indirect bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (nonfasting)	Calcium	ALP	CrCl eGFR by MDRD equation (Appendix 8)
	CK	Lipase	Amylase	Mg
Additional Chemistry at Fasting Visits (fasting for at least 8 h)	Glucose HbA1c (collected regardless of participant’s fasting status) HDL-C LDL-C TGs TC Non-HDL-C Insulin ^b HOMA-IR (calculation)			
Routine Urinalysis (with microscopic exam as needed)	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick			
Pregnancy Testing	Serum and highly sensitive urine hCG (as needed for POCBP)			
Hepatitis B Serology ^c	HBsAg Anti-HBs Anti-HBc			
HBV DNA ^c	HBV DNA			

Laboratory Assessments	Parameters
Hepatitis C Serology ^c	Hepatitis C antibody (if positive perform plasma HCV quantitative test) (at screening only)
HIV-1 and HIV-2 Serology	HIV-1 and HIV-2 antibody test
Virology	HIV-1 viral RNA quantification HIV-1 viral drug resistance
PK	Plasma ISL PK (For Group 1 participants only)
	Plasma Investigational ISL PK (Samples will be collected for participants in Group 1 at Week 36 and for all participants after Week 48. Analysis of these samples will be performed by the Sponsor as needed)
	Plasma ISL and DOR PK (Only participants on DOR/ISL who become pregnant during the study)
Renal Markers	Urine analysis: Albumin/Cr Protein B-2M/Cr RBP/Cr Serum analysis: Cystatin-C Cr Creatinine Clearance by Cockcroft-Gault equation (Appendix 8) eGFR by MDRD equation (Appendix 8)
Energy and Metabolism Markers	Adipokines: Leptin Adiponectin
<p>ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; AST=aspartate aminotransferase; B-2M/Cr=beta-2-microglobulin/creatinine ratio; BUN=blood urea nitrogen; CK=creatinine kinase; Cr=creatinine; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; DOR=doravirine; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; HIV-1=human immune-deficiency virus type 1; HIV-2=human immune-deficiency virus type 2; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; INR=international normalized ratio; ISL=islatravir; LDL-C=low-density lipoprotein cholesterol; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MDRD=Modification of Diet in Renal Disease; Mg=magnesium; non-HDL-C=non-high-density lipoprotein cholesterol; PK=pharmacokinetic(s); POCBP=participant(s) of childbearing potential; PT=prothrombin time; RBC=red blood cell; RBP/Cr=retinol-binding protein/creatinine ratio; RDW=red cell distribution width; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TBNK=T and B Lymphocyte and Natural Killer Cell; TC=total cholesterol; TG=triglyceride; WBC=white blood cell.</p> <p>Notes:</p> <p>^a The central laboratory may reflex to manual differential to further identify atypical or immature forms of leukocytes.</p> <p>^b Participants with type 1 diabetes mellitus should not fast and should not have insulin levels tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing.</p> <p>^c All participants will be screened for HBsAg, anti-HBs, anti-HBc, and HBV DNA. Repeat serology and HBV DNA testing at Weeks 48, 96, 144, and 192 is to be performed for all participants. Participants who are anti-HBc-positive but HBV DNA-negative will have HBsAg and HBV DNA monitored for the duration of the study. Pregnant participants (on DOR/ISL only) will have a sample collected once after pregnancy is confirmed or local laboratory results reported for hepatitis B serology and HBV DNA.</p>	

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

Table 19 Blood Volumes (Efficacy, Safety, and PK) in the Base Study

Study Period	Screen	Intervention (Base Study)															Viremia Confirm	Total Lymphocyte/ CD4+ T-cell Confirm	Early Discon of Treatment	Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL only) ^b	EoT Follow-up ^j
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	Approximate Blood Volume (mL)																				
Plasma HIV-1 RNA Quantification ^a	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6	6	
Blood (Plasma) for HIV-1 Drug Resistance ^b		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		(12)		
Whole Blood for HIV-1 Drug Resistance		4																			
HIV-1 and HIV-2 Serology	1																				
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6	6	(6)	
Hepatitis B and Hepatitis C (Screening only) Serology ^c	4	(4)	(4)	(4)	(4)	(4)	4	(4)	(4)	(4)	(4)	4	(4)	(4)	(4)	4					
HBV DNA ^c	6	(6)	(6)	(6)	(6)	(6)	6	(6)	(6)	(6)	(6)	6	(6)	(6)	(6)	6					
Hepatitis B Serology for Pregnant Participants (DOR/ISL only) ^d		<------(4)----->																			
HBV DNA for Pregnant Participants (DOR/ISL only) ^d		<------(6)----->																			
Plasma HCV Quantitative Test ^c	6																				

Study Period	Screen	Intervention (Base Study)															Viremia Confirm	Total Lymphocyte/ CD4+ T-cell Confirm	Early Discon of Treatment	Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL only) ^b	EoT Follow-up ⁱ
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	Approximate Blood Volume (mL)																				
Chemistry (includes Serum Pregnancy Test at Screening)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			6		
Hematology	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		4	4	4	(4)
HbA1c		2			2		2					2				2					
Fasting Lipids		2			2		2					2				2					
Fasting Insulin ^e		1			1		1					1				1					
PT/INR	3																				
Cystatin-C		2			2		2					2				2					
Blood for Energy and Metabolism Markers		6			6		6					6				6					
Blood (Plasma) for ISL PK (Group 1 only)		4	8	4	4		4										4		4		
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK ^f						4		4	4	4	4	4					4	4	4	4	
Blood (Plasma) for DOR and ISL PK During Pregnancy ^g			<----- (4 or 12, as indicated) ----->																		

Study Period	Screen	Intervention (Base Study)															Viremia Confirm	Total Lymphocyte/ CD4+ T-cell Confirm	Early Discon of Treatment	Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL only) ^b	EoT Follow-up ⁱ
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	Approximate Blood Volume (mL)																				
Approximate Total Blood Volume per Visit (mL)	42	65	52	48	61	48	61	48	48	48	61	44	44	44	57	26	14	42	14	20	
anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; Confirm=Confirmation; Discon=discontinuation; DNA=deoxyribonucleic acid; DOR=doravirine; EoT=End of Treatment; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; INR=international normalized ratio; ISL=islatravir; Monitor=Monitoring; PK=pharmacokinetic(s); PT=prothrombin time; RNA=ribonucleic acid; TBNK=T and B Lymphocyte and Natural Killer Cell.																					
^a Not included in total blood volume per visit: Pregnant participants who require more frequent HIV-1 RNA testing performed per local guidelines or as determined by the investigator.																					
^b Do not collect at Early Discon if collected at previous Viremia Confirm.																					
^c All participants will be screened for HBsAg, anti-HBs, anti-HBc, and HBV DNA as well as hepatitis C antibody (with reflex plasma HCV quantitative test if indicated) at screening. Repeat serology and reflex HBV testing at Weeks 48, 96, and 144 is required. Only participants who are anti-HBc-positive but HBV DNA-negative will have HBsAg and HBV DNA monitored for the duration of the study (participants in Group 2 will begin HBsAg monitoring at Week 36).																					
^d Not included in total blood volume at each visit: Pregnant participants (DOR/ISL only) will have 1 sample collected once after pregnancy is confirmed or local laboratory results reported for HBsAg, anti-HBs, anti-HBc, and HBV DNA during pregnancy.																					
^e Participants with type 1 diabetes mellitus and those who are pregnant should not fast and should not have insulin levels or lipids tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing.																					
^f Investigational ISL PK samples will be collected from Group 1 participants at Week 36 and from Group 1 and Group 2 participants at Weeks 60, 72, 84, and 96. Analysis of these samples will be performed by the Sponsor as needed. See Section 8.6.1.																					
^g Not included in total blood volume at each visit: During pregnancy, blood samples will be collected for PK sampling per Section 8.11.6.1 during the 1 st trimester (4 mL), 2 nd trimester (12 mL), 3 rd trimester (12 mL), and Postpartum (4 mL) study visits. For participants whose pregnancy or Postpartum visit(s) extends beyond Week 144, see Table 21 and Table 22 .																					
^h Blood volumes collected at the Total Lymphocyte Count/CD4+ T-cell Count Monitoring visit (DOR/ISL participants only) represent single monitoring visits every 10 to 14 weeks after discontinuing study intervention.																					
ⁱ For the EoT Follow-up visit, the approximate total volume to be collected is for the assessments in Section 1.3.1 or 1.3.2 or 1.3.3 or 1.3.4 SoA, as indicated.																					

Table 20 Blood Volumes (Genetic Analysis and FBR) in the Base Study

Study Period	Screening	Intervention (Base Study)														Viremia Confirm	Total Lymphocyte/ CD4+ T-cell Confirm	Early Discon of Treatment	Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL only)	EoT Follow-up
Scheduled Day/Week		Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 52 (Group 2 only)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	Approximate Blood Volume (mL)																			
Blood for Genetic Analysis		9																		
Whole Blood for FBR		8			8		8			8		8					8		8	
Approximate Total Blood Volume per Visit (mL)		17			8		8			8		8					8		8	
Confirm=Confirmation; Discon=discontinuation; DOR=doravirine; EoT=End of Treatment; FBR=future biomedical research; ISL=islatravir; Monitor=Monitoring.																				

Table 21 Blood Volumes (Efficacy, Safety, and PK) in the Optional Study Extension

Study Period	Optional Study Extension				Viremia Confirmation	Total Lymphocyte/ CD4+ T-cell Confirmation	Total Lymphocyte/ CD4+ T-cell Monitoring (DOR/ISL only)	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension) ^a
Scheduled Day/Week	Week 168	Week 192	Week 216	Week 240	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	Approximate Blood Volume (mL)^a								
Plasma HIV-1 RNA Quantification (PCR)	6	6	6	6	6			6	(6)
TBNK Panel/CD4+ T-cell Count	6	6	6	6		6	6	6	(6)
Blood (Plasma) for HIV-1 Drug Resistance Testing	12	12	12	12	12			12	(12)
Hematology	2	2	2	2		2	2	2	(2)
Chemistry									(6)
Hepatitis B Serology HBV DNA		10		10					
HBsAg and HBV DNA (Group 2 participants with positive anti-HBc)	(10)	(10)	(10)	(10)					
Blood (Plasma) for Investigational ISL PK					4	4	4		(4)
Blood (Plasma) for DOR and ISL PK						4			
Blood (Plasma) for DOR and ISL PK (pregnant participants on DOR/ISL)					(4)			(4)	(4)
Total Blood Volume per Visit (mL)	26	36	26	36	22	12	12	26	40
anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; DNA=deoxyribonucleic acid; DOR=doravirine; EoT=End of Treatment; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; mL=milliliter; OLE=open-label extension; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid; SoA=Schedule of Activities; TBNK=T and B lymphocyte and natural killer cells. a. For the EoT Follow-up visit, the approximate total volume to be collected is for the assessments in Section 1.3.5 SoA. Alternatively, see Section 1.3.2 or 1.3.3 or 1.3.4 SoA, as indicated									

The assessments in Table 22 are for any participant who is pregnant on or after Week 144 and whose visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum.

Table 22 Blood Volumes: Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 144 (Efficacy, Safety, and PK)

Visit Number	Unscheduled				
Scheduled Week	Pregnancy 1 ^c	Pregnancy 2 ^c	Pregnancy 3 ^c	Pregnancy 4 ^c (Postpartum ≤8 weeks after delivery)	EoT Follow-up ^c
Blood Parameter	Approximate Blood Volume (mL)				
Plasma HIV-1 RNA Quantification	6	6	6	6	
Plasma for HIV-1 Viral Drug Resistance Testing	15	15	15	15	15
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6
Hepatitis B Serology and HBV DNA (DOR/ISL only) ^a	<------(10)----->				
Chemistry	6	6	6	6	6
Hematology	2	2	2	2	2
Blood (Plasma) for DOR and ISL PK ^b	4	12	12	4	4
Approximate Total Blood Volume per Visit (mL)	39	47	47	39	39
DNA=deoxyribonucleic acid; DOR=doravirine; 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 ^a Not included in total blood volume at each visit: Pregnant participants (DOR/ISL only) will have 1 sample collected once after pregnancy is confirmed or local laboratory results reported for HBsAg, anti-HBs, anti-HBc, and HBV DNA during pregnancy. ^b Collect PK samples during pregnancy per Section 8.11.6.1.1. ^c If pregnancy visit occurs at the timeframe of a scheduled optional study extension visit, collection of lab samples should occur per this Table. Collection of laboratory samples should not be duplicated.					

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

Events meeting the AE definition

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.3 Definition of SAE

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

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

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

- c. Requires inpatient hospitalization or prolongation of existing hospitalization
 - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
- d. Results in persistent or significant disability/incapacity
 - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
 - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- e. Is a congenital anomaly/birth defect
 - In offspring of participant taking the product regardless of time to diagnosis.
- f. Other important medical events
 - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
 - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
 - All potential or confirmed DILI events will be reported as an ECI and SAE with OME criteria in the absence of other serious criteria.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

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

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
 - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
 - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with 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 study intervention discontinued or dose/exposure/frequency reduced?
 - If yes, did the AE resolve or improve?
 - If yes, this is a positive dechallenge.
 - If no, this is a negative dechallenge.(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
 - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
 - If yes, did the AE recur or worsen?
 - If yes, this is a positive rechallenge.
 - If no, this is a negative rechallenge.(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
 - Yes, there is a reasonable possibility of study intervention relationship:
 - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
 - No, there is not a reasonable possibility of study intervention relationship:
 - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

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

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

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

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

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

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

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

- Postmenopausal
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
 - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Participants of Nonchildbearing Potential (PONCBP)

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

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

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

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

- Postmenopausal
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
 - Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

As some baseline ART regimens may decrease efficacy of hormonal contraception by potential drug-drug interactions (eg, CYP3A4 inducers), the investigator must assess the need for backup contraception to supplement hormonal contraceptives (preferably penile/external condoms) in accordance with the participant's specific baseline ART regimen and local product labeling. In situations where the PONCBP's baseline ART regimen could reduce their concomitant hormonal contraception efficacy, then penile/external condoms must be used in addition to hormonal contraception.

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency^a <i>Failure rate of <1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Progestogen-only contraceptive implant^b • IUS^c • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
<ul style="list-style-type: none"> • Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent^a <i>Failure rate of <1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception^b <ul style="list-style-type: none"> - Oral - Intravaginal - Transdermal - Injectable
<ul style="list-style-type: none"> • Progestogen-only hormonal contraception^b <ul style="list-style-type: none"> - Oral - Injectable
Sexual Abstinence <ul style="list-style-type: none"> • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective <i>Failure rate of >1% per year when used consistently and correctly.</i>
<ul style="list-style-type: none"> • Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide^d • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
<p>^a Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly)</p> <p>^b If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation</p> <p>^c IUS is a progestin releasing IUD</p> <p>^d Vaginal/internal condom used for contraceptive purposes</p> <p>Note: The following are not acceptable methods of contraception:</p> <ul style="list-style-type: none"> • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)^d

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

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research^{3, 4}

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

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

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

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

3. Summary of Procedures for Future Biomedical Research^{3, 4}

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. **eCRF Documentation for Future Biomedical Research Specimens**

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

d. **Future Biomedical Research Specimen(s)**

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

4. Confidential Participant Information for Future Biomedical Research^{3, 4}

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

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

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

5. Biorepository Specimen Usage^{3, 4}

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

6. Withdrawal From Future Biomedical Research^{3, 4}

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens^{3, 4}

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security^{3, 4}

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

9. Reporting of Future Biomedical Research Data to Participants^{3, 4}

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

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

10. Future Biomedical Research Study Population^{3,4}

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

11. Risks Versus Benefits of Future Biomedical Research^{3,4}

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for Japan

The baseline ART taken by participants in Group 2 until Week 48 is not categorized as “product(s) used in the clinical trial” in Japan.

10.7.2 Country-specific Request for Canada

The baseline ART taken by participants in Group 2 until Week 48 is considered NIMP in Canada, as the ART will be a continuation of prestudy treatment.

In Canada, in addition to the criteria in Section 7.1, a participant must be discontinued from study intervention per Section 8.11.3 for the following reason:

- The participant becomes HBsAg-positive or have confirmed quantifiable HBV DNA after randomization, per Section 8.3.6.

10.7.3 Country-specific Request for South Africa

Study Intervention(s) Administered

Participants in South Africa previously receiving BIC/FTC/TAF in study MK-8591A-020 who enroll in MK-8591A-051 and are randomized to Group 2 will continue to receive MSD-supplied BIC/FTC/TAF as their ART regimen. See Section 6.1 ([Table 2](#)).

10.8 Appendix 8: Calculation of Creatinine Clearance and eGFR

10.8.1 Cockcroft-Gault Equations

- If male:

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

- If female:

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

10.8.2 MDRD Equations

eGFR estimated by MDRD-NKDEP:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{Age [years]})^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if Black)}$$

10.9 Appendix 9: AIDS-defining Opportunistic Infections that Require Discontinuation of Study Intervention

Per Section 7.1, a participant must be discontinued from study intervention if they have a new AIDS-defining opportunistic infection as listed below, ie, a Category C condition according to the CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults [Centers for Disease Control (CDC) 1992].

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

10.10 Appendix 10: Approved HIV-1 RNA Quantification Assays for Local Viral Load Monitoring

For this study, allowed US FDA-approved HIV-1 RNA quantification assays for local viral load monitoring are listed in [Table 23](#).

This list represents the US FDA-approved nucleic acid testing assays for HIV-1 RNA detection and quantification that have a lower limit of detection of <50 copies/mL. Additional details can be found at: www.fda.gov/vaccines-blood-biologics/blood-blood-products/approved-blood-products and www.fda.gov/vaccines-blood-biologics/hiv-1.

Table 23 Approved HIV-1 RNA Quantification Assays for Local Viral Load Monitoring

Tradename	Infectious Agent	Format	Specimen	Use	Manufacturer
APTIMA HIV-1 Quant Assay APTIMA HIV-1 Quant Dx Assay	HIV-1	TMA	Plasma/ Serum	Patient Monitoring: Quantitation of HIV-1 RNA in plasma of HIV-1 infected individuals. Addition of claim for Qualitative detection HIV-1 RNA on Panther platform	Hologic Inc., San Diego, CA US License 1592
COBAS HIV-1		Quantitative PCR	Plasma	Patient Monitoring: Quantitation of HIV-1 RNA in plasma of HIV-1 infected individuals	Roche Molecular Systems, Inc., Pleasanton, CA US License 1636
Abbott RealTime HIV-1					ABBOTT Molecular, Inc., Des Plaines, IL (US License NA)
Amplicor HIV-1 Monitor Test					Roche Molecular Systems, Inc., Pleasanton, CA US License 1636
COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test					Roche Molecular Systems, Inc., Pleasanton, CA US License 1636
FDA=United States Food and Drug Administration; HIV-1=human immunodeficiency virus type 1; NA=not available; PCR=polymerase chain reaction; RNA=ribonucleic acid; TMA=transcription-mediated amplification; US=United States.					

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIDS	acquired immunodeficiency syndrome
albumin/Cr	albumin/creatinine ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
B-2M/Cr	beta-2-microglobulin/creatinine ratio
BIC	bictegravir
BLOQ	below the limit of quantification
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
C ₂₄	concentration after 24 hours
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
C _{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials

Abbreviation	Expanded Term
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
Cr	creatinine
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
C _{trough}	lowest concentration reached before the next dose is administered
CYP	cytochrome P450
DAIDS	Division of AIDS
DAO	data as observed
DDI	drug-drug interaction
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
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQol 5-dimensional descriptive system, 5-level version
EU	European Union
FAS	Full Analysis Set
FAS-E	full analysis set-extension
FBR	future biomedical research

Abbreviation	Expanded Term
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
FSR	first site ready
FTC	emtricitabine
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIV-SI/SDM	Human Immunodeficiency Virus Symptom Index (also known as the Human Immunodeficiency Virus Symptom Distress Module)
HIVTSQ	Human Immunodeficiency Virus Treatment Satisfaction Questionnaire
HIVTSQs	Human Immunodeficiency Virus Treatment Satisfaction Questionnaire status version
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HTA	Health Technology Assessment
IA(s)	interim analysis(es)
IB	Investigator's Brochure
IC ₅₀	inhibitory concentration required for 50% inhibition
ICF	Informed Consent Form

Abbreviation	Expanded Term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir
ISL-TP	islatravir-triphosphate
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LDA	longitudinal data analysis
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantification
M=F	missing data treated as treatment failure
MAR	missing at random
MCAR	missing completely at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing not at random
NIMP	noninvestigational medicinal product
NKDEP	National Kidney Disease Education Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
non-HDL-C	non-high-density lipoprotein cholesterol
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside/nucleotide reverse transcriptase translocation inhibitor

Abbreviation	Expanded Term
OF	observed failure
OME	Other important medical event
PCR	polymerase chain reaction
PDLC	predefined limit of change
PI	protease inhibitor
PK	pharmacokinetic(s)
PLWH	people living with HIV
POCBP	participant(s) of childbearing potential
PONCBP	participant(s) of nonchildbearing potential
PP	per-protocol
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcome
PT	prothrombin time
PTs	preferred terms
QD	once-daily
QM	once-monthly
QW	once-weekly
RBC	red blood cell
RBP/Cr	retinol-binding protein/creatinine ratio
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMQs	Standardized MedDRA Queries
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan

Abbreviation	Expanded Term
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TBNK	T and B Lymphocyte and Natural Killer Cell
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglyceride
TN	treatment-naïve
TP	triphosphate
ULN	upper limit of normal
US	United States
VS	virologically suppressed
WBC	white blood cell
WHO	World Health Organization

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