Official Protocol Title:	A Phase 3 Open-label Clinical Study of Doravirine/ Islatravir (DOR/ISL [100 mg/0.25 mg]) Once Daily for the Treatment of HIV-1 Infection in Participants Who Previously Received DOR/ISL (100 mg/0.75 mg) QD in a Phase 3 Clinical Study
NCT Number:	NCT05766501
Document Date:	20-Nov-2025

TITLE PAGE

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Protocol Title: A Phase 3 Open-label Clinical Study of Doravirine/Islatravir (DOR/ISL [100 mg/0.25 mg]) Once Daily for the Treatment of HIV-1 Infection in Participants Who Previously Received DOR/ISL (100 mg/0.75 mg) QD in a Phase 3 Clinical Study

Protocol Number: 054-04

Compound Number: MK-8591A

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

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

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EU CT	2022-502126-40-00
EudraCT	Not Applicable
JRCT	jRCT2051230002
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UTN	Not Applicable
IND	134036

Approval Date: 20 November 2025

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	20-NOV-2025	To ensure that participants who are pregnant have HIV-1 RNA testing, HIV-1 drug resistance testing, and DOR and ISL PK during the peripartum period; and to add standard-of-care chemistry testing in the optional study extension.
Amendment 3	09-AUG-2024	To extend the study from Week 96 to Week 240 to provide additional safety and efficacy data, and to add an optional study extension with access to DOR/ISL for up to Week 240 or until commercially accessible (whichever comes first).
Amendment 2	01-NOV-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 CD4+ T-cell counts and the management of participants with HIV-1 viremia.
Amendment 1	14-DEC-2022	This protocol is being amended to: (1) modify inclusion criteria to allow for participants to enroll prior to completing their last visit in the prior protocol, (2) add country-specific requirements for Canada and Germany, and (3) increase the screening visit window to ≤45 days.
Original Protocol	19-OCT-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Description of Current Amendment:

Reason(s) for Amendment:	Primary: Other	Secondary: Not Applicable
Amendment Summary:	To ensure that participants who are pregnant have HIV-1 RNA testing, HIV-1 drug resistance testing, and DOR and ISL PK during the peripartum period; and to add standard-of-care chemistry testing in the optional study extension.	
Is this amendment likely to have a substantial impact on the safety or rights of the participants?	No	
Is this amendment likely to have a substantial impact on the reliability and robustness of the data generated in the clinical trial?	No	

Overview of Changes in the Current Amendment:

Section # and Name	Description of Change	Brief Rationale for Change
Section 1.1, Synopsis Section 1.2, Schema Section 5.1, Inclusion Criteria Section 5.2, Exclusion Criteria	Removed mention of MK-8591A-P017 from the text.	Participants from MK-8591A-017 did not directly transition to MK-8591A-054.

Section # and Name	Description of Change	Brief Rationale for Change
Section 1.3.2, Schedule of Activities – Viremia Confirmation and End of Treatment for Participants with Viremia (Except Those With Specified Decreases in CD4+ T-cell or Total Lymphocyte Counts) Section 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 Section 1.3.5, Schedule of Activities – Post-Week 96 Through Week 240 (Optional Study Extension) Section 10.2, Appendix 2: Clinical Laboratory Tests	Added sample collection for chemistry in the optional study extension (including Table 13)	To provide standard-of-care chemistry testing during HIV-1 treatment.
Section 1.3.4, Schedule of Activities for Participants Whose Pregnancy and/or Postpartum Visit(s) Extends Beyond Week 96 Section 8.11.6.1, Continuing Study Intervention in Pregnancy Section 8.11.6.1.1, Collection of Population PK Samples During Pregnancy and Postpartum (Participants Continuing DOR/ISL Only) Section 10.2, Appendix 2: Clinical Laboratory Tests	Added a peripartum visit (if needed) at week 36 of gestation or ≤4 weeks before the planned date of delivery for collection of blood (plasma) samples for HIV-1 RNA testing, HIV-1 drug resistance testing, and DOR and ISL PK in pregnant participants on DOR/ISL (including in Table 5, Table 12 footnote h, and Table 14).	To ensure that participants who are pregnant have specimens collected for testing during the peripartum period.

Section # and Name	Description of Change	Brief Rationale for Change
Section 1.3.5, Schedule of Activities – Post-Week 96 Through Week 240 (Optional Study Extension)	Updated study visit numbers.	To correct visit numbers in the optional study extension to be in sequential order continuing from the base study visit numbers.
Section 3, Hypotheses, Objectives, and Endpoints	Deleted mention of CD4+ T-cell counts that was inadvertently included in the objective for the total lymphocyte count.	To remove redundant text as CD4+ T-cell counts at Week 96 was already listed as a tertiary/exploratory objective.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information Section 8.4.7, Events of Clinical Interest Section 10.3.3, Definition of SAE	Updated periods, duration, reporting requirements, and SAE definition with regard to potential DILI events meeting biochemical criteria of Hy's Law.	To maintain continued regulatory reporting compliance in alignment with Health Authority DILI reporting requirements.
Section 9.6.2.1 Overall Safety Assessment Section 9.6.2.3 Handling of Missing Data and Pregnancies in Safety Analyses	Removed the incidence cutoff for CIs for AE reporting (including Table 8)	As all CIs for AEs are within group CIs, the estimates are valid even when the rates are low.
Section 9.6.2.1 Overall Safety Assessment 9.6.2.3 Handling of Missing Data and Pregnancies in Safety Analyses	Updated text regarding safety analysis in participants who become pregnant.	To clarify the analysis strategy for safety data in participants who become pregnant.

Section # and Name	Description of Change	Brief Rationale for Change
Section 10.2, Appendix 2: Clinical Laboratory Tests	Table 13: Added a row for blood sample collection for participants who have HBsAg and HBV DNA collected during the optional study extension.	To align the blood volumes table with the corresponding SoA (Section 1.3).
Section 10.7.4, Japan-specific Requirements	Added section to clarify that after DOR/ISL is approved for HIV-1 infection in Japan, the terms “clinical study” and “clinical trial” will no longer be applicable in the protocol and “postmarketing clinical study” or "postmarketing clinical trial" would be applicable instead.	To align with Japanese regulations.
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 Open-label Clinical Study of Doravirine/Islatravir (DOR/ISL [100 mg/0.25 mg]) Once Daily for the Treatment of HIV-1 Infection in Participants Who Previously Received DOR/ISL (100 mg/0.75 mg) QD in a Phase 3 Clinical Study

Short Title: Follow-up of Participants Who Received DOR/ISL (100 mg/0.75 mg)

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

There are no hypotheses to be tested in this study. The following objectives will be evaluated in adults with HIV-1 who received DOR/ISL in previous DOR/ISL treatment studies:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of DOR/ISL (100 mg/0.25 mg) as assessed by accumulated safety data through Week 96	Adverse events Adverse events leading to discontinuation of DOR/ISL
Secondary Objectives	**Secondary Endpoints**
To evaluate the antiretroviral activity of DOR/ISL (100 mg/0.25 mg) as assessed by the percentage of participants with the following at Week 96: - HIV-1 RNA ≥50 copies/mL - HIV-1 RNA <50 copies/mL - HIV-1 RNA <200 copies/mL	HIV-1 RNA
To evaluate the development of viral resistance to DOR/ISL (100 mg/0.25 mg)	Viral resistance-associated substitutions

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	HIV infection
Population	Adult participants with HIV-1 who received DOR/ISL (100 mg/0.75 mg tablet) in previous MSD-sponsored treatment studies (MK-8591A-018, -020, and -033 [except for HTE participants]) and agree to continue open-label treatment with DOR/ISL until it becomes commercially accessible.
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Treatment Control
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 650 participants will be enrolled upon completion of studies of DOR/ISL (100 mg/0.75 mg) QD. Enrollment will be adjusted as necessary, based on enrollment in DOR/ISL treatment studies.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
MK-8591A	doravirine/ islatravir	100 mg doravirine/ 0.25 mg islatravir	100 mg doravirine/ 0.25 mg islatravir QD	Oral	Day 1 to Week 96	Test Product
MK-8591A	doravirine/ islatravir	100 mg doravirine/ 0.25 mg islatravir	100 mg doravirine/ 0.25 mg islatravir QD	Oral	Week 96 up to Week 240	Test Product

Admin.=administration; QD=once daily

Note: Study intervention will be dispensed at the last regularly scheduled study visit for participants who become pregnant. The visit schedule for these participants will be extended through the duration of the pregnancy. Study intervention will be dispensed every 12 weeks during pregnancy, as applicable.

Total Number of Intervention Groups/Arms	1
Duration of Participation	Each participant will participate in the base study for approximately 102 weeks from the time the participant provides documented informed consent through the final contact. After confirmation of eligibility, each participant will receive study intervention for approximately 96 weeks. After the end of treatment, all participants will be followed for 6 weeks (42 days). After Week 96, participants will be given the option to continue the study and receive DOR/ISL for up to an additional 144 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	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

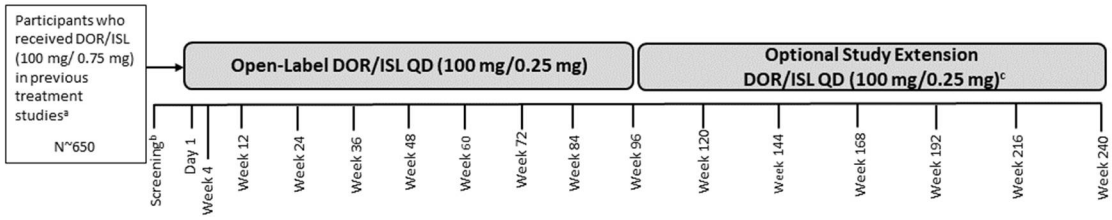
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



DOR/ISL=fixed dose combination of doravirine (100 mg) and islatravir (0.25 mg); EoT=end of treatment; HTE=heavily treatment-experienced; QD=once daily; N=total number of participants in the study.

[a] Includes studies MK-8591A-018, MK-8591A-020, and MK-8591A-033 (except for HTE participants).

[b] Screening visit only applies for participants entering from MK-8591A-033.

[c] For participants who continue optional extension, study visits will occur every 24 weeks.

1.3 Schedule of Activities

1.3.1 Schedule of Activities – Screening Through Week 96 (Base Study)

This SoA applies to all participants in the base study. Manage pregnant participants per Section 8.11.6 (SoA Section 1.3.4). For the optional study extension, see Section 8.11.2.3 (SoA Section 1.3.5)

- The Early Discontinuation of Treatment visit applies to any participant who discontinues study intervention prior to Week 96 (Section 8.11.3).
- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).

Study Period	**Screening[a]**	**Open-label Intervention (Base Study)**										**End of Treatment**		**Notes**
Visit Number/Title	1[a]	2	3	4	5	6	7	8	9	10	11	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	W4	W12	W24 (Fasting)	W36	W48 (Fasting)	W60	W72	W84	W96 (Fasting)	Early Discontinuation Of Treatment	End of Treatment Follow-up (Base Study)	The expected date of each visit should be calculated using the date of Day 1.
Visit Window	≤45 days	NA	± 7 days									NA	42 (+7) days after end of treatment	
	Administrative Procedures													
Informed Consent	(X)	X												(X) = Only for participants entering from MK-8591A-033. Obtain consent on or prior to scheduled visit.
Post-Base Study Disposition Planning									X	X	X			Proactively discuss treatment options prior to the end of the base study (See Section 8.11.2.2).
Informed Consent for Optional Study Extension											X			Obtain prior to dispensing study intervention at Week 96.

Study Period	**Screening[a]**	**Open-label Intervention (Base Study)**										**End of Treatment**		**Notes**
Visit Number/Title	1[a]	2	3	4	5	6	7	8	9	10	11	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	W4	W12	W24 (Fasting)	W36	W48 (Fasting)	W60	W72	W84	W96 (Fasting)	Early Discontinuation Of Treatment	End of Treatment Follow-up (Base Study)	The expected date of each visit should be calculated using the date of Day 1.
Visit Window	≤45 days	NA	± 7 days									NA	42 (+7) days after end of treatment	
Informed Consent for Study Intervention During Pregnancy		<----------X---------->												Obtain upon confirmation of pregnancy. See Section 8.1.1.2
Collect and Enter Data From Prenatal Care Provider		<----------X---------->												For participants who consent to continue study intervention during pregnancy, 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 8.1.1.3 and 8.11.6.4.
Inclusion/Exclusion Criteria		X												To be reviewed predose on Day 1 to ensure no changes and confirm eligibility.
Participant Identification Card		X												Site personnel will add treatment/allocation number.
Medical History		X												
Tobacco and Alcohol Assessments		X					X				X			
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	Collect from 14 days prior to Day 1 through the study treatment period.
Register Study Visit in IRT	(X)	X	X	X	X	X	X	X	X	X	X	X		(X) = Only for participants entering from MK-8591A-033.

Study Period	**Screening[a]**	**Open-label Intervention (Base Study)**										**End of Treatment**		**Notes**
Visit Number/Title	1[a]	2	3	4	5	6	7	8	9	10	11	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	W4	W12	W24 (Fasting)	W36	W48 (Fasting)	W60	W72	W84	W96 (Fasting)	Early Discontinuation Of Treatment	End of Treatment Follow-up (Base Study)	The expected date of each visit should be calculated using the date of Day 1.
Visit Window	≤45 days	NA	± 7 days									NA	42 (+7) days after end of treatment	
Dispense DOR/ISL Using IRT		X	X	X	X	X	X	X	X	X	(X)			(X) = Dispense at Week 96 for eligible participants entering the optional study extension and if needed for those participants whose pregnancy or postpartum visit(s) extends past Week 96 (see Section 1.3.4).
DOR/ISL Compliance Review			X	X	X	X	X	X	X	X	X	X		For participants whose pregnancy or postpartum visit(s) extends past Week 96, 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) = Only for participants entering from MK-8591A-033. See Section 8.2.1. See Section 8.11.6 for HIV-1 RNA testing in participants who become pregnant.
Plasma for HIV-1 Drug Resistance												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.
Safety Procedures														
Weight		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	For all participants, collect weight at Day 1. (X) = Only for participants who become pregnant and consent to continue study intervention.

Study Period	**Screening[a]**	**Open-label Intervention (Base Study)**										**End of Treatment**		**Notes**
Visit Number/Title	1[a]	2	3	4	5	6	7	8	9	10	11	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	W4	W12	W24 (Fasting)	W36	W48 (Fasting)	W60	W72	W84	W96 (Fasting)	Early Discontinuation Of Treatment	End of Treatment Follow-up (Base Study)	The expected date of each visit should be calculated using the date of Day 1.
Visit Window	≤45 days	NA	± 7 days									NA	42 (+7) days after end of treatment	
Directed Physical Examination		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	(X) = Only for participants who become pregnant and consent to continue study intervention.
Vital Signs		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	Includes pulse, BP, temp, and RR. (X) = Only for participants who become pregnant and consent to continue study intervention.
Contraceptive Use Confirmation (POCBP Only)		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 8.3.3).
Urine Pregnancy Test (hCG) (POCBP Only)		X	X	X	X	X	X	X	X	X	X	X	X	Pregnancy must be excluded on Day 1 before treatment allocation. Confirm positive or indeterminate urine test with serum test. If serum test is positive, manage per Section 8.11.6. For participants known to be pregnant, defer urine test until 6 weeks postpartum.
Hepatitis B Serology with Reflex HBV DNA		X					X				X			Encourage vaccination to participants who are not immune to HBV.
HBsAg and HBV DNA			(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]**	**Open-label Intervention (Base Study)**										**End of Treatment**		**Notes**
Visit Number/Title	1[a]	2	3	4	5	6	7	8	9	10	11	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (Fasting)	W4	W12	W24 (Fasting)	W36	W48 (Fasting)	W60	W72	W84	W96 (Fasting)	Early Discontinuation Of Treatment	End of Treatment Follow-up (Base Study)	The expected date of each visit should be calculated using the date of Day 1.
Visit Window	≤45 days	NA	± 7 days									NA	42 (+7) days after end of treatment	
Hepatitis B Serology and HBV DNA in Pregnant Participants		<----------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 testing if indicated per local standard of care.
Chemistry		X	X	X	X	X	X	X	X	X	X	X		Fasting required at Day 1 and Weeks 24, 48, and 96 (see Section 8.11.2.1 and Appendix 2). Pregnant participants should not fast.
Hematology		X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X	X		(X) = For participants who become pregnant and consent to continue study intervention, urinalysis is required at all visits.
TBNK Panel/CD4+ T-cell Count		X	X	X	X	X	X	X	X	X	X	X		
AE/SAE Review		X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics														
Blood (Plasma) for Investigational ISL PK			X									X		Do not collect during pregnancy. Can be collected irrespective of time of last dose. Analysis performed by Sponsor as needed. See Section 8.6.1.

Study Period	**Screening[a]**	**Open-label Intervention (Base Study)**										**End of Treatment**		**Notes**
Visit Number/Title	1[a]	2	3	4	5	6	7	8	9	10	11	Unscheduled		
Scheduled Day/Week	Screening[a]	Day 1 (F[illegible])	W4	W12	W24 (Fasting)	W36	W48 (Fasting)	W60	W72	W84	W96 (Fasting)	Early Discontinuation Of Treatment	End of Treatment Follow-up (Base Study)	The expected date of each visit should be calculated using the date of Day 1.
Visit Window	≤45 days	NA	± 7 days									NA	42 (+7) days after end of treatment	
Blood (Plasma) for DOR and ISL PK in Pregnant Participants			<----------X---------->									X		Participants on DOR/ISL during the 1st, 2nd, and 3rd trimesters and postpartum per Section 8.11.6.1.1 (Table 5).

AE=adverse event; anti-HBc=Hepatitis B core antibody; anti-HBs=Hepatitis B surface antibody; BP=blood pressure; DNA=deoxyribonucleic acid; HBsAg=Hepatitis B surface antigen; HBV=Hepatitis B virus; hCG=human chorionic gonadotropin; DOR=doravirine; HIV-1=human immunodeficiency virus type 1; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; POCBP=participant(s) of childbearing potential; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TBNK=T and B-lymphocyte and natural killer cell; W=week.

[a] Screening visit only applies for participants entering from MK-8591A-033.

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

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 (SoA Section 1.3.3).

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		
DOR/ISL Compliance Review	X	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	
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X	X	See Section 8.2.1. Manage participants with viremia per Section 8.2.2.
Plasma for HIV-1 Drug Resistance	X	(X)		(X)		(X) = Do not collect at Discontinuation of Treatment visit if collected at preceding Viremia Confirmation visit. Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
Safety Procedures						
Directed Physical Examination		X	X	X	X	
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	Contraception is required for 42 days after the last dose of study intervention (see Section 8.3.3).

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	
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		X		
Hematology		X		X		
Urinalysis		X				
TBNK Panel/CD4+ T-cell Count		X		X		
AE/SAE Review	X	X	X	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	
Pharmacokinetics						
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK	X	X				Do not collect during pregnancy. Can be collected irrespective of time of last dose. Analysis performed by Sponsor as needed. See Section 8.6.1.
Blood (Plasma) for DOR and ISL PK in Pregnant Participants	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.

AE=adverse event; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; NA=not applicable; PK=pharmacokinetic; POCBP=participant of childbearing potential; RNA=ribonucleic acid; 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 and 8.11.4 (SoA Section 1.3.2).

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	
Administrative Procedures							
Prior and Concomitant Medications Review	X	X	X	X	X	X	
Register Study Visit in IRT	X	X		X		X	
DOR/ISL Compliance Review	X	X					

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	
Efficacy Procedures							
Plasma HIV-1 RNA Quantification		X	X	X	X		
Plasma for HIV-1 Drug Resistance Testing		X		X			Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
Safety Procedures							
Directed Physical Examination		X	X	X	X		

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	
Contraceptive Use Confirmation (POCBP Only)		X	X	X	X		Contraception is required for 42 days after the last dose of study intervention (see Section 8.3.3).

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	
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		X			
Hematology	X	X	X	X	X	X	

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	
Urinalysis		X					
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X	Manage participants who meet the discontinuation criteria for total lymphocyte count or CD4+ T-cell count (Table 3) per Section 8.11.5
AE/SAE Review	X	X	X	X	X	X	

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	
Pharmacokinetics							
Blood (Plasma) for Investigational ISL PK	X	X					Do not collect during pregnancy. Can be collected irrespective of time of last dose. Analysis performed by Sponsor as needed. See Section 8.6.1.

Study Period	**CD4+ Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment Base Study**		**End Of Treatment (Optional Study Extension)**		**Total Lymphocyte or CD4+ T-cell Count Monitoring**	**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	
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10-14 weeks	

AE=adverse event; hCG=human chorionic gonadotropin; IRT=Interactive Response Technology; NA=not applicable; PK=pharmacokinetics; POCBP=participant of childbearing potential; 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.

1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 96

This SoA applies to eligible participants who are pregnant at Week 96 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, including the peripartum period, 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.

This SoA also applies to eligible participants who become pregnant at any point during the study and who may also require a unscheduled peripartum visit and require a postpartum visit. See Section 8.11.6.1.

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

Study Period	**Pregnancy**			**Peripartum**	**Postpartum**	**End of Treatment[a]**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Peripartum visit is only required if Pregnancy 3 visit occurs prior to week 36 of gestation or does not occur ≤4 weeks before the planned date of delivery.
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	At week 36 of gestation or ≤4 weeks before the planned date of delivery	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.

Study Period	**Pregnancy**			**Peripartum**	**Postpartum**	**End of Treatment[a]**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Peripartum visit is only required if Pregnancy 3 visit occurs prior to week 36 of gestation or does not occur ≤4 weeks before the planned date of delivery.
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	At week 36 of gestation or ≤4 weeks before the planned date of delivery	Pregnancy 4 (Postpartum, ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days					42 (+ 7) days after the end of treatment	
Prior and Concomitant Medications Review	X	X	X		X	X	
Register Study Visit in IRT	X	X	X		X		
Dispense DOR/ISL Using IRT	X	X	X		(X)		(X)=Postpartum participants on DOR/ISL may continue treatment through the optional study extension (Section 1.3.1 or 1.3.5, as appropriate) if not yet commercially accessible.
DOR/ISL Compliance Review	X	X	X		X		
Evaluation to Receive Continued DOR/ISL	X	X	X				At the end of pregnancy, continued access to DOR/ISL may be offered, per Section 6.7.
Efficacy Procedures							
Plasma HIV-1 RNA Quantification	X	X	X	X	X	X	See Section 8.2.1

Study Period	**Pregnancy**			**Peripartum**	**Postpartum**	**End of Treatment[a]**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Peripartum visit is only required if Pregnancy 3 visit occurs prior to week 36 of gestation or does not occur ≤4 weeks before the planned date of delivery.
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	At week 36 of gestation or ≤4 weeks before the planned date of delivery	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 Resistance Testing	X	X	X	X	X	X	Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
Safety Procedures							
Weight	X	X	X		X	X	
Directed Physical Examination	X	X	X		X	X	
Vital Signs	X	X	X		X	X	Includes pulse, BP, temp, and RR.
Hepatitis B Serology with Reflex HBV DNA	<----------X---------->					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	
TBNK Panel/CD4+ T-cell Count	X	X	X		X	X	
AE/SAE Review	X	X	X		X	X	

Study Period	**Pregnancy**			**Peripartum**	**Postpartum**	**End of Treatment[a]**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Peripartum visit is only required if Pregnancy 3 visit occurs prior to week 36 of gestation or does not occur ≤4 weeks before the planned date of delivery.
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	At week 36 of gestation or ≤4 weeks before the planned date of delivery	Pregnancy 4 (Postpartum, ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days					42 (+ 7) days after the end of treatment	
Pharmacokinetics							
Blood (Plasma) for DOR and ISL PK	X	X	X	X	X	X	See Section 8.11.6.1.1 (Table 5).

AE=adverse event; ART= antiretroviral therapy; BP=blood pressure; DNA=deoxyribonucleic acid; DOR=doravirine; HBV=Hepatitis B virus; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; ISL=islatravir; PK=pharmacokinetic(s); RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TBNK=T and B-lymphocyte and natural killer cell; temp=temperature.

[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 – Post-Week 96 Through Week 240 (Optional Study Extension)

This SoA only applies to participants who enter the optional study extension at Week 96.

- Duration of participation in the optional study extension is dependent on when DOR/ISL becomes commercially accessible, with a maximum treatment duration of 144 weeks (ie, total study intervention duration of up to 240 weeks).
- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).
- Manage pregnant participants per Section 8.11.6 (SoA Section 1.3.4).

Study Period	**Optional Study Extension**						**End of Treatment**		**Notes**
Visit Number	12	13	14	15	16	17	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 120	Week 144	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	X	X			Once DOR/ISL is commercially accessible, participants should return to the study site for the Discontinuation of Treatment visit and transition to the local supply.
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X	X		
Dispense Study Intervention Using IRT	X	X	X	X	X	(X)			(X) = Dispense at Week 240 if needed for pregnant participants (see Section 1.3.4).

Study Period	Optional Study Extension						End of Treatment		Notes
Visit Number	12	13	14	15	16	17	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 120	Week 144	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	
Study Intervention Compliance Review	X	X	X	X	X	X	X		
Plasma HIV-1 RNA Quantification	X	X	X	X	X	X	X		See Section 8.2.1.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X	X		
Plasma for HIV-1 Drug Resistance							X		Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
Hepatitis B Serology and Reflex HBV DNA		X		X		X			Encourage vaccination to participants who are not immune to HBV
HBsAg and HBV DNA	(X)	(X)	(X)	(X)	(X)	(X)			Only anti-HBc-positive participants, at each visit. See Section 8.3.6.
Chemistry	X	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X		
Directed Physical Examination							X	X	

Study Period	Optional Study Extension						End of Treatment		Notes
Visit Number	12	13	14	15	16	17	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 120	Week 144	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/SAE Review	X	X	X	X	X	X	X	X	
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	X	X	X	Contraception is required for 42 days after the last dose of study intervention (see Section 8.3.3).
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	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.

AE=adverse event; anti-HBc=hepatitis B core antibodyB; IC=bictegravir; BP=blood pressure; DEXA=dual-energy X-ray absorptiometry; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; 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 visit 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 [Trickey, A., et al 2017]. Anticipating that individuals can receive decades of treatment during their lifetime, long-term tolerability and safety of antiretrovirals have become increasingly important considerations.

There is evidence that 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens, offer 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 due to its potent antiretroviral activity (including activity against common NRTI- and NNRTI-resistant variants) by multiple mechanisms of action, lack of food requirements, and favorable DDI profiles observed to date (see Section 2.2.3).

Previous clinical experience from Phase 2 and Phase 3 studies for DOR/ISL (100 mg/0.75 mg) demonstrated antiretroviral activity in adult populations with HIV-1. However, lymphocyte or CD4+ T-cell reductions were observed with DOR/ISL (100 mg/0.75 mg) QD, the ISL 20 mg QW + MK-8507 (100 mg, 200 mg, and 400 mg), and the ISL 60 mg QM development programs. Therefore, the ISL dose for daily administration for the treatment of HIV-1 was re-evaluated. ISL 0.25 mg is predicted to achieve efficacy comparable to ISL 0.75 mg with no meaningful decreases in total lymphocyte counts or CD4+ T-cell counts (see Section 4.3). The totality of available data for DOR/ISL, including 48 Week results from MK-8591A-017 and -018, supports continued development of DOR/ISL (100 mg/0.25 mg) QD in participants with HIV-1 infection (see Section 2.2.3).

This study will provide long-term safety and efficacy data for DOR/ISL 100 mg/0.25 mg in participants who tolerated DOR/ISL 100 mg/0.75 mg QD in studies for HIV-1 treatment, and who elect to continue DOR/ISL 100 mg/0.25 mg QD as maintenance therapy.

2.2 Background

Refer to approved labeling for DOR and 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_{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 safety and efficacy 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 with HIV-1 (MK-8591A-020) (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 as 3-drug regimens (DOR+ISL+3TC) until virologic suppression (HIV-1 RNA <50 copies/mL) was achieved, at which point the regimen was simplified to a 2-drug regimen (DOR+ISL) 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 ≥200 copies/mL) through Week 144.

The overall AE profile of DOR+ISL (±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 this study (DOR/ISL group), which was considered in both cases 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

No other study-related therapy will be administered.

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 that is suitable across the population of PLWH, including the elderly and those with multiple comorbidities, as an alternative option for HIV-1 treatment. High in vitro potency against wild-type HIV-1 virus and a high barrier to resistance make DOR and ISL suitable candidates for development for treatment of HIV-1 infection. Administration of ISL in dose of 0.25, 0.75, and 2.25 mg with DOR 100 mg and 3TC 300 mg) in a MK-8591-011 achieved virological suppression in >90% treatment-naïve participants by Week 24, which was maintained after switching from the 3-drug regimen (DOR+ISL+3TC) to a 2-drug regimen (DOR+ISL) 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 evaluations of DOR and ISL as mono-entities have 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 subsets 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 DEC 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 were from the studies involves 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 virologically suppressed adults (MK-8591A-017 and -018) are not yet available.

  - Approximately 6 months after discontinuation of ISL 20 mg QW in adult VS participants (MK-8591-013), among those with ≥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 ≥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.

There are no hypotheses to be tested in this study. The following objectives will be evaluated in adults with HIV-1 who received DOR/ISL in previous DOR/ISL treatment studies:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of DOR/ISL (100 mg/0.25 mg) as assessed by accumulated safety data through Week 96	Adverse events Adverse events leading to discontinuation of DOR/ISL
Secondary Objectives	**Secondary Endpoints**
To evaluate the antiretroviral activity of DOR/ISL (100 mg/0.25 mg) as assessed by the percentage of participants with the following at Week 96: - HIV-1 RNA ≥50 copies/mL - HIV-1 RNA <50 copies/mL - HIV-1 RNA <200 copies/mL	HIV-1 RNA
To evaluate the development of viral resistance to DOR/ISL (100 mg/0.25 mg)	Viral resistance-associated substitutions
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the effect of DOR/ISL on total lymphocyte count at Week 96	Total lymphocyte count
To evaluate the immunologic effect of DOR/ISL, as assessed by mean changes from baseline in CD4+ T-cell count at Week 96.	CD4+ T-cell count
To evaluate the long-term antiretroviral activity of DOR/ISL, as assessed by the percentage of participants enrolled in the optional study extension with - HIV-1 RNA ≥50 copies/mL, - HIV-1 RNA <50 copies/mL, - HIV-1 RNA <200 copies/mL	HIV-1 RNA

To evaluate long-term effects of DOR/ISL on total lymphocyte count in participants enrolled in the optional study extension.	Total lymphocyte count
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 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.	Adverse events Adverse events leading to discontinuation of study intervention

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter study for participants with HIV-1 infection who were treated with DOR/ISL (100 mg/0.75 mg) QD in previous DOR/ISL treatment studies. Participants will continue open-label treatment with DOR/ISL (100 mg/0.25 mg). Participants will be assigned a new allocation number.

Participants enrolled in this study will be evaluated for safety and efficacy for a 96-week treatment period (base study), followed by a 144-week optional study extension up to Week 240.

At Week 96, 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. Where local treatment guidelines require study visits more frequently than every 6 months, these visits are permitted and should be conducted by the primary investigator and/or the treating physician following the local standard of care guidance in addition to the study visits.

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

In the global HIV community, uninterrupted access to experimental treatments for participants who are deriving benefit has become an expectation of clinical study participation. After completing participation in prior MSD-sponsored DOR/ISL clinical studies, this study will provide access to DOR/ISL (100 mg/0.25 mg) for eligible participants.

This study will enroll participants with HIV-1 infection who received DOR/ISL (100 mg/0.75 mg) QD in previous DOR/ISL treatment studies (except for HTE participants in MK-8591A-019 and -033). Participants who are considered by the investigator to have derived clinical benefit from study participation and for whom further treatment with DOR/ISL is considered clinically appropriate will be evaluated in this study for long-term safety and efficacy, including lymphocyte/CD4+ T-cell data.

The 0.25 mg dose of ISL in combination with 100 mg DOR is predicted to achieve efficacy comparable to the ISL 0.75 mg dose with no meaningful decreases in total lymphocyte counts or CD4+ T-cell counts (see Section 4.3).

Optional Study Extension

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

4.2.1 Rationale for Endpoints

This study will evaluate the long-term safety and durability of virologic response in participants receiving DOR/ISL (100 mg/0.25 mg). Therefore, the 96-week timepoint was chosen for formal evaluation of safety and efficacy. However, since this is an open-label study, relevant safety and efficacy data may be summarized at other timepoints during the study.

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 HIV-1 RNA Measurements

The efficacy evaluation in this study is based on plasma HIV-1 RNA <50 copies/mL and <200 copies/mL.

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. HIV-1 RNA ≥200 copies/mL are associated with treatment failure and an increased risk of development of HIV-1 drug 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-1 RNA ≥200 copies/mL and do not recommend that low-level viremia (detectable HIV-1 RNA <200 copies/mL)

automatically result 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 an HIV-1 RNA value between ≥50 and <200 copies/mL should continue their current regimen with monitoring of HIV-1 RNA levels as outlined in Section 8.2.2.1.3.

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 directed physical examinations and laboratory tests (eg, hematology, TBNK, chemistry, and urinalysis) performed per SoA (Section 1.3). AEs will be evaluated at each visit and assessed according to the guidelines in Section 8.4 and Appendix 3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring. Due to decreases in total lymphocyte counts and CD4+ T-cell counts observed in clinical studies with DOR/ISL 100 mg/0.75 mg, these parameters will be evaluated as exploratory endpoints at Week 96 and in the optional study extension.

4.2.2 Rationale for Collecting Race and Ethnicity Data

The differential effect on safety and efficacy based on any demographic parameter, including race or ethnicity, cannot be predicted when evaluating a new investigational drug. Therefore, it is important to collect race and ethnicity data to ensure that there is not a differential effect based on these parameters and to gain assurance the results observed in the clinical study will be representative of the drug's use in a broader population. As an example, non-Caucasian females and males were found to have higher plasma concentrations of EFV (an NNRTI) than their Caucasian counterparts, indicating an increased risk of EFV-induced toxicity in non-Caucasian 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 unknown [Weintrob, A. C., et al 2009] [Ribaudo, H. J., et al 2013]. Therefore, subgroup analyses on race and ethnicity will be performed to better understand how these parameters may influence clinical outcome and toxicity.

4.2.3 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 higher prevalence and incidence of HIV infection globally [Poteat, T., et al 2016] [Centers for Disease Control and Prevention 2019] [Department of HIV/AIDS 2015]. When considering HIV treatment, the WHO considers transgender people to be a separate key population because of their specific health needs and vulnerability [Department of HIV/AIDS 2015]. Data will be collected in this study to assess clinical outcomes in the transgender population.

4.2.4 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 consent to continue study intervention (where allowed by local regulations and as appropriate based on available data/local standard of care guidelines) (Sections 8.1.1.3, 8.11.6 and Appendix 7).

There are no clinical data currently available to support breastfeeding by participants who are receiving DOR/ISL; therefore, breastfeeding persons will be discontinued from the study.

4.2.5 Rationale for Infant Safety Data Collection

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

4.2.6 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 of 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 treatment allocation 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 the safety profile of the investigational medicinal product(s) against the background of such comorbid behaviors.

4.3 Justification for Dose

Inhibitory quotient (C_{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 timepoints 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 different daily doses of ISL (0.25, 0.75, and 2.25 mg) QD 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 counts and comparable increases in CD4+ T-cell counts 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 clinical 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 clinical studies [Orkin, C., et al 2019] [Molina, J. M., et al 2018] [Johnson, M., et al 2019]. Of note, in MK-1439A-024 and -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 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 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 as described in Appendix 1.10.

5 STUDY POPULATION

Participants ≥18 years of age with HIV-1 treated with DOR/ISL in previous DOR/ISL treatment studies 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 currently receiving DOR/ISL adult FDC tablet in MSD-sponsored clinical studies (MK-8591A-018, -020, and -033) [except for HTE participants]).

2. Is considered by the investigator to have derived clinical benefit from receiving DOR/ISL and for whom further treatment with DOR/ISL is considered clinically appropriate.

Demographics

3. Is an individual of any sex/gender, at least 18 years of age at the time of providing documented 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 8.3.3.
  - 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.

5.2 Exclusion Criteria

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

1. Has confirmed HIV-1 RNA ≥200 copies/mL in MSD DOR/ISL (100 mg/0.75 mg) MK-8591A-018/-020, or at screening for participants entering from DOR/ISL (100 mg/0.75 mg) MK-8591A-033.

2. Has confirmatory laboratory findings for CD4+ T-cell counts or lymphocyte counts in the prior DOR/ISL study that meet criteria for discontinuation of DOR/ISL.

3. Is a HTE participant receiving treatment in MK-8591A-019 or -033.

Prior/Concomitant Therapy

4. Is taking or is anticipated to require any prohibited therapies outlined in Section 6.5 from 45 days prior to Day 1 through the study treatment period.

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

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.4 Screen Failures

Not applicable.

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 intervention(s) 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 to be used in this study is outlined in Table 1.

Table 1 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
MK-8591A	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg doravirine/ 0.25 mg islatravir	100 mg doravirine/ 0.25 mg islatravir QD	Oral	Day 1 to Week 96	Test Product	IMP	Provided centrally by the Sponsor
MK-8591A	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg doravirine/ 0.25 mg islatravir	100 mg doravirine/ 0.25 mg islatravir QD	Oral	Week 96 up to Week 240	Test Product	IMP	Provided centrally by the Sponsor

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

Study intervention will be extended open-label for participants who become pregnant on-treatment and provide documented informed consent to continue study intervention, as specified in Section 1.3.4 and Section 8.11.6.

All supplies indicated in Table 1 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.

6.1.1 Medical Devices

Not applicable.

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

Participants in this study will be allocated by nonrandom assignment using IRT. There is 1 study intervention arm.

6.3.2 Stratification

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

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 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. 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 SAE or other reason(s) will be reviewed on a case-by-case basis by the investigator. Interruptions from the protocol-specified treatment plan that are expected to be ≥14 consecutive days 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 and/or dose reductions 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.

Concomitant therapies listed in Table 2 are not permitted from 45 days prior to Day 1 through the study treatment period. Table 2 is not comprehensive, and the investigator should use their medical judgment when assessing a participant's concomitant therapy(ies). The Sponsor Clinical Director or designee should be contacted if there are any questions about a therapy not in Table 2 or regarding potential DDI with a specific treatment that the participant may plan to receive.

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

Table 2 Prohibited Therapies

Strong and Moderate CYP3A Inducers	Including, but not limited to: 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 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. *Entecavir therapy for Hepatitis B infection is permitted* Long-acting HIV therapy (eg, cabotegravir, lenacapavir) is not permitted at any time. *Time-limited course of ritonavir as a pharmacokinetic enhancer is permissible (eg, nirmatrelvir/ritonavir for the treatment of COVID-19).*
Immunosuppressive Therapies	Immune therapy agents, immune modulators, or other systemic immunosuppressive therapy, including interferon-based treatment for Hepatitis *Time-limited courses of corticosteroids (eg, for asthma exacerbation) are permitted.*
Investigational Agents	All nonstudy investigational agents including devices *Any agent (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.*
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=intravenously

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)

No dose modification of DOR/ISL is allowed during the study.

6.7 Intervention After the End of the Study

If DOR/ISL is commercially accessible, participants who complete the Week 96 visit should follow the end of treatment procedures outlined in Section 1.3.1, and continue ART therapy with commercially accessible DOR/ISL or transition to local standard of care, as clinically appropriate.

If DOR/ISL is not commercially accessible, participants who complete the Week 96 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 will follow the procedures outlined in Section 1.3.1 and transition to ART therapy per local standard of care as clinically appropriate.

The optional study extension ends at Week 240. Provided DOR/ISL development continues, there will be a future mechanism (eg, prelicense patient access program) beyond the end of the study for participants to continue receiving DOR/ISL 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

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified study intervention regimen will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study Section 7.2.

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.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- 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. Consultation with the Sponsor prior to discontinuation is preferred when medically feasible.
- The participant is considered by the investigator to no longer derive clinical benefit from continued administration of DOR/ISL.
- The participant has a new AIDS-defining opportunistic infection as listed in Appendix 9, ie, a Category C conditions included in 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 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 3 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 3 Discontinuation Criteria for Specified Decreases in Total Lymphocyte Counts or CD4+ T-cell Counts

Laboratory Test	Criterion		Confirmation[a, b]
Total lymphocyte count	A new on-treatment value $<1.0 \times 10^9$ cells/L with a ≥30% decline from baseline (Day 1)		Repeat measurement 10 to 14 weeks later (or at the next scheduled study visit)
CD4+ T-cell count	**If at baseline (Day 1):**	**And on-treatment:**	
	≥500 cells/mm^3	<350 cells/mm^3	
	≥350 to ≤499 cells/mm^3	≥30% decline from baseline and <350 cells/mm^3	
	≥200 to ≤349 cells/mm^3	≥30% decline from baseline and <200 cells/mm^3	
	≤199 cells/mm^3	≥30% decline from baseline	

CD4+=cluster of differentiation 4-positive; SoA=Schedule of Activities.

[a] 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.

[b] 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, treatment nonadherence or other treatment interruption. Allow approximately 4 weeks following resolution of illness, immunization, treatment nonadherence, or other treatment interruption before collecting the confirmation sample.

For country-specific details see 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, 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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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. 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 for Continuation of Study Intervention During Pregnancy

Upon confirming that a participant is pregnant (Section 8.3.3), 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. 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. For country-specific details see Appendix 7.

8.1.1.3 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 infant safety data collection consent to the participant, or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent to collect any data related to infant safety. A copy of the informed consent will be given to the participant. For country-specific details see Appendix 7.

8.1.1.4 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 their 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 allocation, 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.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, and record prior medication taken by the participant within 14 days before first dose of study intervention.

ARTs taken by the participant from 14 days prior to the first dose of study intervention (Day 1) in this study will be recorded. The start/stop date of the MK-8591A taken by participants in the previous DOR/ISL treatment study will also be recorded.

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 intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/allocation number identifies the participant for all procedures occurring after treatment. Once a treatment/allocation number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.8 Study Intervention Administration

DOR/ISL will be provided per Table 1 and dispensed by the site according to the IRT allocation at visits indicated in the SoA (Section 1.3.1). Study intervention should begin within 24 hours of allocation (ie, on the day of treatment allocation 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

From Day 1 and until treatment is discontinued, participants 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.

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.

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 for all remaining study visits as outlined in the SoA and Section 8.11.3.1.

Participants who end study intervention while in the optional study extension (after Week 96 and prior to Week 240) should have a Discontinuation of Study Treatment 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 of Treatment 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 counts or CD4+ T-cell counts 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.

8.1.10 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 (Appendix 2).

8.2.2 Management of Participants With Viremia

When viremia (HIV-1 RNA ≥50 copies/mL) is detected (Section 4.2.1.1.2), the investigator should query the participant regarding adherence to study intervention, intercurrent illness, or

recent immunization. All cases of viremia must be confirmed, and **the participant should continue to take the full assigned dosage of study intervention while awaiting confirmation**.

If a participant has an on-treatment 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. 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 ≥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 (± 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 ≥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 ≥200 copies/mL (on both primary and reflex tests, if available) on consecutive visits 4 weeks (± 1 week) apart, then clinically significant viremia is confirmed, and the participants will be assessed for potential discontinuation from study intervention (Section 7.1 and Section 8.2.2.1.1).

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

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

Participants with confirmed HIV-1 RNA of ≥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 between the investigator and 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.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. 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 12, Table 13, and Table 14 in Appendix 2.

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

8.3.1 Physical Examinations

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 for all participants on Day 1, and participants who become pregnant and consent to continue study intervention at the visits specified in the SoA (Sections 1.3.1 and 1.3.4). 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 body temperature, pulse, RR, and systolic and diastolic BP for participants who become pregnant and consent to continue study intervention at the visits specified in the SoA (Sections 1.3.1 and 1.3.4).

- *Note: Oral temperatures are preferred, but not required.*

8.3.3 Confirmation of Contraception and Pregnancy Testing

POCBP are required to confirm heterosexual abstinence or use 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). POCBP will be tested for pregnancy at each visit as outlined in Section 1.3, Section 5.1, and Appendix 5.

Participants should be asked at study visits per SoA to verbally confirm 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 a 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.

8.3.4 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 42 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.
- A TBNK panel, including CD4+ T-cell count (Table 11), will be performed at the central laboratory as specified in Appendix 2. If laboratory values indicate specified decreases in total lymphocyte count or CD4+ T-cell count (Table 3), 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 (Table 11).

8.3.5 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).

8.3.6 HBV Assessments

Participants coinfected 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) will be closely monitored during the study.

All participants will have repeat hepatitis B serology and HBV DNA annual testing per the SoA Section 1.3.1 and 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.

For the duration of the study (base study and optional study extension), participants who are confirmed to be HBsAg-positive or have confirmed quantifiable HBV DNA during the study 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.

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.

For country-specific details see Appendix 7.

8.3.7 HCV Assessment

HCV serology will be performed on Day 1 and if the individual is HCV antibody positive, reflex testing will be performed for HCV RNA. Repeat testing if indicated per local standard of care.

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 allocation, 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 allocation 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 4.

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

Table 4 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified AE Collection Period**	**Reporting Period: 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 related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Events and Follow-up Information to Sponsor
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 DILI events meeting biochemical criteria of Hy's Law (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – regardless of suspected etiology – 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
ECI (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report if: - requires 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	Previously reported – Follow to completion/ termination; report outcome	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)

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection Period	Time Frame to Report Events and Follow-up Information to Sponsor
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 DILI events meeting biochemical criteria of Hy's Law, 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 allocated 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 is 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 that the 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

Not applicable.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and an SAE with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:

- an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN, and
- an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN, and
- at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

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).

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than twice the prescribed dose of study intervention (3 or more tablets of a single study intervention) in a day. No specific information is available on the treatment of overdose.

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma ISL

Venous blood samples will be collected for measurement of ISL. The Sponsor may assess these samples for DOR PK as needed. Sample collection, storage, and shipment instructions for plasma samples will be provided in the laboratory manual.

Investigational PK samples will be collected from participants as outlined in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). 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 indicated.

The PK samples will be collected from participants as irrespective of time of dose. The time of the doses of study interventions taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

For participants who become pregnant and consent to continue study intervention (base study or optional study extension), PK samples will be collected to evaluate DOR and ISL concentration levels per Table 5 in Section 8.11.6.1.1.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening

Any participant who has completed all visits in a previous DOR/ISL treatment study and is considered by the investigator to have derived clinical benefit from receiving DOR/ISL, and for whom further treatment with DOR/ISL is considered clinically appropriate, will be eligible for enrollment in this study. There is no screening period, except for participants entering from MK-8591A-033. Participants are expected to enroll in this study as soon as they are deemed eligible.

For participants entering from MK-8591A-033, potential participants will be evaluated to determine whether they fulfill the HIV-1 entry requirements as set forth in Section 5.2.

8.11.2 Treatment Period

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

8.11.2.1 Fasting

Visits at Day 1, Week 24, Week 48, and Week 96 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. 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 End-of-Base Study Week 96 Visit

Procedures for the base study are to be conducted per the SoA (Section 1.3.1). Week 96 represents the end of the base study. Prior to the end of the base study/Week 96 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 entering the optional study extension, the Week 96 visit serves as the start of the optional study extension, DOR/ISL will be dispensed, and participants will follow procedures outlined in SoA (Section 1.3.5).

Participants who complete Week 96 should follow End of Treatment Follow-up visit per the Week 96 SoA (Section 1.3.1).

Participants who are pregnant at Week 96 will be managed per Section 8.11.6.

Participants who have laboratory values at the Week 96 visit that meet any of the discontinuation criteria for specified decreases in total lymphocyte counts or CD4+ T-cell counts (Section 7.1, Table 3) must be managed per Section 8.11.5.

8.11.2.3 Optional Study Extension (Week 96 up to Week 240)

If DOR/ISL is not commercially accessible by Week 96, participants will be provided the option to enroll in an optional study extension 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 person 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 (Section 7.1).

Once DOR/ISL becomes commercially available, 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 treatment in the study.

Manage participants with viremia per Section 8.11.4 (SoA Section 1.3.2). Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3). Manage participants who are pregnant per Section 8.11.6 (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 count or CD4+ T-cell counts (Table 3) 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 counts or CD4+ T-cell counts (Table 3) 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 96 for any reason(s) should have an Early Discontinuation of Treatment visit as outlined in the SoA (Section 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 (+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 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) and Sections 4.2.1.1.2 and 8.2.2.1. 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 3) 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 as specified in the SoA (Section 1.3.3) and Table 3.

Management of Participants who Discontinue Study Intervention 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, Table 3) should undergo assessments for the Discontinuation of Treatment visit and the End of Treatment Follow-up visit as specified in the SoA (Sections 1.3.3 and 1.3.5). After discontinuation from study intervention, participants will be managed for treatment of their HIV-1 infection per local standard of care. Consult with Sponsor prior to discontinuation if the investigator believes there is an alternate explanation for the result (eg, COVID-19).

Monitoring of 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 lymphocyte or CD4+ T-cell counts (per Table 3) should have monitoring visits every 10-14 weeks (Section 1.3.3). Participants should be monitored until the total lymphocyte count or CD4+ T-cell count no longer meet the criteria in Section 7.1 Table 3 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 Counts or CD4+ T-Cells Counts

Participants noted to have their first decrease in total lymphocyte or CD4+ T-cell counts that meet the criteria for Table 3 at the Discontinuation of Treatment visit (base study or optional study extension) or at the Week 96 visit, only require monitoring 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 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). Documented informed consent must be obtained to continue study intervention (Section 8.1.1.2).

- 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 PI):

- 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 are eligible to continue their assigned open-label study intervention if they have sustained HIV-1 RNA <50 copies/mL for at least 3 consecutive months and consent to continue study intervention during pregnancy (Section 8.1.1.2). Participants continuing study intervention during pregnancy should complete all remaining protocol-specified visits and procedures per the regular schedule in the applicable SoA (Section 1.3). Participants on DOR/ISL who are pregnant at Week 96 will have the opportunity to continue into the optional study extension.

As specified in the SoA (Section 1.3.4), participants will have study visits at least every 12 weeks (~1 during each trimester and 1 postpartum ≤8 weeks after delivery) in both the base study and the optional study extension (Sections 1.3.1 and 1.3.4, as applicable). An unscheduled peripartum visit at week 36 of gestation or ≤4 weeks before the planned date of delivery may also be required (Section 1.3.4). The peripartum visit is required if the 3rd trimester visit (Pregnancy 3 visit) occurs prior to week 36 of gestation or does not occur ≤4 weeks before the planned date of delivery. At the peripartum visit, blood (plasma) samples will be collected for HIV-1 RNA testing and HIV-1 viral resistance testing, and for DOR and ISL PK. This pregnancy visit schedule also 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 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 hepatitis B serology with reflex HBV DNA, if indicated; 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 96 at the base study or Week 240 at the optional study extension), their visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester, including the peripartum period, and postpartum and, as applicable, a 42-day follow-up period with an End of Treatment Follow-up visit (Section 1.3.4). After the completion of the pregnancy, the participant will have completed the study after either completing the postpartum visit (if the participant chooses to breastfeed) or completing the End of Treatment Follow-up visit (if the participant does not choose to breastfeed and completed the 42-day follow-up period). 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.

For country-specific details see Appendix 7.

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, including the peripartum period and postpartum to evaluate DOR and ISL concentration levels per Table 5. 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 DOR/ISL during the day will have a predose and 2 postdose samples collected per Table 5. Participants that 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, peripartum, 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 5 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
Peripartum[c] (if needed)	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[d]	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

PK=pharmacokinetic(s); DOR= doravirine; ISL= islatravir.

[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 a participant does not learn of their pregnancy until after the first trimester.)

[c] Peripartum visit is only required if 3rd trimester visit (Pregnancy 3 visit) occurs prior to week 36 of gestation or does not occur ≤ 4 weeks before the planned date of delivery.

[d] 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 (+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----------	

Time Point	At Birth[a]	1 Year After Birth[a,b]
Visit Name	NA	Infant Follow-up-1
Administrative and Safety Procedures		

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 KEY STATISTICAL CONSIDERATIONS

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

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 Open-label Clinical Study of Doravirine/Islatravir (DOR/ISL [100 mg/0.25 mg]) Once Daily for the Treatment of HIV-1 Infection in Participants Who Previously Received DOR/ISL (100 mg/0.75 mg) QD in a Phase 3 Clinical Study
Treatment Assignment	All participants will receive DOR/ISL (100 mg/0.25 mg) FDC QD.
Analysis Populations	Safety: APaT, APaT-E Efficacy: FAS, PP, Resistance Analysis Subset, FAS-E
Primary Endpoint(s)	1. AEs 2. AEs leading to discontinuation of DOR/ISL
Secondary Endpoints	Percentages of participants with HIV-1 RNA ≥50 copies/mL, HIV-1 RNA <50 copies/mL and HIV-1 RNA <200 copies/mL.
Statistical Methods for Key Efficacy Analyses	Descriptive statistics will be provided to show the percentage of participants with HIV-1 RNA ≥50 copies/mL, percentage of participants with HIV-1 RNA <50 copies/mL and the percentage of participants with HIV-1 RNA<200 copies/mL at Week 96
Statistical Methods for Key Safety Analyses	Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and AEs leading to discontinuation of DOR/ISL through Week 96. Descriptive statistics will be provided for AE safety parameters.
IAs	An interim analysis will be conducted prior to reaching the planned primary endpoint of Week 96 to support program decisions. The results of this analysis may also be shared with regulatory authorities.
Multiplicity	No hypotheses will be evaluated in this study; therefore, no adjustment for multiplicity is needed.
Sample Size and Power	The sample size is not determined by any statistical considerations; participants with HIV-1 who received DOR/ISL (100 mg/0.75 mg) in previous DOR/ISL treatment studies are eligible to enroll in this study.

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 is an open-label study; all participants will receive DOR/ISL (100 mg/0.25 mg) for the duration of the study.

9.3 Hypotheses/Estimation

There are no hypotheses to be tested in this study.

9.4 Analysis Endpoints

9.4.1 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. A secondary objective will assess the sustained antiretroviral suppression of DOR/ISL after 96 weeks of treatment by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96.

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

The secondary objective to assess the antiretroviral activity of DOR/ISL (100 mg /0.25 mg) will be based on the percentage of participants with HIV-1 RNA <50 copies/mL and the percentage of participants with HIV-1 RNA <200 copies/mL at Week 96.

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.

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 who have evidence of resistance-associated substitutions and will be summarized for Week 96 and optional study extension.

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 adverse events and laboratory values.

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 that 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 tests, participants must have both a baseline and posttreatment allocation on-treatment measurement to be included. Participants' laboratory values (based on their most abnormal laboratory test values in the direction of interest while on study intervention) will be classified as to whether or not they fall outside the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from 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].

Change From Baseline in Total Lymphocyte Count, CD4+ T-cell Count, and TBNK Panel

The mean change from baseline in total lymphocyte count, CD4+ T-cell count and other TBNK parameters (including the observed mean CD4+ T-cell percentage) in the base study and the optional study extension will be summarized at each time point at which TBNK panel/CD4+ T-cell count is scheduled to be collected.

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

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

9.5.1.1 Full Analysis Set

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

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

The composition of the FAS population may vary based on the availability of baseline measurements for the relevant efficacy parameters of interest.

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.

9.5.1.2 Per-protocol Population

The PP population will be the secondary population for the analysis of efficacy data in this study. The PP population will include all participants in the FAS who have not committed any major protocol violations that could impact the assessment of efficacy, including violation of key inclusion/exclusion criteria.

Participants meeting any of the following criteria will be excluded from the PP population:

- Participants who meet the exclusion criteria for receiving any ongoing prohibited therapies listed in Table 2.
- Nonadherence to study intervention: participants with <95% drug compliance rate (see Section 9.11).
- Participants who become pregnant.

The PP analysis will be performed for the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96, the percentage of participants with HIV-1 RNA <50 copies/mL at Week 96, and the percentage of participants with HIV-1 RNA <200 copies/mL.

The final determination of important protocol violations, and thereby the composition of the PP population, will be documented before the final database lock.

The composition of the PP population may vary by the analysis timepoint, based on the number of participants who satisfy the PP criteria at that timepoint.

9.5.1.3 Resistance Analysis Subset

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

9.5.2 Safety Analysis Population

APaT

Safety analyses will be conducted on the APaT population, which consists of all allocated participants who received at least 1 dose of study intervention.

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

9.6.1 Statistical Methods for Efficacy Analyses

Time Windows

Table 6 lists the definition of time windows (day-ranges) and the target day for the scheduled visits in the study, which will be used for all statistical analyses by timepoint. The last available on-treatment measurement within a window will be used for analyses at a specific timepoint, unless otherwise specified. Results from additional timepoints beyond Week 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 6 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	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	≥295 and ≤378	337
		Week 60	≥379 and ≤462	421
		Week 72	≥463 and ≤546	505
		Week 84	≥547 and ≤630	589
		Week 96	≥631 and ≤756	673
Optional Study Extension[b]	DOR/ISL	Week 120	≥757and ≤924	841
		Week 144	925 and ≤1092	1009
		Week 168	≥1093 and ≤1260	1177
		Week 192	≥1261 and ≤1428	1345
		Week 216	≥1429 and ≤1596	1513
		Week 240	≥1597 and ≤1705	1681

DOR=doravirine; ISL=islatravir.
[a] Day-ranges and target days are computed relative to the first day of study intervention.
[b] 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 in the base study is the FDA snapshot algorithm [Food and Drug Administration (CDER) 2015]. Under this approach, for data collected in a given analysis window (see Table 6), the last available measurement while the participant is on-treatment is used to define the virologic outcome. Virologic outcome will be defined according to the following categories:

HIV-1 RNA <50 copies/mL: participants who have the last available on-treatment HIV-1 RNA measurement <50 copies/mL within the time point of interest analysis window specified in Table 6.

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 timepoint of interest analysis window specified in Table 6.

- Who do not have on-treatment HIV-1 RNA data in timepoint of interest analysis window and:
  - Who discontinue study intervention prior to or in the timepoint 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 6 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. Additionally, 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) 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 estimating 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 snapshot algorithm, divided by the number of participants in the FAS.

For estimating 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. Similar logic will also be used for the analysis of the percentage of participants with HIV-1 RNA <200 copies/mL.

A second approach, the missing data treated as treatment failure (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 <50 copies/mL within the timepoint of interest analysis window specified in Table 6, OR 2) are on study intervention and have no HIV-1 RNA measurements within the timepoint of interest analysis window specified in Table 6 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" at the timepoint of interest. Participants with other reasons for missing data will be classified as a virologic failure at the timepoint 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 timepoints thereafter. Participants who discontinue study intervention for reasons other than lack of efficacy and who are not failures at the time of study intervention discontinuation will be excluded from the analyses at subsequent timepoints. Participants with intermittent missing data will be considered to be successes (HIV-1 RNA <50 copies/mL) if both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements are <50 copies/mL; all other intermittent missing results will be imputed as failures.

The same 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/m The relevant percentages will be tabulated, and the within-group nominal 95% CIs will be presented using the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S. 1934] at each timepoint of interest. In addition, for participants who become pregnant and consent to continue study intervention, 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 summarize 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. The relevant percentages will be tabulated, and the within-group nominal 95% CIs will be presented using the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S. 1934] at each timepoint of interest. 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 copies/mL and <200 copies/mL will be summarized in a similar manner as for those with HIV-1 RNA ≥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 ≥400 copies/mL will be summarized by treatment groups at all scheduled study visit timepoints.

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.

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 with primary interest at Week 96, and timepoints of interest during the option 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 who participants 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. Table 7 summarizes the key efficacy analyses of the base study.

Table 7 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Secondary Endpoints				
Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96	P	95% CI (Clopper-Pearson)	FAS	Snapshot
	S	95% CI (Clopper-Pearson)	PP	OF
Percentage of participants with HIV-1 RNA <50 and <200 copies/mL at Week 96	S	95% CI (Clopper-Pearson)	FAS	Snapshot
	S	95% CI (Clopper-Pearson)	FAS	M=F
	S	95% CI (Clopper-Pearson)	PP	OF

FAS=Full Analysis Set; HIV-1=human immunodeficiency virus type 1; M=F=missing equal to failure; OF=Observed Failure; P=primary approach; PP=Per-Protocol; RNA=ribonucleic acid; S=supportive approach.

9.6.2 Statistical Methods for Safety Analyses

9.6.2.1 Overall Safety Assessment

The overall safety evaluation in the base study will include a summary of the number and percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 to 4 AE, with an AE that is both serious and drug-related, with an AE that is both Grade 3 to 4 and drug-related, who discontinued study intervention due to an AE, who discontinued study intervention due to a drug-related AE, and with an AE resulting in death. Point estimates and 95% within-group CIs for 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 within-group 95% CIs for the percentages of participants with specific AEs will be provided for all AEs.

Within-group CIs will be calculated using the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S. 1934]. CIs 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.

For continuous safety measures, such as change from baseline in laboratory parameters, summary statistics for baseline, on-treatment, and change from baseline values will be

provided. For participants who become pregnant during the study, measurements collected from the estimated date of conception through 6 weeks after the date of delivery /termination will be excluded from the analysis.

Safety data for participants who consent to continue in the optional study extension (from post-Week 96 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 are considered safety topics of special interest in the base study.

Opportunistic infections will be summarized by the number and percentage of participants with any opportunistic infection and by the number and percentage of participants with specific opportunistic infections. Point estimates and 2-sided 95% CIs for the percentages of participants with these events will be provided based on the criteria described above for specific AEs. 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.

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 last visit prior to dosing in this study 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.

For participants who become pregnant during the study, safety parameters (collected from the estimated date of conception through six weeks after delivery /termination) will be summarized separately from the primary and secondary safety analyses. Data collected for participants whose pregnancy or postpartum visit(s) extends beyond Week 96 will be reported separately. Infant safety data will be reported separately.

Table 8 summarizes the analysis strategy for safety endpoints in the base study.

Table 8 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Within-group CI
Overall Safety Assessment	Any AE	X	X
	Any drug-related AE	X	X
	Any SAE	X	X
	Any Grade 3-4 AE	X	X
	Any serious drug-related AE	X	X
	Any Grade 3-4 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 that results in death	X	X
	Specific AEs or SOCs	X	X[a]
	PDLCs	X	X[a]
	Change from baseline results (Select laboratory measures including CD4+ T-cell count and total lymphocyte count)	X	
Assessment of Safety Topics of Special Interest	Any opportunistic infection	X	X[a]
	Specific opportunistic infections and corresponding SOCs	X	X[a]

AE=adverse event; CI=Confidence Interval; PDLC=Predefined Limit of Change; SAE=serious adverse event; SOC=system organ class.
[a] Threshold for incidence will be applied for CI.

9.6.3 Summaries of Baseline Characteristics, Demographic, and Other Analyses

The number and percentage of participants screened and randomized and the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, gender, race, region), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables.

9.7 Interim Analyses

An interim analysis is planned to be conducted prior to Week 96. The purpose of this interim analysis is to analyze all data available to inform program decisions. The results may be shared with regulatory authorities.

9.8 Multiplicity

No hypotheses will be evaluated in this study; therefore, no adjustment for multiplicity is needed.

9.9 Sample Size and Power Calculations

This is an estimation study; no statistical testing will be performed. In this study, approximately 650 participants are expected to be enrolled, and the numbers will be adjusted as necessary.

9.9.1 Sample Size and Power for Efficacy Analyses

The estimates of the 95% CIs for the percentage of participants with HIV-1 RNA <50 copies/mL and with HIV-1 RNA <200 copies/mL given various hypothetical observed numbers of participants are provided in Table 9. These estimates are derived based on the snapshot analysis and take into account the expected dropout rate by Week 96. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 9 Estimate of Percentage of Participants With HIV-1 RNA <50 copies/mL or <200 copies/mL

N	Hypothetical Number of Participants With HIV-1 RNA <50 copies/mL or <200 copies/mL	Observed Estimate of Percentage of Participants With HIV-1 RNA <50 copies/mL OR <200 copies/mL(%)	95% Confidence Interval[a]
650	644	99.1	(98.0, 99.6)
	618	95.1	(93.1, 96.6)
	585	90.0	(87.4, 92.2)
	553	85.1	(82.1, 87.7)
	520	80.0	(76.7, 83.0)
	488	75.0	(71.6, 78.4)

HIV=human immunodeficiency virus; N=number of participants; RNA=ribonucleic acid.
[a] Based on the Clopper-Pearson method [Clopper, C. J. and Pearson, E. S. 1934].

9.9.2 Sample Size and Power for Safety Analyses

The estimate of the 95% CI for the underlying percentage of participants with a specific AE given various hypothetical observed numbers of participants with that specific AE is provided in Table 10. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 10 Estimate Incidence of a Specific Adverse Event and 95% Confidence Interval Based on a Hypothetical Number of Participants With That Specific Adverse Event

N	Hypothetical Number of Participants With Adverse Event	Observed Estimate of Incidence Rate (%)	95% Confidence Interval[a]
650	13	2.0	(1.1, 3.4)
	33	5.0	(3.5, 7.1)
	65	10.0	(7.8, 12.6)
	98	15.0	(12.4, 18.0)

HIV=human immunodeficiency virus; N=number of participants; RNA=ribonucleic acid.
[a] Based on the 2-sided exact 95% CI for a binomial proportion. In the 0-event case, the CI is 1-sided (α=0.05 all in the upper tail).

9.10 Subgroup Analyses

Subgroup analyses are not planned.

9.11 Compliance (Medication Adherence)

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

For the analysis of compliance in this study, 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 (eg, Week 96) 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, percent compliance will then be calculated using the following formula:

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

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

9.12 Extent of Exposure

The extent of exposure to study intervention for all treated participants will be summarized in the base study. The number of participants exposed to various doses (actual total daily dose) for defined periods of time in the current study 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 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. 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 11 will be performed by a central laboratory.
  Note: In rare instances, if central laboratory is not feasible, local laboratory tests may be used at scheduled study visits after Sponsor consultation. 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 if 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 12, Table 13, and Table 14.

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

Table 11 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • MCH concentration • RDW	WBC count with Differential[a]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
TBNK Panel/ CD4+ T-cell counts	T and B-Lymphocyte, and Natural Killer Cell profile that 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			
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)[b]	Glucose HDL-C LDL-C TGs TC Non-HDL-C			
Routine Urinalysis (with microscopic exam as needed)	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick			
Pregnancy Testing	Highly sensitive urine hCG pregnancy test (as needed for POCBP)			
Hepatitis B Serology[c]	HBsAg Anti-HBs Anti-HBc			
HBV DNA[c]	HBV DNA			
Hepatitis C Serology[c]	Hepatitis C antibody (if positive perform plasma HCV quantitative test) (at Day 1 only)			
Virology	HIV-1 RNA quantification HIV-1 viral drug resistance			

Laboratory Assessments	Parameters
PK	Plasma investigational ISL PK (Analysis of these samples will be performed by the Sponsor as needed.) Plasma DOR and ISL PK (Only participants on DOR/ISL who become pregnant during the study)

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=creatine kinase; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; DOR=doravirine; 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; 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; PCR=polymerase chain reaction; PK=pharmacokinetic(s); POCBP=participant(s) of childbearing potential; RBC=red blood cell; 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.

[a.] The central laboratory may reflex to manual differential to further identify atypical or immature forms of leukocytes.

[b] Participants with type 1 diabetes mellitus should not fast. 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.

[c] All participants will be tested for HBsAg, anti-HBs, anti-HBc, and reflex HBV DNA as well as hepatitis C antibody (with reflex plasma HCV quantitative test if indicated) at Day 1. Repeat serology and HBV DNA testing at Weeks 48, 96, 144, 192, and 240 to be performed for all participants. Only participants who are anti-HBc-positive will have HBsAg and HBV DNA monitored for the duration of the study.

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

Table 12 Blood Volumes in the Base Study

Study Period	**Screening**	**Open-label Intervention**										**Unscheduled**				
Scheduled Day/Week	Screening[a]	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 60	Week 72	Week 84	Week 96 (fasting)	Viremia Confirm	Total Lymphocyte/ CD4+ T-Cell Confirm	Early Discon of Treatment	Total Lymphocyte/ CD4+ T-Cell Monitor[d]	EoT Follow-Up[e]
Blood Parameter		**Approximate Blood Volume (mL)**														
Blood (Plasma) for HIV-1 RNA Quantification[b] (PCR)	(6)[a]	6	6	6	6	6	6	6	6	6	6	6		6		6
Whole blood for HIV-1 Viral Drug Resistance Testing		4														
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing[c]												15		(15)[c]		
TBNK Panel/CD4+ T-cell Count		6	6	6	6	6	6	6	6	6	6		6	6	6[d]	6
Hepatitis B and Hepatitis C (Day 1 only) Serologies[f]		4	(4)	(4)	(4)	(4)	4	(4)	(4)	(4)	4					
HBV DNA[f]		6	(6)	(6)	(6)	(6)	6	(6)	(6)	(6)	6					
Hepatitis B Serology for Pregnant Participants [g]		<----------(4)---------->														4
HBV DNA for Pregnant Participants[g]		<----------(6)---------->														6
Plasma HCV Quantitative Test[f]		(6)														
Chemistry		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
Fasting Lipids		2			2		2				2					
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK[h]			4									4	4	4		
Blood (Plasma) for DOR and ISL PK in Pregnant Participants			<-------- (4 or 12 as indicated)-------->									4 or 12		4 or 12		

Study Period	Screening	Open-label Intervention										Unscheduled				
Approximate Total Blood Volume per Visit (mL)[d]	**(6)[a]**	**44**	**36**	**32**	**34**	**32**	**34**	**32**	**32**	**32**	**34**	**25**	**14**	**16-41**	**10**	**6-16**

Discon=discontinuation; DNA=deoxyribonucleic acid; EoT=End of Treatment; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV-1=human immunodeficiency virus type 1; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid; TBNK=T and B-lymphocyte and natural killer cell.

[a] Screening visit only applies for participants entering from MK-8591A-033. HIV-1 RNA sample will be collected at the visit.

[b] 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.

[c] If HIV-1 viral drug resistance testing sample is collected at the Viremia Confirmation visit, do not collect at the Early Discontinuation of Treatment visit.

[d] Blood volumes collected at the Total Lymphocyte Count/CD4+ T-cell Count Monitoring Visit represent single monitoring visits every 10-14 weeks after discontinuing study intervention.

[e] Blood volumes indicated for the EoT Follow-Up visit represent the approximate total volume collected per SoA Sections 1.3.1, 1.3.3, or see SoA Section 1.3.2 as indicated.

[f] All participants will be tested for HBsAg, anti-HBs, anti-HBc, and reflex HBV DNV as well as hepatitis C antibody (with reflex plasma HCV quantitative test if indicated) at Day 1. Participants will have repeat testing at Weeks 48 and 96. Only participants who are anti-HBc-positive will have HBsAg and reflex HBV DNA monitored for the duration of the study.

[g] Not included in total blood volume at each visit: Pregnant participants 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.

[h] Not included in the total volume: PK samples collected during pregnancy will be collected per Section 8.11.6.1. During the 1st the 2nd and 3rd trimester, peripartum (if needed), and postpartum study visits, 4 or 12 mL of blood will be collected for PK sampling.

Table 13 Blood Volume for Optional Study Extension

Study Period	**Optional Study Extension**						**Viremia Confirmation**	**Total Lymphocyte/ CD4+ T-cell Confirmation**	**Total Lymphocyte/ CD4+ T-cell Monitoring**	**Discontinuation of Treatment (Optional Study Extension)**	**End of Treatment Follow-up (Optional Study Extension)[a]**
Scheduled Day/Week	Week 120	Week 144	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			6	(6)
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6	6		6	6	6	(6)
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing[b]							12			12[b]	
Hematology	2	2	2	2	2	2		2	2	2	(2)
Chemistry	6	6	6	6	6	6				6	(6)
Hepatitis B Serology HBV DNA		10		10		10					
HBsAg and HBV DNA	(10)	(10)	(10)	(10)	(10)	(10)					
Blood (Plasma) for Investigational ISL (and DOR, if applicable) PK							4	4			
Blood (Plasma) for DOR and ISL PK (pregnant participants on DOR/ISL)							(4)			(4)	(4)
Total Blood Volume per Visit (mL)	20	30	20	30	20	30	22	12	8	32	0-24

Study Period	Optional Study Extension						Viremia Confirmation	Total Lymphocyte/ CD4+ T-cell Confirmation	Total Lymphocyte/ CD4+ T-cell Monitoring	Discontinuation of Treatment (Optional Study Extension)	End of Treatment Follow-up (Optional Study Extension)[a]
Scheduled Day/Week	Week 120	Week 144	Week 168	Week 192	Week 216	Week 240	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled

CD4=cluster of differentiation 4; DNA=deoxyribonucleic acid; DOR=doravirine; HBV=Hepatitis B virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid; TBNK=T and B-lymphocyte and natural killer cell

[a] For the EoT Follow-up visit, the approximate total volume to be collected is for the assessments in SoA Section 1.3.5. Alternatively, see SoA Sections 1.3.2 or 1.3.3 or 1.3.4, as indicated.

[b] If HIV-1 viral drug resistance testing sample is collected at the Viremia Confirmation visit, do not collect at the Early Discontinuation of Treatment visit.

The assessments in Table 14 are for any participant who is pregnant on or after Week 96 and whose visit schedule will be extended through the duration of the pregnancy, to allow assessments through each trimester and postpartum.

Table 14 Blood Volumes: Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 96

Visit Number	**Unscheduled**					
Scheduled Week	**Pregnancy 1[c]**	**Pregnancy 2[c]**	**Pregnancy 3[c]**	**Peripartum** (At week 36 of gestation or ≤4 weeks before planned date of delivery)	**Pregnancy 4 (Postpartum ≤8 weeks after delivery)**	**EoT Follow-up**
Blood Parameter	**Approximate Blood Volume (mL)**					
Plasma HIV-1 RNA Quantification (PCR assay)	6	6	6	6	6	6
TBNK Panel/CD4+ T-cell Count	6	6	6		6	6
Plasma HIV-1 Viral Drug Resistance Testing	15	15	15	15	15	15
Hepatitis B Serology and reflex HBV DNA[a]	<----------(10)---------->			--	--	10
Chemistry	6	6	6	--	6	6
Hematology	4	4	4	--	4	4
Blood (Plasma) for DOR and ISL PK[b]	12	12	12	12	12	12
Approximate Total Blood Volume per Visit (mL)	**49**	**49**	**49**	**33**	**49**	**59**

DNA=deoxyribonucleic acid; DOR=doravirine; HBV=Hepatitis B virus; HIV-1=human immunodeficiency virus Type 1; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid.; mL=milliliter; TBNK=T and B-Lymphocyte and natural killer cell.

[a] Not included in total blood volume at each visit: Pregnant participants will have 1 sample collected once after pregnancy is confirmed or local laboratory results reported for HBsAg, anti-HBs, anti-HBc, and reflex HBV DNA during pregnancy.

[b] Collect PK samples during pregnancy per Section 8.11.6.1.

[c] If pregnancy visit occurs at the timeframe of a scheduled optional study extension visit, collection of laboratory samples should occur per this table. Collection of laboratory samples should not be duplicated. Peripartum visit is only required if Pregnancy 3 visit occurs prior to week 36 of gestation or does not occur ≤4 weeks before the planned date of delivery.

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 DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

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.

Note: For assessing the severity of AEs that are pregnancy-related complications, please refer to the additional guidance provided as part of the DAIDS table version 2.1 "Addendum 1: Female Genital Grading Table for Use in Microbicide Studies", particularly the section "Complications of Pregnancy" (found on pages 11-12 of the Addendum): https://rsc.niaid.nih.gov/sites/default/files/addendum-1-female-genital-grading-table-v1-nov-2007.pdf

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 POCBP:

- 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

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b] • IUS[c] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• 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] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b] - Oral - Injectable
Sexual Abstinence • 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 *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • 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)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [c] IUS is a progestin releasing IUD [d] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • 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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Russia-specific Requirements

If a participant becomes pregnant (has a positive serum pregnancy test), DOR/ISL must be discontinued, and the participant's HIV-1 infection and treatment should be managed per local standard of care. Therefore, the following sections of the protocol are not applicable for participants receiving DOR/ISL:

a. Section 4.2.4: Rationale for Continuing Study Intervention During Pregnancy

b. Section 8.1.1.2 Consent for Continuation of Study Intervention During Pregnancy

c. Section 8.11.6.1 Continuing Study Intervention in Pregnancy

10.7.2 Canada-specific Requirements

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 has confirmed quantifiable HBV DNA after randomization, per Section 8.3.6.

10.7.3 Germany-specific Requirements

Legally Acceptable Representative

Persons of legal age who are incapable of comprehending the nature, significance, and implications of the clinical trial and of determining their will are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Exclusion of Persons who per Order of Court or Authorities Have Been Accommodated in an Institution, as per German Drug Law (AMG) §40(1) Sentence 3 No. 4

Persons who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities are excluded from participation in this clinical trial in Germany.

10.7.4 Japan-specific Requirements

Throughout the Protocol

After DOR/ISL is approved for HIV-1 infection in Japan, the terms “clinical study” and “clinical trial” will no longer be applicable in the protocol and “postmarketing clinical study” or "postmarketing clinical trial" would be applicable instead. The study will continue per protocol.

All applicable laws, rules, and regulations related to the conduct of the clinical trial mentioned in these sections include Japan-specific local regulation, Good Post-Marketing Study Practice (GPSP) in Japan.

10.8 Appendix 8: Calculation of Creatinine Clearance and eGFR

10.8.1 Cockcroft-Gault Equations

- If male:

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

- If female:

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

10.8.2 MDRD Equations

eGFR Estimated by MDRD-NKDEP:

eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine [mg/dL])$^{-1.154}$ × (Age [years])$^{-0.203}$ × 0.742 (if female) × 1.212 (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 15.

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 15 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
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
APaT	All-Participants-as-Treated
APaT-E	All-Participants-as-Treated-Extension
ART	antiretroviral therapy
AST	aspartate aminotransferase
BIC	bictegravir
BP	blood pressure
BLOQ	below the limit of quantification
CD4	cluster of differentiation 4
CI	confidence interval
CL	clearance
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
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
DNA	deoxyribonucleic acid

Abbreviation	Expanded Term
DOR	doravirine
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EEA	European Economic Area
EFV	efavirenz
EMA	European Medicines Agency
EoT	end of treatment
FAS	Full Analysis Set
FAS-E	Full Analysis Set-Extension
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed dose combination
FSH	follicle-stimulating hormone
FTC	emtricitabine
GCP	Good Clinical Practice
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
HRT	hormone replacement therapy
HTE	heavily treatment-experienced
IA(s)	interim analysis(ses)
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
Ig	immunoglobulin
IMP	investigational medicinal product
InSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LDL-C	low-density lipoprotein cholesterol
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	modification of diet in renal disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
NIMP	noninvestigational medicinal product
NNRTI	nonnucleoside reverse transcriptase inhibitor
non-HDL-C	non-high-density lipoprotein cholesterol
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OME	other important medical event
OF	observed failure
PCR	polymerase chain reaction
PDLC	predefined limit of change
PI	protease inhibitor

Abbreviation	Expanded Term
PK	pharmacokinetic
PLWH	people living with HIV
po	orally
POCBP	participant of childbearing potential
PONCBP	participant of nonchildbearing potential
PP	per-protocol
PrEP	pre-exposure prophylaxis
PT	preferred term
QD	once daily
QM	once a month
QW	once a week
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SLAB	supplemental laboratory test(s)
SMQ	standardized MedDRA query
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TBNK	T and B-lymphocyte and natural killer cell
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglyceride
TN	Treatment naive
TP	triphosphate

Abbreviation	Expanded Term
ULN	upper limit of normal
US	United States
VS	virologically suppressed
WHO	World Health Organization

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