Official Protocol Title:	A Phase 3, Randomized, Clinical Study in HIV-1-Infected Heavily Treatment-Experienced Participants Evaluating the Antiretroviral Activity of Blinded Islatravir (ISL), Doravirine (DOR), and Doravirine/Islatravir (DOR/ISL), Each Compared to Placebo, and the Antiretroviral Activity, Safety, and Tolerability of Open-Label DOR/ISL
NCT number:	NCT04233216
Document Date:	26-Sep-2022

Title Page

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Protocol Title: A Phase 3, Randomized, Clinical Study in HIV-1-Infected Heavily Treatment-Experienced Participants Evaluating the Antiretroviral Activity of Blinded Islatravir (ISL), Doravirine (DOR), and Doravirine/Islatravir (DOR/ISL), Each Compared to Placebo, and the Antiretroviral Activity, Safety, and Tolerability of Open-Label DOR/ISL

Protocol Number: 019-09

Compound Number: MK-8591A

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	134,036
EudraCT	2019-000588-26

Approval Date: 26 September 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 09	26-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 08	20-JAN-2022	Given the findings of decreases in CD4+ T-cell and total lymphocyte counts in clinical studies evaluating ISL, the protocol is being amended to increase the frequency of monitoring of CD4+ T-cell and total lymphocyte counts and to specify the management of participants who meet protocol-defined decreases in CD4+ T-cell and/or total lymphocyte counts.
Amendment 07	07-DEC-2021	To increase frequency of monitoring of CD4+ T-cell counts and lymphocyte counts and add criteria for management of participants in response to findings of decreases in CD4+ T-cell counts (in studies of participants with HIV) and lymphocytes (in studies of participants with or without HIV) in ISL clinical studies. **Note: The changes made in Amendment 07 were not implemented at clinical sites. Amendment 08 supersedes Amendment 07.**
Amendment 06	08-JUN-2021	Modified inclusion criteria to clearly characterize the HTE study population as individuals with no more than 2 fully active antiretroviral drugs across all approved antiretroviral classes.
Amendment 05	17-MAY-2021	Modified inclusion criteria for triple-class resistance and number of active ART at study entry. Increased safety monitoring for participants who become pregnant and continue study intervention. Increased safety data collection for infants born to participants who become pregnant.

Document	Date of Issue	Overall Rationale
Amendment 04	16-MAR-2021	A country-specific amendment for Russia. As required by the Russian Ministry of Health, if a participant becomes pregnant (has a positive serum pregnancy test), study intervention must be discontinued.
Amendment 03	29-OCT-2020	Extend Part 2 of the study from 48 weeks to 96 weeks of open-label intervention with DOR/ISL + OBT, permit continued administration of study intervention in participants who become pregnant, add a discontinuation criterion if a participant chooses to breastfeed, and add a Per-Protocol analysis to the SAP.
Amendment 02	12-MAY-2020	Allow participants to rescreen following consultation with the Sponsor. The lower age limit of ≥12 years was removed.
Amendment 01	10-MAR-2020	Assessment of fasting lipid and glucose profiles were added to the protocol to comply with the DHHS "Guidelines For the Use of Antiretroviral Agents in Adult and Adolescents with HIV."
Original Protocol	18-NOV-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Clinical Study in HIV-1-Infected Heavily Treatment-Experienced Participants Evaluating the Antiretroviral Activity of Blinded Islatravir (ISL), Doravirine (DOR), and Doravirine/Islatravir (DOR/ISL), Each Compared to Placebo, and the Antiretroviral Activity, Safety, and Tolerability of Open-Label DOR/ISL

Short Title: DOR/ISL in heavily treatment-experienced participants

Acronym: Not applicable

MK-8591A (hereafter referred to as DOR/ISL) is a novel 2-drug FDC of DOR and ISL.

Hypotheses, Objectives, and Endpoints:

The following objectives will be evaluated in HTE adult participants and in pediatric participants weighing ≥35 kg with pre-study HIV-1 RNA ≥500 copies/mL and currently on failing ART.

Primary Objectives	Primary Endpoints
• To evaluate the antiretroviral activity of DOR/ISL compared to placebo, each given in combination with failing ART as assessed by the percentage of participants achieving ≥0.5 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 (Part 1). Hypothesis: The percentage of participants receiving DOR/ISL and achieving ≥0.5 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 is superior to placebo, each given in combination with failing ART.	• HIV-1 RNA
• To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 25 and Week 49.	• AEs • AEs leading to discontinuation of study intervention

Primary Objectives	Primary Endpoints
Secondary Objectives	Secondary Endpoints
• To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 97.	• AEs • AEs leading to discontinuation of study intervention
• To evaluate the antiretroviral activity of ISL and DOR, each compared to placebo, when each is given in combination with failing ART, as assessed by the percentage of participants achieving ≥0.5 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 (Part 1).	• HIV-1 RNA
• To further evaluate the antiretroviral activity of DOR/ISL, ISL, and DOR each compared to placebo, when each is given in combination with failing ART (Part 1) as assessed by: - mean change in HIV-1 RNA from study baseline (Day 1) to Day 8 - percentage of participants achieving ≥1.0 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8	• HIV-1 RNA
• To further evaluate the antiretroviral activity of DOR/ISL compared to ISL and DOR, when each is given in combination with failing ART (Part 1) as assessed by: - percentage of participants achieving ≥0.5 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 - mean change in HIV-1 RNA from study baseline (Day 1) to Day 8 - percentage of participants achieving ≥1.0 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8	• HIV-1 RNA

Primary Objectives	Primary Endpoints
• To evaluate the antiretroviral activity of DOR/ISL + OBT in Part 2 as assessed by the following at Week 25, Week 49, and Week 97 compared to study baseline (Day 1) and Part 2 baseline (Day 8): - percentage of participants achieving ≥0.5 log10 decrease in HIV-1 RNA - percentage of participants achieving ≥1.0 log10 decrease in HIV-1 RNA - mean change in HIV-1 RNA - percentage of participants achieving HIV-1 RNA <200 copies/mL - percentage of participants achieving HIV-1 RNA <50 copies/mL - percentage of participants achieving HIV-1 RNA <40 copies/mL	• HIV-1 RNA
• To evaluate the development of viral drug resistance to DOR, ISL, or components of OBT through the study duration (Part 1 and Part 2).	• Viral resistance-associated substitutions
• To evaluate the impact of study baseline (Day 1) antiviral resistance on virologic outcome at Week 25, Week 49, and Week 97 (Part 2).	• Viral resistance-associated substitutions • HIV-1 RNA
• To evaluate the change in CD4+ T-cell counts from both study baseline (Day 1) and Part 2 baseline (Day 8) at Week 25, Week 49, and Week 97 (Part 2).	• CD4+ T-cell count

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	HIV-1 infection
Population	HTE adult participants and pediatric participants weighing ≥35 kg currently on failing ART with pre-study HIV-1 RNA ≥500 copies/mL
Study Type	Interventional

Intervention Model	Parallel followed by single-group This is a multi-site study.
Type of Control	Placebo control (Part 1 only)
Study Blinding	Double-blind double-dummy (Part 1) followed by unblinded open-label (Part 2)
Masking	Sponsor (Part 1 only) Investigator (Part 1 only) Participant (Part 1 only)
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact.

Number of Participants:

Approximately 100 participants will be randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Treatment Period	Use
Double-Blind Period (Part 1)						
Group 1	ISL + ART	0.75 mg	QD	Oral	Day 1 to Day 7	Experimental
Group 2	DOR + ART	100 mg	QD	Oral	Day 1 to Day 7	Experimental
Group 3	DOR/ISL + ART	100 mg DOR/0.75 mg ISL	QD	Oral	Day 1 to Day 7	Experimental
Group 4	Placebo + ART	0 mg	QD	Oral	Day 1 to Day 7	Placebo comparison
Open-Label Period (Part 2)						
Open-Label	DOR/ISL + OBT	100 mg DOR/0.75 mg ISL	QD	Oral	Day 8 through Week 97[a]	Experimental

Abbreviations: ART=antiretroviral therapy; DOR=doravirine; ISL=islatravir; OBT=optimized background therapy; QD=once daily.
The Sponsor will not provide ART during Part 1 or OBT during Part 2. Participants will provide their own medications.
[a] For participants who are pregnant at the last regularly scheduled study visit (Week 97), study intervention will be dispensed at Week 97. In addition, their visit schedule will be extended through the duration of the pregnancy and study intervention will be dispensed at Weeks 109, 121, and 133, as applicable.

Total Number

5

Duration of Participation

Each participant will participate in the study for approximately 112 weeks from the time the participant provides documented informed consent/assent through the final contact. After a screening period of up to 60 days and a Run-in Period prior to randomization, each participant will receive assigned double-blind intervention for 7 days in Part 1 and open-label intervention for approximately 96 weeks in Part 2. Participants who discontinue study intervention or who become pregnant will be followed as described in the protocol.

Study Governance Committees:

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

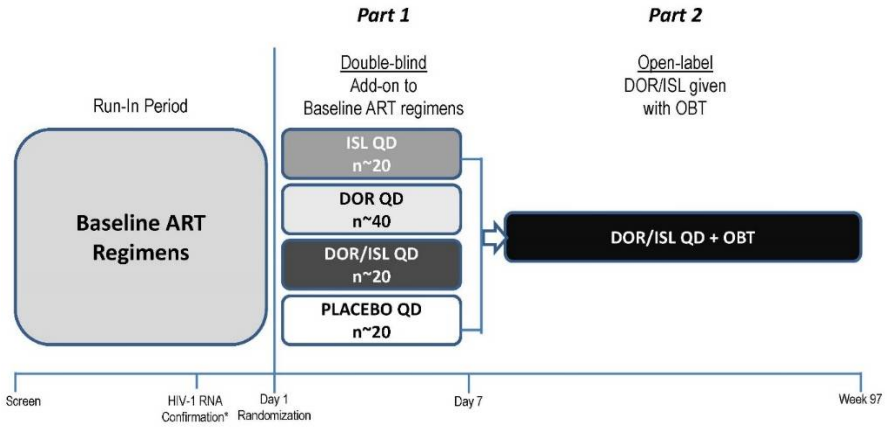
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema and Treatment Plan

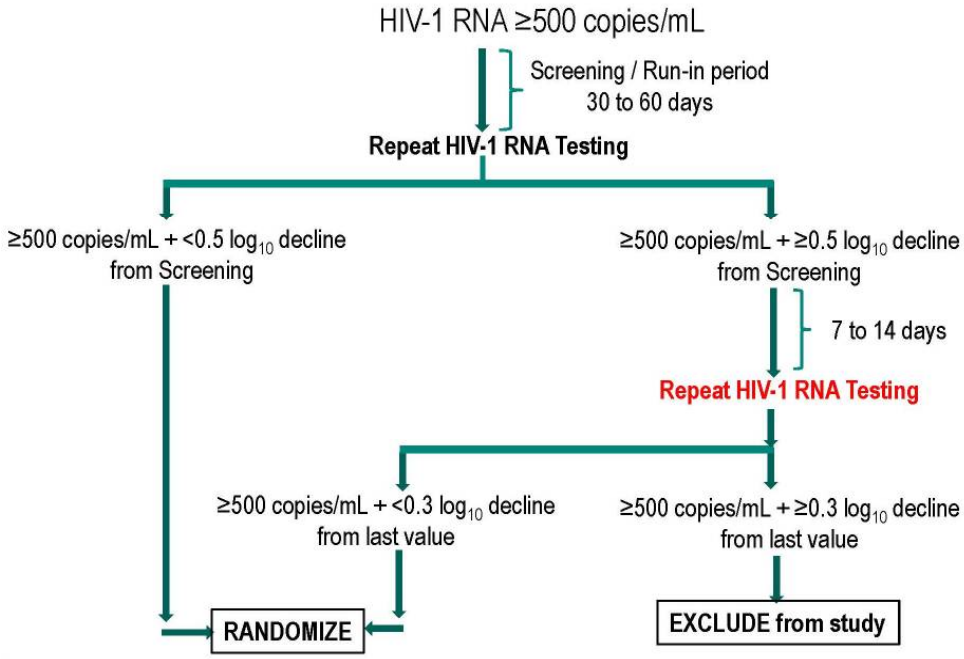


ART=antiretroviral therapy; DOR=doravirine; HIV-1=Human Immunodeficiency Virus Type 1; ISL=islatravir; n=number of participants per group; OBT=optimized background therapy; QD=once daily; RNA=ribonucleic acid.

*HIV-1 RNA testing will be repeated during the Run-in Period to confirm eligibility for randomization (defined as HIV-1 RNA ≥500 copies/mL). Participants with ≥500 copies/mL on confirmation testing but with ≥0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1) will have an additional HIV-1 RNA confirmation test within 7 to 14 days. Participants with a further decline in HIV-1 RNA ≥0.3 $\log_{10}$ compared to the previous confirmation test will be excluded from the study.

Note: Participants are treated with open-label DOR/ISL + OBT for 96 weeks in Part 2.

Figure 2 HIV-1 RNA Study Entry Eligibility Schema



HIV-1=Human Immunodeficiency Virus Type 1; RNA=ribonucleic acid.

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities

Study Period	**Screening/Run-In Period**			**Intervention**												**Notes**
	Screening	**HIV-1 Confirmation Visit[c]**	**Repeat HIV-1 Confirmation Visit[d]**	**Double-blind (Part 1)**	**Open-label (Part 2)**											Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 log_{10} decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Administrative Procedures																	
Informed Consent/Assent	X																
Informed Consent/Assent for Future Biomedical Research	X																
Informed Consent/Assent for Study Intervention During Pregnancy					<----------X---------->												Obtain upon confirmation of pregnancy if participant wants to continue receiving study intervention.

Study Period	Screening/Run-In Period			Intervention												Notes
	Screening	**HIV-1 Confirmation Visit[c]**	**Repeat HIV-1 Confirmation Visit[d]**	**Double-blind (Part 1)**	**Open-label (Part 2)**											Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Collect and enter data from prenatal provider					<----------X---------->												For female participants who become pregnant and consent to continue DOR/ISL, obtain relevant prenatal clinical & laboratory data to monitor the safety of the mother & fetus per Section 8.11.7.
Inclusion/Exclusion Criteria	X	X	X	X													Review prior to randomization on Day 1 to confirm no changes in eligibility.
Participant Identification Card	X			X													At the time of randomization, site personnel will add the randomization number to the participant identification card.
Medical History	X																
Prior/ Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Register study visit in IRT	X			X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Screening/Run-In Period			Intervention												Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)											Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 log_{10} decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Intervention Randomization				X													All procedures should be completed prior to dose on Day 1. Randomization should occur within 10 days of confirmation of HIV-1 RNA eligibility.
Dispense study intervention using IRT				X	X	X	X	X	X	X	X	X	X	X	X		Dispense DOR/ISL at Week 97 to any pregnant participant whose pregnancy or postpartum visit(s) extend beyond Week 97. See Section 1.3.3.
Evaluation to receive continued study intervention																X	See Section 6.7
Study intervention compliance review					X	X	X	X	X	X	X	X	X	X	X	X	Reconcile doses and assess study intervention compliance.

Study Period	Screening/Run-In Period			Intervention													Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)												Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
ART/OBT compliance review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Completion of participant questionnaire (FAHI)				X						X		X				X	Administered to participants ≥18 years of age at the time of consent and prior to being seen by investigator and discussions about medical conditions or test results.
Efficacy/Immunogenicity Procedures																	
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CD4+ T-cell count/TBNK Panel	X			X	X			X		X	X	X	X	X	X	X	Decreases in CD4+ T-cell count that meet ECI criteria should be managed per Section 8.11.6 and Section 1.3.4.

Study Period	Screening/Run-In Period			Intervention												Notes
	Screening	**HIV-1 Confirmation Visit[c]**	**Repeat HIV-1 Confirmation Visit[d]**	**Double-blind (Part 1)**	**Open-label (Part 2)**											Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Blood (plasma) for HIV-1 drug resistance	X			X	X	X	X	X	X	X	X	X	X	X	X	X	Testing performed via central laboratory at Screening, Day 1, Day 8, and thereafter on samples with HIV-1 RNA ≥200 copies/mL for participants who never suppressed at Week 25, Week 49, and Week 97 and those that were collected either to confirm viremia after suppression (VL<50 copies/mL) or at discontinuation.

Study Period	Screening/Run-In Period			Intervention													Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)												Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 log_{10} decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Whole Blood for Proviral DNA Resistance Testing	X									X		X				X	Testing to be performed via central laboratory at a) Screening Visit for all participants and b) on postrandomization samples with HIV-1 RNA ≥200 copies/mL at Week 25, Week 49, and Week 97 and samples collected either to confirm viremia after suppression (VL <50 copies/mL) or at discontinuation.
Safety Procedures																	
Full physical examination				X													
Height				X						X		X					
Weight	X			X						X		X	X	X	X	X	
Directed physical examination	X				X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X			X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse, bp, temp, and rr.
12-lead ECG				X													May be read locally.

Study Period	Screening/Run-In Period			Intervention													Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)												Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Confirmation of menarche status (females only)	X			X	X	X	X	X	X	X	X	X	X	X	X	X	Not required once menarche has been confirmed.
Contraception Use Confirmation (WOCBP only)				X	X	X	X	X	X	X	X	X	X	X	X	X	To be done per local guidelines.
Serum Pregnancy Test (β-hCG; WOCBP only)	X																
Urine Pregnancy Test (WOCBP only)				X	X	X	X	X	X	X	X	X	X	X	X	X	Confirm with serum test if urine test is positive. If confirmatory serum test is positive, participants will be managed per Section 8.11.7 and safety of her infant collected per Section 8.11.7.4.1.

Study Period	Screening/Run-In Period			Intervention													Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)												Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 log_{10} decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Hepatitis Serology (HBsAg, HBsAb, Anti-HBc, HCV Ab)	X											X					Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV.
HBV DNA	X											X					
HCV RNA	X											X					
HIV-1 & -2 Serology	X																
Hematology	X			X	X			X		X	X	X	X	X	X	X	Decreases in total lymphocyte counts that meet ECI criteria should be managed per Section 8.11.6 and Section 1.3.4.
PT/INR	X																
Urinalysis	X			X	X			X		X	X	X	X	X	X	X	
Fasting Lipid/Glucose				X	X							X		X		X	If abnormal profile at Day 8, repeat the abnormal test at TW 25
Chemistry	X			X	X			X		X	X	X	X	X	X	X	
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Screening/Run-In Period			Intervention												Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)											Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Pharmacokinetics																	
Blood (plasma) for DOR and ISL PK				X	X	X		X		X	X	X					At Weeks 25 and 49, a predose and postdose sample will be taken.
Blood (plasma) for Investigational PK							X		X								Analysis triggered by Sponsor as needed.
Blood (Plasma) for DOR and ISL PK in Pregnant Participants					<----------X---------->												Collected during the 1st, 2nd, & 3rd trimesters & postpartum per Section 8.11.7.1.
Biomarkers																	
Blood for Genetic Analysis[b]				X													
Whole Blood for Future Biomedical Research				X						X		X				X	Optional participation; requires FBR consent.

Study Period	Screening/Run-In Period			Intervention													Notes
	Screening	HIV-1 Confirmation Visit[c]	Repeat HIV-1 Confirmation Visit[d]	Double-blind (Part 1)	Open-label (Part 2)												Visit 3 is an additional HIV-1 RNA confirmation test for participants with ≥500 copies/mL on confirmation testing but with ≥0.5 log_{10} decline in HIV-1 RNA from the Screening Visit (Visit 1)
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Each visit should be calculated from date of Randomization (Day 1). A visiting nurse may be used for visits after randomization per Section 8.11.3.4.
Scheduled Day/Week	Screen	NA	NA	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	TW13	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	
Visit Window	≤60 days[a]	≤10 days prior to Day 1	7-14 days after Visit 2	NA	+3 days	±7 days											Adherence to the visit window is critical for study intervention resupply. Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).
Blood for Inflammatory Markers				X						X		X				X	

Anti-HBc=hepatitis B core antibody; ART=antiretroviral therapy; β-hcg-beta human chorionic gonadotropin; bp=blood pressure; D/C=discontinuation; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; ECI=Events of Clinical Interest; FAHI=Functional Assessment of HIV Infection; FBR=Future Biomedical Research; F/U=follow-up; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus Type 1; INR=international normalized ratio; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; OBT=optimized background therapy; PCR=polymerase chain reaction; PK=pharmacokinetic; PT=prothrombin time; RNA=ribonucleic acid; rr=respiratory rate; temp=body temperature; TBNK=T- and B-lymphocyte and natural killer cell profile; TW=treatment week; VL=viral load; WOCBP=women of childbearing potential.

[a] Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 60 days is allowed.

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

[c] Following confirmation of eligibility at Screening, a repeat HIV-1 RNA test will be performed to confirm HIV-1 RNA eligibility for randomization (HIV-1 RNA ≥500 copies/mL with a <0.5 log_{10} decline from the Screening Visit [Visit 1]). If there is ≥0.5 log_{10} decline from the Screening Visit, a repeat confirmation test is required (see footnote d below).

[d] The Repeat HIV-1 Confirmation Visit is only for those participants with HIV-1 RNA ≥500 copies/mL at Visit 2 AND with a ≥0.5 log_{10} decline in HIV-1 RNA from the Screening Visit; these participants will be required to return to the site for a Repeat HIV-1 RNA Confirmation Visit (Visit 3). At Visit 3, in order to be eligible for randomization, participants must have HIV-1 RNA ≥500 copies/mL and a <0.3 log_{10} decline in HIV-1 RNA from the previous result at Visit 2.

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

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		The End of Treatment Follow-up visit should also be performed for participants who will not continue study intervention after Week 97.
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	
Visit Window	Within ~1 month of HIV-1 Initial Viremia	NA	42 (+7) days after the end of treatment	
Administrative Procedures				
Prior and Concomitant Medications Review	X	X	X	
Register Study Visit in IRT	X	X		
Study Intervention Compliance Review	X	X		Reconcile doses and assess study intervention compliance.
ART/OBT compliance review	X	X		
Completion of Participant Questionnaire (FAHI)		X		Administered to participants ≥18 years of age at the time of consent and prior to being seen by investigator and discussions about medical conditions or test results.
Efficacy Procedures				
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	
CD4+ T-cell Count/ TBNK Panel		X		Participants with decreases in CD4+ T-cell count >10% from average baseline value[a] or who meet relevant ECI criteria at the Early Discontinuation of Treatment visit should be managed per Section 8.11.6 and Section 1.3.4.

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		The End of Treatment Follow-up visit should also be performed for participants who will not continue study intervention after Week 97.
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	
Visit Window	Within ~1 month of HIV-1 Initial Viremia	NA	42 (+7) days after the end of treatment	
Blood (plasma) for HIV-1 Drug Resistance Testing	X	X	X	Testing performed on samples with HIV-1 RNA ≥200 copies/mL that were collected either to confirm viremia after suppression (VL <50 copies/mL) or at discontinuation.
Whole Blood for Proviral DNA Resistance Testing	X	X	X	Testing performed on samples with HIV-1 RNA ≥200 copies/mL that were collected either to confirm viremia after suppression (VL <50 copies/mL) or at discontinuation.
Blood (Plasma) for Investigational PK	X	X	X	Analysis triggered by Sponsor as needed.
Safety Procedures				
Directed Physical Examination		X	X	
Vital Signs		X	X	Includes weight, pulse, bp, temp, and rr.
Confirmation of Menarche Status (Females Only)	X	X	X	Not required once menarche has been confirmed.
Contraception Use Confirmation (WOCBP Only)	X	X	X	To be done per local guidelines.
Urine Pregnancy Test (WOCBP Only)		X	X	Confirm with serum test if positive. If serum test is positive, participants will be managed per Section 8.11.7 and safety of her infant collected per Section 8.11.7.4.1.
Chemistry		X	X	

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		The End of Treatment Follow-up visit should also be performed for participants who will not continue study intervention after Week 97.
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	
Visit Window	Within ~1 month of HIV-1 Initial Viremia	NA	42 (+7) days after the end of treatment	
Hematology		X		Participants with decreases in total lymphocyte counts >10% from average baseline value[a] or who meet relevant ECI criteria at the Early Discontinuation of Treatment visit should be managed per Section 8.11.6 and Section 1.3.4.
Urinalysis		X	X	
Review of Adverse Events	X	X	X	
Biomarkers				
Whole Blood for Future Biomedical Research	X	X		If FBR sample was collected at viremia confirmation, it is not necessary to collect another sample at Early Discontinuation visit.

ART=antiretroviral therapy; β-hcg=beta human chorionic gonadotropin; bp=blood pressure; DOR=doravirine; ECI=Events of Clinical Interest; FAHI=Functional Assessment of HIV Infection; FBR=Future Biomedical Research; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus Type 1; IRT=Interactive Response Technology; NA=not applicable; OBT=optimized background therapy; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; rr=respiratory rate; TBNK=T- and B-lymphocyte and natural killer cell profile; temp=body temperature; VL=viral load; WOCBP=a woman/women of childbearing potential.

[a.] The average baseline value is defined as the average value between screening (within 60 days prior to the first dose of study intervention) and Day 1.

1.3.3 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 97

Visit Number	**17**	**18**	**19**	**20**	**Notes**
Scheduled Week	**109**	**121**	**133**	**145**	For any participant who is pregnant at the last regularly scheduled study visit (TW97) and consents to continue DOR/ISL, the visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum. Extension visits will only be performed through pregnancy & a single postpartum timepoint, as applicable for each participant.
Visit Window	± 7 days				
Administrative Procedures					
Collect and enter data from prenatal care provider	<----------X---------->				For female participants who become pregnant and consent to continue DOR/ISL, obtain relevant prenatal clinical & laboratory data to monitor the safety of the mother & fetus per Section 8.11.7
Register Study Visit in IRT	X	X	X	X	
Dispense DOR/ISL Using IRT	X	X	X		
Study intervention compliance review	X	X	X	X	Reconcile doses and assess study intervention compliance.
OBT compliance review	X	X	X	X	
Prior and Concomitant Medications Review	X	X	X	X	
Evaluation to receive continued study intervention	X	X	X	X	At the end of pregnancy, continued access to DOR/ISL will be offered per Section 6.7.
Efficacy Procedures					
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	
CD4+ T-cell Count/TBNK Panel	X	X	X	X	Decreases in CD4+ T cell count that meet ECI criteria should be managed per Section 8.11.6 and Section 1.3.4
Blood (plasma) for HIV-1 drug resistance	X	X	X	X	Testing performed via central laboratory at Screening and thereafter on samples for participants who never suppressed (HIV-1 RNA ≥200 copies/mL) and those that were collected either to confirm viremia after suppression (VL <50 copies/mL) or at discontinuation.
Whole Blood for Proviral DNA Resistance Testing	X	X	X	X	Testing performed via central laboratory on samples for participants who never suppressed (HIV-1 RNA ≥200 copies/mL) and those that were collected either to confirm viremia after suppression (VL <50 copies/mL) or at discontinuation.
Safety Procedures					
Weight	X	X	X	X	
Directed Physical Examination	X	X	X	X	

Visit Number	**17**	**18**	**19**	**20**	**Notes**
Scheduled Week	**109**	**121**	**133**	**145**	For any participant who is pregnant at the last regularly scheduled study visit (TW97) and consents to continue DOR/ISL, the visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum. Extension visits will only be performed through pregnancy & a single postpartum timepoint, as applicable for each participant.
Visit Window	± 7 days				
Vital Signs	X	X	X	X	
Chemistry	X	X	X	X	
Hematology	X	X	X	X	Decreases in total lymphocyte counts that meet ECI criteria should be managed per Section 8.11.6 and Section 1.3.4
Urinalysis	X	X	X	X	
Review of Adverse Events	X	X	X	X	
Pharmacokinetics					
Blood (Plasma) for DOR and ISL PK	X	X	X	X	Collected during the 1st, 2nd, & 3rd trimesters & postpartum per Section 8.11.7.1.
Biomarkers					
Whole Blood for Future Biomedical Research	X	X	X	X	Optional participation; requires FBR consent.
DNA=deoxyribonucleic acid; DOR=doravirine; ECI=Events of Clinical Interest; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; ISL=islatravir; OBT=optimized background therapy; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; TBNK=T- and B-lymphocyte and natural killer cell profile; VL=viral load.					

1.3.4 Schedule of Activities – Participants With Specified Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.6 for details regarding discontinuation and monitoring.**
Visit Window	Within 3-4 weeks of initial decrease	NA	42 (+ 7) days after discontinuing study intervention	Every 4 weeks (± 7 days)	
Administrative Procedures					
Prior and Concomitant Medications Review	X	X	X	X	
Register Study Visit in IRT	X	X		X	
Study Intervention Compliance Review		X			Reconcile doses and assess study intervention compliance.
ART/OBT Compliance Review		X			
Completion of Participant Questionnaire (FAHI)		X			Administered to participants ≥18 years of age prior to being seen by investigator and discussions about medical conditions or test results.
Efficacy Procedures					
Plasma HIV-1 RNA Quantification (Real Time PCR)		X	X		
CD4+ T-cell Count/TBNK Panel	X	X	X	X	

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.6 for details regarding discontinuation and monitoring.**
Visit Window	Within 3-4 weeks of initial decrease	NA	42 (+ 7) days after discontinuing study intervention	Every 4 weeks (± 7 days)	
Blood (plasma) for HIV-1 Drug Resistance Testing		X	X		Analysis of samples collected at End of Treatment visits triggered by Sponsor as needed.
Whole Blood for Proviral DNA Resistance Testing		X	X		Testing performed on samples with HIV-1 RNA ≥200 copies/mL that were collected either to confirm viremia after suppression (VL <50 copies/mL) or at discontinuation.
Safety Procedures					
Directed Physical Examination		X	X		
Vital Signs		X	X		Includes weight, pulse, bp, temp, and rr.
Confirmation of Menarche Status (Females Only)		X	X		Not required once menarche has been confirmed.
Contraceptive Use Confirmation (WOCBP Only)		X	X		To be performed per local guidelines.

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.6 for details regarding discontinuation and monitoring.**
Visit Window	Within 3-4 weeks of initial decrease	NA	42 (+ 7) days after discontinuing study intervention	Every 4 weeks (± 7 days)	
Urine Pregnancy Test (WOCBP Only)		X	X		Confirm with serum test if positive. If serum test is positive, participants will be managed per Section 8.11.7 and safety of her infant collected per Section 8.11.7.4.1.
Chemistry		X	X		
Hematology	X	X	X	X	
Urinalysis		X	X		
Review of Adverse Events	X	X	X	X	
Pharmacokinetics					
Blood (Plasma) for Investigational PK		X	X		Analysis triggered by Sponsor as needed.
Biomarkers					
Whole Blood for Future Biomedical Research		X			

ART=antiretroviral therapy; bp=blood pressure; FAHI=Functional Assessment of HIV Infection; FBR=Future Biomedical Research; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; NA=not applicable; OBT=optimized background therapy; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; rr=respiratory rate; TBNK=T- and B-lymphocyte and natural killer cell profile; temp=body temperature; WOCBP=a woman/women of childbearing potential.

2 INTRODUCTION

DOR/ISL (also known as MK-8591A or MK-8591/DOR) is a novel 2-drug FDC of DOR (a recently approved NNRTI) and ISL (a first-in-class investigational NRTTI). DOR/ISL is being developed for QD treatment of HIV-1 infection in adults and pediatric participants ≥35 kg.

2.1 Study Rationale

Heavily treatment-experienced (HTE) individuals are a small but important population of patients with HIV-1. These individuals have exhausted all or nearly all antiretroviral options for constructing a viable HIV treatment regimen primarily because of extensive multidrug resistance but also because of drug intolerance, lack of access to key drugs, or unacceptability to the participant (eg, parenteral agents). There is consequently an unmet medical need in this population for better treatment options. Preliminary data suggest ISL may be useful in this population and the purpose of the P019 study is to evaluate the safety and efficacy of DOR/ISL in the HTE population.

The HTE population in this clinical study is defined by the following characteristics: 1) HIV heavily treatment-experienced, 2) failing their current antiretroviral regimen, 3) drug resistance to antiretrovirals belonging to at least 3 antiretroviral classes, 4) inability to construct a fully suppressive regimen with available ARTs, and 5) having no more than 2 fully active antiretroviral agents remaining to construct a viable regimen.

DOR/ISL has the potential to be an agent for the treatment of HIV-1 infection in the HTE population 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.

2.2 Background

Refer to the IBs/approved labeling for detailed background information on DOR and ISL.

2.2.1 Islatravir

ISL is the first member of a new class of antiretroviral agents, known as NRTTIs, that block HIV-1 reverse transcriptase by novel mechanisms of action. It is an inactive nucleoside 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 intracellular half-life, and favorable drug resistance profile. ISL (at the proposed dose of 0.75 mg QD) achieves higher steady-state IQs (the ratio of drug exposure to viral susceptibility [Ctrough/IC50]) against wild-type HIV-1 than any NRTI currently approved for treatment. It

also exhibits potent in vitro 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. DOR is differentiated from other NNRTIs by its distinct resistance profile, low likelihood of selection for viral resistance in vivo, and low potential for DDIs. DOR exhibits potent activity against both wild-type HIV-1 virus and frequently transmitted NNRTI-resistant variants including K103N, Y181C, G190A, and E138K.

2.2.3 Doravirine/Islatravir

DOR/ISL is an FDC containing DOR (100 mg) and ISL (0.75 mg), administered as a single tablet QD. DOR and ISL represent 2 distinct classes of antiretrovirals that inhibit reverse transcription by different mechanisms. Based on the profiles of each of these drugs 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 in vitro and has suppressed emergence of resistance at clinically relevant concentrations.

The combination of DOR and ISL (administered as single entities, DOR+ISL) is being evaluated in an ongoing randomized Phase 2 study (MK-8591 Protocol 011) in approximately 90 treatment-naïve adult participants with HIV-1. Participants were initially assigned to receive either DOR+ISL and 3TC or an FDC of DOR, 3TC, and TDF (DOR/3TC/TDF). Participants receiving DOR+ISL+3TC who achieved HIV-1 RNA <50 copies/mL at Week 20 (or later) discontinued 3TC at their next study visit (most were able to discontinue 3TC at Week 24) while continuing DOR+ISL. At Weeks 48 and 96, the percentage of participants with HIV-1 RNA <50 copies/mL among those who received the 2-drug regimen of DOR+ISL was comparable to those who received the 3-drug regimen of DOR/3TC/TDF. The majority of participants maintained virologic suppression through Week 144. None of the participants with protocol-defined virologic failure rebounded above the clinically relevant HIV-1 RNA >200 copies/mL cutoff. As such, no participant met the criteria for resistance testing. DOR+ISL, administered with 3TC or alone as a 2-drug regimen, had a favorable safety and tolerability profile through Week 96, comparable to that of DOR/3TC/TDF. Mean changes from baseline in CD4+ T-cell count were comparable for DOR/3TC/TDF and each dose of ISL as a 3-drug regimen (at Week 24) or a 2-drug regimen (at Weeks 48, 96, 144).

In addition to this study, the clinical development program of DOR/ISL includes ongoing studies in treatment-naïve adults (Protocol 020), virologically suppressed adults (Protocol 017 and Protocol 018), and participants <18 years of age and weighing ≥35 kg (Protocol 028).

2.2.4 Information on Other Study-related Therapy

ART continued at baseline and OBT will be administered at the approved marketed dose. Refer to local labeling for detailed information on baseline ART and OBT.

2.3 Benefit/Risk Assessment

Although 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 in Phase 3 clinical studies.

The comprehensive nonclinical safety evaluations of DOR (an approved NNRTI) and ISL (an investigational NRTTI) as mono-entities have not revealed toxicities of concern for daily dosing. 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 mono-entities are differentiated by a high barrier to resistance in vitro with DOR exhibiting potent activity against the most prevalent NNRTI-resistant mutations (eg, K103N, Y181C, G190A, and E138K) and ISL against common NRTI-resistant mutations (eg, M184V and TAMs). Both may be administered without regard to food, have a low potential for DDIs, and have favorable PK and tolerability profiles.

High potency against wild-type and resistant variants of HIV-1 virus and a long half-life make ISL a suitable candidate for development for the treatment of HIV-1 infection. Across the clinical development program, ISL administered alone or with DOR was generally well-tolerated. In the dose-ranging study (MK-8591 Protocol 011), ISL+DOR+3TC (as a 3-drug regimen) achieved virological suppression in most (>90%) of treatment-naïve participants by Week 24. ISL+DOR (as a 2-drug regimen) maintained virologic suppression of HIV-1 RNA 24 and 48 weeks after switching from the 3-drug regimen and through Week 144. In 2 ongoing Phase 3 studies evaluating DOR/ISL for daily treatment of HIV-1 in virologically suppressed participants (MK-8591A Protocol 017 and MK-8591A Protocol 018), approximately 95% of 658 participants enrolled in the DOR/ISL arm completed the 48 weeks of treatment in both studies. In Protocol 017 and Protocol 018, the percentage of participants with HIV-1 RNA ≥50 copies/mL was <1% for the DOR/ISL group, and a high percentage of participants (>93% to 95%) in the DOR/ISL group maintained virologic suppression (HIV-1 RNA <50 copies/mL) comparable to baseline ART (Protocol 017) and BIC/FTC/TAF (Protocol 018), respectively, at Week 48. To date, no viral resistance to either component of DOR/ISL has been shown in the Phase 2 (Protocol 011) and Phase 3 studies (Protocol 017 and Protocol 018). At the doses administered for daily treatment, DOR/ISL has been well-tolerated and associated with low rates of drug-related AEs.

Downward trends of total lymphocytes counts and CD4+ T-cell counts were observed in studies with ISL alone or in combination with other antiviral agents. In a Phase 2 study (MK-8591 Protocol 013) for once weekly HIV-1 treatment, decreases in total lymphocyte and CD4+ T-cell counts from baseline were observed in the ISL 20 mg + MK-8507 treatment

arms at Week 12 and Week 24. Decreases from baseline in total lymphocyte counts were observed in all dosing arms of ISL+MK-8507 starting at Week 8 with further decreases continuing through Week 24. Twenty of 58 participants on ISL+MK-8507 had a decrease in total lymphocyte counts of >30% (of whom 9 had a >50% reduction) by Week 24. These reductions were more pronounced in the 2 higher MK-8507 dose arms (200 and 400 mg), potentially indicating a dose-response relationship. Dosing of ISL+MK-8507 in Protocol 013 has been discontinued.

In the Phase 2 randomized, double-blind, placebo-controlled study evaluating 60 mg and 120 mg of ISL monthly for PrEP in participants at low-risk of HIV-1 infection (MK-8591 Protocol 016), there was a 21% mean decrease in total lymphocytes observed in the 60 mg arm (the dose being evaluated in Phase 3 PrEP studies) and a 36% decrease in total lymphocytes observed in the 120 mg arm. In this population of HIV-1 uninfected participants, mean decreases were in the normal range and there was no increase in clinical AEs related to infection. Dosing of oral ISL 60 mg QM has been discontinued in PrEP clinical studies.

In an interim analysis for each of the Phase 3 studies studying DOR/ISL 100 mg/0.75 mg for HIV-1 treatment (Protocol 017 and Protocol 018), there were mean decreases from baseline in total lymphocyte counts at Week 48 of 10.6% and 8.5%, respectively, in the DOR/ISL groups compared with mean increases of 2.27% and 3.46% in the comparator arms. In the same studies, DOR/ISL-treated participants had a mean change in CD4+ T-cell counts of -0.7% and +0.9%, compared with an increase of 8.7% in the baseline ART group (Protocol 017) and 12.8% in the BIC/FTC/TAF group (Protocol 018). These decreases in CD4+ T-cell and total lymphocyte counts have not been associated with an increased incidence of infection or other AEs. The clinical impact of these laboratory changes over the long term is unknown, and the Sponsor is assessing the reversibility of the reductions in CD4+ T-cell and total lymphocyte counts. To mitigate the risk, increased monitoring of CD4+ T-cell and total lymphocyte counts and strict stopping rules have been added to DOR/ISL studies. At this time, the data review support continuation of the Phase 3 clinical studies for the DOR/ISL 100 mg/0.75 mg daily HIV-1 treatment program. With regard to this Phase 3 study in the HTE population, review of the available data and benefit/risk assessment support continuing DOR/ISL 100 mg/0.75 mg daily treatment in this important population of patients with multi-drug resistant HIV, who have exhausted all or nearly all antiretroviral options for constructing a viable HIV treatment regimen.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in HTE adult participants and in pediatric participants weighing ≥35 kg with pre-study HIV-1 RNA ≥500 copies/mL and currently on failing ART.

Objectives	Endpoints
Primary	
• To evaluate the antiretroviral activity of DOR/ISL compared to placebo, each given in combination with failing ART as assessed by the percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 (Part 1). **Hypothesis**: The percentage of participants receiving DOR/ISL and achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 is superior to placebo, each given in combination with failing ART.	• HIV-1 RNA
• To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 25 and Week 49.	• AEs • AEs leading to discontinuation of study intervention
Secondary	
• To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 97.	• AEs • AEs leading to discontinuation of study intervention
• To evaluate the antiretroviral activity of ISL and DOR, each compared to placebo, when each is given in combination with failing ART, as assessed by the percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 (Part 1).	• HIV-1 RNA
• To further evaluate the antiretroviral activity of DOR/ISL, ISL, and DOR each compared to placebo, when each is given in combination with failing ART (Part 1) as assessed by: - mean change in HIV-1 RNA from study baseline (Day 1) to Day 8 - percentage of participants achieving ≥1.0 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8	• HIV-1 RNA

Objectives	Endpoints
• To further evaluate the antiretroviral activity of DOR/ISL compared to ISL and DOR, when each is given in combination with failing ART (Part 1) as assessed by: - percentage of participants achieving ≥0.5 log10 decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 - mean change in HIV-1 RNA from study baseline (Day 1) to Day 8 - percentage of participants achieving ≥1.0 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8	• HIV-1 RNA
• To evaluate the antiretroviral activity of DOR/ISL + OBT in Part 2 as assessed by the following at Week 25, Week 49, and Week 97 compared to study baseline (Day 1) and Part 2 baseline (Day 8): - percentage of participants achieving ≥0.5 log10 decrease in HIV-1 RNA - percentage of participants achieving ≥1.0 log10 decrease in HIV-1 RNA - mean change in HIV-1 RNA - percentage of participants achieving HIV-1 RNA <200 copies/mL - percentage of participants achieving HIV-1 RNA <50 copies/mL - percentage of participants achieving HIV-1 RNA <40 copies/mL	• HIV-1 RNA
• To evaluate the development of viral drug resistance to DOR, ISL, or components of OBT through the study duration (Part 1 and Part 2).	• Viral resistance-associated substitutions
• To evaluate the impact of study baseline (Day 1) antiviral resistance on virologic outcome at Week 25, Week 49, and Week 97 (Part 2).	• Viral resistance-associated substitutions • HIV-1 RNA

Objectives	Endpoints
• To evaluate the change in CD4+ T-cell counts from both study baseline (Day 1) and Part 2 baseline (Day 8) at Week 25, Week 49, and Week 97 (Part 2).	• CD4+ T-cell count
Tertiary/Exploratory	
• To evaluate the impact of study baseline (Day 1) resistance on primary efficacy (Day 8) (Part 1): - NRTI resistance on ISL antiviral activity - NNRTI resistance on DOR antiviral activity	• Viral resistance-associated substitutions • HIV-1 RNA
• To evaluate the impact of DOR/ISL + OBT on inflammation as measured by the mean change from study baseline (Day 1) to Week 25, Week 49, and Week 97 (Part 2) in laboratory markers.	• Inflammatory markers
• To describe PROs related to HIV disease-specific QoL assessed at study baseline (Day 1), Week 25, Week 49, and Week 97 (Part 2) for participants ≥18 years of age who received DOR/ISL + OBT.	• FAHI questionnaire: Total score and individual subscale scores
• To evaluate the PK of ISL and DOR, when each is given in combination with failing ART (Part 1).	• PK values, such as AUC, Cmax, and C24
• To evaluate the PK of ISL and DOR, when given in combination with OBT (Part 2).	• PK values, such as AUC, Cmax, and C24
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation

The success of the study is determined by successfully confirming the primary efficacy hypothesis that DOR/ISL is superior to placebo.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, multi-site study in HTE participants infected with HIV-1 currently on failing ART for HIV-1 infection. Following Screening, eligible participants will enter a Run-in Period on current failing baseline ART prior to randomization. Part 1 is a 7-day double-blind period of QD therapy, where the investigational agent (ISL 0.75 mg, DOR 100 mg, or DOR/ISL [100 mg/0.75 mg]) or placebo is added to the participant's current failing ART. In Part 2, all participants receive open-label DOR/ISL (100 mg/0.75 mg) added to OBT through Week 97. The study schema is shown in Figure 1.

Run-in Period: The Run-in Period will start immediately after Screening and end at randomization. During this time, participants will continue their failing ART regimen. Following confirmation of eligibility at the Screening Visit (Visit 1) (test results anticipated to take approximately 30 to 45 days), a repeat measurement for HIV-1 RNA will be performed at Visit 2 to confirm HIV-1 RNA eligibility for randomization (HIV-1 RNA ≥500 copies/mL with a <0.5 $\log_{10}$ decline in HIV-1 RNA from Visit 1). Participants with HIV-1 RNA ≥500 copies/mL and a ≥0.5 $\log_{10}$ decline in HIV-1 RNA from Visit 1 must return to the site 7 to 14 days after Visit 2 for a Repeat HIV-1 RNA confirmation visit (Visit 3). In order to be eligible for randomization, participants must have HIV-1 RNA ≥500 copies/mL and a <0.3 $\log_{10}$ decline in HIV-1 RNA from the previous result at Visit 2 (Figure 2). Randomization of eligible participants must occur within 10 days of Visit 2 (or Visit 3, if required).

Participants must have 2 HIV-1 RNA measurements ≥500 copies/mL to participate in this study: The first measurement at the Screening Visit and the second measurement taken no sooner than 7 days after the first measurement, but ≤10 days prior to randomization.

Double-blind Period, Part 1 (Day 1 to Day 7): Participants will be randomized in a 1:2:1:1 ratio into 1 of 4 treatment groups (Figure 1). The overall goal for this study is to randomize 150 participants; however, a minimum sample size of 100 randomized participants is the target for the planned analyses (40 participants randomized into the DOR treatment group and 20 participants randomized into each of the other treatment groups):

- Group 1 (n ~20): ISL QD + failing baseline ART
- Group 2 (n ~40): DOR QD + failing baseline ART
- Group 3 (n ~20): DOR/ISL QD + failing baseline ART
- Group 4 (n ~20): Placebo QD + failing baseline ART

Randomization will be stratified by age and within the adult strata, the existence of M184V or I substitutions at baseline (see Section 6.3.2).

Baseline ART will not be provided by the Sponsor.

Open-label Period, Part 2 (Day 8 to Week 97): Following the 7-day double-blind treatment period, all participants will be treated with DOR/ISL and OBT from Day 8 through Week 97 (with the opportunity to continue DOR/ISL after Week 97; Section 6.7). OBT options will be driven by historic and baseline resistance as well as drug safety and tolerability, drug access, and acceptability to the participant. In cases where the failing regimen cannot be optimized, participants will continue their failing regimen plus DOR/ISL. OBT will consist of approved and licensed ARTs and will not be provided by the Sponsor.

Participants with confirmed viremia (defined as having 2 consecutive confirmed HIV-1 RNA ≥200 copies/mL [at least 4 weeks apart] after achieving HIV-1 RNA <50 copies/mL) or who discontinued study intervention with HIV-1 RNA ≥200 copies/mL, or who never suppressed (<50 copies/mL) at Week 25, Week 49, and Week 97 with HIV-1 RNA >200 copies/mL, will be assessed for development of viral drug resistance.

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

4.2 Scientific Rationale for Study Design

The study design is based on the schema suggested in the regulatory guidance document [Food and Drug Administration (CDER) 2015] for a study population with multidrug resistant HIV-1 infection failing their current ART, when the study intervention is expected to offer antiretroviral activity. The P019 study design is a modification of the above schema that reflects the use of a combination agent (DOR/ISL) rather than a single new study intervention.

After the Screening Visit, there is a Run-in Period before randomization occurs. After at least 7 days during this period, repeat HIV-1 RNA testing is performed to exclude responders due to possible improved adherence to their ongoing “failing” ART after enrolling in the clinical study. The efficacy analysis (Part 1) will occur after 7 days of functional monotherapy or FDC DOR/ISL and will compare ISL, DOR, or FDC DOR/ISL added to failing baseline ART to placebo. The DOR arm is over-weighted 2:1 to reflect the heterogeneity of resistant mutants typically associated with NNRTI resistance. It is expected that the higher number of participants may allow for the determination of DOR activity over a range of IC50 values and evaluation of the impact and the clinical relevance of NNRTI mutations on DOR activity.

The primary safety evaluation and virologic follow-up will occur after 24 weeks of study intervention (24 weeks of open-label DOR/ISL with an optimized background regimen) to allow for an adequate assessment of safety and a longer observation period for virologic rebound or durability.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 HIV-1 RNA Measurements

The primary efficacy endpoint in this study is the percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, a well-established endpoint for evaluation of efficacy in the HTE population and aligned with regulatory guidance [Food and Drug Administration (CDER) 2015]. The antiretroviral activity of ISL and DOR will be further evaluated through the secondary efficacy endpoints, the percentage of participants achieving ≥1.0 $\log_{10}$ decrease and the mean change in HIV-1 RNA from study baseline (Day 1) to Day 8.

Similar assessments of the antiretroviral activity of DOR/ISL + OBT at Week 25, Week 49, and Week 97 will be performed, along with evaluation of the percentage of participants achieving HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 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. In individuals with no remaining suppressive ART options, decreases in HIV-1 RNA, even if detectable at >50 copies/mL, have been correlated with improved mortality and outcomes.

An HIV-1 RNA level of <200 copies/mL allows for patient monitoring to reduce the risk of developing viral drug resistance and to detect potential treatment failure in a timely manner. It also accounts for isolated detectable HIV-1 RNA after virologic suppression followed by a return to virologic suppression (ie, 'virologic blip') that may not be clinically meaningful.

4.2.1.2 Patient-reported Outcomes

PROs can provide unique information on the impact of HIV disease and its treatment from the patients' perspective as some domains are difficult to observe or are subjective and best collected through patient report. HTE patients have limited treatment options including complex regimens that are associated with adverse effects and consequently impaired HRQoL. PRO data may help clinicians and patients in making informed decision on appropriate combination ART. PROs, including HRQoL data, have been increasingly considered in drug benefit assessment and reimbursement decision-making by HTA authorities. HTA agencies in many countries recommend patient perspectives data and QoL measurement as part of their drug benefit evaluations.

The study will include the Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) for participants ≥18 years of age at the time of consent. The FAHI is a self-administered 47-item questionnaire designed to capture the effects of HIV infection and

treatment-related symptoms on physical, emotional, functional, social, and global well-being as well as cognitive functioning.

4.2.1.3 Safety Endpoints

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

4.2.1.4 Laboratory Markers

The study will assess changes in inflammation after treatment with DOR/ISL + OBT. Causes of persistent inflammation and thrombotic activity in patients with HIV-1 remain topics of debate and ongoing research [Baker, J. V., et al 2011] [Knudsen, T. B., et al 2016] [Wang, H., et al 2016]. The following laboratory markers will be measured:

- IL-6
- D-dimer
- sCD-163
- hs-CRP

4.2.1.5 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoA and Section 8.6.1 will be used to evaluate PK concentrations of ISL and DOR in Part 1 and Part 2, and as appropriate, PK-efficacy, PK-pharmacodynamic, and PK-AE relationships of DOR/ISL. PK values such as AUC, Cmax, and C24 will be explored.

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic

markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

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

4.2.1.7 Future Biomedical Research

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

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

4.2.2 Rationale for the Use of Comparator/Placebo

In alignment with regulatory guidance [Food and Drug Administration (CDER) 2015], Part 1 of this study consists of a brief period (7 days) of functional monotherapy (ie, each component of DOR/ISL), and the FDC DOR/ISL, or placebo added to the participant's current failing ART. Given a non-inferiority comparison is not feasible in this population, to evaluate the efficacy of each component of DOR/ISL, the antiretroviral activity of ISL and DOR at Day 8 are each compared to placebo. The functional monotherapy period is limited to 7 days to minimize the risk for development of resistance to ISL or DOR or additional resistance to the baseline ART.

The uncontrolled (open-label) study design beyond the primary 7-day comparison is deemed appropriate as the modest loss of certainty interpreting study results is outweighed by the unmet medical need in this population and the potential to decrease further development of resistance to the background regimen from this type of study design.

4.2.3 Rationale for the Selected Participant Population

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

- **HTE Participants**: There is an unmet medical need for new treatments in patients with documented baseline resistance to multiple drug classes, who are experiencing an ongoing inability to suppress viral replication on their current regimen and have few if any remaining options to construct a fully suppressive regimen.

Patients with multidrug resistant HIV-1 are at risk of serious illness and death, leading to an urgent need for new antiviral drugs that are active against multidrug resistant virus. In addition to a broad pharmacologic distribution and a long intracellular half-life, ISL has a high IQ (Ctrough/IC50) and the potential to be active against common NRTI-resistant variants (eg, M184I/V, K65R, L74V, Q151M, 69ins). DOR is a potent NNRTI that retains in vitro activity against HIV-1 variants harboring the most common NNRTI resistance mutations (eg, K103N, G190A, Y181C, and E138A/K). Therefore, the FDC of ISL and DOR has the desired properties to meet a critical unmet medical need in this population.

- **Enrollment of Pediatric Participants**: The nonclinical data for DOR/ISL, and its individual components (ISL and DOR), and clinical studies of DOR + ISL conducted to date in adults with and without HIV-1 infection, have not demonstrated significant safety concerns that would preclude evaluation in pediatric participants <18 years of age). Pediatric participants (weighing ≥35 kg) are predicted to have similar plasma ISL and intracellular ISL-TP concentrations to the adults studied in Phase 2 and no dose adjustment is necessary in this age group. The use of a weight limit for pediatric participants is in alignment with WHO pediatric HIV guidance [World Health Organization 2007] to administer antiretrovirals using a weight-band dosing approach.

4.2.4 Rationale for Collecting Race and Ethnicity Data

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

4.2.5 Rationale for Collecting Gender Identity Data

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

health needs and high vulnerability [Department of HIV/AIDS 2015]. Data will be collected in this study to assess clinical outcomes in the transgender population.

4.2.6 Rationale for Infant Safety Data Collection

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

4.2.7 Rationale for Continuing Study Intervention During Pregnancy

The US Department of Health and Human Services guidelines currently advise that women who become pregnant while receiving ART for HIV should continue their regimen provided it is safe, well tolerated, and effective at virologic suppression since 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 consent to continue study intervention (where allowed by local regulations, health authorities, and ethics committees and as appropriate based on available data/local standard-of-care guidelines) (Sections 8.1.1.4 and 8.11.7).

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

4.3 Justification for Dose

IQ (Ctrough/IC50) is the ratio of drug exposure to viral susceptibility. In a Phase 1b proof of concept study (MK-8591 Protocol 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 concentrations achieved at the end of Day 1 after a single dose of 0.75 mg provide IQs of 21 and 4 for wild-type and M184V virus, respectively. After 7 daily doses of 0.75 mg ISL, IQs increase to 113 for wild-type virus and 23 for M184V/I virus. Antiretroviral activity against the exceedingly rare 69ins + M184I/V mutant virus (the NRTI mutant with the highest potency reduction for ISL) is expected to be achieved after 7 QD doses, with an IQ of 5. Steady-state concentrations at later timepoints will produce even higher IQs, as there is additional accumulation of ISL-TP. These simulations support the selection of 0.75 mg ISL as the dose to be studied as monotherapy (in Part 1) and in combination with 100 mg DOR in Part 1 and Part 2.

In the Phase 2 clinical study (MK-8591 Protocol 011), 3 daily doses of ISL (0.25, 0.75, and 2.25 mg) were evaluated in combination with DOR (100 mg) + 3TC for 24 weeks and subsequently with DOR alone through Week 48. All 3 doses of ISL with DOR+3TC demonstrated potent antiretroviral activity comparable with the 3-drug comparator

DOR/3TC/TDF, as demonstrated by the primary efficacy endpoint, the proportion of participants with HIV-1 RNA <50 copies/mL, at both Week 24 and Week 48. Overall, no ISL dose-response for efficacy was observed. Graphical analysis of steady-state ISL-TP trough concentrations and viral load at Week 48 from Protocol 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. Protocol 011 also demonstrated that all doses of ISL studied, when administered with DOR+3TC or DOR alone, had a favorable safety and tolerability profile through Week 48, comparable with that of DOR/3TC/TDF. In addition, a 0.75 mg QD dose of ISL in combination with 100 mg QD DOR is predicted to provide concentrations sufficient to cover mutant virus strains anticipated in an HTE patient population.

Pediatric participants (weighing ≥35 kg) are predicted to have similar plasma ISL and intracellular ISL-TP concentrations to the adults studied in Protocol 011, and no dose adjustment is necessary in this age group (Section 4.2.3).

DOR will be administered at the approved dose of 100 mg. This dose has been studied in Phase 1 to 3 clinical studies in treatment-naïve and virologically suppressed participants with HIV-1 and was selected based on favorable efficacy, safety, tolerability, and metabolic profiles as confirmed in the Phase 3 clinical studies [Orkin, C., et al 2018] [Molina, J. M., et al 2018] and MK-1439A Protocol 024. Of note, among 32 participants in MK-1439A Protocols 024 and 030 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 these 32 participants had been virologically suppressed on PI or InSTI regimens and 8 had been TN). DOR is also expected to have antiviral activity against other prevalent NNRTI-associated reverse transcriptase substitutions including L100I, E138K, H221Y, and P225H when dosed at 100 mg daily.

The DOR dose selection for adolescents was based on a physiologically based PK model that indicated that the 100 mg DOR tablet once daily can be safely and effectively administered in the adolescent population ranging from 12 to 18 years of age, and this dose is currently being studied in MK-1439 Protocol 027.

Therefore, 100 mg DOR has been selected to be studied in monotherapy (in Part 1) and in combination with 0.75 mg ISL in Part 1 and Part 2.

In summary, a 0.75 mg dose of ISL in combination with 100 mg DOR is predicted to provide concentrations that will demonstrate potent activity against both wild-type virus and most common NRTI- and NNRTI-resistance-associated 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/assent. The overall study ends when the last participant completes the last study-related contact, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

Blinded data for participants who fail to achieve ≥0.5 $\log_{10}$ decline in HIV-1 RNA at the end of Part 1 will be communicated to an external unblinded statistician on an ongoing basis to perform the futility assessment. If the futility boundary is met, early study termination may be considered (Section 9.7).

5 STUDY POPULATION

HTE adult participants and pediatric participants weighing ≥35 kg with HIV-1 who are currently on failing ART will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is HIV-1 positive with plasma HIV-1 RNA ≥500 copies/mL at the Screening Visit and confirmed upon repeat testing (Visit 2 [or Visit 3 if required]) during the Run-in Period.

   In addition, the log change in HIV-1 RNA must meet 1 of the following criteria at a confirmation visit:

   - <0.5 $\log_{10}$ decline in HIV-1 RNA from the Screening Visit (Visit 1) to the Confirmation visit (Visit 2)

     OR

   - If ≥0.5 $\log_{10}$ decline in HIV-1 RNA at Visit 2, another confirmation test is required (Visit 3). In this case, there must be <0.3 $\log_{10}$ decline in HIV-1 RNA from Visit 2

   Note: HIV-1 RNA ≥500 copies/mL must be confirmed within 10 days prior to randomization.

   Note: Repeat HIV-1 RNA Confirmation Visit (Visit 3) to occur 7 to 14 days following Visit 2.

2. Has been receiving the same baseline ART for ≥3 months prior to signing the Informed Consent Form/Assent Form.

3. Has at least triple-class resistance (must include NRTI, NNRTI, and resistance to either PI or InSTI) based on any of the following: (a) central laboratory based resistance testing at the Screening Visit, (b) central laboratory based proviral DNA resistance testing at the Screening Visit, or (c) historical resistance testing within 12 months of Screening. Resistance to at least 2 antiretroviral agents in a particular class denotes class resistance. *Note: For purposes of determining NRTI class resistance, resistance to FTC (emtricitabine) and 3TC (lamivudine), resistance associated with MI84V/I substitution must include ≥1 additional NRTI resistance substitution.*

4. Has ≤2 fully active antiretroviral drugs remaining, among all antiretroviral classes, that can be effectively combined to form a viable regimen based on resistance, tolerability, safety, drug access, or acceptability to participant.

Demographics

5. Is male or female, adult (≥18 years of age) or pediatric participants (weighing ≥35 kg and <18 years of age), at the time of signing the informed consent/assent (the Screening Visit).

Contraception/Pregnancy

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

  - Is not a woman of childbearing potential (WOCBP).

    OR

  - Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 6 weeks, corresponding to the time needed to eliminate any study intervention(s) (eg, 5 terminal half-lives) after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

  - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent/Assent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has HIV-2 infection.

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

3. Has HBV co-infection (defined as HBsAg-positive or HBV DNA positive) and is not currently being treated for HBV.
   Note: Participants coinfected with HBV who are currently taking oral antiviral treatment for hepatitis B (eg, tenofovir, entecavir, telbivudine, adefovir, lamivudine, etc.) are eligible for enrollment and should remain on the same treatment for their HBV throughout the study.

   Note: Chronic HCV infection (detectable HCV RNA) and treatment with direct acting antiviral therapies are not exclusionary provided the participant has stable liver function tests and no significant hepatic synthetic dysfunction defined as a serum albumin <2.8 g/dL or an INR >1.7 in the absence of another explanation for the abnormal laboratory value.

4. Has a history or current evidence of any condition (including active TB co-infection), therapy, laboratory abnormality, or other circumstance (including drug or alcohol abuse or dependence) that might, in the opinion of the investigator, confound the results of the study or interfere with study participation for the full study duration.

Prior/Concomitant Therapy

5. Is taking or is anticipated to require any of the prohibited therapies outlined in Section 6.5 from the Screening Visit and throughout the study treatment period. (See Table 3 footnote for special considerations in Part 2 of the study.)

6. Is taking DOR as part of his/her current failing antiretroviral regimen.

7. Is taking EFV, etravirine, or nevirapine.

   Note: Although expected to be rare, these drugs are excluded because of the potential for decreased DOR concentrations when administered with DOR or DOR/ISL). (See Table 3 footnote for more information.)

Prior/Concurrent Clinical Study Experience

8. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device from the Screening Visit through the study treatment period.

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

Diagnostic Assessments

9. Has exclusionary laboratory values at the Screening Visit as listed in Table 1 below.

Table 1 Laboratory Exclusion Criteria

Laboratory Assessment	**Exclusionary Values**
AST SGOT	>5 × ULN
ALT SGPT	>5 × ULN
Hemoglobin	<9.0 g/dL (female) or <10.0 g/dL (male)
Calculated Cr_{CL}	≤30 mL/min based on the Cockcroft-Gault equation (Appendix 8)
ALT SGPT=alanine aminotransferase; AST SGOT=aspartate aminotransferase; Cr_{CL}=creatinine clearance; ULN=upper limit of normal.	

Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results, but the repeat test results must be available within the 60-day screening window.

Other Exclusions

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

    Note: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study treatment. Consistent with the

recommendations for contraceptive use, it is recommended that all female participants refrain from egg donation for 6 weeks following their last dose of study treatment.

Note: Donation of sperm should follow local guidelines for HIV-positive individuals.

5.3 Lifestyle Considerations

There are no lifestyle restrictions for ISL and DOR. Refer to approved labeling for any lifestyle restrictions with administration of ART and OBT.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (study intervention[s] provided by the Sponsor) will be packaged to support enrollment where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.). Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP/ NIMP	Sourcing
All Groups (Group 1, 2, 3, 4)	N/A	Baseline ART regimen[a]	Drug	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Run-in Period through Part 1 Day 7	Background Treatment	NIMP	Local country level Sourcing [b]
Group 1	Experimental	ISL	Drug	Capsule	0.75 mg	0.75 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Experimental	IMP	Provided centrally by Sponsor
Group 1	Experimental	DOR Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 1	Experimental	DOR/ISL Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 2	Experimental	DOR	Drug	Tablet	100 mg	100 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Experimental	IMP	Provided centrally by Sponsor
Group 2	Experimental	ISL Placebo	Drug	Capsule	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 2	Experimental	DOR/ISL Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 3	Experimental	DOR/ISL	Drug	Tablet	100 mg DOR/0.75 mg ISL	100 mg/0.75 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Experimental	IMP	Provided centrally by Sponsor
Group 3	Experimental	DOR Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 3	Experimental	ISL Placebo	Drug	Capsule	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 4	Placebo Comparator	ISL Placebo	Drug	Capsule	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP/ NIMP	Sourcing
Group 4	Placebo Comparator	DOR Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
Group 4	Placebo Comparator	DOR/ISL Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	Part 1: Day 1 to Day 7 (blinded)	Placebo	IMP	Provided centrally by Sponsor
All Groups (Group 1, 2, 3, 4)	Experimental	DOR/ISL	Drug	Tablet	100 mg DOR/0.75 mg ISL	100 mg/0.75 mg QD	Oral	Part 2: Day 8 to Week 97 (open-label)[c]	Experimental	IMP	Provided centrally by Sponsor
All Groups (Group 1, 2, 3, 4	N/A	Optimized Background Treatment[a]	Drug	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Per Approved Product Label	Part 2: Day 8 to Week 97 (open-label)	Background Treatment	NIMP	Local country level sourcing[b]

ART=antiretroviral therapy; CCR5=chemokine receptor type 5; DOR=doravirine; InSTI=integrase strand transfer inhibitor; ISL=islatravir; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; OBT=optimized background therapy; PK=pharmacokinetic; QD=once daily.

[a] Allowed drug classes include NRTIs, NNRTIs, protease inhibitors, InSTIs, fusion inhibitors, CCR5 antagonists, and postattachment inhibitor.

[b] The Sponsor will not provide ART during Part 1 or OBT during Part 2. Participants will provide their own medications.

[c] For participants who are pregnant at the last regularly scheduled study visit (Week 97), study intervention will be dispensed at Week 97. In addition, their visit schedule will be extended through the duration of the pregnancy and study intervention will be dispensed at Weeks 109, 121, and 133, as applicable.

Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

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

All placebos were created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 4 blinded study intervention arms in Part 1. Participants will be assigned randomly in a 1:2:1:1 ratio to ISL, DOR, DOR/ISL, or placebo, respectively. In Part 2, there is 1 open-label study intervention arm; all eligible participants will receive DOR/ISL + OBT.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- **Stratum 1**: Adults (≥18 years of age) with M184V or I substitutions.
  - At least 73 participants will be enrolled into this Stratum.
- **Stratum 2**: Adults (≥18 years of age) without M184V or I substitutions.
- **Stratum 3**: Pediatric participants (<18 years of age).
  - Pediatric participants will not be stratified by M184V or I substitutions as few participants <18 years of age are expected to be enrolled into the study.

Stratification factors help ensure that the blinded treatment arms in Part 1 will be well balanced across the treatment groups within each stratum and the study results will not be confounded by age of the participant or by the existence of M184V or I substitutions at baseline.

6.3.3 Blinding

In Part 1 of this study, a double-blinding technique with in-house blinding will be used. DOR, ISL, DOR/ISL, and placebo will be packaged identically so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Clinical site personnel and participants will remain blinded to Part 1 treatment through Week 97 while Sponsor personnel will remain blinded until the end of Part 1. Sponsor personnel involved in performing and reviewing results of the Part 1 analysis will be unblinded after the Part 1 database lock.

Part 2 of this study is open-label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

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

official memo detailing unblinding procedures will be generated per Sponsor SOP. This memo will list the names of the personnel who will have access to unblinded PK data before database lock.

6.4 Study Intervention Compliance

Participants should be instructed to bring their medication, whether clinical supplies provided by the Sponsor or ART/OBT provided by study participants, to their visits. At each visit, the number of tablets or capsules remaining will be counted, reviewed, and recorded. For any ART/OBT that is received via injection or infusion, the participant will provide information regarding dosing via a conversation with site personnel. 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 AE or other reason will be reviewed on a case-by-case basis by the investigator. Interruptions from the protocol-specified treatment plan that are expected to be 7 consecutive days or longer require consultation between the investigator and the Sponsor, and written documentation of the collaborative decision on participant management.

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.

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

Prior and concomitant therapies listed in Table 3 are not permitted from the Screening Visit and throughout the study treatment period. See footnote in Table 3 for certain exceptions and considerations for Part 2 of the study.

This list of prohibited therapies in Table 3 is not comprehensive, and the investigator should use his/her medical judgment when assessing a participant's prior and concomitant therapy(ies). The Sponsor Clinical Director or designee should be contacted if there are any questions about a therapy not in Table 3 or regarding potential drug interactions with a specific treatment that the participant may be receiving or planning to receive.

Table 3 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 Modafinil Bosentan Nafcillin
Non-Study ART	Use of antiretrovirals other than as components of the baseline ART (Run-in Period and Part 1) or OBT (Part 2) is not allowed, except for treatment of ongoing HBV infection.
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 non-study investigational agents including devices. *Note: For participants with no fully active agents to construct optimized background therapy in Part 2 of the study, consideration will be given to allow use of 1 investigational agent, on a case-by-case basis, but this must first be approved by the study Clinical Director.*
Additional prohibited therapies based on baseline ART (Part 1) or OBT (Part 2)	Refer to the approved local label(s)
Additional prohibited therapies based on ISL	Pentostatin

ART=antiretroviral therapy; CYP3A=cytochrome P450 3A; DOR=doravirine; HBV=hepatitis B Virus; ISL=islatravir; OBT=optimized background therapy.

Note: Efavirenz, etravirine, and nevirapine may lead to decreased DOR concentrations when taken concomitantly with DOR. If use of these agents is considered essential for constructing the OBT in Part 2, investigators should first discuss this with the Sponsor's Clinical Director. Similarly, if use of a moderate CYP3A inducer or immunosuppressive agent is considered essential in Part 2 of the study, this should first be discussed with the Sponsor's Clinical Director.

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 ISL, DOR, or DOR/ISL (during Part 1) or DOR/ISL (during Part 2) is allowed during the study.

6.7 Intervention After the End of the Study

At the end of Week 97, provided development of DOR/ISL continues, all eligible participants will be given the option to continue receiving study intervention without interruption (eg, as part of a rollover study) until it becomes locally available. Eligible participants are those who have completed the last scheduled study visit and are considered by the investigator to derive clinical benefit from continued administration of DOR/ISL.

Participants who complete the Week 97 visit who do not consent to participate in the rollover study should also have an End of Treatment Follow-up visit.

Participants who choose to participate in the rollover study who have decreases in CD4+ T-cell and/or total lymphocyte counts that meet ECI criteria (Section 8.4.7) at Week 97 should have a confirmation visit in this study (per Section 8.11.6 and Section 1.3.4). The confirmatory CD4+ T-cell count and/or total lymphocyte count will be followed in this study, and the participant will be concurrently enrolled in the rollover study.

- Upon repeat testing, if discontinuation criteria (Section 7.1) are confirmed, participation in the rollover study will be stopped. The participant will be followed monthly in this study until 2 values (12 weeks apart) for the CD4+ T-cell and total lymphocyte counts are not decreased by >10% of the average baseline value (Section 8.11.6).

- Upon repeat testing, if discontinuation criteria (Section 7.1) are not confirmed, the participant will continue to participate in the rollover study only.

Participants who decline participation in the rollover study whose Week 97 visit shows decreases in CD4+ T-cell and/or total lymphocyte counts should be managed per Section 8.11.6.3.

6.8 Clinical Supplies Disclosure

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

In Part 1 of the study (Day 1 to Day 7), all study supplies will be double-blinded; therefore, the participant, the study site personnel, the Sponsor and/or designee will be blinded. After Day 7, DOR/ISL will be provided as open-label supplies (Part 2). Study treatment (name, strength, or potency) is included in the label text.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.11.4.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance (for pregnancy, see Section 8.11.7) which, in the opinion of the investigator and/or Sponsor, placed 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 is considered by the investigator to no longer derive clinical benefit from continued administration of DOR/ISL.
- Occurrence of any 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 if the following criteria are met but continue to be monitored per Section 8.11.6:

- A ≥30% reduction from average baseline value* in CD4+ T-cell count OR in total lymphocyte count on 2 consecutive measurements taken 3 to 4 weeks apart.

  *Note: The average baseline value is defined as the average value between screening (within 60 days prior to the first dose of study intervention) and Day 1.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, 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 full 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/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential participant or their legally acceptable representative prior to participating in this clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Informed consent/assent 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 agreement of the person conducting the consent/assent discussion.

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

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

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

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

8.1.1.2 Consent/Assent and Collection of Specimens for Future Biomedical Research

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

8.1.1.3 Consent/Assent for Postnatal Infant Safety Data Collection Through One Year of Age

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

8.1.1.4 Consent/Assent for Continuation of Study Intervention During Pregnancy

Upon learning that a participant is pregnant, the investigator or medically qualified designee and the participant will discuss the potential benefits and risks of continuing (or discontinuing) study intervention (Section 8.11.7). A separate consent/assent is required to continue study intervention in participants who become pregnant. The investigator or medically qualified designee will explain the consent/assent to the participant, or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent/assent before continuing study intervention. A copy of the informed consent/assent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at the Screening Visit. 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/mm^3, the condition as well as a corresponding medical history of AIDS must be reported. In addition, participants' history of smoking and alcohol consumption should be obtained and recorded on the appropriate eCRF as relevant.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant since the Screening Visit through first dose of study intervention.

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

8.1.5.2 Concomitant Medications

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

The ART/OBT taken by the participant during the study will be recorded by the investigator or qualified designee.

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number at the randomization visit (Day 1). The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.8 Study Intervention Administration

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

The first dose of double-blind study intervention will be administered at the study site at the randomization visit (Day 1). Subsequent dosing will be performed once daily by the participant (ie, unsupervised at his/her home) at approximately the same time each day.

8.1.8.1 Timing of Dose Administration

All study interventions should be administered QD at approximately the same time each day without regard to food. The tablets or capsules from each container of study intervention should be taken together.

During the double-blind treatment period (Part 1), all participants will take 1 tablet or capsule from each of the 3 containers QD with their failing ART.

During the open-label treatment period (Part 2), all participants will receive open-label DOR/ISL and will take 1 tablet each day with OBT. If more than 1 bottle is dispensed, the participant is instructed to use all of the medication in a single bottle before opening another bottle.

If a participant misses a dose of any of the study interventions, the following guidance should be followed:

- If ≤12 hours from the missed dose, the missed dose should be taken, and the normal dosing schedule resumed.

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

If a participant misses a dose of baseline ART (during Part 1) or OBT (during Part 2), guidance in the approved label(s) should be followed.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should have an Early Discontinuation visit performed per the SoA (Section 1.3) and be encouraged to continue to be followed as outlined in Section 8.11.4. Participants who discontinue study intervention for decreases in CD4+ T-cell counts and/or total lymphocyte counts or who discontinue study intervention for any other reason and are noted to have a >10% decrease from average baseline value in their CD4+ T-cell and/or total lymphocyte counts or have decreases in CD4+ T-cell and/or total lymphocyte counts that meet ECI criteria at the Early Discontinuation of Treatment Visit should be managed per Section 8.11.6 until the counts recover.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Early Discontinuation visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and participants should attend the End of Treatment Follow-up visit approximately 6 weeks after discontinuing study intervention.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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

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

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel are unblinded so that appropriate follow-up medical care can be provided to the participant.

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

8.1.11 Calibration of Equipment

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

8.1.12 Administration of Patient Questionnaires

Adult participants (≥18 years at the time of consent) will complete the FAHI at Day 1, Week 25, Week 49, Week 97, and/or the Early Discontinuation visit. Participants are to complete the questionnaire on their own at the site on paper during the appropriate study visit (see SoA, Section 1.3) prior to being seen by the investigator, receiving study intervention, discussing any medical conditions with the study personnel, or receiving any medical results. The questionnaire will not be administered to participants if native language translation is not available.

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

8.2 Efficacy Assessments

The primary efficacy measurement is HIV-1 RNA. Additional efficacy measurements include CD4+ T-cell counts, viral resistance testing, and proviral DNA resistance testing. Blood will be collected as indicated in the SoA (Section 1.3).

8.2.1 HIV-1 RNA

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

8.2.2 Management of Study Participants with Viremia

When viremia (HIV-1 RNA ≥200 copies/mL after participant has achieved HIV-1 RNA of <50 copies/mL) is detected, the investigator should query the participant regarding adherence to study therapy, intercurrent illness, or recent immunization. All cases of viremia must be confirmed, and **the participant should continue to take the assigned dosage of study intervention while awaiting confirmation**.

HTE patients may derive clinical benefit from declining HIV-1 RNA levels even if complete viral suppression is not achieved. Participants with HIV-1 RNA ≥200 copies/mL during the open-label treatment period (Part 2) who are considered by the investigator to derive clinical benefit may continue treatment with DOR/ISL.

8.2.2.1 Viremia Confirmation

Confirmation of viremia requires 2 consecutive plasma HIV-1 RNA results of ≥200 copies/mL after a participant previously achieved HIV-1 RNA of <50 copies/mL. The second sample collected at a “Viremia Confirmation” visit at least 4 weeks from the date of the initial sample. This timeframe may be extended if study intervention is interrupted for one of the following circumstances:

- **Intercurrent illness**: Redraw 2 to 4 weeks following resolution of the illness, during which time the participant should continue to receive the assigned dosage of study intervention without interruption;

- **Immunization**: Redraw approximately 4 weeks following any immunization, during which time the participant should continue to receive the assigned dosage of study intervention without interruption;

- **Toxicity management, noncompliance, or other reason**: Redraw 2 to 4 weeks following resuming the assigned dosage of study intervention.

8.2.2.2 Viral Drug Resistance Testing

Phenotypic and genotypic HIV-1 drug resistance testing will be performed on plasma samples per the SoA (Section 1.3) to determine resistance to ISL, DOR, and other ARTs. Samples collected at Day 1 (baseline), Day 8, and samples with HIV-1 RNA ≥200 copies/mL for participants who never suppressed at Week 25, Week 49, and Week 97 and those that were collected either to confirm viremia or at discontinuation will be sent for genotypic and phenotypic resistance testing.

Whole blood samples for proviral DNA resistance testing will be collected and analyzed at Screening for all participants. In addition, postrandomization samples for proviral DNA resistance testing will be collected per the SoA (Section 1.3). Postrandomization whole blood samples in participants with plasma HIV-1 RNA ≥200 copies/mL at Week 25, Week 49, and Week 97 and those that were collected either to confirm viremia or at discontinuation will be analyzed for proviral DNA resistance testing.

All viral resistance testing will be performed by the central laboratory.

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

A TBNK Panel, including CD4+ T cell count, will be performed at the central laboratory (Appendix 2). Refer to Section 8.11.6 for guidance on management of participants with decreased CD4+ T-cell counts and/or decreased total lymphocyte counts.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted at the randomization visit (Day 1) by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. The complete physical examination will include examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system).

A directed physical examination will be conducted as indicated in the SoA (Section 1.3) by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, 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. This does not preclude examination of any of the body system as clinically indicated.

Height and weight will also be measured and recorded at the visits specified in the SoA (Section 1.3). Height measurements are recommended to be taken by use of a stadiometer, however not required.

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

8.3.2 Vital Signs

Vital signs will be measured after approximately 5-10 minutes of rest and will include temperature, pulse, respiratory rate, and systolic and diastolic blood pressure.

Note: Oral temperatures are preferred, but not required.

8.3.3 Electrocardiograms

A single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 1.3.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.3.4 Confirmation of Menarche, Contraception, and Pregnancy Testing

To determine if a participant is of child bearing potential, female participants should be asked to confirm their menarche status. Once menarche has been established and recorded in source documents, a participant is considered a WOCBP, and is required to use contraception to prevent pregnancy during the study and will be tested for pregnancy at each visit as outlined in Section 1.3, Section 5.1, and Appendix 5.

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

Urine pregnancy test kits will be provided by the central laboratory, and routine testing will be performed by the local laboratory. In the event of a positive urine pregnancy test result, serum pregnancy testing must be performed by the central laboratory. If a participant becomes pregnant, refer to Section 8.11.7.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (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.

  Note: Management of decreases in CD4+ T-cell and/or total lymphocyte counts is described in Section 8.11.6.

8.3.6 HBV Assessments

Participants who become HBsAg or HBV DNA positive after study entry may be allowed to continue study treatment if deemed medically appropriate upon consultation with the Sponsor.

8.3.7 Tobacco and Alcohol Assessments

Participants’ use of tobacco and alcohol will be obtained and recorded at Week 97.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

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

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

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

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

For infants born to participants who become pregnant 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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 4.

For participants who continue in a rollover study, the collection requirements of AEs, SAEs, and other reportable safety events in this protocol are amended as follows:

- AEs, SAEs, and other reportable safety events will be collected and recorded through the last study visit in this protocol.
- Pregnancy outcome and infant SAEs will be captured in this protocol, if pregnancy exposure is reported in this protocol.
- The last collection of nonserious AEs (including cancer that does not meet serious criteria) will be at the last study visit in this protocol.

  Note: All new SAEs (including those considered related to study intervention) and other new reportable safety events (including pregnancy exposure) that occur after the last study visit will be collected in the rollover study.

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

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (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
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply wth 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

For infants born to participants who become pregnant 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.

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

This section is not applicable to the study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

- A ≥30% decrease from average baseline** values of CD4+ T-cell count or total lymphocyte count values while on study intervention.

  ** The average baseline value is defined as the average value between screening (within 60 days prior to the first dose of study intervention) and Day 1.

Note: The first on-treatment value that meets the above CD4+ T-cell or total lymphocyte criteria should be reported as an ECI. See Section 8.11.6 for further guidance on the management of participants meeting CD4+ T-cell or total lymphocyte criteria.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the prescribed dose of study intervention.

No specific information is available on the treatment of overdose.

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma ISL and DOR

Venous blood samples will be collected for measurement of ISL and DOR. Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

Population PK samples will be collected from all participants as outlined in Table 5. 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.

Investigational PK samples will be collected from all participants as outlined in the SoA (Section 1.3). Analysis of these samples will be triggered by the Sponsor as needed.

For participants who become pregnant and consent to continue DOR/ISL, PK samples will be collected to evaluate DOR and ISL concentration levels per Table 6 in Section 8.11.7.1.

Table 5 Collection of Population PK Samples

Study Visit	**Time relative to dose**
Day 1	Predose
Day 8	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented), but prior to initiation of open-label DOR/ISL + OBT (Part 2)
Week 3	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
Week 13	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
Week 25	Sample to be collected predose and within 0.5 and 2 hours postdose*

Study Visit	Time relative to dose
Week 37	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
Week 49	Sample to be collected predose and within 0.5 and 2 hours postdose*
* For participants who take their study intervention during the day, samples should be collected predose and postdose. For participants who take their study intervention in the evening, only a postdose sample should be collected the following day irrespective of time of dose (time of last dose and time of PK sample collection must be documented).	

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

8.8.1 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

8.8.2 Inflammation

Blood samples will be collected to evaluate the inflammatory and thrombotic response as measured by the following laboratory markers as indicated in the SoA (Section 1.3).

- IL-6
- D-dimer
- sCD-163
- hs-CRP

8.8.3 Fasting Lipid and Metabolic Profiles

Participants will be asked to fast for at least 8 hours prior to Day 1 (Visit 4) and Day 8 (Visit 5) where blood will be taken to measure glucose, HDL-C, TGs, TC, and non-HDL-C.

Participants with normal fasting lipid and metabolic profiles will repeat measurements at Week 49 (Visit 12), Week 73 (Visit 14), and Week 97 (Visit 16). Participants with abnormal measurements at Day 8 will also have repeat testing at Week 25 (Visit 10).

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of future biomedical research:

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

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

8.10 Health Economics Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening/Rescreening

Screening

Approximately 60 days prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Participants are expected to enroll within 10 days after confirmatory HIV-1 RNA result has been obtained and all other eligibility criteria have been met.

A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results, but the repeat test results must be available within the 60-day screening window.

Rescreening

Since HTE participants have few or no options for an effective treatment, it is necessary to consider the circumstances where a participant may not meet eligibility criteria at the current time, but due to the progression of their HIV-1 disease, they may qualify at a later time (eg, a participant not having a high enough HIV-1 RNA at Screening or a participant not having NRTI or NNRTI resistance on the screening resistance test). Participants may be allowed to rescreen following consultation with the Sponsor. Once a participant has started the rescreening process, a new screening period (ie, an additional ≤60-day window) will begin, during which time screening procedures may be repeated.

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

- Vital signs, weight, and directed physical examination
- Review medical history and prior/concomitant medications for new information
- All laboratory assessments (includes serum β hCG pregnancy testing for WOCBP)
- HIV-1 drug resistance testing will be repeated only if determined to be required
- Review of AEs

Documented informed consent/assent provided during the original screening period should be reviewed with the participant and verbal reconsent to continue in the study should be documented.

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

8.11.2 Run-in Period

The Run-in Period begins immediately after Screening and ends at randomization. This period is designed to allow detection of participants who are failing their baseline regimen due to nonadherence. HIV-1 RNA testing will be repeated at Visit 2 to confirm study eligibility (HIV-1 RNA ≥500 copies/mL with a <0.5 $\log_{10}$ decline in HIV-1 RNA from Visit 1). Participants at Visit 2 who have HIV-1 RNA ≥500 copies/mL and a ≥0.5 log10 decline from Visit 1, must return to the site 7 to 14 days after Visit 2 for a Repeat HIV-1 RNA confirmation visit (Visit 3). In order to be eligible for randomization, participants must have HIV-1 RNA ≥500 copies/mL and a <0.3 log10 decline in HIV-1 RNA from the previous result at Visit 2. Participants should be instructed to maintain strict adherence to their baseline ART regimen during this Run-in Period.

8.11.3 Treatment Period

8.11.3.1 Fasting

Visits at Day 1 (Visit 4), Day 8 (Visit 5), Week 49 (Visit 12), Week 73 (Visit 14), and Week 97 (Visit 16) require that participants fast (ie, do not consume any food or beverages except water) for at least 8 hours prior to the visit. The investigator/study coordinator are responsible to remind participants to fast prior to these visits and to confirm with participants their fasting status in the appropriate source documentation.

Participants may need to fast at the Week 25 (Visit 10) visit as well depending on the outcome of the fasting lipid profile and fasting glucose measurement at Day 8 (see Section 8.8.3).

8.11.3.2 Double-blind (Part 1)

All procedures should be completed prior to intervention randomization as per the SoA (Section 1.3.1). Randomization should occur within 10 days after confirmation of HIV-1 RNA eligibility. Participants who are eligible will enter the 7-day double-blind treatment period (Part 1). Participants will continue on their failing ART during Part 1 and should be instructed to maintain strict adherence to both their failing ART and to the study intervention during this period.

The Visit at Day 1 requires that participants fast (ie, do not consume any food or beverages except water) for at least 8 hours prior to the visit. The investigator/study coordinator are responsible to remind participants to fast prior to this visit and to confirm with participants their fasting status in the appropriate source documentation.

8.11.3.3 Open-label (Part 2)

Participants who complete the 7-day double-blind treatment period (Part 1) will continue to the open-label treatment period (Part 2). Participants will take OBT along with open-label DOR/ISL for 96 weeks.

8.11.3.4 Optional Nurse Visits and Telephone Visits

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

For visits conducted by the visiting nurse, whole blood for proviral DNA resistance and FBR samples (for those participants who consent to FBR) will not be collected by the visiting nurse. Participants should be instructed to return to the site within 2 to 4 weeks from the scheduled visit for collection of whole blood for proviral DNA resistance and FBR, when possible. If an unscheduled visit for collection of whole blood for proviral DNA resistance

testing and FBR is not possible, the sample should be drawn at the next scheduled visit at the site.

8.11.3.5 End of Study Week 97 Visit

Week 97 represents the end of this study.

Participants will be given 2 options at the Week 97 visit:

1. End participation in this study and resume locally available treatment of their choice. These participants should have an End of Treatment Follow-up visit approximately 42 (+ 7) days (6 weeks) after the last dose of study intervention.

2. Provide documented consent to participate in the rollover study. The rollover study will provide open-label DOR/ISL to participants.

Participants who are pregnant at Week 97 will be managed per Section 8.11.7.

Management of participants with decreased CD4+ T-cell counts and/or total lymphocyte counts is as follows:

- See Section 6.7 for management of participants entering the rollover study who have CD4+ T-cell count and/or total lymphocyte count decreases that meet ECI criteria at their last study visit in this study (ie, rollover enrollment visit).

- Participants not participating in the rollover study who have decreases in CD4+ T-cell and/or total lymphocyte counts that meet ECI criteria or are decreased by >10% of their average baseline value require additional follow-up monitoring of CD4+ T-cell and lymphocyte counts per Section 6.7 and Section 8.11.6.

8.11.4 Participants Who Discontinue Study Intervention

A participant must be discontinued from study intervention but continue to be monitored 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 8.11.4.1) and an End of Treatment Follow-up visit (Section 8.11.4.2) conducted. After the visit procedures are completed, the participant will be withdrawn from the study and managed for treatment of HIV-1 per local standard-of-care.

- Guidance for management of participants who discontinue study intervention due to confirmed decreased CD4+ T-cell counts and/or decreased total lymphocyte counts is provided in Section 8.11.6.

- If participants discontinue study intervention for other reasons and the CD4+ T-cell counts and/or total lymphocyte counts at Early Discontinuation of Treatment visit are

decreased by >10% of their average baseline value, additional monitoring is required per Section 8.11.6.

8.11.4.1 Early Discontinuation of Treatment

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

8.11.4.2 End of Treatment Follow-Up Visit

Participants who discontinue study intervention at any time prior to the Week 97 visit for any reason(s) and participants who will not continue study intervention after Week 97 will have an End of Treatment Follow-up visit in the clinic approximately 42 days after the last dose of study intervention. Assessments for this visit are outlined in Section 1.3.2. Participants who complete the Week 97 visit who do not consent to participate in the rollover study should also have an End of Treatment Follow-up visit.

Participants discontinuing study intervention with specified decreases in CD4+ T-cell and/or total lymphocyte counts will be followed monthly for monitoring of CD4+ T-cell and/or total lymphocyte counts per Section 8.11.6.

8.11.5 Viremia Confirmation

If a participant meets the criteria for viremia (see Section 8.2.2), a Viremia Confirmation visit must be conducted at least 4 weeks of the initial HIV-1 viremia. If a scheduled visit is to occur within the timeframe that a participant would return for a viremia confirmation visit, the assessments for the scheduled visit should be conducted, and the HIV viral drug resistance sample from the viremia confirmation visit must be collected.

8.11.6 Management of Participants with Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts

Management of participants with decreases in CD4+ T-cell counts and/or total lymphocyte counts is explained below.

8.11.6.1 Participants Whose CD4+ T-cell Count and/or Total Lymphocyte Count Decreases Meet Criteria for Events of Clinical Interest While on Study Intervention

Participants whose decreases in CD4+ T-cell counts and/or total lymphocyte counts meet ECI criteria (Section 8.4.7) must have a confirmation visit in 3 to 4 weeks*.

Upon repeat testing at the confirmation visit (Section 1.3.4), if the discontinuation criteria are met (Section 7.1), participants must be discontinued from study intervention and managed per Section 8.11.6.2.

8.11.6.2 Participants Discontinued from Study Intervention Due to Decreased CD4+ T-cell Count and/or Total Lymphocyte Count

After discontinuation from study intervention, participants will be managed for treatment of HIV-1 per local standard of care.

Participants discontinued from study intervention due to specified decreases in CD4+ T-cell and/or total lymphocyte counts should undergo assessments as specified for the Early Discontinuation of Treatment Visit and the End of Treatment Follow-up Visit (Section 1.3.4). Participants will then be monitored monthly until 2 values (12 weeks apart) of CD4+ T-cell counts and total lymphocyte counts are not decreased by >10% of the average baseline value.

8.11.6.3 Participants Discontinued from Study Intervention For Other Reasons AND Have Decreases in CD4+ T-cell Count and/or Total Lymphocyte Count

Participants who discontinue study intervention for any other reason or decline participation into the rollover study who are found to have decreases in CD4+ T-cell and/or total lymphocyte counts >10% of average baseline values, or that meet ECI criteria at the Early Discontinuation of Treatment Visit should undergo assessments specified at the End of Treatment Follow-up at Day 42 (Section 1.3.5).

- If the decrease of >10% of average baseline is confirmed at this visit, participants should continue to be monitored monthly until 2 values 12 weeks apart of CD4+ T-cell counts and total lymphocyte counts are not decreased by >10% of the average baseline value.
- If the decrease of >10% of average baseline is not confirmed at this visit, then no further follow-up for CD4+ T cell and/or total lymphocyte counts is required.

8.11.7 Clinical Management of Participants Who Become Pregnant

If a participant becomes pregnant (confirmed by a positive serum pregnancy test), the investigator should refer her to a local provider for appropriate obstetric (prenatal) care per local standard-of-care. 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 version 2.1 “Addendum 1: Female Genital Grading Table for Use in Microbicide Studies,” particularly the section “Complications of Pregnancy.”

The site will discuss with the participant:

- Joining a pregnancy registry (the Antiretroviral Pregnancy Registry), which collects information about the outcome of the pregnancy,
- Consenting to infant safety data collection per Sections 8.1.1.3 and 8.11.7.4,
- Her intended breastfeeding status (Section 8.11.7.3),

- 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).

8.11.7.1 Continuing Study Intervention

Participants who become pregnant and consent to continue study intervention (Section 8.1.1.4) should complete all remaining protocol-specified visits and procedures per the regular schedule in the SoA (Section 1.3.1). As the SoA specifies study visits at least every 12 weeks, participants will have a study visit approximately during each trimester and postpartum (ie, the first visit after delivery [~12 weeks after the 3rd trimester visit and ≤8 weeks after delivery]).

The participant's prenatal care should be coordinated between the investigator and the local obstetric care provider. The investigator (or designee) is responsible for 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
- Plasma HIV-1 RNA level
- Results of Week 20 to 22 or second 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 (TW 97), their visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum (Section 1.3.3). At the completion of the pregnancy, continued access to DOR/ISL will be offered per Section 6.7.

For participants who continue DOR/ISL, PK samples will be collected at their scheduled visit during the 1st, 2nd, and 3rd trimesters and postpartum to evaluate DOR and ISL concentration levels per Table 6. These samples will be used to characterize the PK profile of DOR/ISL during pregnancy.

Table 6 Collection of Population PK Samples During Pregnancy and Postpartum

Study Visit	Time Relative to Dose
1st Trimester[a]	Predose
2nd Trimester	Predose AND 0.5 to 2 hours AND 4 to 6 hours postdose
3rd Trimester	Predose AND 0.5 to 2 hours AND 4 to 6 hours postdose
Postpartum[b]	Predose

PK=pharmacokinetic.

[a] Collected in the 1st trimester at a scheduled visit when a participant reports gravid status.

[b] The first visit after delivery; ~12 weeks after the 3rd trimester visit and ≤8 weeks after delivery.

8.11.7.2 Discontinuing Study Intervention

Participants who become pregnant and discontinue study intervention should have an Early Discontinuation of Treatment visit per the SoA (Section 1.3.2). If the decision to discontinue study intervention occurs during the timeframe of a scheduled study visit, the assessments for the Early Discontinuation of Treatment visit should be conducted at that time. In addition, these participants will have an End of Treatment Follow-up visit in-clinic 42 (+7) days after the last dose of study intervention (Section 1.3.2).

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.

8.11.7.3 Participants Who Choose to Breastfeed

If a participant chooses to breastfeed, she should discontinue study intervention before initiating breastfeeding (Section 7.1) and be followed in the study per Section 8.11.7.2. The investigator (or local HIV care provider, if not the study site) should make every effort to develop a new treatment plan (per local guidelines) within sufficient time prior to delivery to minimize the likelihood of a gap in ART.

8.11.7.4 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 8.11.7.4.1 should be obtained by the site and entered into the appropriate CRF and source documentation. In addition, study staff should obtain results from any ultrasounds performed per local standard-of-care.

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 in this study, if exposure during pregnancy is reported in this study.

8.11.7.4.1 Schedule of Activities: Infant Safety Data Collection

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

HIV=human immunodeficiency virus; SAE=serious adverse event.

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

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

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

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

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes are made to primary hypothesis, or the statistical methods related to this hypothesis, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to final database lock, 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.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Randomized, Clinical Study in HIV-1-Infected Heavily Treatment-Experienced Participants Evaluating the Antiretroviral Activity of Blinded Islatravir (ISL), Doravirine (DOR), and Doravirine/Islatravir (DOR/ISL), Each Compared to Placebo, and the Antiretroviral Activity, Safety, and Tolerability of Open-Label DOR/ISL.
Treatment Assignment	**Run-in Period**: Participants will continue to take their current failing baseline ART. **Part 1**: Participants will be randomized in a 1:2:1:1 ratio into 1 of 4 treatment groups stratified by factors in Section 6.3.2. The goal is to randomize 150 participants; however, a minimum of 100 randomized participants is targeted for the planned analyses. • Group 1 (n ~20): ISL QD + failing baseline ART • Group 2 (n ~40): DOR QD + failing baseline ART • Group 3 (n ~20): DOR/ISL QD + failing baseline ART • Group 4 (n ~20): Placebo QD + failing baseline ART **Part 2**: All participants will be treated with DOR/ISL and OBT for 96 weeks (with the opportunity to continue DOR/ISL after Week 97). OBT options will be driven by historic and baseline resistance as well as safety and tolerability considerations.
Analysis Populations	**Efficacy:** FAS, Per-Protocol Analysis Set, and Resistance Analysis Subset **Safety**: APaT
Primary Endpoint(s)	• Percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 in the DOR/ISL group • Number of participants experiencing AEs and discontinuing study intervention due to AEs through Week 25 and Week 49.
Key Secondary Endpoints	• Percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 in the ISL group and DOR group • Percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) and Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97 • Percentage of participants achieving ≥1.0 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97, and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97 • Percentage of participants with HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL at Week 25, Week 49, and Week 97 • Mean change in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97 and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97 • Mean change in CD4+ T-cell count from study baseline (Day 1) and Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97 • Viral resistance-associated substitutions • Number of participants experiencing AEs and discontinuing study intervention due to AEs through Week 97.

Statistical Methods for Key Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	To evaluate the primary efficacy hypothesis, superiority of DOR/ISL compared to placebo with respect to the percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 will be calculated using the stratified Miettinen and Nurminen method with CMH weights (stratified by stratification factors in Section 6.3.2). Superiority will be concluded if the lower bound of the multiplicity-adjusted 95% CI for the difference is greater than 0. To assess the secondary efficacy objective regarding the treatment effect of ISL and DOR each compared to placebo with respect to the percentage of participants achieving ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, the stratified Miettinen and Nurminen method with CMH weights will be used to estimate the nominal 95% CI for the difference. Similar methodology will be used to estimate all other between-group differences and the associated nominal 95% CIs with respect to the percentage of participants achieving ≥0.5 $\log_{10}$ decrease and ≥1.0 $\log_{10}$ decrease in HIV-1 RNA from baseline to the analysis time points of interest. For participants with HIV-1 RNA <200 copies/mL, those with HIV-1 RNA <50 copies/mL, and those with HIV-1 RNA <40 copies/mL at Week 25, Week 49, and Week 97, the relevant percentages will be tabulated, and the within-group nominal 95% CIs will be presented using the Clopper Pearson method.
Statistical Methods for Key Safety Analyses	Safety and tolerability will be assessed by clinical review of all relevant parameters. Of primary interest will be a descriptive summary of the safety and tolerability of DOR/ISL. Safety summaries will be presented by treatment group through Day 8; in addition, a pooled summary will be presented for data collected through Week 25 and Week 49. The Clopper Pearson method will be used to compute within-group nominal 95% CIs for selected binary parameters. CIs for change from baseline parameters will be computed based on the t-distribution.
Interim Analyses	Three types of interim analyses are planned in this study. • **Periodic reviews of safety and efficacy data** (conducted by an independent, unblinded eDMC). • **Futility assessment**. HIV-1 RNA at the end of Part 1 will be tracked and provided to an external unblinded statistician to perform the futility assessment. Details on futility boundaries are presented in Section 9.7.2. If any of the futility boundaries are met, an ad hoc eDMC review will be triggered and the eDMC may recommend the study be stopped; the eDMC will review the totality of the available data at the time of this ad hoc interim analysis before making such a recommendation. • **Analysis for testing the primary efficacy hypothesis.** This analysis will be conducted by Sponsor at the end of Part 1. Results will be shared with the eDMC.
Multiplicity	For statistical rigor, a small amount of alpha (α=0.00001) will be set aside for the futility assessment and each eDMC evaluation. The Type I error rate for testing the primary hypothesis at Day 8 will be adjusted depending on the number of eDMC reviews conducted prior to completion of the testing of the primary hypothesis.
Sample Size and Power	The study power to establish superiority under various assumptions is presented in Section 9.9.1.

9.2 Responsibility for Analyses/In-house Blinding

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

Part 1 of this study (Day 1 through Day 8) will be conducted as a double-blind study under in-house blinding procedures. The official, final database for Part 1 will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete for Part 1. The clinical database and all Sponsor personnel will become unblinded to Part 1 intervention assignment at the time of the Part 1 analysis, although study participants and site personnel will remain blinded until Week 97. Part 2 of this study (Day 8 through Week 97) will be conducted as an open-label study. Results of Part 2 will be presented in the CSR along with results of Part 1.

PK data may be unblinded earlier for the purpose of preparing a population PK model. A separate team from the Sponsor protocol team will be unblinded for the purpose of preparing the population PK model. Efficacy and safety data will not be unblinded for the purpose of PK analysis. Interim data or results will not be shared with the Sponsor protocol team before unblinding of the Sponsor.

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

9.4.1 Efficacy/Pharmacokinetics Endpoints

9.4.1.1 Primary Efficacy Endpoint

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

Percentage of participants with ≥0.5 $\log_{10}$ decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 in the DOR/ISL group

The Abbott RealTime PCR assay with a reliable lower limit of quantification of 40 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The evaluation of the primary efficacy objective (including the primary efficacy

hypothesis) will be based on the percentage of participants with ≥0.5 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 in the DOR/ISL group.

9.4.1.2 Secondary Efficacy Endpoints

Percentage of participants with ≥0.5 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 in the ISL group and DOR group

Percentage of participants with ≥0.5 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) and Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97

Percentage of participants with ≥1.0 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97 and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97

Percentage of participants with HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL at Week 25, Week 49, and Week 97

Antiretroviral activity will also be assessed on the basis of the percentage of participants with HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL. These endpoints will be estimated at each time point at which HIV-1 RNA is measured, with primary interest at Week 25, Week 49, and Week 97 to support the secondary objectives.

Change in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97 and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97

For calculations of change from baseline in HIV-1 RNA, both study baseline (Day 1) and the Part 2 baseline (Day 8) HIV-1 RNA measurements will be used. In the rare event when baseline data are missing, the last measurement within the screening window will be used as the study baseline (Day 1) when available, and the last measurement in Part 1 prior to Day 8 intervention will be used as Part 2 baseline (Day 8) when available. These rules will also apply to define the baseline measurements for calculation of change from baseline in CD4+ T-cell count, and for other laboratory tests.

Change in CD4 + T-cell Count from study baseline (Day 1) and Part 2 baseline (Day 8) at Week 25, Week 49, and Week 97

Change in CD4+ T-cell count from baseline will be estimated at each time point at which CD4+ T-cell count is collected. A secondary objective will assess the change in CD4+ T-cell count from study baseline (Day 1) and Part 2 baseline (Day 8) baseline at Week 25, Week 49, and Week 97.

Viral resistance-associated substitutions

Participants who meet the definition of confirmed viremia (defined as having 2 consecutive confirmed HIV-1 RNA ≥200 copies/mL [at least 4 weeks apart] after achieving HIV-1 RNA <50 copies/mL), or who discontinue study intervention with HIV-1 RNA ≥200 copies/mL, or who never suppressed (<50 copies/mL) at Week 25, Week 49, and Week 97 with HIV-1

RNA >200 copies/mL, will be assessed for development of viral drug resistance. Among such participants, those with HIV-1 RNA ≥400 copies/mL will be included in 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 resistance analyses. The resistance analysis will summarize the number of participants who have resistance-associated substitutions associated with each study intervention and will be summarized with primary interest at Day 8, Week 25, Week 49, and Week 97.

9.4.1.3 Pharmacokinetics Endpoints

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

9.4.2 Safety Endpoints

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

Adverse Events

The following clinical and laboratory adverse events 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 to 4 AE; 5) participants with at least 1 serious and drug-related AE; 6) participants with at least 1 AE which is both Grade 3 to 4 and drug-related; 7) participants who discontinued study intervention due to a drug-related and nondrug-related AE; and 8) participants with AE(s) leading to death.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a study baseline (Day 1) or Part 2 baseline (Day 8) and postrandomized 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 of the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, Version 2.1 (Appendix 3). A listing of the participants who meet the criteria will also be provided.

These PDLC summaries will be performed for the following:

- Day 1 (study baseline) to Day 8 (end of blinded treatment period)
- Day 1 (study baseline) to Week 25
- Day 1 (study baseline) to Week 49
- Day 1 (study baseline) to Week 97

- Day 8 (Part 2 baseline) to Week 25
- Day 8 (Part 2 baseline) to Week 49
- Day 8 (Part 2 baseline) to Week 97

Measures of Inflammation

Change from baseline in IL-6, D-dimer, sCD-163, and hs-CRP from study baseline (Day 1) to Week 25, Week 49, and Week 97 will be analyzed.

9.4.3 Patient-reported Outcome Endpoints

An initial description of patient-reported outcome measures is provided in Section 4.2.1.2 of the protocol.

Patient-reported outcomes from each questionnaire at Day 1, Week 25, Week 49, and Week 97 will be summarized for participants ≥18 years of age at the time of consent in each treatment group. A total FAHI score and score for individual subscales (physical, emotional, functional, social, and global well-being as well as cognitive functioning) will be summarized.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

Details on the approach to handling missing data for efficacy analyses are provided in Section 9.6.1.

9.5.1.1 Full Analysis Set

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

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

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

9.5.1.2 Per-protocol Analysis Set

The secondary analysis set for the efficacy analyses is defined as the PP analysis set, which will include all participants in the FAS who have not committed any major protocol violations that could impact the assessment of efficacy. Participants will be grouped according to the treatment to which they are randomized.

Participants who are nonadherent to study intervention (ie, participants with a study intervention compliance rate <95%) or who become pregnant will be excluded from the PP analysis set.

The additional criteria resulting in exclusion from the PP analysis set will be provided in the sSAP and will be identified prior to unblinding and completion of Part 1.

The composition of the PP analysis set will 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 participant for whom available genotypic or phenotypic data show evidence of resistance irrespective of viral load.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received.

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

Details on the approach to handling missing data for safety analyses are provided in Section 9.6.2.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to PK analysis and modeling will be described in a separate modeling and simulation plan authored by the department of Quantitative Pharmacology and Pharmacometrics (QP2). Methods related to other exploratory objectives will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analyses

Time Window

The definition of time windows that will be used for the purposes of the statistical analyses and the target relative day for the scheduled visits in the study which will be used for all analyses by time point are presented in Table 7. The last available on-treatment measurement

within a window will be used for analyses at a specific time point, unless otherwise specified. Results from additional time points beyond Week 97 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 7 Definitions of Study Time Points

Treatment Phase	Treatment Period	Visit	Day-Range Rules	Target Day[a]
Pretreatment	Screening	Day 1[b]	≤1	1
Treatment	Part 1	Day 8‡	≥2 and ≤14	8
	Part 2	Week 3	≥15 and ≤35	22
		Week 7	≥36 and ≤70	50
		Week 13	≥71 and ≤112	92
		Week 19	≥113 and ≤154	134
		Week 25	≥155 and ≤217	176
		Week 37	≥218 and ≤301	260
		Week 49	≥302 and ≤385	344
		Week 61	≥385 and ≤469	428
		Week 73	≥470 and ≤553	512
		Week 85	≥554 and ≤637	596
		Week 97	≥638 and ≤721	680

a Relative days and target days are computed from the first day of study intervention. Participants have to complete Day 8 assessment before entering study Part 2; Day 8 window will not overlap with start of OBT.

b Day 1 is also referred to as the Study Baseline. Day 8 is also referred to as the Part 2 Baseline.

FDA Snapshot Algorithm and Missing Data Approaches

There are 3 types of missing values:

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

Three approaches will be used to handle missing values. The primary approach for the analysis of binary efficacy endpoints (eg, assessing percentage of participants with ≥0.5 log_{10} or a ≥1.0 log_{10} decrease in HIV-1 RNA from baseline; assessing the percentages of participants with HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL) is the FDA "snapshot" algorithm [Food and Drug Administration (CDER) 2015]. Under this approach, the binary outcomes will be defined according to the following categories:

- Success: depending on the analysis and endpoint, success could mean ≥0.5 log10 decrease in HIV-1 RNA from baseline; ≥1.0 log10 decrease in HIV-1 RNA from baseline; HIV-1 RNA <200 copies/mL, <50 copies/mL, or <40 copies/mL. This category includes participants who have the last available on-treatment HIV-1 RNA measurement meeting the success criteria within the time point of interest analysis window specified in Table 7.

- Failure: depending on the analysis and endpoint, failure could mean <0.5 log10 decrease in HIV-1 RNA from baseline; <1.0 log_{10} decrease in HIV-1 RNA from baseline; HIV-1 RNA ≥200 copies/mL, ≥50 copies/mL, or ≥40 copies/mL. This category includes the following participants:

  1) Those whose last available on-treatment HIV-1 RNA fails to meet the success criteria within the time point of interest analysis window specified in Table 7

  2) Those who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window and

     - Who discontinue study intervention prior to or in the time point of interest analysis window due to lack of efficacy, or

     - Who discontinue study intervention prior to or in the time point of interest analysis window due to reasons other than lack of efficacy and AE/death and whose last available on-treatment HIV-1 RNA fails to meet the success criteria.

- **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 because of the following:

  1) 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 virologic data during the specified window.

  2) 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 or AE/Death (ie, lost to follow-up, noncompliance with study intervention, physician decision, protocol deviation, withdrawal by participant, etc.) and have the last available on-treatment HIV-1 RNA meeting the success criteria.

3) 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 of this window will be classified as "on study intervention, but missing data in window" regardless of the HIV-1 RNA results.

In Part 2 of the study, any changes to the OBT regimen due to lack of efficacy will be imputed as failure using the FDA snapshot approach. For participants who become pregnant during the study, modification of the OBT will not be imputed as failure unless the change was due to lack of efficacy. Additionally, changes to the OBT regimen due to delayed drug sourcing or other extraneous circumstances will not be imputed as failure.

For the primary evaluation of superiority based on those with a $\geq$0.5 $\log_{10}$ decrease in HIV-1 RNA, the parameter for evaluation is the number of participants classified as "success" according to the FDA snapshot algorithm defined above, divided by the number of participants in the FAS. Similar logic will also be used to define the percentage of participants with a $\geq$1.0 $\log_{10}$ decrease in HIV-1 RNA from baseline and the percentage of participants with HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL in accordance with the relevant secondary endpoints. It is noted that those classified as having no data in the specified analysis window will contribute to the denominator (as these participants are included in the FAS), but are effectively treated as failures under this approach as they do not contribute to the numerator.

A second approach, the missing data treated as treatment failure (M=F) approach, will be performed as a sensitivity analysis. Under this approach, participants who 1) have at least one on-treatment HIV-1 RNA measurement within the time point of interest analysis window specified in Table 7 and have the last available on-treatment measurement within the window meeting the success criterion for the endpoint will be classified as "success" at the time point of interest, OR 2) are on study intervention and have no HIV-1 RNA measurements within the time point of interest analysis window specified in Table 7 and have both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements meeting the success criterion will be classified as "success" at the time point of interest. Participants with other reasons for missing data will be classified as a "failure" at the time point of interest.

A third approach, the Observed Failure (OF) approach will also be performed as a sensitivity analysis for these efficacy endpoints. Under this approach, participants with nonintermittent missing data who prematurely discontinue study intervention due to lack of efficacy or who discontinue study intervention for other reasons and are failures at the time of study intervention discontinuation are considered as failures at time points thereafter. Participants who discontinue study intervention for reasons other than lack of efficacy and who are not failures at the time of study intervention discontinuation will be excluded from the analyses at subsequent time points. Participants with intermittent missing data will be considered as successes if both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements meet the success criterion; all other intermittent missing results will be imputed as failures.

In accordance with the FDA snapshot algorithm and to provide a full picture of virologic outcomes at Day 8, Week 25, Week 49, and Week 97, participants will be classified as either "success", "failure", or as having "no virologic data within the time window". Participants with no virologic data within the time window will be further classified by reason: 1) discontinued study intervention due to AE or death, 2) discontinued study intervention for other reasons (includes withdrawal of consent, loss to follow-up, moved, etc.), or 3) on study intervention, but missing data in window.

Percentage of participants achieving ≥0.5 log_{10} or ≥1.0 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) and Part 2 baseline (Day 8)

For the evaluation of the primary hypothesis, superiority of DOR/ISL compared to placebo with respect to the percentage of participants achieving ≥0.5 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8 will be calculated using the Miettinen and Nurminen method with CMH weights (stratified by the factors specified in Section 6.3.2). Superiority will be concluded if the lower bound of the multiplicity-adjusted 95% CI for the difference (DOR/ISL minus placebo) is greater than 0.

To assess the secondary objective regarding estimation of the treatment effect of ISL monotherapy and DOR monotherapy compared to placebo with respect to the percentage of participants achieving ≥0.5 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, the Miettinen and Nurminen method with CMH weights will also be used to estimate the nominal 95% CI for the treatment difference (ISL minus placebo, DOR minus placebo).

Similar methodology will be used to estimate between-group differences and the associated nominal 95% CIs for the percentage of participants achieving ≥0.5 log_{10} decrease from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97, as well as for the percentage of participants achieving ≥1.0 log_{10} decrease from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97, and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97.

It is noted that the enrollment into Stratum 2 and Stratum 3 (as defined in Section 6.3.2) are likely to be low. If there are fewer than 5 participants randomized into one of these strata (which would be a complete randomization block), Strata 2 and 3 will be combined for the purposes of conducting all stratified analyses. If after combining Strata 2 and 3 there are still <2 participants in a treatment group, the unstratified Miettinen and Nurminen method would be used instead for that analysis.

Percentages of participants with HIV-1 RNA <200 copies/mL, <50 copies/mL, and <40 copies/mL

For the secondary endpoints associated with Week 25, Week 49, and Week 97, the relevant percentages will be tabulated and the within-group 95% CIs will be presented using the Clopper Pearson method. Since all participants will have received DOR/ISL, these results will also be pooled across the original treatment groups at Week 25, Week 49, and Week 97.

Mean change in HIV-1 RNA from study baseline (Day 1) and Part 2 baseline (Day 8)

Change in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97, and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97, will be summarized by treatment groups. The treatment differences in change in HIV-1 RNA from baseline will be estimated between treatment groups using ANCOVA models.

The DAO approach will be used to handle missing data for these analyses. Under the DAO approach, participants must have both a baseline measurement and at least one postbaseline measurement within the time point of interest analysis window specified in Table 7 in order to be included in the analyses of the mean change from baseline in HIV-RNA. Supportive analyses will also be provided using the LOCF method to account for missing data.

Mean change in CD4+ T-cell count from study baseline (Day 1) and Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97

Change from baseline in CD4+ T-cell count will be summarized at each time point at which CD4+ T-cell count is collected with primary interests at Week 25, Week 49, and Week 97. Descriptive statistics will be provided including point estimates and corresponding confidence intervals based on the t-distribution. Change from baseline in CD4+ T-cell count will be summarized by Part 1 treatment group as well as pooled across groups.

The DAO approach will be used to handle missing data for these analyses. Under the DAO approach, participants must have both a baseline measurement and at least one postbaseline measurement within the time point of interest analysis window specified in Table 7 in order to be included in the analyses of the mean change from baseline in CD4+ T-cell count. Supportive analyses will also be provided using the baseline observation carried forward (BOCF) method to account for missing data.

Viral resistance-associated substitutions

The number of participants in the resistant analysis subset with genotypic and/or phenotypic resistance to each study intervention will be summarized for each treatment group with primary interests at Day 1, Day 8, Week 25, Week 49, and Week 97.

Unblinding of Participants During the Study

Given the objective nature of the efficacy endpoint HIV-1 RNA, if a participant becomes unblinded during the study for any reason not related to efficacy (eg, due to a safety event, acute infection/reactivation of HBV or pregnancy that requires unblinding, or accidental unblinding), such participants will not be treated as treatment failures in the primary efficacy analyses on the FAS population due to the unblinding alone. If the unblinding is due to acute infection/reactivation of HBV or pregnancy that requires discontinuation of study intervention or if the clinical management of the HBV requires the addition of a concomitant therapy that is also active against HIV-1, such participants will be censored from that point forward and will be handled in the primary efficacy analyses according to the FDA snapshot algorithm classification rules.

Participants Who Become Pregnant or Choose to Breastfeed

Efficacy assessments in participants who become pregnant and discontinue study intervention or choose to breastfeed will be censored from that point forward and will be handled in the primary efficacy analyses following the FDA snapshot algorithm classification rules.

Table 8 summarizes the key efficacy analyses of the study.

Table 8 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method[a]	Analysis Population	Missing Data Approach
Percentage of participants achieving ≥0.5 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97, and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97	P	M&N method with CMH weights	FAS	Snapshot[b]
	S	M&N method with CMH weights	FAS	M=F
	S	M&N method with CMH weights	PP	OF
Percentage of participants achieving ≥1.0 log_{10} decrease in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97, and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97	P	M&N method with CMH weights	FAS	Snapshot[b]
	S	M&N method with CMH weights	FAS	M=F
	S	M&N method with CMH weights	PP	OF
Percentage of Participants with HIV-1 RNA <200 copies/mL, those with HIV-1 RNA <50 copies/mL, and those with HIV-1 RNA <40 copies/mL at Week 25, Week 49, and Week 97	P	Clopper Pearson	FAS	Snapshot[b]
	S	Clopper Pearson	FAS	M=F
	S	Clopper Pearson	PP	OF
Change in HIV-1 RNA from study baseline (Day 1) to Day 8, Week 25, Week 49, and Week 97, and from Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97	P	ANCOVA	FAS	DAO
	S	ANCOVA	FAS	LOCF

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method[a]	Analysis Population	Missing Data Approach
Change in CD4+ T-cell count from study baseline (Day 1) and Part 2 baseline (Day 8) to Week 25, Week 49, and Week 97	P	Within-group summaries using the t-distribution	FAS	DAO
	S	Within-group summaries using the t-distribution	FAS	BOCF

ANCOVA=analysis of covariance; BOCF=Baseline Observation Carried Forward; CMH=Cochran-Mantel-Haenszel; DAO=Data as Observed; FAS=Full Analysis Set; HIV-1=human immunodeficiency virus Type 1; LOCF=Last Observation Carried Forward; M=F=Missing=Failure; OF=Observed Failure; P=Primary approach; PP=Per-Protocol Analysis Set; RNA=ribonucleic acid; S=Supportive approach.

a The Miettinen and Nurminen method with CMH weights will be stratified by stratification factors specified in Section 6.3.2

b Number of participants that meet the endpoint clinical response criteria over total FAS population.

9.6.2 Statistical Methods for Safety Analyses

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

Of primary interest will be a descriptive summary of the safety and tolerability of DOR/ISL. Upon the completion of Part 1, safety data from Day 1 through Day 8 will be summarized by treatment group. At Week 25, Week 49, and Week 97, safety data will be summarized by treatment group as well as pooled across treatment groups; the safety data from Day 8 in the placebo group and the safety data from Day 1 in all other treatment groups will be pooled for these summaries. A summary of the analysis strategy for the safety parameters is provided in Table 9. The Clopper Pearson method will be used to compute within-group 95% CIs for selected binary parameters. Confidence intervals for change from baseline parameters will be computed using the t-distribution.

Missing values will be handled using the DAO approach, that is, any participant with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. Baseline measurements are defined as either the Day 1 value (study baseline) or Day 8 value (Part 2 baseline) for each participant, depending on the analysis/summary. In the rare event when study baseline data are missing, the value obtained at the most recent Screening Visit will be used as the Day 1 baseline. If no pretreatment result is available, that participant will not be included in the summary. Similarly, if no Day 8 value is available, that participant will not be included in summaries involving the Part 2 baseline.

For participants who become pregnant during the study, safety parameters assessed during the pregnancy period (estimated date of conception to date of conclusion of the pregnancy) may be summarized separately from the primary and secondary safety analyses. For continuous measures that are considered to be Tier 2 events, data collected after the estimated date of conception will be excluded from the analyses. Infant safety data will be reported separately. Additional details on how pregnancy and infant data will be handled in safety analyses will be provided in the sSAP and/or CSR.

Table 9 Analysis Strategy for Safety Parameters

Safety Parameters	Within-Group 95% CI[a]	Descriptive Statistics
• The percentage of participants with an AE in each of the following categories: one or more AE(s); drug-related AE(s), serious AE(s), Grade 3 to 4 AE(s), AE(s) which are both drug-related and serious, AE(s) which are both Grade 3 to 4 and drug-related, AE(s) [drug-related and nondrug-related] leading to discontinuation of study intervention, and AE(s) leading to death • The percentage of participants with a cardiac SAE • Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence ≥10% in one of the groups • Change from baseline in markers of inflammation	X	X
• Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence <10% in all groups • Change from baseline in laboratory measurements and vital signs		X

AE(s)=adverse event(s); CI=confidence interval; PDLC=Predefined Limit of Change; SAE=serious adverse event; SOC=System Organ Class; X=results will be provided.

a 95% CIs will be calculated using the Clopper Pearson method for binary parameters and the t-distribution for change from baseline measures.

9.6.3 Summaries of Baseline Characteristics, Demographic, and other Analyses

9.6.3.1 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

There are possibly 4 types of analysis that will be performed at interim time points (Section 9.7.1 to Section 9.7.4). Study enrollment is likely to be ongoing at the time of some interim analyses. Blinding to Part 1 treatment assignment will be maintained at all investigational sites.

An eDMC will serve as the primary reviewer of the results of the interim analyses of the study and may make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor. If the eDMC recommends

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

Treatment-level results from the interim analyses will be provided to the eDMC by the external unblinded statistician until the Sponsor is unblinded at the time of the Part 1 analysis. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses. Following the unblinding of the Sponsor after Part 1 analysis, the responsibility for providing subsequent interim analysis results to the eDMC may transfer to unblinded Sponsor personnel.

9.7.1 Safety Monitoring

A periodic review of safety and efficacy data will be conducted by an independent, unblinded, eDMC. A description of the structure and function of the eDMC, along with the timing and content of the review, will be outlined in the DMC charter.

9.7.2 Futility Monitoring

HIV-1 RNA at Day 8 (the end of Part 1) will be tracked and provided to an unblinded statistician on an ongoing basis to perform futility assessment. Table 10 lists the futility boundaries corresponding to each possible sample size in the DOR/ISL group. For example, based on the futility boundary with a sample size of up to and including 20, if 12 or more participants who receive DOR/ISL in the double-blind treatment period (Part 1) fail to achieve $\geq$0.5 $\log_{10}$ decline in HIV-1 RNA at the end of Part 1, an eDMC review will be triggered. This futility criterion corresponds to an OF rate of 60%. If such a futility analysis is triggered, the results will be shared with the eDMC who will make recommendations for discontinuation of the study or protocol modifications to the study Executive Oversight Committee (EOC). The Sponsor will not be informed if an eDMC review is triggered due to meeting the futility boundaries.

Table 10 Futility Boundary That Would Trigger Ad Hoc eDMC Review Corresponding to Current Possible Sample Size in DOR/ISL Group

Current Sample Size in DOR/ISL Group	**Futility Boundary (Number of Participants with <0.5 log_{10} Decline in HIV-1 RNA at Day 8)**	**Observed Failure Rate (<0.5 log_{10} Decline in HIV-1 RNA)**	**Observed Rate with ≥0.5 log_{10} Decline in HIV-1 RNA**
≤20	12	≥60.0%	≤40.0%
21	12	57.1%	42.9%
22	13	59.1%	40.9%
23	13	56.5%	43.5%
24	14	58.3%	41.7%
25	14	56.0%	44.0%
26	15	57.7%	42.3%
27	15	55.6%	44.4%
28	16	57.1%	42.9%
29	16	55.2%	44.8%
30	17	56.7%	43.3%
DOR=doravirine; HIV-1=human immunodeficiency virus Type 1; ISL=islatravir; RNA=ribonucleic acid.			

9.7.3 Interim Analysis for Potential Marketing Authorization Application

Prior to the formal unblinded IA in Section 9.7.4, a blinded interim data summary may be conducted to support any potential marketing authorization application of DOR/ISL. In such an event, blinded efficacy and safety summaries from Part 1 will be presented along with open-label efficacy and safety summaries from Part 2. This analysis will be prepared by the blinded team of the Sponsor.

9.7.4 Interim Analysis for Testing the Primary Hypothesis

An analysis will be conducted to test the primary efficacy hypothesis after all participants have completed Part 1. This will be the formal evaluation of the primary efficacy hypothesis and the Sponsor will become unblinded at that time. The analysis of Part 1 data will be performed by the unblinded team of the Sponsor. All available efficacy and safety data will be reviewed at this interim time point. Treatment-level results from this analysis will also be provided to the eDMC. Following the unblinding of the Sponsor after Part 1, the responsibility for providing subsequent interim analysis results to the eDMC may transfer to unblinded Sponsor personnel.

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

9.8 Multiplicity

As noted in Section 9.7, an eDMC will convene at routine intervals to monitor efficacy, safety, and tolerability. There is no intention of stopping the study due to positive efficacy at any of these reviews. Nevertheless, since unblinded summaries of HIV-1 RNA values may be included in these reviews, a small amount of alpha (α=0.00001) will be allocated for each of these looks, purely for statistical rigor. An allowance will be made such that a total of up to 5 of these unblinded eDMC reports (including the futility assessment if the eDMC review is triggered) may be presented prior to the evaluation of the primary efficacy hypothesis (DOR/ISL vs. placebo) at Day 8.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

9.9.1.1 Futility Criteria and Superiority Testing

All the calculations in this section are conservatively based on a sample size of 20 in the DOR/ISL group. As the sample size may be larger, these calculations are expected to represent the minimum power.

As described in Section 9.8, the alpha level used in the final analysis (corresponding to the multiplicity-adjusted 95% CI) will account for the actual number of eDMC evaluations conducted in the study. For the purposes of the power calculations, 5 eDMC evaluations are assumed, leaving α=0.02495 (one-sided) available for the final analysis of the Part 1 hypothesis.

The power calculations shown in Table 11 incorporate the futility stopping rule. Based on the futility rule, the study may stop if 12 or more out of 20 participants who receive DOR/ISL in the double-blind treatment period (Part 1) fail to achieve $\geq$0.5 $\log_{10}$ decline in HIV-1 RNA at the end of Part 1. Table 11 displays the probability of this study meeting the stopping rule, and the overall power to demonstrate superiority of DOR/ISL compared to placebo under a variety of response assumptions. For example, if the true response rate for DOR/ISL recipients in Part 1 is 80%, there is a 0.01% chance of meeting the futility rule. In addition, if the true response rate for the placebo recipients is 3%, the probability of demonstrating superiority of DOR/ISL compared to placebo at Day 8 is >99.9%.

Table 11 Probability of Meeting Futility Criteria and the Overall Study Power for Various Underlying True Response Rates Assuming the Response Rate is 3% or 10% for Placebo Recipients

True Response Rate for Placebo Recipients (N=20)	True Response Rate for DOR/ISL Recipients (N=20)	Probability of Meeting Futility Criteria[a]	Probability Of Demonstrating Superiority Of DOR/ISL Over Placebo At Day 8[b]
3%	30%	88.7%	7.3%
	40%	59.6%	33.9%
	50%	25.1%	71.3%
	60%	5.6%	93.6%
	70%	0.5%	99.4%
	80%	0.01%	>99.9%
	90%	<0.001%	≥99.9%
10%	30%	88.7%	3.9%
	40%	59.6%	24.1%
	50%	25.1%	60.9%
	60%	5.6%	89.1%
	70%	0.5%	98.7%
	80%	0.01%	>99.9%
	90%	<0.001%	≥99.9%

DOR=doravirine; HIV-1=human immunodeficiency virus Type 1; ISL=islatravir; RNA=ribonucleic acid.

a Calculated using the binomial distribution. Under the minimum sample size of 20, the cutoff for futility is 12 participants, meaning if 12 or more out of 20 participants who receive DOR/ISL in the double-blind treatment period (Part 1) fail to achieve ≥0.5 $\log_{10}$ decline in HIV-1 RNA at the end of Part 1, the study may be stopped.

b Overall power to demonstrate superiority of DOR/ISL compared to placebo are calculated based on one-sided α=0.02495.

9.9.1.2 Evaluation of the Primary Hypotheses

This section provides further description of the power calculations for the primary analysis of superiority of DOR/ISL over placebo. In contrast to the power shown in Table 11, the power calculations shown in Table 12 do not account for the futility analysis and instead assume the futility criteria are not met.

The study power of demonstrating superiority of DOR/ISL over placebo under various assumptions is presented in Table 12, with assumed true response rates ranging from 70% to 90% for DOR/ISL and rates from 3% to 25% for placebo. For example, if the true rate of DOR/ISL participants achieving a ≥0.5 $\log_{10}$ decrease in HIV-1 RNA is 83%, and the corresponding true rate in placebo recipients is 3%, this study has >99.9% power to demonstrate superiority of DOR/ISL over placebo.

Table 12 Power (%) to Establish Superiority† Under Various Response Rate Assumptions (20 DOR/ISL Recipients and 20 Placebo Recipients)

True Response Rate for Placebo Recipients	True Response Rate for DOR/ISL Recipients				
	70%	78%	83%	88%	90%
3%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%
10%	99.2%	>99.9%	>99.9%	>99.9%	>99.9%
20%	92%	98.2%	99.5%	>99.9%	>99.9%
25%	84%	95%	98.3%	99.6%	99.8%

DOR=doravirine; ISL=islatravir.
† Overall power to demonstrate superiority of DOR/ISL compared to placebo is calculated based on one-sided α=0.02495.

9.9.2 Sample Size and Power for Safety Analyses

A summary of the probability of observing at least one AE for a given incidence rate is summarized in Table 13 for a variety of underlying AE incidence rates. For example, in a treatment group with 20 participants (such as Group 1 in the double-blind treatment period [Part 1]), if the underlying incidence of a particular AE is 10%, there is a 87.8% chance of observing at least 1 participant with that particular AE among 20 participants receiving DOR/ISL through Day 8.

Table 13 Probability of Observing At Least One Event in a Treatment Group for a Given Sample Size and a Variety of Underlying AE Incidence Rates

Underlying AE Incidence Rate	Probability of Observing At Least One Event in a Treatment Group of Size N=20	Probability of Observing At Least One Event in a Treatment Group of Size N=40	Probability of Observing At Least One Event in a Treatment Group of Size N=100
0.1%	2.0%	3.9%	9.5%
0.5%	9.5%	18.2%	39.4%
1.0%	18.2%	33.1%	63.4%
3.0%	45.6%	70.4%	95.2%
5.0%	64.2%	87.1%	99.4%
10.0%	87.8%	98.5%	>99.99%

AE=adverse event.

The estimate and associated upper bound of the 95% CI for the underlying percentage of participants with an AE given various hypothetical observed number of participants with the AE are provided in Table 14 for treatment groups of varying size. These calculations are

based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

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

Sample Size	Hypothetical Number of Participants with Adverse Event	Observed AE Incidence Rate	95% CI Upper Bound[a]
20	0	0%	13.9%
	1	5%	24.8%
	2	10%	31.7%
	3	15%	37.9%
	4	20%	43.7%
	5	25%	49.1%
40	0	0%	7.2%
	1	2.5%	13.2%
	2	5%	16.9%
	4	10%	23.7%
	8	20%	35.6%
	12	30%	46.5%
	15	37.5%	54.2%
100	0	0%	2.9%
	1	1%	5.4%
	2	2%	7.0%
	4	4%	9.9%
	8	8%	15.2%
	12	12%	20.0%
	15	15%	23.5%
	20	20%	29.2%

AE=adverse event; CI=confidence interval

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

9.10 Subgroup Analyses

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% Miettinen and Nurminen CI unadjusted for stratification factors) for the primary endpoint will be calculated within each category of the following classification variables:

- Age group (<18, ≥18 years of age)
- Sex at birth
- Gender identity
- Race (White, Black, Asian, Other)
- Region (North America, South America, Europe, Asia, Africa, etc.)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Randomization stratum
- Number of fully active and available drugs in the OBT
- Baseline CD4+ T-cell count category (50 to <200 cells/mm^3, <50 cells/mm^3)
- Baseline HIV-1 RNA (≤100,000, >100,000 copies/mL)
- Baseline NNRTI mutations
- Baseline NRTI mutations

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

9.11 Compliance (Medication Adherence)

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

For the main 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 or capsule from any bottle provided for this 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 date of the scheduled Week 97 visit for those participants who are on study intervention for the entire study period.

For participants who discontinue study intervention early (ie, prior to completion of the study at Week 97), 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 on percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations, and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

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

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will

review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

10.1.9 Source Documents

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

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
    - Pregnancy testing:
    - Pregnancy testing requirements for study inclusion are described in Section 5.1.
    - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 15 Protocol-required Laboratory Assessments

Laboratory Assessments	**Parameters**
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit RBC Indices: • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • MCH concentration • Red cell distribution width (RDW) White blood cell (WBC) count with Differential (%; absolute): • Neutrophils, total • Lymphocytes • Monocytes • Eosinophils • Basophils

Laboratory Assessments	**Parameters**
CD4+ T-cell count/TBNK Panel	T-cell, B-cell and Natural Killer cell panel includes: CD3+ Percent CD3+ Value/Absolute Count CD3+CD4+ Percent CD3+CD4+ Value/Absolute Count CD3+CD8+ Percent CD3+CD8+ Value/Absolute Count CD3-CD19+ Percent CD3-CD19+ Value/Absolute Count CD16+CD56+ Percent CD16+CD56+ Value/Absolute Count CD3+CD4+CD8+ Percent CD3+CD4+CD8+ Value/Absolute Count CD4/CD8 Ratio
Coagulation	Prothrombin time/International normalized ratio (INR)
Chemistry (nonfasting)	Alanine Aminotransferase (ALT) Albumin Alkaline Phosphatase Amylase Aspartate Aminotransferase (AST) Bicarbonate Blood Urea Nitrogen (BUN) Calcium Chloride Creatinine Creatine Kinase Glucose (nonfasting) Lipase Magnesium Phosphorous Potassium Sodium Total bilirubin • Direct bilirubin • Indirect bilirubin Total Protein

Laboratory Assessments	Parameters
Additional chemistry at fasting visit (fasting for at least 8h)	Glucose [fasting] High-density lipoprotein (HDL-C) Low-density lipoprotein (LDL-C) Triglycerides (TGs) Total Cholesterol (TC) Non-HDL-C
Renal Function	Creatinine clearance will be measured by Cockcroft-Gault (see Appendix 8) and estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) equation
Routine Urinalysis	Blood Bilirubin Glucose Ketones Leukocytes Nitrite pH Protein Specific gravity Urobilinogen
Pregnancy Testing	Serum β human chorionic gonadotropin (β hCG) test (as needed for WOCBP) Urine β human chorionic gonadotropin (β hCG) test (as needed for WOCBP)
Hepatitis Serology (at Screening)	Hepatitis B virus surface antigen (HBsAg) Hepatitis B virus (HBV) surface antibody Anti-HBc (hepatitis B core antibody) HBV DNA Hepatitis C antibody plasma HCV RNA (hepatitis C virus quantitative test)
HIV-1 Serology	HIV-1/-2 antigen/antibody screen
Virology	HIV-1 viral RNA quantification (Real time polymerase chain reaction [PCR]) HIV-1 drug resistance Proviral DNA Resistance Testing (GenoSure Archive)
Inflammatory Markers	D-dimer IL-6 Soluble CD163 hs-CRP
PK	ISL DOR

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

Table 16 Blood Volume by Visit

Study Period	Screening	HIV-1 RNA Confirmation	Repeat HIV-1 RNA Confirmation[a]	Intervention													End of Treatment				
				Double-Blind (Part 1)	Open-Label (Part 2)												Viremia Confirmation	CD4+ T-cell / Lymphocyte Confirmation	Early D/C of Treatment	CD4+ T-cell / Lymphocyte Monitoring[d]	End of Treatment F/U
Scheduled Day/Week	Screen	≤10 days prior to Day 1	7-14 days after Visit 2	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	Unscheduled	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																				
Hematology	2			2	2			2		2	2	2	2	2	2	2		2	2	2	2
Chemistry (includes serum pregnancy at Screening and Early Discontinuation)	6			6	6			6		6	6	6	6	6	6	6			6		6
Renal Function	NA; eGFR by MDRD equation																				
Serum Pregnancy Test (β-hCG; WOCBP only)	Included in Chemistry																				
Fasting Lipids/Glucose	Included in Chemistry																				
PT/INR	2.7																				
HIV-1/2 and hepatitis serology[b]	6																				
HBV DNA	6											6									
HCV RNA	6											6									
HIV-1 viral RNA Quantification (Real Time PCR)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6		6
HIV Confirmation Geenius	1																				
CD4+ T-cell count/TBNK Panel	4			4	4			4		4	4	4	4	4	4	4		4	4	4	4

Study Period	Screening	HIV-1 RNA Confirmation	Repeat HIV-1 RNA Confirmation[a]	Intervention													End of Treatment				
				Double-Blind (Part 1)	Open-Label (Part 2)												Viremia Confirmation	CD4+ T-cell / Lymphocyte Confirmation	Early D/C of Treatment	CD4+ T-cell / Lymphocyte Monitoring[d]	End of Treatment F/U
Scheduled Day/Week	Screen	≤10 days prior to Day 1	7-14 days after Visit 2	Day 1 (Fasting)	Day 8 (Fasting)	TW3	TW7	Unscheduled	TW19	TW25	TW37	TW49 (Fasting)	TW61	TW73 (Fasting)	TW85	TW97 (Fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
HIV-1 drug resistance	16			16	16	16	16	16	16	16	16	16	16	16	16	16	16		16		16
Whole blood for Proviral DNA resistance testing	3									3		3				3	3		3		3
Blood (plasma) for ISL and DOR PK				4	4	4		4		8	4	8									
Blood (plasma) for Investigational PK							4		4								4		4		4
Blood (Plasma) for DOR and ISL PK During Pregnancy					<----------X[c]---------->																
Genetic Analysis				8.5																	
FBR				8						8		8				8	8		8		
Inflammatory Markers				10.7						10.7		10.7				10.7					
Total Blood Volume per Visit	**58.7**	**6**	**6**	**65.2**	**38**	**26**	**26**	**38**	**26**	**63.7**	**38**	**75.7**	**34**	**34**	**34**	**55.7**	**37**	**6**	**49**	**6**	**41**

anti-HBc=hepatitis B core antibody; DNA=deoxyribonucleic acid; DOR=doravirine; eGFR=estimated glomerular filtration rate; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus-1; INR=international normalized ratio; ISL=islatravir; MDRD=Modification of Diet in Renal Disease; NA=Not Applicable; PCR=polymerase chain reaction; PK=pharmacokinetic(s) PT=prothrombin time; RNA=ribonucleic acid; TBNK=T- and B-lymphocyte and natural killer cell profile; WOCBP=women of childbearing potential.

[a] The Repeat HIV-1 Confirmation Visit is only for those participants with HIV-1 RNA ≥500 copies/mL at Visit 2 AND with a ≥0.5 log10 decline in HIV-1 RNA from the Screening Visit; these participants will be required to return to the site for a Repeat HIV-1 RNA Confirmation Visit (Visit 3). At Visit 3, in order to be eligible for randomization, participants must have HIV-1 RNA ≥500 copies/mL and a <0.3 log10 decline in HIV-1 RNA from the previous result at Visit 2.

[b] HIV-1/2 and hepatitis serology includes: HBsAg, HBsAb, anti-HBc total, HCV Ab, and HIV-1/2 antigen/antibody test.

[c] PK samples collected during pregnancy per Section 8.11.7.1. During the 1st trimester and postpartum study visits, 4 mL of blood will be collected for PK sampling. During the 2nd and 3rd trimester study visits, 12 mL of blood will be collected for PK sampling.

[d] Blood volumes collected at the CD4+ T-cell Count/Lymphocyte Count Monitoring Visit represent single monthly monitoring visits.

The assessments in Table 17 are for any participant who is pregnant at the last regularly scheduled study visit (ie, Week 97) and whose visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum.

Table 17 Blood Volumes: Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 97

Visit Number	**17**	**18**	**19**	**20**
Scheduled Week	**Week 109**	**Week 121**	**Week 133**	**Week 145**
Blood Parameter	**Approximate Blood Volume (mL)**			
Plasma HIV-1 RNA Quantification (Real Time PCR)	6	6	6	6
CD4+ T-cell Count/TBNK panel	4	4	4	4
Plasma for HIV Viral Drug Resistance Testing	15	15	15	15
Chemistry	6	6	6	6
Hematology	2	2	2	2
Blood (Plasma) for DOR and ISL PK	<----------X[a]---------->			
Whole Blood for FBR	8	8	8	8
Total Blood Volume per Visit (mL)[a]	53	53	53	53

DOR=doravirine; FBR=future biomedical research; 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 profile.

[a] PK samples collected during pregnancy will be collected per Section 8.11.7.1. During the 1st trimester and postpartum study visits, 4 mL of blood will be collected for PK sampling. During the 2nd and 3rd trimester study visits, 12 mL of blood will be collected for PK sampling.

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

10.3.1 Definition of AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

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

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

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

Assessment of intensity/toxicity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. Any AE which changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

  - Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.

  - Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.

  - Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.

  - Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care funtions with intervention indicated to prevent permanent impairment, persistent disability, or death.

  - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and

their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

Women of Childbearing Potential (WOCBP)

A woman (including a transgender man who is assigned female gender at birth and is transitioning toward maleness) is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

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

Women in the following categories are not considered WOCBP:

Transgender women (assigned male gender at birth and transitioning toward femaleness).

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include[a]:

Highly Effective Contraceptive Methods That Have Low User Dependency[b]
Failure rate of <1% per year when used consistently and correctly.

- Progestogen- only contraceptive implant[c]
- IUS[d]
- Non-hormonal IUD
- Bilateral tubal occlusion

- Azoospermic partner (vasectomized or secondary to medical cause)
  This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.

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

Highly Effective Contraceptive Methods That Are User Dependent[b]
Failure rate of <1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen- containing) hormonal contraception[c]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormonal contraception[c]
  - Oral
  - Injectable

Sexual Abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Contraceptive Methods
Failure rate of >1% per year when used consistently and correctly.

- Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[e]

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.
b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).
c. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.
d. IUS is a progestin releasing IUD.
e. A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.

Note: The following are not acceptable methods of contraception:
- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.
- Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for Russia

In Russia, only adult (≥18 years of age) participants will be enrolled in this study.

In Russia, if a participant becomes pregnant (has a positive serum pregnancy test), study intervention 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:

- Section 4.2.7: Rationale for Continuing Study Intervention During Pregnancy
- Section 8.1.1.4: Consent/Assent for Continuation of Study Intervention During Pregnancy
- Section 8.11.7.1: Continuing Study Intervention

10.7.2 Country-specific Request for Australia

In Australia, only adult (≥18 years of age) participants will be enrolled in this study.

10.7.3 Country-specific Request for Germany

In Germany, only adult (≥18 years of age) participants will be enrolled in this study.

10.7.4 Country-specific Request for Ukraine

In Ukraine, only adult (≥18 years of age) participants will be enrolled in this study.

10.8 Appendix 8: Calculation of Creatinine Clearance

Cockcroft-Gault equations

- If male:

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

- If female:

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

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
3TC	Lamivudine
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APaT	All Participants as Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
BOCF	baseline observation carried forward
C24	concentration after 24 hours
CI	confidence interval
Cmax	maximum (peak) observed drug plasma concentration
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CR_{CL}	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
eCTA	exploratory Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
Ctrough	lowest concentration reached by a drug before the next dose is administered
DAIDS	The Division of AIDS
DAO	data as observed
DDI	drug-drug interaction
DHHS	US Department of Health and Human Services
DMC	Data Monitoring Committee
DOR	Doravirine
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	External Data Monitoring Committee
EE	ethinyl estradiol
EFV	Efavirenz
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FAHI	Functional Assessment of Human Immunodeficiency Virus Infection
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FSH	follicle stimulating hormone
FTC	emtricitabine
GCP	Good Clinical Practice
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol

Abbreviation	Expanded Term
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIV-2	Human Immunodeficiency Virus Type 2
HRQoL	health-related quality of life
hs-CRP	High Sensitivity C-Reactive Protein
HTA	Health Technology Assessment
HTE	Heavily Treatment-Experienced
IB	Investigator's Brochure
IC50	concentration of drug needed to inhibit 50% of viral growth
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-6	interleukin-6
INR	international normalized ratio
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
LNG	Levonorgestrel
LOCF	last observation carried forward
NNRTI	non-nucleoside reverse transcriptase inhibitor
Non-HDL-C	nonhigh-density lipoprotein cholesterol
NRTI	nucleoside reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OBT	Optimized Background Therapy
OF	Observed Failure
PCR	polymerase chain reaction
PDLC	predefined limit of change
PI	protease inhibitor
PK	pharmacokinetic
PP	per-protocol
PrEP	preexposure prophylaxis
PROs	patient-reported outcomes
QD	once daily
QoL	quality of life
QW	once weekly
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
sCD-163	soluble CD-163
SoA	schedule of activities
SOP	Standard Operating Procedure
sSAP	supplemental statistical analysis plan
SUSARs	suspected unexpected serious adverse reactions
TAMs	thymidine analog mutations
TB	tuberculosis
TBNK	T- and B- Lymphocyte and Natural Killer Cell Profile

Abbreviation	Expanded Term
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	Triglycerides
TN	treatment-naïve
TP	Triphosphate
TW	treatment week
ULN	upper limit of normal
VL	viral load
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCB	woman/women of nonchildbearing potential

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