Official Protocol Title:	A Phase 2 Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Doravirine/Islatravir in Pediatric Participants with HIV-1 Infection who are Virologically Suppressed or Treatment-Naïve, are Less Than 18 Years of Age, and Weigh Greater Than or Equal to 35 kg
NCT number:	NCT04295772
Document Date:	08-Feb-2022

Title Page

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Protocol Title: A Phase 2 Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Doravirine/Islatravir in Pediatric Participants with HIV-1 Infection who are Virologically Suppressed or Treatment-Naïve, are Less Than 18 Years of Age, and Weigh Greater Than or Equal to 35 kg

Protocol Number: 028-03

Compound Number: MK-8591A

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	134036
EudraCT	2019-003597-10

Approval Date: 08 February 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
Protocol Amendment 03	08-FEB-2022	The protocol was amended to: (1) discontinue dosing of study intervention in all participants based on Sponsor's acceptance of recommendations by the eDMC for pediatric HIV treatment trials (2) specify plans for detection of and follow-up of participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.
Protocol Amendment 02	12-MAR-2021	The protocol was amended to: (1) include an assessment of the palatability of a split tablet, (2) update inclusion criteria to include only participants who have no prior history of treatment failure, (3) add documented M184V/I substitution to exclusion criterion 9, and (4) add clarity around safety data collection for participants continuing study intervention after the last visit.
Protocol Amendment 01	12-AUG-2020	The protocol was primarily amended to: (1) include a new cohort of 15 participants who are naïve to ART, (2) adapt the study visit schedule removing Week 12 and adding Week 8 and Week 16 visits, (3) remove the 12-year-old lower age limit, (4) remove DOR PK assessments, and (5) extend the overall duration of the study to a total of 96 weeks.
Original Protocol	09-JAN-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

The protocol was amended to: (1) discontinue dosing of study intervention in all participants based on Sponsor's acceptance of recommendations by the eDMC for pediatric HIV treatment trials (2) specify plans for detection and follow-up of participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.1 Study Rationale 3 Hypotheses, Objectives, and Endpoints 4 Study Design (Sections 4.2, 4.2.1.2, 4.2.1.3, 4.2.1.4) 4.3 Justification for Dose 6 Study Intervention (Sections 6.1, 6.2, 6.3, 6.4, 6.5, 6.7, 6.8) 7.1 Discontinuation of Study Intervention 8 Study Assessments and Procedures (Sections 8.3.5, 8.4.7, 8.6.1, 8.11.3) 9 Statistical Analysis Plan (Sections 9.4.3, 9.6.1, 9.6.1.1, 9.6.2, 9.6.3, 9.6.4, 9.9, and 9.10)	• Notes were added to multiple sections to indicate that study intervention administration has been discontinued in all participants and all participants will be switched to non-study ART. • Study endpoints that are no longer applicable were noted as such. • Duration and details of safety follow-up were added where relevant.	To make updates consistent with Sponsor's acceptance of the recommendations by the eDMC to discontinue study intervention for all participants, and to specify plans to monitor CD4+ T-cell and total lymphocyte counts.

Section # and Name	Description of Change	Brief Rationale
1.3.2 SoA - Viremia Confirmation and End of Treatment	• Expanded lymphocyte analysis to include B-cells and NK cells.	• Given the decreases in total lymphocyte count observed in the ISL program, to assess for changes in other subpopulations of lymphocytes in addition to T-cells.
	• Changed the laboratory procedure name from "CD4+ T cell count" to "CD4+ T cell count/TBNK panel".	• To clarify that CD4+ T-cell count is part of the TBNK panel, which measures different T-cell, B-cell, and NK-cell types.
	• Added notes for CD4+ T-cell count/TBNK panel testing and Hematology assessments to refer to Section 8.11.5 and Section 1.3.3 for participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.	• To refer to additional follow-up needed for participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.
	• Added random PK sample collection to the End of Treatment Follow-up Visit.	• A plasma sample for PK will be collected at the End of Treatment Follow-up Visit to determine whether there is prolonged ISL exposure in pediatric participants.
	• Deleted previous notes for HIV viral resistance and revised the note for PK sample collection.	• For clarity

Section # and Name	Description of Change	Brief Rationale
1.3.3 SoA - Participants with Specified Decreases in CD4+ T-cell Counts and/or Lymphocyte Counts	• Added new Schedule of Activities	• To specify visits and assessments associated with confirming and monitoring decreases in CD4+ T-cell counts and/ or total lymphocyte counts. • To determine whether there is prolonged ISL exposure in pediatric participants.
2.2.3 Doravirine/Islatravir	• Updated results for MK-8591 Protocol 011.	• To provide most current information on DOR/ISL clinical studies.
2.3 Benefit/Risk Assessment	• Updated text based on CD4+ T cell and total lymphocyte findings. • Updated text to state that dosing of ISL QM 60 mg in the HIV-1 PrEP program has been discontinued. • Specified DOR/ISL QD doses (100 mg/0.75 mg) used in the Phase 3 studies (MK-8591A Protocol 017 and MK-8591A Protocol 018)	• To account for new safety and efficacy information from the ISL clinical development program that is relevant to the population in this study. • To provide current status of ISL dosing in the PrEP program. • DOR/ISL doses were specified to provide context for changes from baseline in CD4+ T-cell and/or total lymphocytes

Section # and Name	Description of Change	Brief Rationale
5 Study Population	• Clarified that no new participants will be enrolled into the study	• To align with Sponsor's acceptance of the recommendations by the eDMC to discontinue study intervention for all participants
5.2 Exclusion Criteria	• Updated exclusion criterion #9 (prior to Sponsor decision to discontinue dosing in the study) to allow resistance testing results from a local laboratory to determine participant eligibility, if the results were obtained <90 days prior to Screening Visit through Day 1.	• To align the protocol text with a Protocol Clarification Letter that took effect when participant enrollment was ongoing.
5.2 Exclusion Criteria	• The text in parentheses, "(based on central laboratory results)", was removed from exclusion criterion #10	• To align the protocol text with a Protocol Clarification Letter that took effect when participant enrollment was ongoing. This update was made to clarify that central laboratory results are not needed for the exclusionary laboratory values in Table 1. Although the exclusion criterion has been revised to remove the parenthetical statement, any laboratory tests related to study endpoints (eg, HIV-1 RNA or CD4+ T-cell count) must be performed at the central laboratory.

Section # and Name	Description of Change	Brief Rationale
8.2.3 T- and B-Lymphocyte and Natural Killer Cell Profile (TBNK)	• Updated section title and text to reflect TBNK panel (changed from "CD4+ T-cell Counts" to "T- and B-Lymphocyte and Natural Killer Cell Profile [TBNK])".	• Revised for clarity and accuracy of laboratory test nomenclature.
8.3.4 Clinical Safety Laboratory Assessments	• Added note to cross-reference to Section 8.11.5 Management of Participants with Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts	• To clarify additional follow-up needed for participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.
8.6.1 Blood Collection for Plasma ISL measurements	• Added PK sample collection at the End of Treatment Follow-up Visit • Removed footnote in Table 6 for the Week 24 visit	• To determine whether there is prolonged ISL exposure in pediatric participants. • Random samples were no longer taken at that visit.
8.11.3.1 Clinical Management of Participants Who Become Pregnant	• Updated text to include guidance for assessment of AEs that are pregnancy-related complications	• To clarify the reference (within the DAIDS table) when assessing AEs that are pregnancy-related complications.

Section # and Name	Description of Change	Brief Rationale
8.11.3.2 Early Discontinuation of Treatment 8.11.3.3 End of Treatment Follow-up Visit	• Added guidance that additional monitoring after discontinuation of DOR/ISL is required for participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts per Section 8.11.5.	• To clarify management of participants who discontinue study intervention and emphasize additional requirements to monitor decreases in CD4+ T-cell and/or total lymphocyte counts for recovery after DOR/ISL discontinuation.
8.11.5 Management of Participants with Decreases in CD4+ T-cell count Counts and/or Total Lymphocyte Counts	• New section added to define methods for confirming and monitoring decreases in CD4+ T-cell counts and/or total lymphocyte counts	• To guide the management of participants with decreases in CD4+ T-cell counts and/or lymphocyte counts.
9 Statistical Analysis Plan	• Clarified which analyses will be performed based on available data and indicated the sections that are no longer applicable.	• To clarify the statistical analysis plan for the study.
10.2 Appendix 2: Clinical Laboratory Tests	• Added details on TBNK panel to Table 13 • Added a bullet referencing the central laboratory requirements for testing study endpoints. • Added Table 15	• Added for completeness; TBNK panel measures different T-cell, B-cell, and NK cell types. • To improve clarity. • To specify the timing and volume of blood collection at Early Discontinuation of Treatment, End of Treatment Follow-up and Extended Monitoring of CD4+ T-cell and/or Total Lymphocyte Count visits

Section # and Name	Description of Change	Brief Rationale
10.5.2 Contraception Requirements	• Added footnote “d” to describe IUS	• To update standard template language
Throughout as applicable	• Minor changes made to correct typographical and editorial errors	• To provide consistency and/or clarity within the document.
Throughout as applicable	• Notes were added to indicate certain sections of the protocol that are no longer applicable due to discontinuation of DOR/ISL dosing.	• For clarity

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Clinical Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Doravirine/Islatravir in Pediatric Participants with HIV-1 Infection who are Virologically Suppressed or Treatment-Naïve, are Less Than 18 Years of Age, and Weigh Greater Than or Equal to 35 kg

Short Title: DOR/ISL in Pediatric Participants with HIV-1, Less Than 18 Years of Age and Greater Than or Equal to 35 kg

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

Note: As of amendment 028-03, the safety, tolerability, and antiviral activity of DOR/ISL will not be evaluated at Weeks 48 and 96 as dosing has been discontinued in all participants. Updated analyses are described in Section 9.

There are no hypotheses in this study. The following objectives will be evaluated in pediatric participants with HIV-1, who are <18 years of age, weigh ≥35 kg, are treatment-naïve or have been virologically suppressed on stable combination ART for ≥3 months.

Primary Objectives	Primary Endpoints
- To evaluate the steady-state plasma pharmacokinetic profile of ISL as assessed by intensive pharmacokinetic sampling on Day 28 in the Intensive PK Cohort	- ISL AUC0-24, Cmax, Tmax, t1/2, CL/F, Vz/F
- To evaluate the steady-state intracellular pharmacokinetic profile of ISL-triphosphate in peripheral blood mononuclear cells on Day 28 in the Intensive PK Cohort	- ISL-triphosphate AUC0-24, Cmax, and C24
- To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 24	- Adverse events - Adverse events leading to discontinuation of study intervention
Secondary Objectives	Secondary Endpoints
- To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through study duration	- Adverse events - Adverse events leading to discontinuation of study intervention

- To evaluate the antiretroviral activity of DOR/ISL in virologically suppressed and treatment-naïve participants, separately, as assessed by the percentage of participants with the following at Weeks 24, 48, and 96: Virologically Suppressed Cohort: - HIV-1 RNA ≥50 copies/mL - HIV-1 RNA <50 copies/mL Treatment-Naïve Cohort: - HIV-1 RNA <50 copies/mL	- HIV-1 RNA
- To evaluate the immunologic effect of DOR/ISL in the Treatment-Naïve and Virologically Suppressed Cohorts separately as measured by change from baseline in CD4+ T-cell count at Weeks 24, 48, and 96	- CD4+ T-cell count
- To evaluate the development of viral drug resistance to DOR or ISL in participants who receive DOR/ISL	- Viral resistance-associated substitutions
- To evaluate the acceptability and palatability of the DOR/ISL tablet (whole and split)	- Score on a palatability acceptability assessment scale

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	HIV-1 Infection
Population	Pediatric participants with HIV-1, who are <18 years of age, weigh ≥35 kg, are treatment-naïve or have been virologically suppressed on stable combination ART for ≥3 months.
Study Type	Interventional

Intervention Model	Single Group **Note: As of Amendment P028-03, all participants will have switched to non-study ART**. This is a multi-site study
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years from the time the first participant (or legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 45 participants (30 virologically suppressed, 15 treatment-naïve) will be enrolled. As of Amendment 028-03 enrollment was closed with 42 participants enrolled in the study (39 virologically suppressed, 3 treatment-naïve).

Intervention Groups and Duration:

Intervention Groups

Note: As of Amendment 028-03, all cohorts have discontinued study intervention administration. All participants will have switched to non-study ART.

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin-istration	Treatment Period	Use
DOR/ISL	DOR/ISL	100 mg / 0.75 mg	QD	Oral	Day 1 to Week 96	Experimental

DOR/ISL=fixed dose combination of doravirine and islatravir, also known as MK-8591A; QD=once daily

Total Number

1

Note: As of Amendment 028-03, all cohorts have discontinued study intervention administration. All participants will have switched to non-study ART.

Duration of Participation	**Note: As of Amendment 028-03, all cohorts have discontinued study intervention administration. All participants will have switched to non-study ART. Participants with CD4+ T-cell and/or total lymphocyte counts that are not decreased by >10% of the average baseline value at the Early Discontinuation of Treatment Visit will discontinue from the study at the End of Treatment Follow-up Visit. Participants who have CD4+ T-cell and/or total lymphocytes decreased by >10% of the average baseline value at the Early Discontinuation of Treatment Visit and confirmed at the End of Treatment Follow-up Visit will continue on the study with extended monitoring until both the CD4+ T-cell and total lymphocyte count reductions are ≤10% of the average baseline value on 2 measurements 12 weeks apart. Extended monitoring will continue for 6 months, if needed. If the CD4+ T-cell and/or total lymphocyte counts remain decreased by >10% of the average baseline value at 6 months, the Investigator should consult with the Sponsor.** Each participant will participate in the study for approximately 108 weeks from the time the participant provides documented informed consent/assent through the final contact. After a screening phase of up to 45 days, participants will receive daily study intervention for approximately 96 weeks. Participants who discontinue study intervention will be followed as described in the protocol.

Study Governance Committees:

[redacted]

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

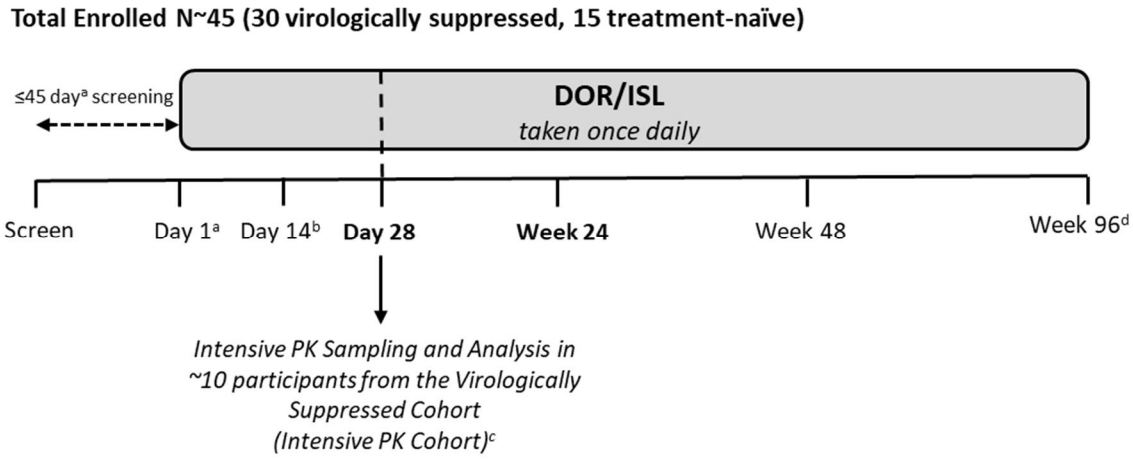
Study Accepts Healthy Volunteers: No

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



DOR/ISL=fixed dose combination of doravirine and islatravir, also known as MK-8591A; n=number; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic

The visits specified in the Study Schema are not comprehensive. See Section 1.3 Schedule of Activities for additional details for the scheduled visits, which include the following: Screening, Day 1, Day 14, Day 28, Week 8, Week 16, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, and Week 96.

[a] A screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.

[b] A qualified medical designee will be responsible for a phone call to the participant on Day 14 to collect information on the use of concomitant medications and AEs since the prior visit. Medication adherence assessment and counseling will also be performed.

[c] Approximately 10 participants in the Virologically Suppressed Cohort who provide consent for Day 28 intensive PK sampling (Plasma and PBMC) (at sites that can perform PBMC processing) will comprise the Intensive PK Cohort. All participants, including those in the Intensive PK Cohort, will undergo sparse PK sampling at prespecified visits during the study.

[d] At the end of Week 96, there will be a mechanism for all eligible participants to continue receiving study intervention without interruption until it becomes commercially accessible.

1.3 Schedule of Activities

1.3.1 Schedule of Activities

Note: As of Amendment 028-03, all participants should follow the SoAs in Sections 1.3.2 and 1.3.3.

Study Period	**Screen**	**Treatment Period: Open-Label DOR/ISL**												**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	
Scheduled Day/Week	Screen	Day 1 (Fasting)	Day 14 Phone Call	Day 28	Week 8	Week 16	Week 24	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	
Visit Window	≤45 days[a]	NA	±4 days	+14 days	±7 days									Each visit should be calculated from date of Day 1
Administrative Procedures														
Informed Consent/Assent	X													
Informed Consent/Assent for Intensive PK Cohort	X													
Informed Consent/Assent for FBR	X													
Inclusion/Exclusion Criteria	X	X												Review before allocation in IRT on Day 1 to confirm eligibility
Participant Identification Card	X	X												At the time of allocation, site will add allocation number to identification card
Medical History	X													
Prior and Concomitant Medications Review	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	
Intervention Allocation via IRT		X												
Dispense DOR/ISL Using IRT		X		X	X	X	X	X	X	X	X	X		
Observed Dosing in-Clinic		X		X			X		X					See Section 8.1.8.1 and 8.6.1 for more information (including instructions for participants dosing in the evening)

Study Period	**Screen**	**Treatment Period: Open-Label DOR/ISL**												**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	
Scheduled Day/Week	Screen	Day 1 (Fasting)	Day 14 Phone Call	Day 28	Week 8	Week 16	Week 24	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	
Visit Window	≤45 days[a]	NA	±4 days	+14 days	±7 days									Each visit should be calculated from date of Day 1
Palatability and Acceptability Assessment		X		X			X							Day 1 and Day 28 whole tablet assessment. Week 24 assessment for split tablet only. See Section 8.1.9.
DOR/ISL Compliance Assessment			X	X	X	X	X	X	X	X	X	X	X	Reconcile doses and assess DOR/ISL compliance. Day 14 phone call should include compliance counseling
Evaluation to receive continued DOR/ISL													X	See Section 6.7
Efficacy Procedures														
Plasma HIV-1 RNA Quantification (RealTime PCR)	X	X		X	X	X	X	X	X	X	X	X	X	Day 1 collection must be prior to first dose of DOR/ISL.
CD4+ T-cell Count	X	X					X		X				X	Day 1 collection must be prior to first dose of DOR/ISL.
Plasma for HIV Viral Drug Resistance Testing	X	X		X	X	X	X	X	X	X	X	X	X	**Screening collection is only required in Treatment-Naïve Cohort (n=15)**. Day 1 collection must be prior to first dose of DOR/ISL.
Safety Procedures														
Full Physical Examination	X												X	
Directed Physical Examination		X		X	X	X	X	X	X	X	X	X		Day 1 exam must be prior to first dose of DOR/ISL
Height	X	X		X	X	X	X	X	X	X	X	X	X	
Weight	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	Day 1 vitals must be prior to first dose of DOR/ISL. Includes pulse, blood pressure, body temperature, and respiratory rate.

Study Period	**Screen**	**Treatment Period: Open-Label DOR/ISL**												**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	
Scheduled Day/Week	Screen	Day 1 (Fasting)	Day 14 Phone Call	Day 28	Week 8	Week 16	Week 24	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	
Visit Window	≤45 days[a]	NA	±4 days	+14 days	±7 days									Each visit should be calculated from date of Day 1
Confirmation of menarche	X	X		X	X	X	X	X	X	X	X	X	X	Day 1 collection must be prior to first dose of DOR/ISL. Females only; not required once menarche has been confirmed
Contraceptive Use Confirmation (WOCBP only)	X	X		X	X	X	X	X	X	X	X	X	X	Day 1 collection must be prior to first dose of DOR/ISL.
Urine Pregnancy Test (WOCBP only)	X	X		X	X	X	X	X	X	X	X	X	X	Confirm with serum test if urine test is positive. Day 1 testing must be prior to first dose of DOR/ISL
HIV-1 & -2 Serology	X													
Hepatitis Serology (B and C)	X													
HCV RNA		X												Only hepatitis C antibody positive participants will undergo testing at Day 1.
HbsAg	X	X		X	X	X	X	X	X	X	X	X	X	All participants will be tested at screening. Only anti-HBc-positive participants will undergo testing at subsequent visits
HBV DNA	X	X		X	X	X	X	X	X	X	X	X	X	
Chemistry & Hematology	X	X		X	X	X	X	X	X	X	X	X	X	Day 1 collection must be prior to first dose of DOR/ISL. Fasting is required at Day 1, Week 48 & 96 visits to evaluate fasting lipid profile, and blood glucose. Participants with abnormal results will be required to fast for periodic testing at other visits (Section 8.11.2.3).
PT/INR	X													
Urinalysis	X			X			X		X		X		X	
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	**Screen**	**Treatment Period: Open-Label DOR/ISL**												**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	
Scheduled Day/Week	Screen	Day 1 (Fasting)	Day 14 Phone Call	Day 28	Week 8	Week 16	Week 24	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	
Visit Window	≤45 days[a]	NA	±4 days	+14 days	±7 days									Each visit should be calculated from date of Day 1
Pharmacokinetics														
Blood (Plasma) for Intensive ISL PK				X										Collected from participants in the Intensive PK Cohort only: • Plasma: Predose & 0.5, 1, 2, 4, 8, 12, 24 hours postdose on Day 28 • PBMC: Predose & 4, 24 hours postdose on Day 28
Blood (PBMC) for ISL-TP PK[b]				X										
Blood (Plasma) for Sparse ISL PK		X		X	X	X	X	X	X	X	X	X	X	See Section 8.6.1 Collected from all participants: • Day 1: predose • Day 28: predose • Week 8 and 16: random • Week 24: predose & 0.5 to 2 hours postdose • Week 36: random • Week 48: predose & 0.5 to 2 hours postdose • Weeks 60-96: random.
Biomarkers														
Buccal swab (DNA) for Genetic Analysis[c]		X												

Study Period	**Screen**	**Treatment Period: Open-Label DOR/ISL**												**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	
Scheduled Day/Week	Screen	Day 1 (Fasting)	Day 14 Phone Call	Day 28	Week 8	Week 16	Week 24	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	
Visit Window	≤45 days[a]	NA	±4 days	+14 days	±7 days									Each visit should be calculated from date of Day 1

antiHBc=hepatitis B core antibody; ART=antiretroviral therapy; DNA=deoxyribonucleic acid; DOR=doravirine; FBR=future biomedical research; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IRT=Interactive Response Technology; ISL=islatravir; ISL-TP=islatravir-triphosphate; NA=not applicable; PBMC = peripheral blood mononuclear cell; PCR=polymerase chain reaction; PK=pharmacokinetic; PT=prothrombin time; RNA=ribonucleic acid; WOCBP=a woman/women of childbearing potential.

A A screening period of up to 45 days is allowed, but participants are expected to enroll as soon as possible after eligibility is confirmed.

B PBMC samples will also be analyzed for islatravir-diphosphate (ISL-DP) to ensure proper sample stabilization. No ISL-DP PK parameters will be reported.

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

1.3.2 SoA – Viremia Confirmation and End of Treatment

Note: As of Amendment 028-03, the Viremia Confirmation Visit is no longer applicable.

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	
Visit Window	Within 2 to 4 weeks of Viremia (≥50 copies/Ml)	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		
DOR/ISL Compliance Review	X	X		Reconcile doses and assess DOR/ISL compliance
Efficacy Procedures				
Plasma HIV-1 RNA Quantification (RealTime PCR)	X	X	X	
CD4+ T-cell Count/TBNK panel		X	X	Decreases in CD4+ T-cell count at the Early Discontinuation of Treatment visit and End of Treatment Follow-up visits should be managed per Section 1.3.3 and Section 8.11.5.
Plasma for Viral Drug Resistance Testing	X	X	X	
Whole Blood for Proviral DNA Archive Resistance Testing	X			Testing performed via central laboratory once per confirmed low-level viremic episode.
Pharmacokinetic Procedures				
Blood (Plasma) for Investigational PK	X	X	X	A random sample will be collected.
Safety Procedures				
Full Physical Examination		X	X	
Weight	X	X	X	
Height	X	X	X	
Vital Signs		X	X	Includes pulse, blood pressure, body temperature, and respiratory rate

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	
Visit Window	Within 2 to 4 weeks of Viremia (≥50 copies/Ml)	NA	42 (+7) days after the end of treatment	
Confirmation of Menarche	X	X	X	Females only; not required once menarche has been confirmed
Contraception Use Confirmation (WOCBP only)	X	X	X	
Urine Pregnancy Test (WOCBP only)		X	X	Confirm with serum test if urine test is positive
Chemistry/Hematology		X	X	Decreases in total lymphocyte counts at the Early Discontinuation of Treatment visit and End of Treatment Follow-up visit should be managed per Section 1.3.3 and Section 8.11.5.
Urinalysis		X		
Review of Adverse Events	X	X	X	

DOR=doravirine; HIV-1=human immunodeficiency virus type 1; IRT=interactive response technology; ISL=islatravir; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells; WOCBP=woman/women of childbearing potential.

1.3.3 SoA – Monitoring of Participants with Confirmed Specified Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts

Study Period	**Extended Monitoring of CD4+ T-cell Count and/or Total Lymphocyte Count**	**Notes**
Visit Number	**Unscheduled**	
Scheduled Day/Week	Monitoring for CD4+ T-cell and/or Total Lymphocytes	
Visit Window	Every 4 to 6 weeks after End of Treatment Follow-up Visit	**See Section 8.11.5 for details.**
Prior and Concomitant Medications Review	X	
Register Study Visit in IRT	X	
CD4+ T-cell Count/TBNK Panel	X	
Hematology	X	
Review of Adverse Events	X	
Blood (Plasma) for Investigational PK	X	A PK sample (random) will be collected at the first monitoring visit only.
IRT=interactive response technology; TBNK=T and B lymphocyte and natural killer cells		

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 once daily treatment of HIV-1 infection in adults and pediatric patients.

2.1 Study Rationale

Rationale for Amendment 028-03:

Downward trends of total lymphocytes and CD4+ T-cell counts were observed in some participants, which triggered ad hoc pediatric eDMC recommendations to discontinue study intervention administration for all participants and to initiate safety monitoring of participants. The Sponsor accepted these recommendations.

Original Study Rationale:

As treatment regimens have improved, infection with HIV-1 has become a chronic, manageable condition, and those receiving effective ART regimens can now expect to live a near-normal lifespan [Trickey, A., et al 2017]. With anticipation of lifelong treatment and near-normal lifespans, the long-term tolerability and safety of antiretrovirals are increasingly important considerations for pediatric patients living with HIV-1.

The current standard of care for the treatment of HIV-1 infection is the use of a combination of 2 NRTIs with a third agent (eg, InSTI, NNRTI, or PI) [AIDS info 2017] [European AIDS Clinical Society 2016] [World Health Organization 2016]. Although such regimens have become increasingly well tolerated and highly efficacious, the current paradigm of lifelong daily treatment is associated with a need for simpler and safer regimens, with reduced drug exposure.

There is accumulating evidence that simplified 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens; improve tolerability and quality of life; and increase medication adherence; all of which can help to sustain virologic suppression [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. The durability of 2-drug regimens depends on both components having distinct mechanisms of action with at least 1 of the components having a relatively high barrier to resistance.

DOR/ISL has the potential to be an ideal agent for the treatment of HIV-1 infection due to its potent in vitro antiretroviral activity of each component (including activity against common NRTI- and NNRTI resistance-associated substitutions), inhibition of reverse transcriptase by multiple mechanisms of action, lack of food requirements, and favorable safety and DDI profile 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, which block HIV-1 reverse transcriptase by novel mechanisms of action. ISL is an inactive nucleoside analog that is converted to the pharmacologically active triphosphate (ISL-TP) form via endogenous intracellular kinases. It acts through multiple mechanisms, including immediate chain termination by blocking translocation and delayed chain termination by preventing nucleotide excision [Michailidis E 2014].

ISL is differentiated from other HIV-1 antiretrovirals by its high potency, long half-life, favorable drug resistance profile, and broad pharmacologic distribution. 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-associated mutations, including M184V/I and TAMs.

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 the 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. As compared with Efavirenz, DOR had fewer CNS-related AEs in Phase 3 studies. DOR exhibits potent activity against both wild-type HIV-1 virus and frequently transmitted NNRTI-resistance-associated substitutions (eg, K103N, Y181C, G190A, and E138K). The safety and efficacy profiles of DOR have been well characterized in Phase 3 clinical studies conducted in treatment-naïve adult participants [Orkin, C., et al 2018] [Molina, J. M., et al 2018] and in virologically suppressed adult participants switching from a stable antiretroviral regimen (MK-1439A Protocol 024) [Johnson, M., et al 2019].

An ongoing Phase 1/2 clinical study (MK-1439 Protocol 027; IMPAACT 2014) is evaluating the PK, safety, and tolerability of DOR (100 mg) in children and adolescents. Modeling and simulation predicted that adolescents (≥12 to <18 years of age who weigh ≥35 kg) would have similar exposures as adults with the DOR 100 mg dose including adolescents who weigh between 35 and 45 kg. Initial results from MK-1439 Protocol 027 confirm that projected steady-state PK after a single-dose of DOR (100 mg) is similar to that observed in adults (9 adolescents living with HIV-1 (≥12 to <18 years of age who weigh ≥45 kg). The safety assessment in these 9 participants demonstrated 1 AE of Grade 1 diarrhea, which was considered unrelated to study intervention by the investigator.

2.2.3 Doravirine/Islatravir

DOR/ISL is an FDC tablet 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.

DOR and ISL have been studied in a Phase 1 fixed-sequence, 2-period, multiple-dose, drug-drug interaction clinical study (MK-8591 Protocol 10). This study indicated no clinically meaningful interactions between DOR and ISL.

The combination of DOR and ISL (administered as single-entities, ISL+DOR) 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 ISL+DOR and 3TC or an FDC of DOR, 3TC, and TDF (DOR/3TC/TDF). Participants receiving ISL+DOR+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 Week 48 and 96, the percentage of participants with HIV-1 RNA <50 copies/mL among those who received the 2-drug regimen of ISL+DOR 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 >200 copies/mL cutoff. As such, no participant met the criteria for resistance testing. ISL+DOR, 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).

The clinical development program of DOR/ISL includes ongoing studies in virologically suppressed adults (P017 and P018), treatment-naïve adults (P020), heavily treatment experienced participants (P019), and participants <18 years of age and weighing at least 35 kg (P028).

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.

In preclinical rat studies, chronic dosing of ISL at very high exposure levels (~204 fold greater than the estimated exposure in humans dosed at 0.75 mg) caused incisor breakage and molar discoloration. Incisor breakage or molar discoloration were not observed in studies conducted with other species including mice or monkeys. In the study with monkeys, no effects of ISL on dentition (unerupted dental buds) were observed based on results of micro-CT scans. These findings are not considered to present a risk to the human pediatric population based on the high safety multiples, the lack of changes in developing teeth in juvenile rats, and the lack of dental changes in monkeys (monkey dentistry being evolutionarily and anatomically more similar to humans than rodents) and mice.

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 P017 and MK-8591A P018), approximately 95% of 658 participants enrolled in the DOR/ISL arm completed the 48-week treatment period in both studies. In P017 and P018, 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 and BIC/FTC/TAF, respectively, at Week 48. To date, no viral resistance to either component of DOR/ISL has been shown in the Phase 2 (MK-8591A Protocol 011) and Phase 3 studies (MK-8591A Protocols 017 and 018).

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 count 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 count of >30% (of which 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, the decreased values remained 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 of MK-8591A Protocols 017 and 018, (DOR/ISL 100 mg/0.75 mg QD for HIV-1 treatment), mean decreases from baseline in total lymphocyte counts were observed 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 baseline ART group and 12.8% in BIC/FTC/TAF group. 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 longer-term is unknown, and the Sponsor is assessing the reversibility of the reductions in CD4+ T-cell counts 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 supports continuation of the Phase 3 clinical studies for the DOR/ISL 100 mg/0.75 mg HIV-1 once-daily treatment program.

With regard to this Phase 2 study in the pediatric population, the Sponsor decided to discontinue DOR/ISL dosing following review of the available data and benefit/risk assessment.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Note: As of amendment 028-03, the safety, tolerability, and antiviral activity of DOR/ISL will not be evaluated at Weeks 48 and 96 as dosing has been discontinued in all participants. Updated analyses are described in Section 9.

There are no hypotheses in this study. The following objectives will be evaluated in pediatric participants with HIV-1, who are <18 years of age, weigh ≥35 kg, are treatment-naïve or have been virologically suppressed on stable combination ART for ≥3 months.

Objectives	Endpoints
Primary	
• To evaluate the steady-state plasma pharmacokinetic profile of ISL as assessed by intensive pharmacokinetic sampling on Day 28 in the Intensive PK Cohort	• ISL AUC0-24, Cmax, Tmax, t1/2, CL/F, Vz/F

Objectives	Endpoints
• To evaluate the steady-state intracellular pharmacokinetic profile of ISL-triphosphate in peripheral blood mononuclear cells on Day 28 in the Intensive PK Cohort	• ISL-triphosphate AUC0-24, Cmax, and C24
• To evaluate the safety and tolerability of DOR/ISL as assessed by review of the accumulated safety data through Week 24	• Adverse events • Adverse events 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 study duration	• Adverse events • Adverse events leading to discontinuation of study intervention
• To evaluate the antiretroviral activity of DOR/ISL in virologically suppressed and treatment-naïve participants, separately, as assessed by the percentage of participants with the following at Weeks 24, 48, and 96: Virologically Suppressed Cohort: - HIV-1 RNA ≥50 copies/mL - HIV-1 RNA <50 copies/mL Treatment-Naïve Cohort: - HIV-1 RNA <50 copies/mL	• HIV-1 RNA
• To evaluate the immunologic effect of DOR/ISL in the Treatment-Naïve and Virologically Suppressed Cohorts separately as measured by change from baseline in CD4+ T-cell count at Weeks 24, 48, and 96	• CD4+ T-cell count
• To evaluate the development of viral drug resistance to DOR or ISL in participants who receive DOR/ISL	• Viral resistance-associated substitutions

Objectives	Endpoints
• To evaluate the acceptability and palatability of the DOR/ISL tablet (whole and split)	• Score on a palatability acceptability assessment scale
Tertiary/Exploratory	
• To evaluate the pharmacokinetics of ISL as assessed by sparse PK sampling through Week 96	• Plasma concentration of ISL
• 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

4 STUDY DESIGN

4.1 Overall Design

Amendment 028-03

As of Amendment 028-03, all participants will have been brought to the clinic for an Early Discontinuation of Treatment visit so that non-study ART could be initiated. Participants who have CD4+ T-cell and/or total lymphocyte counts that are not decreased by >10% of the average baseline value at this visit will discontinue participation from the study at the End of Treatment Visit. Participants who have CD4+ T-cell and/or total lymphocyte values that are decreased by >10% of the average baseline value will have confirmation testing at the End of Treatment Follow-up Visit. If that decrease in CD4+ T-cell and/or total lymphocyte count is not confirmed at the End of Treatment Visit, the participant will not require further monitoring. If that decrease in CD4+ T-cell and/or total lymphocyte count is confirmed at the End of Treatment Visit, the participants will continue on the study with extended monitoring every 4 to 6 weeks until two samples 12 weeks apart show a recovery of the counts to ≤10% of the average baseline value. After 6 months, if decreased counts persist, the Sponsor should be consulted. Participants who no longer want to undergo extended monitoring should be advised to follow up with their HIV care provider.

Original Design

This is a Phase 2 nonrandomized, noncomparative, multisite, open-label study to evaluate ISL and ISL-TP PK and the safety, tolerability, and efficacy of DOR/ISL in pediatric

participants with HIV-1 who are treatment-naïve or virologically suppressed for ≥3 months with no history of treatment failure.

Approximately 45 participants (30 virologically suppressed, 15 treatment-naïve) will be enrolled to receive DOR/ISL at the adult dose [DOR (100 mg)/ISL (0.75 mg) FDC tablet administered QD] through Week 96.

Virologically Suppressed Cohort participants will be required to discontinue use of their current suppressive ART regimen and receive only DOR/ISL as ART during the study. Approximately 10 of the 30 participants from the Virologically Suppressed Cohort who provide consent for intensive PK sampling (plasma and PBMC) on Day 28 will comprise the Intensive PK Cohort. Results from evaluation of the Intensive PK Cohort will be used for dose confirmation of ISL (Section 9.6.1.1). Both Intensive PK Cohort and non-Intensive PK Cohort will enroll concurrently. If all 20 non-Intensive PK participants are enrolled prior to completing enrollment of the Intensive PK Cohort, then the non-Intensive PK Cohort will close to enrollment, and only the Intensive PK Cohort will remain open to enrollment. All participants, including those in the Intensive PK Cohort, will undergo sparse plasma PK sampling at prespecified visits during the study (Section 8.6).

Enrollment of the Treatment-Naïve Cohort will only begin when the adult Phase 3 ISL/DOR treatment-naïve study (P020) is open to full enrollment (see Section 4.2 below for additional details).

All participants will be evaluated for efficacy of DOR/ISL to maintain virologic suppression based on predefined, clinically significant, and confirmed viremia. Any participants with confirmed viremia, as described in Section 4.2.1.3.1, will be assessed for development of viral drug resistance and potential discontinuation from study intervention.

Participant safety will be monitored by an eDMC who will perform periodic reviews of safety data throughout the study (Section 9.7; Appendix 1). Details regarding eDMC will be provided in a charter.

At the end of Week 96, there will be a mechanism for all eligible participants to continue receiving study intervention without interruption until it becomes commercially accessible (Section 6.7).

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

Amendment 028-03

Based on the Sponsor acceptance of the pediatric eDMC recommendation to stop study intervention administration in this study, Amendment 028-03 is designed to allow for discontinuation of study intervention for all participants, the follow-up of all participants with specified decreases in CD4+ T-cell and/or total lymphocyte count, and the discontinuation from the study of participants who did not have these specified decreases.

Original rationale:

The open-label, nonrandomized, PK-confirmatory study design is consistent with recent published regulatory guidance for conducting clinical studies in the pediatric population [Food and Drug Administration 2019]. Aligned with this guidance, the known clinical and pharmacological profile of DOR/ISL provides sufficient support to safely evaluate DOR/ISL in pediatric patients living with HIV-1 in parallel with the pivotal Phase 3 clinical studies in adults. Conducting adult and pediatric studies in parallel accelerates the development of antiretrovirals in the pediatric population, providing clinically meaningful information about the use of DOR/ISL for the treatment of HIV-1 in pediatric patients earlier and more efficiently.

The design is considered appropriate for a treatment experienced study population that is switching from another stable ART regimen with HIV RNA <50 copies/mL and for a study population with HIV-1 who are naïve to antiretroviral therapy. The Phase 3 study in treatment-naïve adults (MK-8591A Protocol 020) is ongoing, and the P028 Treatment-Naïve Cohort will not begin enrollment until supportive data from the Sentinel Cohort in P020 is available.

As HIV-1 is a chronic viral infection for which antiretroviral treatment is administered indefinitely, participants will be treated for 96-weeks in this study to assess the durability of efficacy, emergence of resistance, and long-term safety.

4.2.1 Rationale for Endpoints

4.2.1.1 Pharmacokinetic Endpoints

Plasma PK

PK samples collected for analysis of ISL plasma concentrations will be used to calculate the steady-state plasma AUC0-24 and Cmax. These results will confirm that adequate exposures of ISL are achieved in pediatric participants <18 years of age weighing ≥35 kg and will support dosing recommendations in the pediatric population. As DOR/ISL is anticipated to be chronically dosed, steady-state PK endpoints are the most appropriate endpoints.

Intensive plasma PK samples will be collected from the Intensive PK Cohort participants (Section 8.6). In addition to these results, data from sparse plasma PK sampling collected from all participants will be used in population PK models for ISL levels.

PBMC PK

PBMC PK samples collected from the Intensive PK Cohort participants (Section 8.6) will be used to evaluate intracellular ISL-TP levels, the active anabolite resulting from ISL dosing. Intracellular PBMC trough levels (C24) are a better predictor of efficacy than the exposure (AUC) and can be used along with in vitro potency values to predict efficacy against both wild-type virus and drug resistant variants.

4.2.1.2 Safety Endpoints

Note: As of Amendment 028-03, study intervention administration has been discontinued, but the study will continue so that participants can be monitored for decreases in CD4+ T-cell and/or total lymphocyte counts. If the specified decreases are present, those participants will be managed per Section 8.11.5.

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

4.2.1.3 Efficacy Endpoints

Note: As of Amendment 028-03, HIV-1 RNA measurements will not be collected beyond the Early Discontinuation of Treatment Visit. Management of viremia after that visit will be at the discretion of the Investigator outside of the study.

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.

Plasma HIV-1 RNA <50 copies/mL is a well-established clinically meaningful endpoint for treatment-naïve patients. Plasma HIV-1 RNA ≥50 copies/mL is a clinically meaningful endpoint in virologically suppressed populations, as it reflects inability to maintain virologic suppression after switching to a new antiretroviral regimen.

4.2.1.3.1 Definition of Clinically Significant Confirmed Viremia

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

- **Virologic Rebound**: A participant who is virologically suppressed and has 2 consecutive (2 to 4 weeks apart) occurrences of HIV-1 RNA ≥200 copies/mL at any time during the study.

  Note: This definition is applicable to participants who are virologically suppressed at baseline and participants who are treatment-naïve at baseline and have achieved viral suppression (HIV-1 RNA <50 copies/mL).

or

- **Incomplete Virologic Response**: A participant who is treatment-naïve at baseline and has 2 consecutive (2 to 4 weeks apart) occurrences of HIV-1 RNA ≥200

copies/mL at or after Week 24 in the absence of previous suppression of HIV-1 RNA to <50 copies/mL.

There is currently no global standard for definition of patients with low-level viremia (viral load ≥50 and <200 copies/mL), and the predictive implication of such low-level viremia is uncertain [Vandenhende, M. A., et al 2015] [Charpentier, C., et al 2014]. The US Department of Health and Human Services guidelines currently define virologic failure as confirmed HIV RNA ≥200 copies/mL and do not recommend that low-level viremia (detectable HIV RNA <200 copies/mL) automatically result in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. Participants with HIV-1 RNA between 50 and 200 copies/mL have a lower risk of developing resistance compared to those with HIV-1 RNA >200 copies/mL and should continue on their current regimen, with HIV-1 RNA levels monitored as outlined in Section 8.2.2.

4.2.1.4 Palatability and Acceptability Assessment Endpoints

Note: As of Amendment 028-03, study intervention administration has been discontinued, so palatability and acceptability assessments will no longer be performed.

Acceptability may play an important role in adherence to treatment in the pediatric population as it does in the adult population. Acceptability and swallowability of the whole and split tablet will be evaluated in all participants using the most frequently reported assessment to measure acceptability in pediatric participants, consisting of a visual analog scale that was modified by including a 5-point facial hedonic scale (FHS), an expression scale depicting various degrees of pleasure [Thompson, C., et al 2015].

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 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.

4.2.1.6 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 Collecting Race and Ethnicity Data

The differential effect on the safety and efficacy based on any demographic parameter, including race or ethnicity, cannot be predicted when evaluating a new investigational drug. Therefore, it is important to collect race and ethnicity data to ensure there is not a differential effect based on these parameters and to gain assurance the results observed in the clinical study will be representative of the drug's use in a broader patient population. As an example, non-Caucasian females and males were found to have higher plasma concentrations of EFV (an NNRTI) than their Caucasian counterparts, indicating an increased risk of EFV-induced toxicity in non-Caucasian patients [Burger, D., et al 2005]. As another example, among the population with HIV in the 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, race and ethnicity data will be collected in this study to characterize baseline demographics, and analyses on race and ethnicity may be performed to better understand how these parameters influence clinical outcome and toxicity.

4.2.3 Rationale for Collecting Gender Identity Data

Transgender people, defined as those whose gender identities and/or expressions differ from the sex assigned to them at birth, have a 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 World Health Organization considers transgender people to be a separate key population because of their specific health needs and high vulnerability [Department of HIV/AIDS 2015]. Thus, gender identity data will be collected in this study to characterize baseline demographics and assess clinical outcomes in the transgender population.

4.2.4 Rationale for Collecting Infant Safety Follow-up Data

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

4.3 Justification for Dose

Note: As of Amendment 028-03, study intervention administration has been discontinued.

Pediatric patients treated for HIV have response rates similar to adults when given a dose regimen that achieves exposures similar to those observed in adult patients. Pediatric participants who are <18 years of age and weigh ≥35 kg, are predicted to have similar plasma ISL and intracellular ISL-TP concentrations to adults and no dose adjustment is expected to be necessary in this population.

In the MK-8591 Protocol 011 of treatment-naïve adults, at Week 48, DOR+ISL maintained virologic suppression in participants who achieved <50 copies/mL on DOR+ISL+3TC by Week 24 and were maintained on DOR+ISL. All 3 dose levels of ISL (0.25, 0.75, and 2.25 mg) administered with DOR±3TC in adults demonstrated potent antiretroviral activity comparable to DOR/3TC/TDF, as demonstrated by the proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 24 and 48. Overall, no ISL dose-response for efficacy was observed. Graphical analysis of steady-state ISL-TP trough concentrations and response at Week 48 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. ISL 0.75 mg was selected for study in adults who are naïve to treatment (Protocol 020), virologically suppressed (Protocols 017 and 018), and heavily treatment experienced (Protocol 019) in the Phase 3 clinical program. Protocol 011 also demonstrated that all doses of ISL studied, when administered with DOR±3TC, had a favorable safety and tolerability profile through Week 48, comparable with that of DOR/3TC/TDF. Thus, based on projected exposure in this population, similar safety and tolerability is expected in pediatric participants enrolled in Protocol 028 as adults enrolled in Protocol 011.

A population PK model for ISL and ISL-TP was simulated at the 0.25, 0.75, and 2.25-mg doses for an adult population using demographic data from the NHANES database. The allometrically scaled model was also simulated with a 0.75-mg dose for a population of pediatric participants (who are <18 years of age and weigh ≥35 kg), also using data selected from the NHANES database. ISL plasma AUC0-24, the PK parameter most closely associated with ISL safety, was estimated for pediatric participants after ISL 0.75 mg QD dosing and compared with that from adults after ISL 2.25 mg QD dosing (a dose found to have a favorable safety and tolerability profile in adults in MK-8591A Protocol 011). Plasma

ISL AUC0-24 (geometric mean estimated to be 0.12 µM·hr) for pediatric participants (who are <18 years of age and weigh ≥35 kg) is expected to be approximately 2.3-fold lower than that at the 2.25-mg dose in adults (N=1000 simulated geometric mean of 0.28 µM·hr).

ISL-TP PBMC C24, the PK parameter most closely associated with ISL efficacy, was estimated for pediatric participants (who are <18 years of age and weigh ≥35 kg) after ISL 0.75 mg QD dosing and compared to that from adults after ISL 0.25 mg dosing (a dose found to be on the plateau of efficacy in adults in MK-8591A Protocol 011). The ISL-TP PBMC C24 expected in pediatric participants (who are <18 years of age and weigh ≥35 kg) after daily dosing of ISL 0.75 mg (11.2 µM or 2.2 pmol/10^6 cells) is approximately 4.1-fold higher than that at the 0.25-mg dose in adults (N=1000 simulated geometric mean of 2.7 µM or 0.54 pmol/10^6 cells).

Therefore, it is expected that ISL 0.75 mg QD is safe to study in pediatric participants weighing ≥35 kg and sufficient levels of ISL-TP will be generated to provide efficacy comparable to the adult population.

The approved dose of DOR 100 mg has been studied in Phase 1 to 3 clinical studies in treatment-naïve and virologically suppressed participants with HIV-1. It was selected based on favorable efficacy, safety, tolerability, and metabolic profiles as confirmed in the Phase 3 clinical studies conducted in adults [Orkin, C., et al 2018] [Molina, J. M., et al 2018] (MK-1439A Protocol 024). Initial results from MK-1439 Protocol 027 indicate that projected steady-state PK after a single-dose of DOR (100 mg) in 9 adolescents living with HIV-1 (<18 years of age, weighing ≥45 kg) is similar to that observed in adults. DOR plasma C24 is the PK parameter most closely associated with efficacy. It is expected that pediatric participants dosed with DOR 100 mg QD will have C24 values ≥560 nM, corresponding to 0.6-fold the steady-state mean C24 for the 100-mg dose in adults.

In summary, a 0.75-mg dose of ISL in combination with 100 mg DOR is predicted to be tolerable and provide ISL-TP concentrations in participants <18 years of age, weighing ≥35 kg that will demonstrate potent antiretroviral activity against both wild-type HIV-1 virus and most common NRTI- and NNRTI-resistance substitutions. Specific criteria for dose confirmation after PK evaluation in the Intensive PK Cohort are provided in Section 9.6.1.1.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or 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, GCP, and/or

other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Note: As of Amendment 028-03, the study has closed to enrollment.

Pediatric participants with HIV-1 who are <18 years of age, weigh ≥35 kg, and are treatment-naïve or have been virologically suppressed for ≥3 months on any stable oral 2-drug or 3-drug combination ART (± PK booster) and have not failed prior ART therapy 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. Meets one of the following:

    a) Virologically Suppressed: Is HIV-1 positive at screening with plasma HIV-1 RNA <50 copies/mL at screening

    AND

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

    Note: A single episode of nonclinically significant HIV-1 RNA result (defined as 1 or more measurement(s) of HIV-1 RNA above the limit of quantification, but <200 copies/mL returning to levels below the lower limit of quantification; ie, transient detectable viremia) during the 3 months prior to screening is acceptable.

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

    Note: Any prior change of a single drug or multiple drugs simultaneously must have occurred due to tolerability or safety, access to medications, or simplification, and must not have been done for treatment failure.

    OR

b) Treatment-Naïve: Is HIV-1 positive with plasma HIV-1 RNA ≥500 copies/mL at screening

AND

Is naïve to ART defined as having received ≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection, except for use of PrEP or PEP.

Note: The use of any PrEP or PEP prior to diagnosis of HIV-1 infection is permissible up to 1 month prior to screening.

Note: Treatment-naïve participants will only be allowed to enroll when the Phase 3 ISL/DOR treatment-naïve study in adults (MK-8591A Protocol 020) is open to full enrollment after the Sentinel Cohort Week 24 interim analysis. Sites will be informed when treatment-naïve enrollment can begin.

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

2. Able and willing to swallow available tablet formulation.

Demographics

3. Is male or female, <18 years of age, and weighing ≥35 kg at the time of signing the informed consent/assent.

Contraception/Pregnancy

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

   Is not a WOCBP

   OR

   Is a WOCBP and using 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

5. The participant and legally acceptable representative have 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 drugs as determined by the investigator.

3. Has an active diagnosis of hepatitis due to any cause, including active HBV infection (defined as HBsAg-positive or HBV DNA positive).

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

   Note: Participants who do not demonstrate immunity to HBV are encouraged to be vaccinated against HBV.

   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. Significant hepatic synthetic dysfunction is defined as a serum albumin <2.8 g/dL or an INR >1.7 in the absence of another explanation for the abnormal laboratory value.

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

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

Prior/Concomitant Therapy

6. Is taking or is anticipated to require systemic immunosuppressive therapy, immune modulators, or any prohibited therapies outlined in Section 6.5 from 45 days prior to Day 1 through the study treatment period.

   Note: Time-limited courses (≤7 consecutive days) of systemic corticosteroids (eg, for asthma exacerbation), topical steroids for the treatment of skin conditions, and systemic steroids <0.5 mg/kg/day or <30 mg maximum daily prednisone equivalent dose (whichever is less) are permitted.

7. Is currently taking long-acting cabotegravir-rilpivirine.

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 45 days prior to Day 1 through the study treatment period.

   Note: Concurrent participation in observational studies are to be discussed with the Sponsor prior to enrollment and through the study treatment period.

Diagnostic Assessments

9. Has a documented or known virologic resistance to components of DOR/ISL, as demonstrated by any of the following:

   - DOR resistance substitutions in reverse transcriptase: V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L, or Y318F
   - ISL resistance substitution in reverse transcriptase: M184V/I

   Note: Virologically Suppressed Cohort participants who do not have documentation of resistance testing may enroll.

   Note: Treatment-Naïve Cohort participants will have resistance testing performed by the central laboratory as part of the screening assessments. However, if resistance testing results obtained from a local laboratory <90 days prior to the Screening Visit date through Day 1 are available prior to the availability of the central laboratory screening resistance results, the local results can be used to determine participant eligibility.

10. Has exclusionary laboratory values within 45 days prior to Day 1 as listed in Table 1.

Note: A single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results, but the repeat test results must be available within the 45-day screening window.

Table 1 Laboratory Exclusion Criteria

Laboratory Assessment	**Exclusionary Values**
AST SGOT	>5 × ULN
ALT SGPT	>5 × ULN
Lipase	≥ 3× ULN
eGFR	≤59 mL/min/1.73 m^2 *based on the Schwartz equation (Appendix 8)*
Hemoglobin	<8.5 g/dL (female) or <9.00 g/dL (male)
ALT SGPT=alanine aminotransferase; AST SGOT=aspartate aminotransferase; eGFR= estimated glomerular filtration rate; ULN=upper limit of normal.	

Other Exclusions

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

Note: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study 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 individuals who are HIV-positive*

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

If a participant in the Intensive PK Cohort discontinues from study intervention OR withdraws from the study OR has nonevaluable intensive PK data, a replacement participant may be enrolled if deemed appropriate by the Sponsor. The replacement participant will be assigned a unique treatment number by the IRT. Participants will not be replaced in any other circumstances.

6 STUDY INTERVENTION

Note: As of Amendment 028-03, study intervention administration has been discontinued and all participants will have switched to non-study ART.

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

Clinical supplies (DOR/ISL provided by the Sponsor) will be packaged to support enrollment and replacement participants as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

Note: As of Amendment 028-03, study intervention administration has been discontinued and all participants will have switched to non-study ART.

The study intervention to be used in this study is outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Treatment Period	Use	IMP/ NIMP	Sourcing
DOR/ ISL	Experi mental	DOR/ISL	Drug	Tablet	100 mg/ 0.75 mg	100 mg/ 0.75 mg QD	Oral	Day 1 to Week 96	Experi mental	IMP	Provided centrally by Sponsor

DOR=doravirine; ISL=Islatravir; QD=once daily

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

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

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

6.2 Preparation/Handling/Storage/Accountability

Note: As of Amendment 028-03, study intervention administration has been discontinued and all participants will have switched to non-study ART.

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

Note: As of Amendment 028-03, study intervention administration has been discontinued and all participants will have switched to non-study ART.

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IRT system. All participants will be allocated by nonrandom assignment to receive DOR/ISL FDC.

6.3.2 Stratification

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

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Note: As of Amendment 028-03, study intervention administration has been discontinued and all participants will have switched to non-study ART.

Participants/guardians should bring the study intervention bottle(s) to their visits. At each visit, the number of doses remaining in the study packaging will be counted, reviewed, and recorded. The results will be used to assess participant compliance. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant/guardian, and the explanation must be documented. When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

Participants/guardians should be reminded of the importance of taking the study intervention as instructed for the entire duration of the study.

Decisions to temporarily withhold study intervention because of an AE or other reasons 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

Note: As of Amendment 028-03, there are no study defined prohibited medications. The local label for the non-study ART should be consulted for potential drug interactions.

Medications specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant/guardian.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with: reason for use, dates of administration (including start and end dates), and dosage (information including dose and frequency).

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

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

Table 3 Prohibited Therapies

Strong and moderate CYP3A inducers based on potential to reduce DOR concentrations	Including, but not limited to: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Enzalutamide Rifabutin Rifampin Rifapentine Mitotane St. John's Wort Herbal remedies Modafinil Bosentan Nafcillin
Additional prohibited therapies based on ISL	Pentostatin

Nonstudy ART	All nonstudy antiretrovirals (with the exception of study drugs and baseline ART during the screening period) including treatments for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1 (eg, adefovir, TDF, TAF, FTC, or 3TC). *Entecavir therapy for acquired HBV infection during the study is permitted.*
Immunosuppressive therapies	Immune therapy agents, immune modulators or other systemic immunosuppressive therapy, including interferon-based treatment for hepatitis and maintenance glucocorticoid therapy (≥0.5 mg/kg/day prednisone equivalent dose or ≥30 mg daily dose for >7 consecutive days). *Note: Time-limited courses (≤7 consecutive days) of systemic corticosteroids (eg, for asthma exacerbation), topical steroids for the treatment of skin conditions, and systemic steroids <0.5 mg/kg/day or <30 mg maximum daily prednisone equivalent dose (whichever is less) are permitted.*
Investigational agents	All nonstudy investigational agents including devices
3TC=lamivudine; ART=antiretroviral therapy; CYP3A=cytochrome P450 3A; DOR=doravirine; FTC= emtricitabine, HIV-1=human immunodeficiency virus-1; ISL=islatravir; TAF= tenofovir alafenamide; TDF= tenofovir disoproxil fumarate	

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification

No dose modification is allowed during the study.

6.7 Intervention After the End of the Study

Note: As of Amendment 028-03, this section is no longer applicable.

At the end of Week 96, provided development of DOR/ISL continues, there will be a mechanism for all eligible participants to continue receiving study intervention without interruption until it becomes commercially accessible. 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.

6.8 Clinical Supplies Disclosure

Note: As of Amendment 028-03, this section is no longer applicable.

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Note: As of Amendment 028-03, as study intervention administration will have discontinued for all participants, this section is no longer applicable.

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 8.11.3.

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has confirmed HIV-1 virologic rebound as defined in Section 4.2.1.3.1.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a positive confirmatory serum pregnancy test.

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

- The participant requires treatment for active tuberculosis infection.

- The participant has an estimated eGFR of ≤59 mL/min/1.73m^2 based on the Schwartz equation.

  - Note: eGFR should be confirmed by repeat analysis prior to discontinuing

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 8.1.10. 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, 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 maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 521 mL for all participants in the Intensive PK Cohort or approximately 483 mL for all other participants (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 consent, and assent if applicable, from each potential participant and each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

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

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

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

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

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

8.1.1.2 Consent/Assent for Intensive PK Cohort Blood Sample Collection for Plasma and PBMCs

The investigator or medically qualified designee will explain the Intensive PK Cohort blood sample collection for plasma and PBMCs to the participant and participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent and assent before performing any procedure related to the Intensive PK Cohort blood sample collection. After applicable consent and assent are obtained, these participants will have additional PK blood sample collection as specified in the SoA (Section 1.3) and Section 8.6. A copy of the signed informed consent and assent will be given to the participant and participant's legally acceptable representative.

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

The investigator or medically qualified designee will explain the infant safety data collection consent to the participant, answer all questions, and obtain documented informed consent before collecting any data related to infant safety (Section 8.3.6). A copy of the informed consent will be given to the participant.

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

Note: As of Amendment 028-03, specimens for FBR will not be collected, so this section is no longer applicable.

The investigator or medically qualified designee will explain the future biomedical research consent/assent to the participant/legal guardian, 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/legal guardian.

8.1.2 Inclusion/Exclusion Criteria

Note: As of Amendment 028-03, this section is no longer applicable.

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

Note: As of Amendment 028-03, this section is no longer applicable.

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 allocation, 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

Note: As of Amendment 028-03, this section is no longer applicable.

A medical history will be obtained by the investigator or qualified designee. The medical history should include information pertaining to the diagnosis of HIV-1 and AIDS (if applicable) and year diagnosed. If the participant has been previously diagnosed with any AIDS-defining conditions or CD4+ T-cell count <200 cells/mm^3, the condition as well as a corresponding medical history of AIDS must be reported.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

Note: As of Amendment 028-03, this section is no longer applicable.

The investigator or qualified designee will review prior medication use and record prior medication taken by the participant within 45 days before first dose of study intervention.

All prior HIV medication use, regardless of timing, including PrEP or PEP, must be recorded.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

Note: As of Amendment 028-03, this section is no longer applicable.

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

Any participant who is screened more than once 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/Allocation Number

Note: As of Amendment 028-03, this section is no longer applicable.

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

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

8.1.8 Study Intervention Administration

Note: As of Amendment 028-03, study intervention administration will have discontinued, so this section is no longer applicable.

Study intervention will be provided as per Table 2 and dispensed through the IRT system at visits indicated in the SoA (Section 1.3).

The first dose of study intervention will be administered at the study site at Visit 2 (Day 1). Subsequent dosing will be performed once daily by the participant at his/her home at approximately the same time each day unless otherwise specified in Section 8.1.8.1.

8.1.8.1 Timing of Dose Administration

Note: As of Amendment 028-03, this section is no longer applicable.

Participants will take (at their home) 1 tablet of study intervention (DOR/ISL) QD at the same time each day (with the exception of days where study intervention is to be observed at the site). Study intervention will be taken without regard to food. If more than 1 bottle of

study intervention is dispensed, the participant is instructed to use all study intervention in the bottle before opening another bottle.

Participants in the Intensive PK Cohort will be required to take their daily dose of DOR/ISL in the morning. All other participants may follow an alternative dosing schedule for DOR/ISL (eg, afternoon or evening).

The timing of dosing will be aligned with the timing of blood collection for PK analyses (see Sections 8.6.1 and 8.6.2 for timing of blood collection for PK).

- Intensive PK Cohort Participants:
    - **Participants in the Intensive PK Cohort are required to take DOR/ISL in the morning Day 1 through Day 29 to facilitate the scheduling of blood collection during the day on Day 28 and Day 29**
    - Dose administration of DOR/ISL on Day 28 will be observed at the study site and must be planned to allow a **predose** PK blood draw (plasma), and a **4-hour postdose** blood draw (PBMC) according to Sponsor instructions
    - Dose administration of DOR/ISL on Day 29 must be planned such that the Day 28 **24-hour postdose** PK blood draw (plasma) can be obtained **prior** to taking the DOR/ISL dose on Day 29.

      Note: Participants will be allowed to transition to an alternate dosing schedule for DOR/ISL (eg, afternoon or evening) beyond Day 29. Participants should take the dose of DOR/ISL at approximately the same time, each day.
- All Participants:
    - DOR/ISL dosing for Day 1, Day 28, Week 24 and Week 48 visits will be observed at the study site and must be planned such that a predose PK blood draw (plasma) can be obtained prior to the daily dose of DOR/ISL.

      Note: If participants (excluding those in the Intensive PK Cohort) take their dose of DOR/ISL without observation at the study site, and prior to the predose PK blood draw, then the timing of dose will be verbally reported to study staff by the participant or guardian and recorded in the appropriate source documentation.
    - For Week 8, 16, 36, 60, 72, 84, and 96 visits, the timing of DOR/ISL dose administration should be verbally reported to study staff by the participant or guardian and recorded in the appropriate source documentation

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

- <u>If ≤12 hours from the missed dose</u>, the missed dose should be taken, and the normal dosing schedule resumed

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

8.1.9 Palatability and Acceptability Assessment

Note: As of Amendment 028-03, this section is no longer applicable.

The questionnaire to assess palatability and acceptability is to be completed for all participants at the time of DOR/ISL administration on Days 1 and 28 (whole tablet), and Week 24 (split tablet). The following recommendations should be considered when completing the questionnaire:

- **Age of less than 12 years**: Combined completion where the participant completes the faces question, and the observer completes the remaining questions.

- **Ages 12 to less than 18 years**: Completion directly by the participant, preferred when possible.

Observer assessments should be based on what the legally acceptable representative/caregiver/healthcare provider directly observed during and after intervention administration, including the participant's facial expressions, behavior, and what the participant says. Only individuals who have actually observed the participant taking the intervention should complete the assessment.

Week 24 Assessment: The palatability of a split tablet is being evaluated at Week 24. The study staff will split the tablet using a pill splitter immediately prior to administration at the Week 24 visit. Both halves should be taken immediately after splitting. The splitting tool should be wiped immediately following each use. The tablet should only be split at Week 24 for the palatability assessment, and not at any other time.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

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

8.1.10.1 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) and have their specimens and all derivatives destroyed. 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@merck.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 or their legal guardian 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.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 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.

8.1.13 Domiciling

Note: As of Amendment 028-03, this section is no longer applicable.

For Intensive PK Cohort participants who will undergo intensive PK sampling, the investigator may make arrangements (including local accommodations outside the context of hospitalization, if needed/warranted) such that all PK sampling at specified timepoints can be performed as scheduled.

8.2 Efficacy Assessments

8.2.1 HIV-1 RNA Quantification

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

8.2.2 Management of Study Participants with Viremia

Note: As of Amendment 028-03, this section is no longer applicable.

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

For Virologically Suppressed Cohort participants, when viremia (HIV-1 RNA ≥50 copies/mL) is detected (Section 4.2.1.3.1), the investigator should query the participant regarding adherence to study intervention, intercurrent illness, or recent immunization

For Treatment-Naïve Cohort participants, when viremia (HIV-1 RNA ≥50 copies/mL) is detected (Section 4.2.1.3.1) following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression to <50 copies/mL, the investigator should query the participant regarding adherence to study intervention, intercurrent illness, or recent immunization.

8.2.2.1 Viremia Confirmation

Note: As of Amendment 028-03, this section is no longer applicable.

Confirmation of viremia requires 2 consecutive plasma HIV-1 RNA results of ≥50 copies/mL (Section 4.2.1.3.1) with the second sample collected at a "Viremia Confirmation" visit at least 2 weeks, but not more than 4 weeks from the date of the initial sample. This timeframe may be extended if study intervention is interrupted for 1 of the following circumstances:

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

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

Note: As of Amendment 028-03, this section is no longer applicable.

Study participants with confirmed HIV-1 RNA of ≥200 copies/mL (following prior suppression to HIV-1 RNA to <50 copies/mL OR at or after Week 24 in the absence of previous suppression to HIV-1 RNA <50 copies/mL) will be assessed for development of viral drug resistance (Section 8.2.2.4) and discontinuation from study intervention (Section 7.1). Once it is determined that study intervention discontinuation is appropriate, Early Discontinuation and End of Treatment visit procedures should be completed (Sections 1.3.2 and 8.11.3) and the participant managed by the investigator per local standard of care.

8.2.2.3 Participants With Low-Level Viremia (≥50 and <200 Copies/mL)

Note: As of Amendment 028-03, this section is no longer applicable.

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

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

8.2.2.4 Viral Drug Resistance Testing

Participants with confirmed virologic rebound or incomplete virologic response (Section 4.2.1.3.1), or who discontinue study intervention for another reason and have HIV-1 RNA ≥200 copies/mL at the time of discontinuation, will be assessed for development of viral drug resistance. Samples with HIV-1 RNA ≥200 copies/mL that were collected either to confirm viremia or at discontinuation will be sent for genotypic and phenotypic resistance testing. Samples will be collected for genotypic and phenotypic HIV-1 drug resistance testing per SoA (Section 1.3) and used to assess resistance-associated substitutions as applicable during the study.

Whole blood samples will be collected per the SoA (Section 1.3) for proviral DNA archive resistance testing. The proviral DNA archive resistance testing sample will be collected at the viremia confirmation visit and only sent for analysis if the HIV-1 RNA is confirmed to be ≥50 and <200 copies/mL at the viremia confirmation visit. The proviral DNA archive resistance testing sample should only be sent once per confirmed low-level viremic episode.

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

A TBNK panel, including CD4+ T cell count, will be performed at the central laboratory (Appendix 2).

Refer to Section 8.11.5 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 to be drawn over the course of the study, including

approximate blood volumes drawn by visit and by sample type per participant, can be found in Table 14 in Appendix 2.

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

8.3.1 Physical Examinations

A full physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at the visits specified in the SoA (Section 1.3). The full physical examination will include examination of body systems including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system.

Height will be measured and recorded at the visits specified in the SoA (Section 1.3). Height measurements should be taken using a stadiometer (recommended, but not required). Participants should remove their shoes and stand as tall and straight as possible.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the visits specified in the SoA (Section 1.3). This examination will be sign- and symptom-directed and based on the participant's condition and circumstances. The investigator should note any changes in the participant's condition (body systems) since the last examination, not precluding examination of any body system(s) as clinically indicated.

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

8.3.1.1 Weight

Weight will be measured and recorded at the visits specified in the SoA (Section 1.3). Participants should remove their shoes and wear a single layer of clothing at each measurement.

8.3.2 Vital Signs

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

8.3.3 Confirmation of Menarche, Contraception, and Pregnancy Testing

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

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

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

Urine pregnancy test kits will be provided by the central laboratory, and routine testing will be performed by the local laboratory. In the event of a positive urine pregnancy test result, serum pregnancy testing must be performed by the central laboratory. If a participant becomes pregnant, refer to Section 7.1 and Section 8.11.3.1.

8.3.4 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Table 13 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: Decreases in CD4+ T-cell and/or lymphocyte counts should be managed per Section 8.11.5.

8.3.5 HBV Assessments

Note: As of Amendment 028-03, HBV monitoring will not be performed after the Early Discontinuation of Treatment visit.

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

All eligible participants must be HBsAg-negative at screening. Participants who are antiHBc positive and HBV DNA positive at screening are excluded. Participants who are antiHBc positive but HBV DNA negative at screening are eligible to enroll. For the duration of the

study, participants positive for antiHBc should be monitored for possible HBV reactivation. Samples will be taken to monitor HBsAg and HBV DNA each visit per SoA (Section 1.3). Investigators should also pay close attention to changes from baseline in ALT, AST, bilirubin, and alkaline phosphatase (included in chemistry laboratory assessments).

Participants who become HBsAg or HBV DNA positive during the study will be managed by the investigator per local standard of care and/or referred for management of their HBV infection. Participants may be allowed to continue study intervention if deemed medically appropriate upon consultation with the Sponsor.

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

8.3.6 Infant Safety Follow-up Assessments

Infants, born to participants who become pregnant while receiving study intervention or during the protocol-specified follow-up period and consent to infant follow-up, will have safety follow-up through approximately 1 year of age as outlined in Table 4. This infant safety follow-up data may be collected by phone call. Gestational age, Apgar score, length, weight, head circumference measurements, directed pediatric examination, concomitant medications and infant SAEs will be collected at birth. Infant informed consent, length, weight, head circumference measurements, concomitant medications and infant SAEs will be collected at 1 year of age. Infant SAEs, including congenital anomalies identifiable on physical examination at birth or shortly after birth, will be collected as per Section 8.4.1.

Table 4 Infant Safety Data Collection Through 1 Year of Age

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 ----------	

Timepoint	At Birth[a]	1-Year After Birth[a,b]
Visit Name	N/A	Infant Follow-Up 1
Administrative and Safety Procedures		

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.

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

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

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

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

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

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

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

From the time of intervention allocation through the 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 follow-up, 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 5.

For participants that continue to receive study intervention in a rollover study, the collection requirements of AEs, SAEs and other reportable safety events are amended as follows:

- AEs, SAEs and other reportable safety events will be collected and recorded through the last treatment visit in this protocol.
- All new SAEs (including those considered related to study intervention) and new other reportable safety events (including pregnancy exposure) that occur after the last treatment visit will be collected in the rollover study.
- Pregnancy outcome and infant SAEs will be captured in this protocol, if pregnancy exposure is reported in this protocol.
- The last collection of non-serious SAEs will be at the last treatment visit in this protocol.

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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
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
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, 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 allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

For infants born to participants who become pregnant and consent to infant follow-up, 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 this study.

8.4.7 Events of Clinical Interest

Note: As of Amendment 028-03, ECIs will be reported through 42 days after the last dose of study intervention.

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

Events of clinical interest for this study include:

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

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

8.5 Treatment of Overdose

Note: As of Amendment 028-03, as administration of study intervention will have discontinued, this section is no longer applicable.

In this study, an overdose is any dose higher than the prescribed dose of DOR/ISL (100 mg/0.75 mg daily).

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 Measurements

Note: As of Amendment 028-03, plasma PK sample collection has been revised and will be collected only at the Early Discontinuation of Treatment and End of Treatment Follow-Up visits.

Venous blood samples will be collected from all participants for the measurement of ISL concentrations in plasma (Table 6).

The timing of blood collection will be aligned with the timing of dose administration as outlined in Section 8.1.8.1. Study staff will observe and record the timing of DOR/ISL doses administered to all participants at the investigational site on Day 1, Day 28, Week 24, and Week 48, which are PK sample collection days.

For participants who take DOR/ISL at night, there will be an exception to the time points outlined in the SoA. For these participants, 1 blood sample (assigned as "random") will be collected at the Week 48 visit irrespective of time of the last dose. If participants administered their dose of DOR/ISL without observation at the study site at Week 48, then the dose timing will be verbally reported (Section 8.1.8) and the PK sample will be assigned as "random".

For Week 8, 16, 36, 60, 72, 84, and 96 visits, the timing of DOR/ISL dose administration prior to the PK sample collection will be verbally reported to study staff by the participant or guardian and recorded in the appropriate source documentation.

Sample collection, storage, and shipment instructions for plasma samples will be provided in a separate manual.

Intensive blood sampling on Day 28 will be conducted only for participants in the Intensive PK Cohort. Participants in the Intensive PK Cohort will be required to take their daily dose of DOR/ISL in the morning. Sparse PK samples (plasma) will be collected from all participants. Of note, a single predose sample on Day 28 will be collected from all participants (regardless of their participation in the Intensive PK Cohort).

PK samples (investigational, time relative to dose not specified) will also be drawn at the Viremia Confirmation Visit, Early Discontinuation of Treatment Visit, and the End of Treatment Follow-up Visit, (Section 1.3.2). The timing of DOR/ISL dose administration prior to the PK sample collection at these visits will be verbally reported to study staff by the participant or guardian and recorded in the appropriate source documentation. Analysis of these samples will be triggered by the Sponsor as needed.

Table 6 Plasma Sample Collection Schedule for ISL Concentrations

Intensive PK Cohort Participants	**All Participants**
Day 28: • 1 sample predose[a] • 1 sample postdose, each for the following timepoints: o 0.5 hour (±10 min) o 1 hour (±15 min) o 2 hours (±15 min) o 4 hours (±1 hour) o 8 hours (±2 hours) o 12 hours (±2 hours) o 24 hours (±4 hours)	• **Day 1**: 1 sample predose • **Day 28[a]**: 1 sample predose • **Week 8 and Week 16[c]**: 1 sample, "random" • **Week 24**: o 1 sample predose o 1 sample at 0.5 hour (±10 min) to 2 (±15 min) hours postdose • **Week 36[c]**: 1 sample, "random" • **Week 48[b]**: o 1 sample predose o 1 sample 0.5 hour (±10 min) to 2 (±15 min) hours postdose • **Week 60-96**: 1 sample, "random"
PK=Pharmacokinetic Note: All predose samples will be collected up to 3 hours prior to dosing [a] A single predose sample will be taken from every participant on Day 28. Intensive PK Cohort Participants do not require 2 samples predose [b] Participants who routinely take their study intervention in the evening should continue to do so and only 1 sample will be taken at Week 48 visit irrespective of time of last dose. If participants administered their dose of DOR/ISL without observation at the study site at Week 48, then the dose timing will be verbally reported and the PK sample will be assigned as "random". [c] The time of the dose of DOR/ISL taken prior to the random PK sample collection on the Week 8,16, 36, 60, 72, 84, and 96 visits will be verbally reported to study staff by the participant or guardian and recorded in the appropriate source documentation.	

8.6.2 Blood Collection for ISL-TP Measurements in PBMCs

Note: As of Amendment 028-03, this section is no longer applicable.

On Day 28, venous blood samples will be collected from participants in the Intensive PK Cohort for the measurement of ISL-TP (and ISL-DP for proper stabilization confirmation) concentrations in PBMCs.

One blood sample for PBMCs will be collected at each of the following timepoints on Day 28: Predose (up to 3 hours prior to dosing), 4 hours (±1 hour), and 24 hours (±4 hours) postdose. The timing of blood collection will be aligned with the timing of dose administration as outlined in Section 8.1.8.1.

Sample collection, storage, and shipment instructions for PBMC samples will be provided in a separate manual.

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 collected for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for 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 instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

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

- Buccal swabs for genetic analysis

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, 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

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

Note: As of Amendment 028-03, this section is no longer applicable.

Screening

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

Rescreening

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

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

- Vital signs, weight, height and directed physical examination
- Review medical history and prior/concomitant medications for new information
- All laboratory assessments (includes urine pregnancy testing for WOCBP), with the exception of HIV-1 drug resistance testing
- Review of AEs

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

8.11.2 Treatment Period

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

8.11.2.1 Optional Nurse Visits and Telephone Visits

A visiting nurse service may be used (if locally available and approved for use) under extenuating circumstances and with Sponsor approval. If a visiting nurse service is utilized 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.

8.11.2.2 Day 14 Telephone Call

Note: As of Amendment 028-03, this section is no longer applicable.

A qualified medical designee noted on the study delegation log will be responsible for the Day 14 telephone call. During the call, participants will be asked about the use of concomitant medications in Section 8.1.5.2 and AEs experienced as described in Section 8.4.2. The participant/guardian will be reminded of the scheduled Day 28 visit date and planned dosing schedule for Day 28 and scheduled domiciling (as applicable). Adherence assessment and counseling will also be performed. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adherence to study intervention.

8.11.2.3 Fasting

Note: As of Amendment 028-03, this section is no longer applicable.

On Day 1, Week 48, and Week 96 visits, participants are required to fast (ie, do not consume any food or beverages except water) for at least 8 hours prior to the visit. Fasting chemistry tests for lipid profile and glucose will be performed at these visits. If the measurements are normal at baseline, then these measurements will be repeated only at 48 and 96 weeks. If the baseline fasting lipid profile or fasting glucose is abnormal, then the participant will be tested again at Week 24.

The investigator/study coordinator are responsible to remind participants to fast prior to these visits and to confirm with participants their fasting status in the appropriate source documentation.

8.11.3 Participants Who Discontinue Study Intervention

Note: As of Amendment 028-03, all participants should be managed per Sections 8.11.3.2, 8.11.3.3, and 8.11.5.

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

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

8.11.3.1 Participants Who Become Pregnant

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

The participant should not be withdrawn from the study but should have an Early Discontinuation of Treatment visit (Section 8.11.3.2). If the pregnancy is reported at a scheduled study visit, the assessments for the Early Discontinuation of Treatment visit and the End of Treatment Follow-up (42 days after End of Treatment) should be conducted at that time (Section 1.3.2). These visits will be registered in IRT, concomitant medications will be reviewed, and safety assessments will be completed.

All reported pregnancies occurring during the study must be followed to the completion/termination of the pregnancy (Section 8.4.5). When assessing the severity of AEs that are pregnancy-related complications, please refer to the additional guidance provided as part of the DAIDS table version 2.1 "Addendum 1: Female Genital Grading Table for Use in Microbicide Studies", particularly the section "Complications of Pregnancy" (found on pages 11-12 of the Addendum).

The participant will be asked to join a pregnancy registry, which collects information about the outcome of the pregnancy. Infants born to participants who become pregnant while receiving study intervention and consent/assent to infant follow-up will have follow-up data collected up to approximately 1 year of age (Section 8.3.6).

8.11.3.2 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.

Decreases in CD4+ T-cell and/or total lymphocyte counts at the Early Discontinuation of Treatment visit should be managed per Section 8.11.5.

8.11.3.3 End of Treatment Follow-up Visit

Participants who discontinue study intervention at any time (including at the Week 96 visit) for any reason(s) not related to pregnancy will have a safety follow-up visit in-clinic approximately 42 days after the last dose of study intervention. Assessments for this visit are outlined in Section 1.3.2.

Participants with decreases in CD4+ T-cell and/or total lymphocyte counts at the Early Discontinuation of Treatment Visit and confirmed at the End of Treatment Follow-up Visit will be followed every 4 to 6 weeks (Section 8.11.5 and Section 1.3.3). The End of Treatment Follow-up Visit will be conducted approximately 42 days after the last dose of study intervention. All activities outlined in Section 1.3.2 for the End of Treatment Follow-up Visit should be performed at this time.

8.11.4 Viremia Confirmation

Note: As of Amendment 028-03, this section is no longer applicable.

For the Virologically Suppressed Cohort, if a participant has a viral load of ≥50 copies/mL at any time during the study, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (Section 1.3.2 and 4.2.1.3.1).

For the Treatment-Naïve Cohort, if a participant has a viral load of ≥50 copies/mL following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (see Section 1.3.2 and Section 4.2.1.3.1).

For both cohorts, 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 and whole blood for proviral DNA archive resistance test sample must be collected.

8.11.5 Management of Participants with Regards to CD4+ T-Cell Counts and/or Total Lymphocyte Counts

- Participants discontinued from DOR/ISL should undergo assessments for CD4+ T-cell and total lymphocyte counts at the Early Discontinuation of Treatment Visit. The average baseline value (defined as the average of the screening [within 45 days prior to the first dose of study intervention] and Day 1 values) for CD4+ T-cells and total lymphocytes will be compared to the values at the Early Discontinuation of Treatment Visit.

    - If the CD4+ T-cell and/or total lymphocyte counts at the Early Discontinuation of Treatment Visit are not decreased by >10% of the average baseline value, the participant will proceed to an End of Treatment Follow-Up visit approximately 42 days later and will discontinue from the study at that visit. If the CD4+ T-cell and/or total lymphocyte counts at the Early Discontinuation of Treatment Visit are >10% below average baseline value, the participant will need to have the decrease in counts confirmed at the End of Treatment Follow-up Visit. If at the End of Treatment Follow-up visit the counts are not decreased by >10% of the average baseline value, then the participant will discontinue from the study at the End of Treatment visit.

    - If the CD4+ T-cell and/or total lymphocyte counts at the Early Discontinuation of Treatment Visit are >10% below average baseline value, the participant will need to have the decrease in counts confirmed at the End of Treatment Follow-up Visit. If at the End of Treatment Follow-up visit the counts are still decreased by >10% of the average baseline value, then the CD4+ T-cell and total lymphocyte counts should be monitored every 4 to 6 weeks (per Section 1.3.3) until both the CD4+ T-cell count and total lymphocyte count are not decreased by >10% of the average baseline value on 2 measurements 12 weeks apart.

Note: If a participant has 2 values 12 weeks apart that are ≤10% below average baseline value, but has more than 1 value >10% below average baseline value during the 12-week interval, then the participant will require continued monitoring.

If the CD4+ T-cell and/or total lymphocyte counts remain decreased by >10% of the average baseline value at 6 months, the Investigator should consult with the Sponsor.

9 STATISTICAL ANALYSIS PLAN

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

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 2 nonrandomized, noncomparative, open-label clinical study to evaluate the PK, safety, and efficacy of DOR/ISL in participants with HIV-1 who are <18 years of age, weighing ≥35 kg, and have been virologically suppressed for ≥3 months or are treatment-naïve.
Treatment Assignment	All participants will receive DOR (100 mg)/ISL (0.75 mg) FDC QD.
Analysis Populations	**PK**: PP; **Safety**: APaT; **Efficacy**: FAS, and Resistance Analysis Subset.
Primary Endpoint(s)	**PK:** 1. ISL steady-state AUC0-24, Cmax, Tmax, CL/F, Vz/F, t1/2 after administration of DOR/ISL QD for 28 days in the Intensive PK Cohort. 2. ISL-triphosphate steady-state AUC0-24, Cmax, and C24 after administration of DOR/ISL QD for 28 days in the Intensive PK Cohort. **Safety:** 1. Percentage of participants experiencing AEs or discontinuing study intervention due to an AE through Week 24.
Key Secondary Endpoints	**Safety:** 1. Percentage of participants experiencing AEs or discontinuing study intervention due to an AE through study duration. **Efficacy:** 1. Percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 24, 48, and 96 (for Virologically Suppressed Cohort only). 2. Percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 24, 48, and 96. 3. Change from baseline in CD4+ T-cell count at Weeks 24, 48, and 96. 4. Development of viral drug resistance to DOR or ISL in participants treated with DOR/ISL. **Palatability and Acceptability of the Tablet (whole and split)** 1. 5-point facial hedonic scale

Statistical Methods for Key Analyses	**PK (Intensive PK Cohort):** PK data from the Intensive PK Cohort will be used to estimate the posterior probabilities that in pediatric participants the true steady-state plasma ISL AUC0-24 is <0.28 µM·hr (ie, GM of plasma ISL AUC0-24 in adults following ISL 2.25 mg QD); the true steady-state PBMC ISL-TP C24 is >2.68 µM (or 0.54 pmol/10^6 cells) (ie, GM of PBMC ISL-TP C24 in adults following ISL 0.25 mg QD). The PK profile is considered acceptable if the posterior probabilities are greater than 90% and 90% respectively. **Safety:** Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Descriptive statistics will be provided for these safety parameters. **Efficacy:** The percentage of participants with HIV-1 RNA ≥50 and <50 copies/mL will be estimated with a 95% CI (via the Clopper-Pearson method). The primary missing data approach will be the FDA snapshot approach. Change from baseline in CD4+T-cell counts will be estimated using the DAO approach with a 95% CI based on the t-distribution.
Interim Analyses	An eDMC will review the safety and tolerability data at regular intervals throughout the study. After the target enrollment has been met and all the participants have completed the Week 24 Visit, the primary safety and the secondary efficacy analysis at Week 24 will be conducted by the Sponsor and results will be shared with the eDMC.
Multiplicity	No multiplicity adjustment is needed as there are no hypotheses to be tested in the study.
Sample Size	The Intensive PK Cohort size is supported by clinical trial simulations using the ISL population PK model based on adult data (from MK-8591-001, 002, 003, 009, and 011) that indicated N=10 is required to estimate clearance in pediatric participants with adequate precision (relative standard error <30%).

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. The statistical analyses of the PK data will be conducted in collaboration with the departments of Quantitative Pharmacology and Pharmacometrics and Clinical Research of the Sponsor.

This study will be conducted as a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will know the intervention administered.

The Clinical Biostatistics department will generate the allocation schedule for study intervention assignment. Allocation number will be assigned via an IRT.

9.3 Hypotheses/Estimation

There are no hypotheses to be tested in this study.

9.4 Analysis Endpoints

Initial descriptions of PK, safety, and efficacy measures are provided in Section 4.

9.4.1 Pharmacokinetic Endpoints

Plasma PK Profile

Endpoints for the intensive plasma PK sampling (Intensive PK Cohort) are ISL steady-state AUC0-24, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F after administration of DOR/ISL QD in pediatric participants for 28 days.

Intracellular PK Profile

Endpoints for the PBMC PK sampling (Intensive PK Cohort) are ISL-TP steady-state AUC0-24, Cmax, and C24 after administration of DOR/ISL QD in pediatric participants for 28 days.

Population PK Modeling

Endpoints for the sparse plasma PK sampling for all participants are ISL plasma concentrations through Week 48.

9.4.2 Safety Endpoints

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

Adverse Events

The following AEs will be summarized: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 serious and drug-related AE; 5) participants with at least 1 Grade 3 to 4 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 an AE; 8) participants who discontinued study intervention due to a drug-related AE; 9) 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 baseline and postallocation on-treatment measurement to be included. Participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study intervention) will be classified as to whether or not they fall outside the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3). A listing of the participants who meet the criteria will also be provided.

9.4.3 Efficacy Endpoints

Note: As of Amendment 028-03, the available efficacy data will be summarized.

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

The Abbott RealTime PRC 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 percentage of participants with HIV-1 RNA <50 copies/mL will be estimated separately for Treatment-Naïve and Virologically Suppressed Cohorts at each visit time point in the SoA. A second objective will be assessed based on the percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 24, 48, and 96.

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

The percentage of participants with ≥50 copies/mL will be estimated at each visit time point in the SoA for Virologically Suppressed Cohort. A second objective will be assessed based upon the percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 24, 48, and 96.

Change From Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be assessed at Weeks 24, 48, and 96 in the Virologically Suppressed Cohort and the Treatment-Naïve Cohort separately.

For analyses of change from baseline (eg, change in CD4+ T-cell count, change in laboratory tests, etc.), baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available.

Clinically Significant Confirmed Viremia

Participants with confirmed virologic rebound or incomplete virologic response as defined in Section 4.2.1.3.1 will be identified.

Viral Resistance-associated Substitutions

Participants who meet the definition of confirmed virologic rebound or incomplete virologic response (Section 4.2.1.3.1), or who discontinue study intervention for another reason and have HIV-1 RNA ≥200 copies/mL at the time of discontinuation, will be assessed for development of viral drug resistance. Among such participants, those with HIV-1 RNA ≥400 copies/mL or anyone for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load, will be included for resistance analyses. The resistance analysis will summarize the number and percentage of participants who have evidence of resistance-associated substitutions with primary interest at Weeks 24, 48, and 96.

9.5 Analysis Populations

9.5.1 Pharmacokinetic Analysis Population

Pharmacokinetic analyses will be conducted in a PP population, which consists of a subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of the study intervention, according to the underlying scientific model. Compliance with the protocol includes considerations such as exposure to study intervention, availability of measurements, and absence of important protocol deviations that may impact PK analyses.

At the end of the study, all participants who are compliant with the study procedures as aforementioned and have available data from at least 2 PK time points will be included in the PP dataset. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR.

9.5.2 Safety Analysis Population

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

At least 1 laboratory, or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of those respective safety parameters. For safety analyses that assess change from baseline, a baseline measurement is also required.

9.5.3 Efficacy Analysis Population

Details on the approach to handling missing data for efficacy analyses are provided in Section 9.6.3.

9.5.3.1 Full Analysis Set

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

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

9.5.3.2 Resistance Analysis Subset

The resistance analysis subset will include 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.

9.6 Statistical Methods

9.6.1 Pharmacokinetic Analyses

Note: As of Amendment 028-03, only descriptive statistics based on available data is applicable for this section. Both non-model based and model-based analysis will be performed on available data, as applicable.

Individual values will be listed for each PK parameter and the following (non-model-based) descriptive statistics will be provided: N (number of participants with nonmissing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt (exp(s2) - 1), where s2 is the observed variance on the natural log scale).

ISL plasma concentrations from sparse PK sampling will be summarized by nominal timepoint with the following descriptive statistics: N (number of participants with nonmissing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, IQR (interquartile range), and geometric percent CV (calculated as: 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log scale).

ISL PK data will also be added to the ISL population PK model along with data collected from other studies. The analysis plan for the population PK analysis will be described in a separate MAP.

9.6.1.1 Dose Confirmation

Note: As of Amendment 028-03, this section is no longer applicable.

In the Intensive PK Cohort, posterior probabilities with a noninformative flat prior will be used to assess whether pediatric participants have acceptable PK. Acceptable PK is defined as follows:

- A posterior probability that the true ISL steady-state plasma exposure (AUC0-24) in pediatric participants does not exceed 0.28 µM·hr (corresponding to the GM exposure simulated using the population PK model for adults at ISL 2.25 mg QD) at Day 28 greater than 90%

- A posterior probability that the true ISL-TP steady-state PBMC trough concentration (C24) in pediatric participants exceeds 2.68 µM (or 0.54 pmol/10^6 cells) (corresponding to the GM exposure simulated using the population PK model for adults at ISL 0.25 mg QD) at Day 28 greater than 90%

If the participants in the Intensive PK Cohort meet the acceptable PK definition and there are no safety concerns, then the ISL dose will be established.

If any of the acceptable PK definitions are not met, then an intensive review of all PK, safety, and efficacy data will be conducted.

The simulation-based justification for the posterior probability thresholds is provided in Section 9.9.1.

9.6.2 Safety Analyses

Note: As of Amendment 028-03, only descriptive statistics based on available data is applicable for this section. Events that are described below as either Tier 1, 2, or 3 events will now all be summarized descriptively.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. The analysis of safety results will follow the strategy in Table 7 at Week 24, 48, and 96.

Adverse Events

Percentage of participants with AEs in the broad categories of: any AE, a drug-related AE, an SAE, an AE, which is both drug-related and serious, a Grade 3 to 4 AE, an AE that is both Grade 3 to 4 and drug-related, discontinuation of study intervention due to an AE, discontinuation of study intervention due to a drug-related AE, an AE leading to deaths, and specific AEs occurring with an incidence ≥ 10% will be provided along with the corresponding 95% CIs (Table 7). The 95% CIs for the safety parameters will be estimated using the Clopper-Pearson method [Clopper, C. J. 1934].

Continuous Measures

For continuous measures such as changes from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided (Table 7). Missing safety laboratory, or vital signs will be handled using the DAO approach, ie, any missing value will be excluded from the analysis, with the exception that a missing Day 1 result will be replaced with the value obtained at the most recent screening visit will be used as baseline, when available. If no baseline result is available, that participant will not be included in the summary.

For PDLC assessments, participants' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study intervention) will be classified as to whether or not they fall outside the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from 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.

Table 7 Analysis Strategy for Safety Parameters

Safety Endpoint	Within Group 95% CI	Descriptive Statistics
Any AE	X	X
Any Drug-Related AE	X	X
Any SAE	X	X
Any Drug-Related SAE	X	X
Discontinuation due to an AE	X	X
Discontinuation due to a Drug-Related AE	X	X
Any Grade 3 to 4 AE	X	X
Any Grade 3 to 4 Drug-Related AE	X	X
Death	X	X
Specific AEs, SOCs or PDLCs occurring with an incidence ≥ 10%	X	X
Specific AEs, SOCs or PDLCs occurring with an incidence < 10%		X
Change from Baseline Results (Labs, Vital Signs)		X
AE=adverse event; CI=confidence interval; SAE=serious adverse event; SOC=System Organ Class; PDLC=Predefined Limit of Change; X = results will be provided. 95% CIs will be calculated using the Clopper-Pearson method [Clopper, C. J. 1934].		

9.6.3 Efficacy Analyses

Note: As of Amendment 028-03, this section is no longer applicable. Only descriptive statistics for all available data is applicable for this section.

Time Windows for Analyses

Table 8 lists 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. The last available on-treatment measurement within a window will be used for analyses at a specific time point, unless otherwise specified. Results from additional time points beyond Week 96 may be summarized, and day-range rules for determining the analysis time windows will follow the same pattern where the ranges start and end at the midpoints between target days.

Table 8 Definitions of Study Time Points for Analyses

Treatment Phase	Visit	Day-Range Rules	Target Day[a]
Baseline	Day 1	≤1	1
Treatment	Day 28	≥2 and ≤42	28
	Week 8	≥43 and ≤84	57
	Week 16	≥85 and ≤126	113
	Week 24	≥127 and ≤210	169
	Week 36	≥211 and ≤294	253
	Week 48	≥295 and ≤378	337
	Week 60	≥379 and ≤462	421
	Week 72	≥463 and ≤546	505
	Week 84	≥547 and ≤630	589
	Week 96	≥631 and ≤714	673

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

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 discontinuations because of treatment-associated reasons including adverse events (regardless of relationship to study intervention) or lack of efficacy
- Nonintermittent missing values due to premature 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 (Table 9). The primary approach for the analysis of the percentage of participants with HIV-1 RNA ≥50 copies/mL and the percentage of participants with HIV-1 RNA<50 is the FDA snapshot approach [Food and Drug Administration (CBER) 2015]. Under this approach, virologic outcome will be defined according to the following categories:

- **HIV-1 RNA <50 copies/mL**: Participants who have the last available on-treatment HIV-1 RNA measurement < 50 copies/mL within the analysis window specified in Table 8 for the time point of interest.

- **HIV-1 RNA ≥50 copies/mL**: This includes participants who:

    1) Have the last available on-treatment HIV-1 RNA measurement ≥50 copies/mL within analysis window specified in Table 8 for the timepoint of interest.

    2) Do not have on-treatment HIV-1 RNA data in the window of interest and

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

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

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

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

    2) Discontinued study intervention for other reasons: This includes participants who discontinued study intervention 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.) prior to or in the analysis window for the time point of interest and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL

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

The number of participants classified as "HIV-1 RNA ≥50 copies/mL" according to the FDA snapshot algorithm defined above, divided by the number of participants in the FAS, is the percentage of participants with HIV-1 RNA ≥50 copies/mL at a timepoint. Similarly, the percentage of participants with HIV-1 RNA <50 copies/mL at a timepoint is calculated using the number of participants classified as "HIV-1 RNA <50 copies/mL" according to the FDA snapshot algorithm defined above, divided by the number of participants in the FAS.

A second approach, the missing data treated as treatment failure (M=F) approach, will be performed as a sensitivity analysis for the percentage of participants achieving HIV-1 RNA

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

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

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

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

The percentage of participants with HIV-1 RNA ≥50 copies will be estimated at Weeks 24, 48, and 96. For each time point of interest, the associated 95% CI will be calculated based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934]. Virologic response over all time points will also be summarized in a similar fashion.

Percentage of Participants with HIV-1 RNA <50 copies/mL

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA <50 copies/mL. The percentage of participants with HIV-1 RNA <50 copies/mL will be estimated at Weeks 24, 48, and 96. For each time point of interest, the associated 95% CI will be calculated based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934]. Virologic response over all time points will also be summarized in a similar fashion. The supportive analysis using the OF approach (as defined above) will also be presented.

Change From Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be summarized at Weeks 24, 48, and 96 with the associated 95% CI calculated based on the t-distribution (Table 9).

The DAO approach will be used to handle missing data for these analyses. Under the DAO approach, participants must have both a baseline measurement and at least 1 postbaseline measurement within the analysis window specified in Table 8 for the time point of interest 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 LOCF and BOCF methods to account for missing data.

Clinically Significant Confirmed Viremia

The number of participants with confirmed virologic rebound or incomplete virologic response, as defined in Section 4.2.1.3.1, will be summarized.

Viral Drug Resistance

The number of participants in the resistance analysis subset with genotypic and/or phenotypic resistance to the study intervention will be summarized.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 24, 48, and 96	P (for the Virologically Suppressed Cohort)	95% CI (Clopper-Pearson)	FAS	Snapshot[a]
Percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 24, 48, and 96	P (for the Treatment-Naïve Cohort) S (for the Virologically Suppressed Cohort)	95% CI (Clopper-Pearson)	FAS	Snapshot[a]
	S	95% CI (Clopper-Pearson)	FAS	M=F
	S	95% CI (Clopper-Pearson)	FAS	OF
Change from baseline in CD4+ T-cell counts at Weeks 24, 48, and 96	P	95% CI (t-distribution)	FAS	DAO
	S	95% CI (t-distribution)	FAS	LOCF
	S	95% CI (t-distribution)	FAS	BOCF

BOCF=Baseline Observation Carried Forward; CI=confidence interval; DAO=Data As Observed; FAS=Full Analysis Set; FDA=Food and Drug Administration; HIV=human immunodeficiency virus; LOCF=Last Observation Carried Forward; OF= Observed Failure; P=Primary approach; RNA=ribonucleic acid; S=Supportive approach; vs=versus.
[a] Number of participants who meet the endpoint clinical response criteria over total number in the FAS.

9.6.4 Palatability and Acceptability Assessment of the Tablet (Whole and Split)

Note: As of Amendment 028-03, study intervention administration will have been discontinued, so descriptive statistics will be prepared on available data.

Each participant will rate the palatability and respond to questions on the acceptability of treatment with oral DOR/ISL FDC tablet as outlined in the SoA (Section 1.3). This assessment will be based on the 5-point facial hedonic scale (FHS), an expression scale depicting various degrees of pleasure as an assessment of palatability (Section 4.2.1.4 and Section 8.1.9).

Descriptive statistics will be used to summarize the palatability and acceptability responses by cohorts on Day 1 and Day 28 for full tablet, and on Week 24 for split tablet. Missing data will not be imputed, and the analyses will be based on observed data only. These analyses will be based on the APaT population.

9.7 Interim Analyses

An eDMC will review accumulating safety data throughout the study as detailed in the eDMC Charter and will make recommendations for discontinuation of the study or protocol modifications to an executive committee of the Sponsor (Appendix 1).

9.8 Multiplicity

There will be no multiplicity adjustments in the analysis of this study.

9.9 Sample Size Calculations

Note: As of Amendment 028-03, the study has closed to enrollment therefore the following sample size calculations are no longer applicable.

9.9.1 Sample Size for PK Analysis

The Intensive PK Cohort size is supported by clinical trial simulations using the ISL population PK model based on adult data (from MK-8591-001, 002, 003, 009, and 011) that indicated N=10 is required to estimate clearance in pediatric participants with adequate precision (relative standard error <30%).

In addition, the operating characteristics of posterior probability-based thresholds for acceptable PK (defined in 9.6.1.1) are provided below. With approximately 10 participants in Intensive PK Cohort:

- Assuming the log scale SD of steady-state plasma ISL AUC0-24 in pediatric participants (<18 years of age, weighing ≥35 kg) is 0.285 after the administration of DOR/ISL (100 mg/0.75 mg) QD, if the true steady-state ISL AUC0-24 is 0.12 μM·hr, the probability that this PK endpoint will be deemed within the acceptable range is >99%. The true SS plasma ISL AUC0-24 can be as high as 0.23 μM·hr to still have a conclusion of acceptable PK with 80% probability.

- Assuming the log scale SD of steady-state PBMC ISL-TP C24 in pediatric participants is 0.496 after the administration of DOR/ISL (100 mg/0.75 mg) QD, if the true SS PBMC ISL-TP C24 is 11.22 µM (2.24 pmol/10^6 cells), the probability that this PK endpoint will be deemed within the acceptable range is >99%. The true SS PBMC ISL-TP C24 can be as low as 3.76 µM (0.75 pmol/10^6 cells) to still have a conclusion of acceptable PK with 80% probability.

9.9.2 Sample Size for Safety Analysis

The probability of observing at least 1 of a particular type of AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population.

If the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving DOR/ISL), there is a 36.4% chance of observing at least 1 of that particular AE among the 45 participants in the study. If no AE of that particular type is observed among the 45 participants in the study, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <6.4% (1 in every 16 participants).

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

Table 10 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs

	Hypothetical Number of Participants with an AE (Estimate of Incidence, %)	**95% Upper Confidence Bound[a]**
N=30 (Virologically Suppressed Cohort)	0 (0)	9.5
	1 (3.3)	17.2
	2 (6.7)	22.1
	3 (10.0)	26.5
N=15 (Treatment-Naïve Cohort)	0 (0)	18.1
	1 (6.7)	31.9
	2 (13.3)	40.5
	3 (20.0)	48.1
N=45 (Pooled)	0 (0)	6.4
	1 (2.2)	11.8
	3 (6.7)	18.3
	5 (11.1)	24.1

AE=adverse event; CI=confidence interval.
[a] Based on the 2-tailed exact CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. 1934]). In the 0 event case, the 95% CI is one sided (α=0.05 all in the upper tail).

9.9.3 Sample Size for Efficacy Analysis

The key efficacy objective for the Virologically Suppressed Cohort will be assessed based on the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 24. The anticipated virologic failure rate for the study population is approximately 2%. With 30 participants, the maximum half-width of the 95% exact CI will be no greater than 19%. The calculation is based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934] and is performed using SAS v9.4. Table 11 shows the 95% CIs for percentage of participants with HIV-1 RNA ≥50 copies/mL given varying assumptions of numbers of responders in 30 participants. Note that the intervals are not symmetric around the point estimate.

Table 11 Two-Sided 95% CIs for the Percentage of Participants With HIV-1 RNA ≥50 copies/mL at Week 24 (FAS)

	Number of Responses[a] (%)	**Two-Sided 95% CI[b]**
N=30 (Virologically Suppressed Cohort)	0 (0)	(0, 9.5)
	1 (3.3)	(0.1, 17.2)
	2 (6.7)	(0.8, 22.1)
	3 (10.0)	(2.1, 26.5)
	4 (13.3)	(3.8, 30.7)

a. CI=confidence interval; FAS=full analysis set; HIV=human immunodeficiency virus.

b. [a] Based on FDA snapshot approach; response refers to participants with HIV-1 RNA≥50 copies/mL.

[b] Based on the 2-tailed exact CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. 1934]). In the 0-event case, the 95% CI is one sided (α=0.05 all in the upper tail).

The key efficacy objective for the Treatment-Naïve Cohort will be assessed based on the percentage of participants with HIV-1 RNA <50 copies/mL at Week 24. The anticipated rate of participants with HIV-1 RNA <50 copies/mL for the study population is approximately 80% to 90%, based on experience from MK-8591 Protocol 011 and assuming DOR/ISL will be similarly active in adults and pediatric participants. With 15 participants, the maximum half-width of the 95% exact CI will be no greater than 26%. The calculation is based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934] and is performed using SAS v9.4. Table 12 shows the 95% CIs for percentage of participants with HIV-1 RNA <50 copies/mL given varying assumptions of numbers of responders in 15 participants. Note that the intervals are not symmetric around the point estimate.

Table 12 Two-Sided 95% CIs for the Percentage of Participants With HIV-1 RNA <50 copies/mL at Week 24 (FAS)

	Number of Responses[a] (%)	Two-Sided 95% CI[b]
N=15 (Treatment-Naïve Cohort)	10 (66.7)	(38.4, 88.2)
	11 (73.3)	(44.9, 92.2)
	12 (80.0)	(51.9, 95.7)
	13 (86.7)	(59.5, 98.3)
	14 (93.3)	(68.1, 99.8)

c. CI=confidence interval; FAS=full analysis set; HIV=human immunodeficiency virus.

d. [a] Response refers to participants with HIV-1 RNA<50 copies/mL.

[b] Based on the 2-tailed exact CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. 1934]).

9.10 Subgroup Analyses

Note: As of Amendment 028-03, subgroup analyses will no longer be conducted.

To assess the consistency of the response across various subgroups, the percentage of participants with HIV-1 RNA ≥50 copies/mL (Virologically Suppressed Cohort only) and HIV-1 RNA <50 copies/mL, and associated 95% CIs will be estimated within each category of the following classification variables:

- Age category (≤ median, > median)
- Sex at birth
- Gender identity
- Region (North America, South America, Europe, Asia, Africa, etc.)

The consistency of the response will be assessed descriptively via summary statistics by category for the classification variables listed above as applicable based on the number available in each potential subgroup. Other clinically relevant variables may be identified for which additional subgroup analyses may be performed. Subgroup summaries will be presented separately for the Virologically Suppressed and Treatment-Naïve Cohorts.

9.11 Compliance (Medication Adherence)

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

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 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 96 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 96), 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 for the FAS and will be presented separately for the Virologically Suppressed and Treatment-Naïve Cohorts.

9.12 Extent of Exposure

The extent of exposure to study intervention will be evaluated by summary statistics (N, mean, and range) for the "Number of Days on Therapy".

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 and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection 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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participant's 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 13 will be performed by the central laboratory.

- Local laboratory results are only required if the central laboratory results are not available in time for either study intervention administration (including Day 1), 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.

- Any laboratory test results related to study endpoints (eg, HIV-1 RNA and CD4+ T-cell counts) must be provided by the central laboratory.

- 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 13 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count 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: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
CD4+ T-cell/(T-Cell and B-Cell and Natural Killer Cell) TBNK panel	CD3+CD4+ T cell Count CD3+CD8+ T cell Count CD4/CD8 ratio CD3+ CD45+ CD3- CD19+ CD16+ CD56+ CD3+CD4+ CD8+			
Coagulation	Prothrombin time (PT)/ international normalized ratio (INR)			
Chemistry (nonfasting)	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin • Direct bilirubin • Indirect bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	estimated Glomerular Filtration Rate (eGFR)
	Creatinine Kinase	Lipase	Amylase	Magnesium
Additional Chemistry at fasting visits (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			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase			
Pregnancy testing	Serum (conducted by central lab) and urine (conducted by local lab) β human chorionic gonadotropin (β hCG) pregnancy test (for a woman/women of childbearing potential [WOCBP])			
Hepatitis screening and monitoring[a]	Hepatitis B virus surface antigen (HBsAg) Hepatitis B virus (HBV) surface antibody AntiHBc (hepatitis B core antibody) HBV DNA Hepatitis C antibody (if positive perform plasma hepatitis C virus quantitative test- not required for study inclusion)			
Human immunodeficiency virus-1 (HIV-1) serology	HIV 1/2 antibody test			

Laboratory Assessments	Parameters
Virology	HIV-1 viral ribonucleic acid (RNA) quantification (RealTime polymerase chain reaction [PCR]) HIV-1 viral resistance Proviral DNA archive resistance testing
Pharmacokinetics (PK)	Islatravir (ISL) Sparse PK, Intensive PK, and Investigational PK[b] ISL-triphosphate in PBMCs (Intensive PK Cohort only)
[a] All participants will be screened for HBsAg, HBV surface antibody, antiHBc and HBV DNA. Participants that are antiHBc positive, but HBV DNA negative will have HBsAg and HBV DNA monitored for the duration of the study. [b] Investigational PK samples will be collected per the SoA (Section 1.3). Analysis of these samples will be triggered by the Sponsor as needed.	

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

Table 14 Estimated Blood Volumes

Note: As of Amendment 028-03, Table 14 is no longer applicable. Table 15 outlines the blood volume collection for the remainder of the study per the SoA in Sections 1.3.2 and 1.3.3.

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	**Viremia Confirmation**	**Treatment Discontinuation**	**End of Treatment Follow-up**
Scheduled Day/Week	**Screening**	**Day 1 (Fasting)**	**Day 14 Phone Call**	**Day 28**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48 (Fasting)**	**Week 60**	**Week 72**	**Week 84**	**Week 96 (Fasting)**			
Visit Window	≤45 days	NA	±4 days	+14 days	±7 days									w/in 2-4 wks of Viremia	NA	42 (+7) days after EOT
Blood Parameter	Approximate Blood Volume (mL)															
Blood (Plasma) HIV-1 RNA Quantification (Real Time PCR)	6	6		6	6	6	6	6	6	6	6	6	6	6	6	6
CD4+ T-cell Count	4	4					4		4				4		4	
Blood (Plasma) for HIV Viral Drug Resistance Testing[a]	12	6		6	6	6	6	6	6	6	6	6	6	12	12	6
Serology: HIV-1 & 2; Hepatitis (B and C)	5															
HIV-1 Confirmation	1															
HCV RNA (perform only if hepatitis C antibody positive - not required for study inclusion)		6														
PT/INR 2.7 mL	2.7															

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	**Viremia Confirmation**	**Treatment Discontinuation**	**End of Treatment Follow-up**
Scheduled Day/Week	**Screening**	**Day 1 (Fasting)**	**Day 14 Phone Call**	**Day 28**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48 (Fasting)**	**Week 60**	**Week 72**	**Week 84**	**Week 96 (Fasting)**			
Visit Window	≤45 days	NA	±4 days	+14 days	±7 days									w/in 2-4 wks of Viremia	NA	42 (+7) days after EOT
HBsAg (as required, at baseline part of Serology 2 mL)[b]		2		2	2	2	2	2	2	2	2	2	2			
HBV DNA (as required)	6	6		6	6	6	6	6	6	6	6	6	6			
Chemistry (after baseline, additional 2 mL is required if serum pregnancy needed)	3	3		3	3	3	3	3	3	3	3	3	3		3	3
Hematology	1	1		1	1	1	1	1	1	1	1	1	1		1	1
Blood (Plasma) for Sparse ISL PK		2		2	2	2	4	2	4	2	2	2	2			
Blood (Plasma) for Investigational PK														2	2	
Whole Blood for Proviral DNA Archive Resistance Testing														4		
Maximum Total Blood Volume per Visit in mL (not in Intensive PK Cohort)	**40.7**	**36**	**0**	**26**	**26**	**26**	**32**	**26**	**32**	**26**	**26**	**26**	**30**	**24**	**28**	**16**

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	**Viremia Confirmation**	**Treatment Discontinuation**	**End of Treatment Follow-up**
Scheduled Day/Week	**Screening**	**Day 1 (Fasting)**	**Day 14 Phone Call**	**Day 28**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48 (Fasting)**	**Week 60**	**Week 72**	**Week 84**	**Week 96 (Fasting)**			
Visit Window	≤45 days	NA	±4 days	+14 days	±7 days									w/in 2-4 wks of Viremia	NA	42 (+7) days after EOT
Pharmacokinetic Samples Intensive PK Cohort																
Blood (Plasma) for Intensive ISL[c]				16												
Blood (PBMC) for ISL-TP PK				24												
Total Blood Volume per Visit in mL (Intensive PK Cohort)	**40.7**	**36**	**0**	**64**	**26**	**26**	**32**	**26**	**32**	**26**	**26**	**26**	**30**	**24**	**28**	**16**
Maximum Blood Volume in mL (Intensive PK Cohort) for Study Duration	**459**															
Maximum Blood Volume in mL (Participants not in Intensive PK Cohort) for Study Duration	**421**															

[a] Screening collection is only required in Treatment-Naïve Cohort (n=15)
[b] indicates collection only in participants meeting certain criteria (HCV RNA, HBsAg and HBV DNA)
[c] Day 28 Plasma for Intensive ISL PK total is 16 mL (2 mL noted for Sparse PK is not duplicated for Intensive PK Cohort)

Table 15 Estimated Blood Volumes for Early Discontinuation of Treatment, End of Treatment Follow-up, and Extended Monitoring of CD4+ T-cell and/or Lymphocyte Counts

Visit Name	**Treatment Discontinuation**	**End of Treatment Follow-up**	**Extended Monitoring of CD4+ T-cell and/or Lymphocyte Counts**
Visit Window	NA	42 (+7) days after EOT	4 to 6 weeks
Blood Parameter	Approximate Blood Volume (mL)		
CD4+ T-cell/TBNK Count	4	4	4
Blood (Plasma) for HIV Viral Drug Resistance Testing[a]	12	6	
Chemistry (Additional 2 mL is required if serum pregnancy needed)	3		
Hematology	1	1	1
Blood (Plasma) for Investigational PK	2	2	2 [a]
Maximum Total Blood Volume per Visit in mL	**22**	**13**	**5**[b]
Maximum Blood Volume in mL for those who end at End of Treatment Follow-up	**35**		
Maximum Blood Volume in mL for those who require extended monitoring[a]	**67**		

[a] Taken at the first monitoring visit only
[b] For 6 blood draws for those who qualify for extended monitoring for 6 months (5 mL per month). Total of 7 mL at the first monitoring visit only.

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

10.3.1 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

  Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- 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."

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

SAE reporting to the Sponsor via paper CRF

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

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

This appendix is not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
Progestogen- only contraceptive implant[c,d] IUS[c,d,e] 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,d] - Oral - Intravaginal - Transdermal - Injectable
Progestogen-only hormonal contraception[c,d] - 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 8.8 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirement for Russia

In Russia, only participants ≥12 to <18 years of age weighing ≥35 kg at the time of signing the informed consent/assent will be enrolled in this study.

10.8 Appendix 8: Calculation of Estimated Glomerular Filtration Rate

Schwartz Bedside equation [Schwartz, G. J. 2009]:

eGFR = 0.413 X Height (cm)/Scr

- eGFR (estimated glomerular filtration rate) in units of mL/min/1.73 m^2
- Scr (standardized serum creatinine) in units of mg/dL

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
antiHBc	hepatitis B core antibody
APaT	All Participants as Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-24	area under the curve from 0 to 24 hours postdose
BIC	bictegravir
BMI	body mass index
BOCF	baseline observation carried forward
C24	concentration after 24 hours
CD4+	CD4-positive
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
Cmax	maximum (peak) observed drug plasma concentration
CL/F	apparent total clearance of the drug from plasma after oral administration
CNS	central nervous system
Crcl	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
Ctrough	lowest concentration reached by a drug before the next dose is administered
CYP	cytochrome P450
DAIDS	The Division of AIDS
DAO	Data As Observed
DDI	drug-drug interaction
DEXA	Dual X-ray Absorptiometry
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravirine
DTG	dolutegravir
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research Consent
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation	Expanded Term
FDC	fixed dose combination
FSH	follicle stimulating hormone
FTC	emtricitabine
GCP	Good Clinical Practice
HBc	hepatitis B core
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV-1	human immunodeficiency virus type 1
HIV	human immunodeficiency virus
HIV-SI	Human Immunodeficiency Virus Symptom Index
HIVTSQ	Human Immunodeficiency Virus Treatment Satisfaction Questionnaire
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC50	concentration of drug needed to inhibit 50% of viral growth
IC90	concentration of drug needed to inhibit 90% of viral growth
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IL-6	interleukin-6
IND	Investigational New Drug
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
ISL	Islatravir
ISL-DP	Islatravir-diphosphate
ISL-TP	Islatravir-triphosphate
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LDL-C	low-density lipoprotein cholesterol
LNG/EE	levonorgestrel/ethinyl estradiol
LOCF	last observation carried forward
M=F	missing data treated as treatment failure
MSD	Merck Sharp & Dohme, Corp.
NHANES	National Health & Nutrition Examination Survey
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OF	Observed Failure
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PDLC	predefined limit of change
PEP	potentially exposed person
PI	protease inhibitor
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
QD	once daily

Abbreviation	Expanded Term
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
t1/2	elimination half-life of the drug
TAF	tenofovir alafenamide
TAM	thymidine analog mutation
TBNK	T and B lymphocyte and natural killer cell
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglyceride
TLOVR	Time to Loss of Virologic Response
Tmax	time at which the maximum plasma concentration of the drug is achieved
US	United States
Vz/F	apparent volume of distribution during terminal phase after non-intravenous administration
WOCBP	woman/women of childbearing potential

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