Official Protocol Title:	A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate a Switch to Doravirine/ Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)
NCT number:	NCT05630755
Document Date:	08-Aug-2024

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)

Protocol Number: 052-02

Compound Number: MK-8591A

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	NCT05630755
EU CT	2022-502079-49-00
EudraCT	Not Applicable
JRCT	JRCT2051230003
WHO	Not Applicable
UTN	Not Applicable
IND	134,036

Approval Date: 08 August 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	08-AUG-2024	To extend the blinded comparison period from Week 96 to Week 144 (Base Study) to provide additional safety and efficacy data, and to add an optional open-label extension (OLE) with access to DOR/ISL for up to Week 240 or until commercially available (whichever comes first).
Amendment 1	20-OCT-2023	To provide for increased HIV-1 RNA monitoring during pregnancy (if recommended in local guidelines), to clarify the management of participants with decreases in total lymphocyte and CD4+ T-cell counts and the management of participants with HIV-1 viremia.
Original Protocol	03-NOV-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

To extend the blinded comparison period from Week 96 to Week 144 (Base Study) to provide additional safety and efficacy data and to add an optional open-label extension (OLE) with access to DOR/ISL for up to Week 240 or until commercially available (whichever comes first).

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 4.1 Overall Design	Extended the blinded comparison period from Week 96 to Week 144 and added an optional OLE up to Week 240 or until DOR/ISL is commercially accessible (whichever comes first).	Study extension added to provide long-term comparative efficacy and safety data.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 1.1 Synopsis	Revised objectives, endpoints, study duration, duration of participation, and treatment period to reflect the extended base study and the added OLE.	Refer to rationale for Section 4.1.
Section 1.2 Schema	Updated the study schema to reflect the extended base study and the added OLE.	Refer to rationale for Section 4.1.
Section 1.3 Schedule of Activities	Added text above each SoA explaining the purpose of each SoA and relocated section references from notes	To clarify the applicability of each SoA.
1.3.1 Schedule of Activities – Screening Through Week 144 – (Base Study)	Added visits and study procedures for Weeks 108, 120, 132, 144, Early Discontinuation of Treatment, and End of Treatment Follow Up visits .	Refer to rationale for Section 4.1.
	Added rows for Post-Base Study Disposition Planning at Weeks 120, 132 and 144 and for Unblinding of Treatment Group Assignment at Week 144.	Refer to rationale for Section 4.1.
	Added note to administer EQ-5D-5L and HIV-SI/SDM questionnaires only through Week 96.	Refer to rationale for Section 4.1.
	Updated to collect HBV serology and HBV DNA for all participants annually.	To allow for annual hepatitis B surveillance to detect new exposures or change in immune status.
	Added note for Chemistry to clarify that pregnant participants should not fast.	To avoid hypoglycemia and nonfasting results that could compromise analysis.
	Added row for informed consent for the optional OLE (at Week 144).	Refer to rationale for Section 4.1.
	Added note to specify that samples for inflammatory, renal, and energy and metabolism markers should not be collected from pregnant participants.	To reduce blood volume collection from pregnant participants.
	Added note to specify that waist and hip measurements are not applicable for pregnant participants.	Results in pregnant participants would confound analysis.
	Added footnote to clarify that the scheduled visit assessments should be performed if early discontinuation occurs at a scheduled visit.	Refer to rationale for Section 4.1.

Section Number and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities – Viremia Confirmation and End of Treatment for Participants With Viremia (Except Those With Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count	Updated the End of Treatment activities for the base study and added End of Treatment activities for the OLE.	Refer to rationale for Section 4.1.
	Replaced full with directed physical examination at the End of Treatment Follow-up (Base Study) visit.	To allow directed physical examinations to be performed if clinically indicated.
	Added DOR investigational PK assessment, as needed, using the same blood (plasma) sample collected for investigational ISL PK..	To characterize both DOR and ISL PK in the setting of viremia.
	Removed blood sample collection for investigational PK at the End of Treatment Follow-Up (Base Study) visit.	ISL plasma concentrations are expected to be BLOQ by 42 days after the end of DOR/ISL study treatment.
Section 1.3.3 Schedule of Activities for Participants Who Meet the Discontinuation Criteria for Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count	Revised the End of Treatment activities for the base study and added End of Treatment activities for the OLE.	Refer to rationale for Section 4.1.
	Added study intervention compliance review at the Total Lymphocyte Count and/or CD4+ T-Cell Count Confirmation visit. To assess compliance in the setting of confirmed specified decreases in total lymphocyte count and/or CD4+ T-cell count.	To assess compliance in the setting of confirmed specified decreases in total lymphocyte count and/or CD4+ T-cell count.
	Removed DOR/ISL-only specification from Hematology and TBNK Panel/ CD4+ T-cell Count assessments at the End of Treatment Follow-Up (Base Study) visit.	To collect comparative data in both treatment groups at all visits.
	Replaced full physical examination with directed physical examination to be performed if clinically indicated at the End of Treatment Follow-up (Base Study) visit.	Refer to rationale for Section 1.3.2 regarding directed physical examination.
	Removed investigational ISL PK blood sample collection at the End of Treatment Follow-Up (Base Study) visit.	See rationale for Section 1.3.2 regarding investigational ISL PK.
Section 1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 144	Removed week numbers for pregnancy visits.	To provide flexibility in timing of pregnancy visits in each trimester.
	Extended the time period from Week 96 to Week 144 to consent to continue study intervention beyond Week 144.	Refer to rationale for Section 4.1.
	Added dispensing of study intervention at the Pregnancy 4 visit for participants on DOR/ISL who opt to continue study intervention in the OLE, and noted that those on BIC/FTC/TAF should transition to commercially accessible ART.	Refer to rationale for Section 4.1.
	Removed whole blood for FBR sample collection for participants whose pregnancy and/or postpartum visit(s) extends beyond Week 144.	Refer to rationale for section 1.3.1 regarding reducing blood volume collected from pregnant participants.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.5 Schedule of Activities – Week 148 Through Week 240 (Open-Label Extension)	Added SoA for the optional OLE.	Refer to rationale for Section 4.1.
Section 2.2.3 Doravirine/Islatravir	Updated the number of participants with viral resistance across the program.	To update with new information.
Section 2.3 Benefit/Risk Assessment.	Updated the number of participants with viral resistance across the program.	Refer to rationale for Section 2.2.3.
Section 3 Hypotheses, Objectives, and Endpoints	Revised previously specified secondary and tertiary objectives to include Week 144 and added hypothesis 4.	Refer to rationale for Section 4.1.
	Added a tertiary objective and endpoint to evaluate total lymphocyte count.	To assess the effect of DOR/ISL vs BIC/FTC/TAF on total lymphocyte count through Week 144.
	Added tertiary objectives and endpoints to evaluate the long-term efficacy and safety of DOR/ISL in the OLE.	Refer to rationale for Section 4.1.
	Added a tertiary objective and endpoint to evaluate viral drug resistance in the OLE.	To assess long-term efficacy of DOR/ISL.
Section 4.2 Scientific Rationale for Study Design	Added rationale for the blinded treatment period (base study) through Week 144 and the added optional OLE from Week 144 up to Week 240.	Refer to rationale for Section 4.1.
Section 4.2.1.2 Safety Endpoints	Added TBNK to list of safety endpoints and explanation of new safety endpoint for total lymphocyte count.	Refer to rationale for Section 3 regarding evaluation of total lymphocyte count.
Section 4.2.1.3 Weight, Body Composition, and Radiological and Laboratory Markers	Added Week 144 time point to rationale for assessment of weight, body composition, and radiological and laboratory markers.	Refer to rationale for Section 4.1.
Section 4.2.1.5 Patient-reported Outcomes	Added clarification that PROs should not be collected after Week 96.	Refer to rationale for Section 4.1.
Section 4.2.1.6 Planned Exploratory Biomarker Research	Removed sub-section 4.2.1.6.2 as not applicable.	Only genetic analysis and FBR are exploratory biomarker assessments.
Section 4.2.2 Rationale for the Use of Comparator/Placebo	Added reference supporting rationale for use of comparator (BIC/FTC/TAF) and matching placebo use in blinded therapy period through Week 144.	Refer to rationale for Section 4.1.
Section 4.3 Justification for Dose	Updated the number of participants with viral resistance across the program.	Refer to rationale for Section 2.2.3.
Section 6.1 Study Interventions Administered	Extended treatment period for all blinded study intervention in the base study from Week 96 to Week 144 and added open-label DOR/ISL from Week 144 up to Week 240.	Refer to rationale for Section 4.1.
Section 6.3.3 Blinding	Extended blinding through Week 144.	Refer to rationale for Section 4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 6.5 Concomitant Therapy	Noted that recommendations for timing of medications or supplements containing polyvalent cations apply only to base study and that dofetilide is allowed during the OLE.	To clarify BIC/FTC/TAF dosing timing recommendations and contraindications.
	Added metamizole, a strong CYP3A inducer, as a prohibited medication.	Metamizole is contraindicated to use with DOR.
Section 6.7 Intervention After the End of the Study	Revised end of study treatment and treatment transition procedures, as clinically appropriate and depending on whether or not DOR/ISL is commercially accessible, in the base study and OLE.	Refer to rationale for Section 4.1.
Section 7.1 Discontinuation of Study Intervention	Updated footnote a in Table 4 to add that total lymphocyte and/or CD4+ T-cell count discontinuation criteria will be established at Week 144 for participants in the OLE.	Refer to rationale for Section 4.1.
Section 8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy	Added note that pregnant participants cannot switch study intervention.	Refer to rationale for Section 4.1.
Section 8.1.1.5 Consent for Open-Label Extension	Added section on consent for the optional OLE.	Refer to rationale for Section 4.1.
Section 8.1.8.1 Timing of Dose Administration	Clarified timing of dose administration during the base study and added timing of dose administration during the OLE.	Refer to rationale for Section 4.1.
Section 8.1.9 Discontinuation and Withdrawal	Added discontinuation or withdrawal procedure during the OLE.	Refer to rationale for Section 4.1.
Section 8.3.4 Confirmation of Contraception and Pregnancy Testing	Updated to include the OLE in the Contraception requirement for 42 days after the last dose of study intervention.	Refer to rationale for Section 4.1.
Section 8.3.6 HBV Assessments	Revised to indicate that HBV serology and HBV DNA is to be checked annually for all participants.	Refer to rationale for Section 1.3.1 regarding Hepatitis B surveillance.
	Clarified that participants confirmed to be HBsAg-positive or to have quantifiable HBV DNA after randomization may be unblinded or allowed to continue study intervention, as deemed medically appropriate.	To avoid unnecessary unblinding if the principal investigator does not deem it necessary to guide care.
Section 8.3.9 Exploratory Clinical Marker Assessments	Added heading and relocated information from Section 8.8 about sample collection and assessments for inflammation, renal function, fasting lipid and metabolic profiles, (including waist/ and hip measurements, and DEXA.	Refer to rationale for Section 4.2.1.6.
Section 8.3.9.3 Fasting Lipid and Metabolic Profiles	Added to note that insulin-dependent diabetic participants and pregnant participants should not fast and should not have insulin levels and lipids measured.	To avoid hypoglycemia, as nonfasting results could compromise analysis.
Section 8.3.10 Administration of Patient Questionnaires	Relocated section (moved from Section 8.1.12).	To group PROs with safety assessments..

Section Number and Name	Description of Change	Brief Rationale
Section 8.6.1 Blood Collection for Plasma ISL	Added DOR PK assessment (as needed).	Refer to rationale for Section 1.3.2 regarding DOR PK assessment in the setting of viremia.
	Added sample collection for DOR and ISL PK assessment in pregnancy/postpartum in the OLE.	Refer to rationale for Section 4.1.
Section 8.9 Future Biomedical Research Sample Collection	Updated FBR-specific specimens collection description to include leftover specimens.	To update information regarding FBR consent and FBR-specific specimens collection.
Section 8.11.2.1 Fasting	Added additional fasting visit at Week 144.	Refer to rationale for Section 4.1.
	Noted that pregnant participants should not fast or have fasting laboratory assessments performed or insulin and lipids measured.	Refer to rationale for Section 1.31 regarding hypoglycemia and nonfasting results.
Section 8.11.2.2. End of Base Study Week 144 Visit	Updated title and content to explain end of blinded base study procedures.	Refer to rationale for Section 4.1.
Section 8.11.2.3 Optional Open Label Extension Period (Week 144 up to Week 240)	Added section to explain OLE activities.	Refer to rationale for Section 4.1.
Section 8.11.3.1 Discontinuation of Treatment	Updated title and content to explain Discontinuation of Treatment procedures for the base study (Early Discontinuation) and OLE (Discontinuation).	Refer to rationale for Section 4.1.
Section 8.11.3.2 End of Treatment Follow up	Updated title and content to explain end of treatment follow-up procedures for the base study and OLE.	Refer to rationale for Section 4.1.
Section 8.11.4 Viremia Confirmation	Noted that both DOR and ISL PK are to be collected at viremia confirmation.	To inform proper clinical management of participants with viremia.
Section 8.11.5 Management of Participants With Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count	Updated to specify that the same monitoring and discontinuation criteria/procedures apply in the base study and OLE.	Refer to rationale for Section 4.1.
Section 8.11.6 Clinical Management of Participants Who Become Pregnant	Clarified unblinding of participants who become pregnant prior to Week 144.	Refer to rationale for Section 4.1.
Section 8.11.6.1 Continuing Study Intervention in Pregnancy	Added management of participants who become pregnant and are eligible and consent to continue DOR/ISL during pregnancy in the OLE and beyond Week 240, as applicable.	Refer to rationale for Section 4.1; the frequency of visits (every 3 months) will remain the same in the OLE as in the base study due to limited data on DOR/ISL use during pregnancy.
	Specified that participants on BIC/FTC/TAF who are pregnant at Week 144 will continue on BIC/FTC/TAF through the postpartum visit and complete the study.	Refer to rationale for Section 4.1.
Section 8.11.6.2 Discontinuing Study Intervention for Pregnancy	Clarified discontinuation procedures for participants who become pregnant and discontinue their assigned study intervention during the base study (Section 1.3.1) or OLE (Section 1.3.5).	Refer to rationale for Section 4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 9 Key Statistical Considerations	Added clarification on how the data collected from the OLE will be summarized.	Refer to rationale for Section 4.1.
Section 9.1 Statistical Analysis Plan Summary	Updated to include extended study duration.	Refer to rationale for Section 4.1.
	Multiplicity: Revised multiplicity strategy.	To enhance statistical rigor, a small alpha (0.00001) will be allocated for the Week 24 interim analysis.
Section 9.2 Responsibility for Analyses/In-house Blinding	Updated to reflect that study participants and site personnel will remain blinded until Week 144.	Refer to rationale for Section 4.1.
Section 9.4.1.1 Efficacy Endpoints	Added Week 144 to the secondary efficacy objectives and endpoints and define the baseline for continuous parameters for OLE analyses.	Refer to rationale for Section 4.1.
Section 9.4.2 Safety Endpoints	Added Week 144 to the applicable safety objectives and endpoints and defined the baseline for OLE analyses.	Refer to rationale for Section 4.1.
	Added base study objective and endpoints to assess total lymphocyte count for DOR/ISL vs BIC/FTC/TAF.	Refer to rationale for Section 3.
Section 9.5.1 Efficacy Analysis Populations	Removed the postbaseline data requirements for the FAS population and added PP analysis population.	To align with the FDA snapshot approach, participants who do not have on treatment postbaseline data will be categorized under "no data" in the window.
	Added FAS and APaT for the OLE.	Refer to rationale for Section 4.1.
Section 9.5.2 Safety Analysis Populations	Added APaT-E population to analyze safety data from the OLE.	Refer to rationale for Section 4.1.
Section 9.6.1 Statistical Methods for Efficacy Analyses	Updated Table 8 (Definitions of Study Time Points) to include Week 108 through Week 240.	Refer to rationale for Section 4.1.
	Specified Base Period or base study and added Week 144 for efficacy analyses in the base study and added efficacy analyses in the OLE.	Refer to rationale for Section 4.1.
	Added text on how HBV acute infection/ reactivation will be handled in the OLE.	Refer to rationale for Section 4.1.
	Updated Table 9 (Analysis Strategy for Key Efficacy Variables) to include Week 144 for the secondary endpoints and H4.	Refer to rationale for Section 4.1.
	Added efficacy analyses at Week 144 and in the OLE.	Refer to rationale for Section 4.1.
Section 9.6.2 Statistical Methods for Safety Analyses	Updated Table 10 (Definition of Study Time Points for DEXA Analyses) to include Week 144.	Refer to rationale for Section 4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 9.6.2.1 Overall Safety Assessment	Added safety analyses at Week 144 and in the OLE.	Refer to rationale for Section 4.1.
	Excluded participants who become pregnant during the study from the analyses of continuous safety measures.	Refer to rationale for Section 3 regarding evaluation of total lymphocyte count.
	Added assessment of mean change from baseline in lymphocyte and lymphocyte subset counts in the base study.	Refer to rationale for Section 4.1.
Section 9.6.2.2 Assessment of Safety Topics of Special Interest	Specified time period (base study) and added Week 144 for assessments of opportunistic infections.	Refer to rationale for Section 4.1.
Section 9.6.2.3 Handling of Missing Data and Pregnancies in Safety Analyses	Added missing safety data handling in the OLE and extended base study period to Week 144 for data collection for pregnant participants.	Refer to rationale for Section 4.1.
	Table 11: Added mean change from baseline safety parameters for lymphocytes.	Refer to rationale for Section 3 regarding evaluation of total lymphocyte count.
Section 9.7 Interim Analyses	Updated to reflect that the study participants and site personnel will remain blinded until Week 144 and added H4.	Refer to rationale for Section 4.1.
Section 9.8 Multiplicity	Added a Type I error adjustment for the futility analysis, for statistical rigor.	To enhance statistical rigor, a small alpha (0.00001) will be allocated for the Week 24 IA.
	Added the hypothesis 4 testing superiority of Group 1 to Group 2 as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 144.	Refer to rationale for Section 4.1.
Section 9.9.1.1 Sample Size and Power Calculations	Tables 12 and 13: Updated to accommodate the Type I error adjustment.	Refer to rationale for Section 9.8 regarding Type I error adjustment.
Section 9.9.1.2 Evaluation of the Futility Criterion and Non-Inferiority at Week 48	Table 15: Updated to accommodate the Type I error adjustment.	Refer to rationale for Section 9.8 regarding Type I error adjustment.
Section 9.11 Compliance (Medication Adherence)	Updated the computation for blinded study intervention compliance in the base study and added Week 144 time point.	Refer to rationale for Section 4.1.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Table 18 Protocol-required Laboratory Assessments: Moved HbA1c to the Additional Chemistry at Fasting Visits row.	To clarify that HbA1c can be collected regardless of fasting or nonfasting status.
	Updated footnote c to apply for all participants.	Refer to rationale for Section 1.3.1 regarding HBV.
	Updated blood volumes: Added table for OLE (Table 21), updated tables for base study (Tables 19 and 20), and removed table for FBR in pregnancy beyond Week 144, that is no longer applicable.	Refer to rationale for Section 4.1 regarding removal of FBR sample collection in pregnancy/postpartum post-Week 144.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Who Are Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)

Short Title: DOR/ISL 100 mg/0.25 mg QD Blinded Switch

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in participants ≥18 years of age with HIV-1 who have been virologically suppressed (ie, HIV-1 RNA <50 copies/mL) for ≥3 consecutive months on BIC/FTC/TAF.

Primary Objective	**Primary Endpoint**
To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 **Hypothesis (H1)**: DOR/ISL is non-inferior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48. A margin of 4 percentage points is used to define non-inferiority. **Hypothesis (H2)**: DOR/ISL is superior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48.	HIV-1 RNA
To evaluate the safety and tolerability of a switch from BIC/FTC/TAF to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by review of the safety data accumulated through Week 48	Adverse events Adverse events leading to discontinuation of study intervention

Secondary Objectives	Secondary Endpoints
To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96 and Week 144 **Hypothesis (H3)**: DOR/ISL is superior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96. **Hypothesis (H4)**: DOR/ISL is superior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 144.	HIV-1 RNA
To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the percentage of participants with the following at Week 48, Week 96, and Week 144: - HIV-1 RNA <200 copies/mL - HIV-1 RNA <50 copies/mL	HIV-1 RNA
To evaluate the immunologic effect of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the mean change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144	CD4+ T-cell count
To evaluate the development of viral drug resistance to any study intervention at Week 48, Week 96, and Week 144	Viral resistance-associated substitutions
To evaluate the safety and tolerability of a switch from BIC/FTC/TAF to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by review of the safety data accumulated through Week 144	Adverse events Adverse events leading to discontinuation of study intervention

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	HIV infection
Population	Participants ≥18 years of age with HIV-1 who have been virologically suppressed for ≥3 consecutive months on BIC/FTC/TAF
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Sponsor Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 501 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Group 1	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Day 1 to Week 144	Test Product
Group 1	placebo to bictegravir/ emtricitabine/ tenofovir alafenamide	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo
Group 1	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg. 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product
Group 2	bictegravir/ emtricitabine/ tenofovir alafenamide	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg QD	Oral	Day 1 to Week 144	Comparator
Group 2	placebo to doravirine/ islatravir	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo
Group 2	doravirine/ islatravir	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product

QD=once-daily.

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

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

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

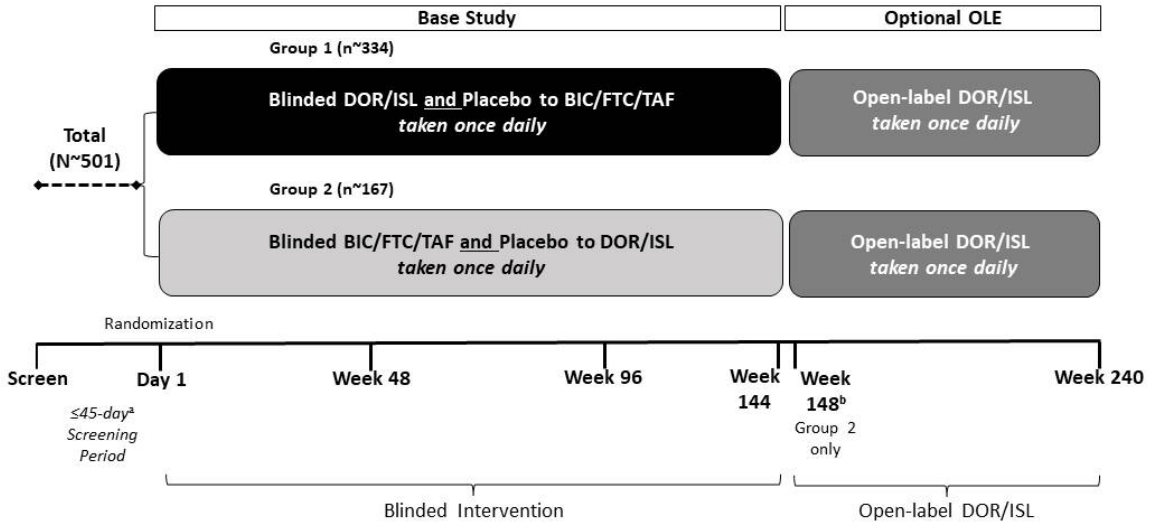
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema and Treatment Plan



BIC=bictegravir; DOR=doravirine; FTC=emtricitabine; HIV-1= human immunodeficiency virus type 1; ISL=islatravir; N=total number of participants in the study; n=number of participants in the intervention group; OLE=open-label extension; TAF=tenofovir alafenamide.

a. Participants are expected to enroll as soon as possible after eligibility is confirmed. In cases of unexpected delays in receiving repeat screening laboratory results, a screening period of up to 45 days is allowed.
b. Only Group 2 participants in the OLE (ie, switch to DOR/ISL) have an extra visit at Week 148.

1.3 Schedule of Activities

1.3.1 Schedule of Activities – Screening Through Week 144 – (Base Study)

This SoA applies to all participants in the blinded comparison period (Base Study).

- The Early Discontinuation of Treatment Visit applies to any participant who discontinues study intervention prior to Week 144 (Section 8.11.3). Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section1.3.3).
- Manage pregnant participants per Section 8.11.6.
- For the OLE, see Sections 8.11.2.3 (SoA Section 1.3.5).

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for FBR	X																	

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Post Base Study Disposition Planning													X	X	X			Proactively discuss prior to the Week 144 visit (see Section 8.11.2.2).
Unblinding of Treatment Group Assignment															X			Complete after documenting all AEs (including causality).
Informed Consent for OLE															X			Obtain prior to dispensing study intervention at Week 144.
Informed Consent for Study Intervention During Pregnancy			<----------X---------->															Obtain upon confirmation of pregnancy. See Section 8.1.1.3.
Collect and Enter Data From Prenatal Care Provider			<----------X---------->															See Section 8.11.6 for prenatal safety monitoring.
Informed Consent for Infant Data Safety Collection			<----------X---------->															Obtain after confirmation of continuing pregnancy. See Sections 8.1.1.4 and 8.11.6.4.

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

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Prior and Concomitant Medications Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Intervention Randomization		X																All pretreatment procedures should be completed prior to randomization on Day 1.
Dispense Study Intervention Using IRT		X	X	X	X	X	X	X	X	X	X	X	X	X	(X)			(Dispense at Week 144 for participants entering the OLE and if needed for those whose pregnancy or Postpartum visit(s) extends past Week 144 see Section 1.3.4).

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

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

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

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Hepatitis B Serology and HBV DNA in Pregnant Participants (DOR/ISL Only)		<----------(X)---------->																Collect once after pregnancy is confirmed or report local laboratory results. See Section 8.11.6.1.
Hepatitis C Serology	X																	See Section 8.3.7. Repeat screening if indicated per local standard of care.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Fasting required at Day 1 and Weeks 24, 48, 96, and 144 (see Section 8.3.9.3 and Appendix 2). Pregnant participants should not fast.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PT/INR	X																	
Urinalysis		X			X		X		X		X		X		X	X		
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Blood (Plasma) for ISL PK		X	X	X	X		X											At Week 4, if daytime dosing, obtain pre- and postdose or, if evening dosing, collect only 1 sample irrespective of time of last dose. See Section 8.6.1 (Table 6). Do not collect if participant unblinded and assigned to BIC/FTC/TAF.
Blood (Plasma) for Investigational ISL PK						X		X	X	X	X							Do not collect during pregnancy or if participant unblinded and assigned to BIC/FTC/TAF. Analysis performed by Sponsor as needed. See Section 8.6.1.

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Blood (Plasma) for DOR and ISL PK in Pregnant Participants (DOR/ISL Only)			<----------X---------->													X		Collect during the 1st, 2nd, and 3rd trimesters and postpartum. See Section 8.11.6.1 (Table 7).
Waist and Hip Measurements		X					X				X				X			Not applicable to pregnant participants

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
DEXA Scan (Only Where Permitted by Local Law)		X					X				X				X			Perform after <u>all</u> eligibility criteria are confirmed. Must be performed prior to 45 days after Day 1 and ±45 days of the Weeks 48, 96, and 144 visits. Perform only for participants with valid baseline images. Do not perform on pregnant participants. See Appendix 7 for country-specific requirements.
Blood and Urine for Renal Markers		X			X		X				X				X			Do not collect during pregnancy.
Blood for Inflammatory Markers		X			X		X				X				X			Do not collect during pregnancy.

Study Period:	Screening[a]	**Blinded Intervention (Base Study)**														**End of Treatment**		**Notes**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	Unscheduled		
Scheduled Day/Week:	Screening	Day 1 (Fasting)	Week 4	Week 12	Week 24 (Fasting)	Week 36	Week 48 (Fasting)	Week 60	Week 72	Week 84	Week 96 (Fasting)	Week 108	Week 120	Week 132	Week 144 (Fasting)	Early Discontinuation of Treatment[b]	End of Treatment Follow-Up (Base Study)	
Visit Window	≤45 day	NA	±7 days (Calculate each visit from date of Day 1)													NA	42 (+7) days after end of treatment	
Blood for Energy and Metabolism Markers		X			X		X				X				X			Do not collect during pregnancy.
Biomarkers																		
Blood for Genetic Analysis[c]		X																Collect predose. See Section 8.8.1.
Whole Blood for FBR		X			X		X				X				X	X		Optional participation; requires FBR consent. Collect Day 1 sample predose; remaining samples may be collected at any time irrespective of last dose.

AE=adverse event; anti-HBc=hepatitis B core antibody; BIC=bictegravir; BP=blood pressure; DEXA=dual x-ray absorptiometry; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; FTC=emtricitabine; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IEC=Independent Ethics Committee; INR=international normalized ratio; IRB=Institutional Review Board; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participant(s) of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TAF=tenofovir alafenamide; TBNK=T and B Lymphocyte and Natural Killer Cell; temp=body temperature.

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

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

[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 the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant (or their legally acceptable representative) provides documented informed consent for FBR. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

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

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

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

Study Period	**Viremia Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Administrative Procedures						
Prior and Concomitant Medications Review	X	X	X	X	X	
Register Study Visit in IRT	X	X		X		
Study Intervention Compliance Review	X	X				
Administration of EQ-5D-5L, HIVTSQ, and HIV-SI/SDM Patient Questionnaires		(X)				Administer in the order listed, before the participant is seen by the investigator and before discussing medical conditions or test results. (Do not administer after Week 96 visit).

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X	X	See Section 8.2.1.
Plasma for HIV-1 Drug Resistance	X	(X)		(X)		(Do not collect at Discontinuation of Treatment Visit if collected at the Viremia Confirmation Visit.) Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
TBNK Panel/CD4+ T-cell Count		X		X		
Safety Procedures						
Full Physical Examination		X				
Directed Physical Examination			X	X	X	
Weight		X	X			
Vital Signs		X	X			
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	Contraception required for 42 days after the last dose of study intervention (Section 8.3.4).

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	Confirm positive or indeterminant urine test with serum. If positive, manage participant per Section 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.
Chemistry		X				
Hematology		X		X		
Urinalysis		X				
AE/SAE Review	X	X	X	X	X	
Pharmacokinetics						
Blood (Plasma) for Investigational ISL PK (and DOR, if applicable)	X	X				Do not collect during pregnancy or if participant unblinded and assigned to BIC/FTC/TAF. Analysis performed by Sponsor as needed. see Section 8.6.1.
Blood (Plasma) for DOR and ISL PK	X	X		X		Only for pregnant participants on DOR/ISL. Collect irrespective of time of last dose and record time of last dose of study intervention in appropriate source documentation.

Study Period	Viremia Confirmation	End of Treatment (Base Study)		End of Treatment (OLE)		Notes
Visit Number	Unscheduled	Unscheduled		Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-Up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-Up (OLE)	
Visit Window	Within 4 weeks (±1 week) of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after end of treatment	NA	42 (+7) days after end of treatment	
Biomarkers						
Whole Blood for FBR	X	(X)				Optional participation; requires FBR consent. Collect irrespective of time of last dose. (If collected at preceding Viremia Confirmation Visit, do not collect at Early Discontinuation of Treatment visit).

AE=adverse event; BIC=bictegravir; BP=blood pressure; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; FTC=emtricitabine; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TAF=tenofovir alafenamide; TBNK=T and B Lymphocyte and Natural Killer Cell; temp=body temperature.

[a] Participants who discontinue at a Scheduled Visit, should complete the assessments for the scheduled visit as well as for the Early Discontinuation of Treatment Visit. Collection of laboratory samples should not be duplicated.

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

This SoA only applies to participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts in the base study and/or OLE per Section 8.11.5.

- Manage participants with Viremia per Sections 8.2.2 and 8.11.4 (SoA Section1.3.2).

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

Study Period	**Total Lymphocyte Count or CD4+ T-cell Count Confirmation**	**End of Treatment (Base Study)**		**End of Treatment (OLE)**		**Total Lymphocyte Count or CD4+ T-cell Count Monitoring (DOR/ISL Only)**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled		Unscheduled	
Visit Name	Total Lymphocyte Count or CD4+ T-cell Count Confirmation	Early Discontinuation of Treatment (Base Study)[a]	End of Treatment Follow-up (Base Study)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)	Total Lymphocyte Count or CD4+ T-cell Count Monitoring	See Sections 7.1, 8.1.9, and 8.11.5 for details regarding discontinuation and monitoring.
Visit Window	Within 10 to 14 weeks after initial decrease	NA	42 (+7) days after discontinuing study intervention	NA	42 (+7) days after discontinuing study intervention	Every 10 to 14 weeks after discontinuing study intervention	
Study Intervention Compliance Review	X	X					
Administration of EQ-5D-5L, HIVTSQ, and HIV-SI/SDM Patient Questionnaires		(X)					Administer in the order listed, before the participant is seen by the investigator and before discussing medical conditions or test results. (Do not administer after the Week 96 visit).
Efficacy Procedures							
Plasma HIV-1 RNA Quantification		X	X	X	X		See Section 8.2.1.
Plasma for HIV-1 Drug Resistance		X		X			Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.

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

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

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

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

AE=adverse event; BIC=bictegravir; BP=blood pressure; DOR=doravirine; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; FTC=emtricitabine; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IRT=Interactive Response Technology; ISL=islatravir; NA=not applicable; PK=pharmacokinetic(s); POCBP=participants/participants of childbearing potential; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TAF=tenofovir alafenamide; TBNK=T and B Lymphocyte and Natural Killer Cell; temp=body temperature.

[a] Participants who discontinue at a Scheduled Visit, should complete the assessments for the scheduled visit as well as for the Early Discontinuation of Treatment Visit. Collection of laboratory samples should not be duplicated.

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

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

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

Study Period	**Pregnancy**			**Postpartum**	**End of Treatment[a]**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days				42 (+7) days after the end of treatment	
Administrative Procedures						
Collect and Enter Data From Prenatal Care Provider	<----------X---------->					Obtain relevant prenatal clinical and laboratory data to monitor the safety of the mother and fetus per Section 8.11.6.
Register Study Visit in IRT	X	X	X	X		
Dispense Study Intervention Using IRT	X	X	X	(X) (DOR/ISL Only)		(Postpartum participants on DOR/ISL may continue treatment through the OLE [Section 1.3.5] if not yet commercially accessible; those on BIC/FTC/TAF should transition to commercially accessible ART at their postpartum visit per Section 8.6.11.1).

Study Period	**Pregnancy**			**Postpartum**	**End of Treatment[a]**	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days				42 (+7) days after the end of treatment	
Study Intervention Compliance Review	X	X	X	X		
Prior and Concomitant Medications Review	X	X	X	X	X	
Efficacy Procedures						
Plasma HIV-1 RNA Quantification	X	X	X	X	X	See Section 8.2.1. Manage participants with viremia per Section 1.3.2 and 8.2.2.
Plasma for HIV-1 Drug Resistance	X	X	X	X	X	Analysis performed by Sponsor if indicated per Section 8.2.2.1.2.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	
Safety Procedures						
Weight	X	X	X	X	X	
Directed Physical Examination	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Hepatitis B Serology and HBV DNA (DOR/ISL only)	<----------X---------->					Collect once after pregnancy is confirmed or report local laboratory results. See Section 8.11.6.1.
Chemistry	X	X	X	X	X	
Hematology	X	X	X	X	X	
Urinalysis	X	X	X	X	X	
AE/SAE Review	X	X	X	X	X	

Study Period	**Pregnancy**			**Postpartum**	**End of Treatment**[a]	**Notes**
Visit Number	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled	
Scheduled Week	Pregnancy 1	Pregnancy 2 (12 weeks from Pregnancy 1)	Pregnancy 3 (12 weeks from Pregnancy 2)	Pregnancy 4 (Postpartum ≤8 weeks after delivery)	End of Treatment Follow-up	
Visit Window	±7 days				42 (+7) days after the end of treatment	
Pharmacokinetics						
Blood (Plasma) for DOR and ISL PK	X	X	X	X	X	Collect only for participants on DOR/ISL during the 1st, 2nd, and 3rd trimesters and postpartum per Section 8.11.6.1.1 (Table 7).

AE=adverse event; BIC=bictegravir; BP=blood pressure; DNA=deoxyribonucleic acid; DOR=doravirine; FBR=future biomedical research; FTC=emtricitabine; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus type 1; IRT=Interactive Response Technology; ISL=islatravir; PK=pharmacokinetic(s); OLE=open-label extension; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TAF=tenofovir alafenamide; TBNK=T and B Lymphocyte and Natural Killer Cell; temp=temperature.

[a] The procedures in this End of Treatment Follow-up Visit should be followed for those participants not continuing in the OLE.

1.3.5 Schedule of Activities – Week 144 Through Week 240 (Open-label Extension)

This SoA only applies to participants who enter the optional OLE at Week 144.

- Duration of participation in the OLE is dependent on when DOR/ISL becomes commercially accessible, with a maximum treatment duration of 96 weeks (ie, total study intervention duration of up to 240 weeks).
- Manage participants with viremia per Sections 8.2.2 and 8.11.4 (SoA Section 1.3.2).
- Manage participants with specified decreases in total lymphocyte and/or CD4+ T-cell counts per Section 8.11.5 (SoA Section 1.3.3).
- Manage pregnant participants per Section 8.11.6 (SoA Section 1.3.4).

Study Period	**Optional OLE**					**End of Treatment**		**Notes**
Visit Number	16	17	18	19	20	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 148 (Group 2 Only)	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (OLE)[a]	End of Treatment Follow-up (OLE)	
Visit Window	±14 days (Calculate each visit from date of Day 1)					NA	42 (+7) days after end of treatment	
Evaluate Local Accessibility of DOR/ISL	X	X	X	X	X			Once DOR/ISL is commercially accessible, participants should return to the study-site for the Discontinue of Treatment visit and transition to the local supply.
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X		
Dispense Study Intervention Using IRT	X	X	X	X	(X)			(Dispense at Week 240 if needed for pregnant participants see Section 1.3.4).
Study Intervention Compliance Review	X	X	X	X	X	X		

Study Period	Optional OLE					End of Treatment		Notes
Visit Number	16	17	18	19	20	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 148 (Group 2 Only)	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (OLE)[a]	End of Treatment Follow-up (OLE)	
Visit Window	±14 days (Calculate each visit from date of Day 1)					NA	42 (+7) days after end of treatment	
Plasma HIV-1 RNA Quantification	X	X	X	X	X	X		See Section 8.2.1.
TBNK Panel/CD4+ T-cell Count	X	X	X	X	X	X		
Blood (Plasma) for HIV-1 Drug Resistance	X	X	X	X	X	X		Analysis will be performed by Sponsor if indicated per Section 8.2.2.1.2.
Hepatitis B Serology and HBV DNA			X		X			Encourage HBV vaccination to participants who are not immune to HBV. Repeat serology and HBV DNA testing at Weeks 192 and 240 (annual surveillance).
HBsAg and HBV DNA	(X)	(X)	(X)	(X)	(X)			(Only anti-HBc-positive participants, at each visit.) See Section 8.3.6.
Hematology	X	X	X	X	X	X		
Directed Physical Examination	X	X	X	X	X	X	X	
AE/SAE Review	X	X	X	X	X	X	X	
Contraceptive Use Confirmation (POCBP Only)	X	X	X	X	X	X	X	Contraception is required 42 days after the last dose of study intervention.
Urine Pregnancy Test (hCG) (POCBP Only)	X	X	X	X	X	X	X	Manage participants who have a positive or indeterminant urine test per Sections 1.3.4 and 8.11.6. For participants known to be pregnant, defer until 6 weeks postpartum.

Study Period	Optional OLE					End of Treatment		Notes
Visit Number	16	17	18	19	20	Unscheduled	Unscheduled	
Scheduled Day/Week	Week 148 (Group 2 Only)	Week 168	Week 192	Week 216	Week 240	Discontinuation of Treatment (OLE)[a]	End of Treatment Follow-up (OLE)	
Visit Window	±14 days (Calculate each visit from date of Day 1)					NA	42 (+7) days after end of treatment	
Informed Consent for Study Intervention During Pregnancy	< ----------X---------- >							Obtain upon confirmation of pregnancy. See Sections 1.3.4 and 8.1.1.3.

AE=adverse event; anti-HBc=hepatitis B core antibody; BIC=bictegravir; BP=blood pressure; DEXA=dual-energy X-ray absorptiometry; DNA=deoxyribonucleic acid; DOR=doravirine; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensional descriptive system, 5-level version; FBR=future biomedical research; FTC=emtricitabine; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HIV-1=human immunodeficiency virus type 1; HIV-2= human immunodeficiency virus type 2; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/symptom distress module; INR=international normalized ratio; IRT=interactive response technology; ISL=islatravir; NA=not applicable; OLE=open-label extension PK=pharmacokinetic(s); POCBP=participant/participants of childbearing potential; PT=prothrombin time; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; TAF=tenofovir alafenamide; TBNK=T and B lymphocyte and natural killer cells; temp=body temperature.

[a] If discontinuation occurs at a scheduled visit, perform Discontinuation of Treatment (OLE) visit assessments.

2 INTRODUCTION

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

2.1 Study Rationale

As treatment regimens have improved, HIV-1 infection has become a chronic, manageable condition, and PLWH receiving effective ART regimens can expect to live near-normal lifespans [Trickey, A., et al 2017]. Anticipating that individuals can receive decades of treatment during their lifetime, long-term tolerability and safety of antiretrovirals have become increasingly important considerations.

The current standard of care for the treatment of HIV-1 is a combination of 2 NRTIs with a third agent (eg, InSTI, NNRTI, or PI) [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022] [European AIDS Clinical Society 2021] [World Health Organization 2021]. Although these 3-drug regimens are well tolerated and highly efficacious, the current paradigm of lifelong daily treatment is associated with a need for simpler and safer regimens that reduce overall drug exposure [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. As this population ages, there is increasing concern about polypharmacy, long-term toxicity, and DDIs related to comorbidity and multimorbidity and risks associated with the emergence of HIV-1 variants resistant to InSTI, NRTI, and NNRTI treatments.

There is evidence that 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens, offer better tolerability, and improve quality of life; all of which can support adherence and help to sustain virologic suppression [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. The effectiveness of 2-drug regimens depends on both components having distinct mechanisms of action with at least 1 of the components having a relatively high barrier to resistance.

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

2.2 Background

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

2.2.1 Islatravir

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

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

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

2.2.2 Doravirine

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

2.2.3 Doravirine/Islatravir

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

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

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

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

2.2.4 Information on Other Study-related Therapy

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

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

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

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

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

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

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

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

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

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

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

- No changes in general hematology parameters (including hemoglobin, basophils, eosinophils, monocytes, leukocytes, neutrophils, platelets) were observed for participants receiving ISL alone or in combination with other ART in any study.

- ISL dose-dependent decreases from baseline were observed in mean total lymphocyte counts and lymphocyte subset (CD4+ T-cell, CD8+ T-cell, B-cell) counts, with greater decreases observed at the higher ISL doses administered QW (20 mg) and QM (60 mg) compared with QD (0.75 mg) administration.

    - In VS participants in MK-8591A-017 and MK-8591A-018 receiving DOR/ISL 100 mg/0.75 mg QD, mean percent changes from baseline were observed in total lymphocyte (-10.6% and -8.4%, respectively), CD4+ T-cell (-0.68% and +0.87%, respectively), CD8+ T-cell (-8.2% and -7.4%, respectively), and B-cell (-4.4% and -8.6%, respectively) counts at Week 48.

    - In VS participants in MK-8591-013 receiving ISL 20 mg + MK-8507 100 to 400 mg QW, mean percent changes from baseline were observed in total lymphocyte (-15.1% to -30.9%), CD4+ T-cell (-7.6% to -28.1%), CD8+ T-cell (-18.1% to -32.8%), and B-cell (-36.8% to -46.3%) counts were observed at Week 24.

  - In participants with low risk of HIV-1 infection receiving ISL 60 or 120 mg QM for PrEP, the on-treatment mean decreases from baseline in total lymphocyte count were -21.3% and -35.6% at Week 24, respectively.

- Stabilization of the decreases from baseline in mean total lymphocyte count and lymphocyte subset counts observed for the DOR/ISL 100 mg/0.75 mg QD program occurred between Weeks 48 and 72, depending on the lymphocyte subset.

- Decreases from baseline in mean total lymphocyte count and lymphocyte subset counts were not associated with increased incidence of infection.

- A return toward baseline in lymphocyte and lymphocyte subset counts has been observed across the ISL clinical development program. However, a full recovery was not observed by 24 weeks after stopping ISL. The most robust data on recovery of the lymphocyte counts available at this point was from the studies involving administration of ISL QW (20 mg) and QM (60-120 mg), as detailed below. Data on recovery to baseline following discontinuation of DOR/ISL 100 mg/ 0.75 mg QD in VS adults (MK-8591A-017 and MK-8591A-018) is not yet available.

- Approximately 6 months after discontinuation of ISL 20 mg QW in adult VS participants (MK-8591-013), among those with ≥30% decrease in total lymphocyte or CD4+ T-cell counts at their last on-treatment measurement and at least 1 follow-up result, 10/40 (25%) and 15/32 (47%) participants demonstrated an increase in total lymphocyte and CD4+ T-cell counts, respectively, to within 10% of baseline.

- Approximately 5 months after discontinuation of ISL 60 mg QM in adults at risk of HIV-1 infection, 43 (29.9%) of the 144 participants in MK-8591-022 and MK-8591-024 with a ≥30% decrease in total lymphocyte count at the last on-treatment visit demonstrated an increase in total lymphocyte counts to within 10% of baseline.

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

BIC/FTC/TAF is currently an approved InSTI based single-tablet regimen for the treatment of HIV-1 infection in patients naïve to ART or to replace the current ART regimen in those who are virologically suppressed. Refer to the approved local labeling for detailed benefit-risk information on BIC/FTC/TAF.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in participants ≥18 years of age with HIV-1 who have been virologically suppressed (ie, HIV-1 RNA <50 copies/mL) for ≥3 consecutive months on BIC/FTC/TAF.

Primary Objective	**Primary Endpoint**
To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 **Hypothesis (H1)**: DOR/ISL is non-inferior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48. A margin of 4 percentage points is used to define non-inferiority. **Hypothesis (H2)**: DOR/ISL is superior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48.	HIV-1 RNA
To evaluate the safety and tolerability of a switch from BIC/FTC/TAF to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by review of the safety data accumulated through Week 48	Adverse events Adverse events leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96 and Week 144 **Hypothesis (H3)**: DOR/ISL is superior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96. **Hypothesis (H4)**: DOR/ISL is superior to BIC/FTC/TAF, as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 144.	HIV-1 RNA

To evaluate the antiretroviral activity of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the percentage of participants with the following at Week 48, Week 96, and Week 144: - HIV-1 RNA <200 copies/mL - HIV-1 RNA <50 copies/mL	HIV-1 RNA
To evaluate the immunologic effect of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the mean change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144	CD4+ T-cell count
To evaluate the development of viral drug resistance to any study intervention at Week 48, Week 96, and Week 144	Viral resistance-associated substitutions
To evaluate the safety and tolerability of a switch from BIC/FTC/TAF to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by review of the safety data accumulated through Week 144	Adverse events Adverse events leading to discontinuation of study intervention
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the effects on weight, body composition, fasting lipid and metabolic profiles, bone density, renal function, and inflammation of a switch to DOR/ISL compared with continued BIC/FTC/TAF, as assessed by the mean change in these parameters from baseline at Week 48, Week 96, and Week 144	Weight, body composition, BMD, and laboratory markers
To evaluate the effect of DOR/ISL compared with BIC/FTC/TAF on total lymphocyte count at Weeks 48, 96, and 144	Total lymphocyte count
To describe PROs (HRQoL, HIV treatment satisfaction, and HIV symptoms) after a switch to DOR/ISL compared with continued BIC/FTC/TAF at Week 48 and Week 96	EQ 5D 5L, HIVTSQ, and HIV SI/SDM
To evaluate the pharmacokinetics of ISL when administered as a component of DOR/ISL	Pharmacokinetic values, e.g. AUC, Cmax, and C24

To evaluate the long-term antiretroviral activity of DOR/ISL in participants initially randomized to Group 1 and the antiretroviral activity of a switch to DOR/ISL in participants initially randomized to Group 2, as assessed by the percentage of participants with - HIV-1 RNA ≥50 copies/mL, - HIV-1 RNA <50 copies/mL, - HIV-1 RNA <200 copies/mL in those enrolled in the open-label extension	HIV-1 RNA
To evaluate the long-term immunologic effect of DOR/ISL, as assessed by mean changes in CD4+ T-cell count over time in participants enrolled in the open-label extension	CD4+ T-cell count
To evaluate the long-term effect of DOR/ISL on total lymphocyte count in participants enrolled in the open-label extension	Total lymphocyte count
To evaluate the development of viral drug resistance to DOR/ISL in the open-label extension	Viral resistance associated substitutions
To evaluate the long-term safety and tolerability of DOR/ISL, as assessed by review of the safety data accumulated in participants enrolled in the open-label extension	Adverse events Adverse events leading to discontinuation of study intervention
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 and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, multi-site, double-blind study to evaluate a switch from BIC/FTC/TAF QD to DOR/ISL (100 mg/0.25 mg QD) in participants with HIV-1 who have been virologically suppressed on BIC/FTC/TAF for ≥3 consecutive months with no history of virologic treatment failure.

The study consists of a screening period of up to 45 days and a blinded treatment period (base study) of 144 weeks with participants receiving either DOR/ISL or BIC/FTC/TAF, followed by an optional OLE of up to 96 weeks with participants continuing on or switching to DOR/ISL (Figure 1).

Base Study

A total of approximately 501 participants will be randomized in a 2:1 ratio into 1 of 2 treatment groups (Figure 1):

- Group 1 (n=approximately 334): Switch from BIC/FTC/TAF QD to DOR/ISL (100 mg/0.25 mg QD) on Day 1 and continue DOR/ISL QD through Week 144 (taken with matching placebo to BIC/FTC/TAF through Week 144).

- Group 2 (n=approximately 167): Continue BIC/FTC/TAF QD through Week 144 (taken with matching placebo to DOR/ISL (100 mg/0.25 mg QD) through Week 144).

All participants will receive 144 weeks of assigned blinded therapy in the base study. Participants who complete the last visit in the base study (Week 144) will be given an option to receive open-label DOR/ISL until it is commercially accessible (Section 6.7). Study intervention will be extended open-label for participants who become pregnant on treatment and provide documented informed consent to continue their assigned study intervention (DOR/ISL or BIC/FTC/TAF in the base study or open-label DOR/ISL in the OLE), as specified in Sections 1.3.4 and 8.11.6.Clinical site personnel and participants will remain blinded through Week 144 while Sponsor personnel will remain blinded through Week 48. Efficacy and safety laboratory results, including HIV-1 RNA, will remain unmasked throughout the study. At Week 144, all participants and site personnel will be unblinded.

Participants and all field and study-site personnel will remain blinded through the end of the base study (Week 144). Any participants with clinically significant confirmed viremia (Section 4.2.1.1.2) will be assessed for development of viral drug resistance and discontinuation from study intervention per the SoA (Section 1.3.2) and Section 7.1.

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

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

Open-Label Extension (OLE)

At Week 144, participants from both groups who meet criteria in Section 8.11.2.3 and consent to enter the OLE will continue (Group 1) or switch to (Group 2) open label DOR/ISL up to Week 240 or until it is commercially accessible (whichever comes first). Procedures to be followed upon exiting the OLE are outlined in Section 6.7.

Consistent with global HIV-1 treatment guidelines [Food and Drug Administration (CDER) 2015] [European AIDS Clinical Society 2021] the OLE consists of in-clinic visits every 6 months to assess maintenance of virologic suppression, CD4+ T-cell count and tolerability. Group 2 (BIC/FTC/TAF) participants who switch to DOR/ISL at Week 144 will have a follow-up visit at Week 148 to assess, for continued viral suppression and tolerability 4 weeks after the switch, in accordance with HIV-1 treatment guidelines. Where local treatment guidelines require visits more frequently than every 6 months, these are permitted and should be conducted by the primary investigator and/or the treating physician.

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

4.2 Scientific Rationale for Study Design

Base Study

The randomized, active-controlled, non-inferiority study design is consistent with the FDA CDER 2015 Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment [Food and Drug Administration (CDER) 2015] and is considered appropriate for a treatment-experienced study population that is switching from another stable ART regimen with HIV RNA <50 copies/mL. Small differences in virologic efficacy, emergence of resistance, and loss of tolerability or safety may be detected prior to 48 weeks of treatment, particularly for therapies with largely comparable characteristics. Thus, an efficacy and safety outcome through 48 weeks is aligned with current regulatory guidance [Food and Drug Administration (CDER) 2015], and the primary efficacy and safety analyses will occur after 48 weeks of treatment with DOR/ISL or BIC/FTC/TAF. A 2:1 randomization ratio optimizes collection of efficacy and safety data on the DOR/ISL investigational product relative to the approved BIC/FTC/TAF comparator product taken by the Group 2 participants in this study. The blinded treatment (base study) duration is 144 weeks to allow for collection of long-term comparative efficacy

and safety data for DOR/ISL vs. BIC/FTC/TAF. Participants and investigators remain blinded for the duration of comparative data collection to minimize potential bias.

Open-Label Extension (OLE)

The primary rationale for the OLE is to provide access to DOR/ISL until it is commercially accessible. Participation in the OLE is optional and allows eligible participants who are deriving benefit from treatment in the DOR/ISL group to continue DOR/ISL and avoid interruption of treatment. The OLE also allows participants assigned to the comparator to have the option to switch to DOR/ISL at the completion of the base study in accordance with standard practice in HIV trials. The OLE will also allow for long-term efficacy and safety data collection for DOR/ISL.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 HIV-1 RNA Measurements

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

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

The secondary efficacy endpoint of plasma HIV-1 RNA <200 copies/mL corresponds to the clinically relevant threshold. With values ≥200 copies/mL, there is an increased risk of development of resistance.

4.2.1.1.2 Definition of Clinically Significant Confirmed Viremia

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

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

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

results in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. PLWH with HIV-1 RNA ≥50 and <200 copies/mL have a lower risk of developing resistance compared with those with HIV-1 RNA ≥200 copies/mL. Therefore, study participants with HIV-1 RNA ≥50 and <200 copies/mL should continue their current regimen, with HIV-1 RNA levels monitored as outlined in Section 8.2.2.

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

4.2.1.2 Safety Endpoints

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

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

4.2.1.3 Weight, Body Composition, and Radiological and Laboratory Markers

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

Inflammation

Causes of persistent inflammation and thrombotic activity in patients with HIV-1 remain topics of debate and ongoing research [Baker, J. V., et al 2011] [Knudsen, T. B., et al 2016] [Wang, H., et al 2016]; thus, key indicators of inflammation will be measured (Section 8.3.9.1).

Weight

Increases in body weight have been reported in PLWH on long-term ART and have long been considered a return-to-health phenomenon. However, evidence suggests that excess weight gain may be associated with certain ARV agents, which may have long-term health effects [Bailin, S. S., et al 2020] [Shah, S., et al 2021] [Buzon-Martin, L. 2020] [Wood, B. R. 2021]. In contrast, other ARV drugs, such as TDF and EFV, may have an anti-obesogenic effect [Hill, A., et al 2019]. Compared with other antiretroviral classes, use of integrase inhibitors in patients with HIV-1 has been associated with greater increases in body weight [Hill, A., et al 2019]. The mean change in weight will be compared between participants who switch to DOR/ISL and participants who continue taking BIC/FTC/TAF (Sections 8.3.1 and 8.3.9.4).

Body Composition

Decreases in BMD and lipodystrophy (peripheral and central fat redistribution) have been reported in patients with HIV-1 receiving ART [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022] [McComsey, G. A., et al 2018], particularly with the use of certain NRTIs. Key indicators of body composition (including waist-to-hip ratio and DEXA assessments) will be measured (Sections 8..3.9.4 and 8.3.9.5, respectively).

Fasting Lipid and Metabolic Profiles

Some antiretrovirals have been associated with lipid abnormalities [U.S. Prescribing Information 2017]; thus, key indicators of fasting lipid profiles will be measured (Section 8.3.9.3).

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

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

Renal Function

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

4.2.1.4 Pharmacokinetic Endpoints

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

4.2.1.5 Patient-reported Outcomes

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

HRQoL data are used to estimate health utility scores, which inform cost-effectiveness model analysis.

This study will include 3 self-administered PRO questionnaires (Sections 1.3 SoA, 8.1.12, and 9.4.3). The EQ-5D-5L, a generic HRQoL questionnaire, will provide a simple descriptive profile and index value for health status used to compute health utilities for health economic analyses. The HIVTSQ is a 10-item instrument used to measure satisfaction with medications for people with HIV infection. The status version (HIVTSQs) will be used to evaluate treatment satisfaction over time. The HIV-SI (also known as the HIV-SDM) is a 20-item HIV disease-specific questionnaire designed to assess the prevalence and burden of adverse effects associated with ART regimens. The PRO questionnaires will be completed up to Week 96 at the time points specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3).

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

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

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

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

See Section 8.8.1.

4.2.1.7 Future Biomedical Research

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

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

the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

The 3-drug regimen of BIC/FTC/TAF will be the comparator in this study. BIC/FTC/TAF has been approved by the EMA and the FDA for both treatment-naïve and switch patients and is a recommended initial regimen for most people infected with HIV-1 [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]. Although some previous switch studies have been conducted within-class (eg, from one NNRTI to another), this study is designed to compare switching to DOR/ISL from an InSTI-containing regimen. The InSTI-containing regimen was chosen as the comparator because the InSTI class is recommended by both the US Department of Health and Human Services [Panel on Antiretroviral Guidelines for Adults and Adolescents 2022] and the European AIDS Clinical Society [European AIDS Clinical Society 2021] as part of all first-line, standard-of-care treatment regimens. However, emerging data suggest that some InSTIs may have tolerability issues including possible weight gain and CNS side effects. Furthermore, long-term renal and bone defects have been associated with the use of TAF [U.S. Prescribing Information 2016]. Thus, some patients may want to switch from the combination of BIC/FTC/TAF [Norwood, J., et al 2017] [Hoffmann, C., et al 2017].

Matching placebo will be used to provide a robust evaluation of the safety and tolerability profile of DOR/ISL by maintaining double-blind, double-dummy therapy through Week 144.

4.2.3 Rationale for the Selected Participant Population

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

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

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

  Life expectancy for PLWH receiving suppressive ART is generally similar to people without HIV infection [Farahani, M., et al 2017] [Wandeler, G., et al 2016]. The leading cause of mortality in PLWH is no longer attributed to HIV-related complications, but

rather to comorbid conditions commonly associated with an aging population (eg, diabetes, cardiovascular disease, renal disease, cancer).

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

4.2.4 Rationale for Collecting Race and Ethnicity Data

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

4.2.5 Rationale for Collecting Gender Identity Data

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

4.2.6 Rationale for Infant Safety Data Collection

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

4.2.7 Rationale for Continuing Study Intervention During Pregnancy

The US Department of Health and Human Services guidelines currently advise that persons who become pregnant while receiving ART for HIV infection should continue their regimen provided it is safe, well tolerated, and effective at virologic suppression, because altering the regimen could cause an increase in viral load [Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]. Nonclinical developmental and reproductive toxicology studies did not identify any teratogenicity or other clinically relevant concerns that would preclude continued dosing of DOR/ISL in participants who become pregnant and provide documented informed consent to continue study intervention (where allowed by local regulations, health authorities, and ethics committees and as appropriate based on available data/local standard-of-care guidelines) (Sections 8.1.1.3 and 8.11.6).

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

4.2.8 Rationale for Collecting Alcohol and Tobacco Use

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

4.3 Justification for Dose

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

In the Phase 2 clinical study (MK-8591-011), 3 daily doses of ISL (0.25, 0.75, and 2.25 mg) were evaluated in combination with DOR (100 mg) + 3TC for 24 weeks and subsequently

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

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

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

4.4 Beginning and End-of-Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

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

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

5 STUDY POPULATION

Participants ≥18 years of age with HIV-1 who have been virologically suppressed for ≥3 consecutive months on BIC/FTC/TAF will be enrolled in this study.

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Is HIV-1 positive with plasma HIV-1 RNA <50 copies/mL at screening.
   Note: A single repeat of the plasma HIV-1 RNA screening test will be allowed, provided results are available within the 45-day screening window.

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

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

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

Demographics

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

Participants Assigned Female Sex at Birth

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

- Is not a POCBP

  OR

- Is a POCBP and:

  - Uses an acceptable contraceptive method or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 42 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours (for urine test) or 72 hours (for serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4 and Appendix 2.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

5. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.
   Note: See Appendix 7 for country-specific requirements.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has HIV-2 infection.
2. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.
3. Has a diagnosis of an active AIDS-defining opportunistic infection within 30 days prior to screening.
4. Has active HBV infection (defined as HBsAg-positive or HBV DNA-positive).

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

5. Has chronic HCV infection (detectable HCV RNA) with laboratory values consistent with cirrhosis (serum albumin <2.8 g/dL or INR >1.7 or platelets $<100 \times 10^9$ cells/L in the absence of another explanation for the abnormal laboratory values).

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

6. Has a history of malignancy ≤5 years prior to providing documented informed consent except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or cutaneous Kaposi's sarcoma.
7. Has a history or current evidence of any condition (including active tuberculosis), therapy, laboratory abnormality, or other circumstance (including drug or alcohol use or dependence) that might, in the opinion of the investigator, confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate.

Prior/Concomitant Therapy

8. Is taking or is anticipated to require systemic immunosuppressive therapy, immune modulators, or strong and moderate CYP3A inducers (or any other prohibited therapies outlined in Section 6.5) from 45 days prior to Day 1 through the study treatment period.

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

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

Prior/Concurrent Clinical Study Experience

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

    Notes:

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

    BIC/FTC/TAF is not considered investigational in countries where it has received health authority approvals, regardless of commercial availability.

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

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

Diagnostic Assessments

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

    Notes:

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

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

12. Has exclusionary laboratory values (completed by the central laboratory) within 45 days prior to Day 1 as listed in Table 1.

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

Table 1 Laboratory Exclusion Criteria

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

Other Exclusions

None

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Day 1 to Week 144	Test Product	IMP	Provided centrally by the Sponsor
Group 1	Experimental	placebo to bictegravir/ emtricitabine/ tenofovir alafenamide	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo	IMP	Provided centrally by the Sponsor
Group 1	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg. 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product	IMP	Provided centrally by Sponsor
Group 2	Active Comparator	bictegravir/ emtricitabine/ tenofovir alafenamide	Drug	Tablet	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg QD	Oral	Day 1 to Week 144	Comparator	IMP	Provided centrally by the Sponsor
Group 2	Active Comparator	placebo to doravirine/ islatravir	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 144	Placebo	IMP	Provided centrally by the Sponsor
Group 2	Experimental	doravirine/ islatravir	Drug	Tablet	100 mg/ 0.25 mg	100 mg/ 0.25 mg QD	Oral	Week 144 up to Week 240	Test Product	IMP	Provided centrally by Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; QD=once-daily.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

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

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to Group 1 (DOR/ISL) or Group 2 (BIC/FTC/TAF), respectively.

6.3.2 Stratification

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

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. DOR/ISL and BIC/FTC/TAF will be packaged identically relative to their matching placebos so that the blind is maintained.

As described in Section 4.1, clinical site personnel and participants will remain blinded through Week 144, while Sponsor personnel will remain blinded through Week 48. Sponsor personnel involved in performing and reviewing results of the Week 48 analysis will be unblinded at the time of the Week 48 database lock.

The Sponsor may have a limited unblinded team not involved with day-to-day conduct of the study that will review unblinded data for internal programmatic decision-making. Participants and all field and study-site personnel will remain blinded through Week 144.

Restricted Sponsor personnel involved in performing and reviewing PK data may be unblinded before the Week 48 database lock to allow timely completion of population PK modeling. No personnel directly associated with study conduct will be unblinded before the database lock at Week 48. Before granting select personnel access to unblinded PK data, an official memo detailing unblinding procedures will be generated per Sponsor SOP. This memo will list the names of the personnel who will have access to unblinded PK data before the Week 48 database lock.

6.4 Study Intervention Compliance

Participants should be instructed to bring the study intervention bottles to their visits. At each visit, the number of tablets remaining in the study packaging will be counted, reviewed, and recorded. The results will be used to assess participant compliance. If a discrepancy is noted, the investigator/study coordinator must discuss the discrepancy with the participant and the explanation must be documented. All participants should be reminded of the importance of taking their study intervention as instructed for the entire duration of the study.

Decisions to temporarily withhold study intervention because of an AE or other reason(s) will be reviewed on a case-by-case basis by the investigator.

Interruptions from the protocol-specified treatment plan that are expected to be ≥7 consecutive days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

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

- A record of the number of DOR/ISL/placebo and BIC/FTC/TAF/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the CRF.

6.5 Concomitant Therapy

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

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use

- Dates of administration including start and end dates

- Dosage information including dose and frequency

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

Prior and concomitant therapies listed in Table 3 are not permitted from 45 days prior to Day 1 through the study treatment period. Table 3 is not comprehensive, and the investigator should use their medical judgment when assessing a participant's prior and concomitant therapy(ies). The Sponsor Clinical Director or designee should be contacted if there are any

questions about a therapy not on the list below or regarding potential DDIs with a specific treatment that the participant may plan to receive.

In instances where the local product circular for DOR or BIC/FTC/TAF is more restrictive with regard to prohibited (ie, contraindicated or not recommended) therapy(ies), the local product circular supersedes this section. In addition, the below recommendations for coadministration with BIC/FTC/TAF should be followed for all participants receiving blinded study intervention:

- For participants taking metformin, close monitoring is recommended (BIC/FTC/TAF may increase metformin levels). Sucralfate and inhibitors of P-gp and/or BCRP should be used with caution. Refer to the local product circular for BIC/FTC/TAF for additional information.

- For participants taking medications or oral supplements containing polyvalent cations (eg, Mg, Al, Ca, Fe) during the base study, study intervention should be taken either 2 hours before or 6 hours after taking any polyvalent cation-containing medicine.

Concomitant medications (i.e. dofetilide), prohibited during the base study due to interaction with BIC/FTC/TAF will be allowed during the OLE.

Table 3 Prohibited Therapies

Therapy Type	**Prohibited Therapy(ies)**
Strong and moderate CYP3A inducers	Including, but not limited to: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Enzalutamide Rifabutin Rifampin Rifapentine Mitotane St. John's Wort Herbal remedies *(only those that are strong or moderate CYP3A inducers)* Modafinil Bosentan Nafcillin Lumacaftor Metamizole

Therapy Type	Prohibited Therapy(ies)
Nonstudy ART	All nonstudy antiretrovirals (with the exception of BIC/FTC/TAF during the screening period and intrapartum treatment [eg, IV AZT] in the case of pregnancy) including treatments for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1. Long-acting HIV therapy (eg, cabotegravir, lenacapavir) is not permitted at any time. *Time-limited course of ritonavir as a pharmacokinetic enhancer is permissible (eg, nirmatrelvir/ritonavir for the treatment of COVID-19).*
Immunosuppressive therapies	Immune therapy agents, immune modulators, or other systemic immunosuppressive therapy, including interferon-based treatment for hepatitis *Time-limited courses of corticosteroids (eg, for asthma exacerbation) are permitted.*
Investigational agents	All nonstudy investigational agents including devices *Any agents (eg, vaccine or therapy for COVID-19) approved locally for Emergency Authorized Use, or equivalent, that do not have a known or anticipated DDI with study intervention, are permitted.*
Antiarrhythmics	Dofetilide
Additional prohibited therapies based on ISL	Pentostatin
ART=antiretroviral therapy; AZT=zidovudine; BIC=bictegravir; COVID-19=coronavirus disease caused by severe acute respiratory syndrome coronavirus 2; CYP3A=cytochrome P450 3A; DDI=drug-drug interaction; FTC=emtricitabine; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; IV=intravenous; TAF=tenofovir alafenamide.	

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification of DOR/ISL or BIC/FTC/TAF is allowed during the study (see Section 4.3 for dose justification).

6.7 Intervention After the End of the Study

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

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

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

participants to continue receiving DOR/ISL until it becomes commercially accessible. The details of this mechanism will vary per local regulations.

6.8 Clinical Supplies Disclosure

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

Clinical site personnel and participants will remain blinded through Week 144 while Sponsor personnel will remain blinded through Week 48.

6.9 Standard Policies

At the close of the study after unblinding, a letter is to be sent by the investigator to those participants who received placebos in the image of the comparator product to provide the following advice:

"You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug/vaccine BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE) as much as possible. You did not receive the active drug/vaccine BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE) as manufactured by Gilead Sciences, Inc."

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- After prolonged study intervention interruption that prohibits restarting study intervention (per Section 6.4).

- The participant has a medical condition or personal circumstance (for pregnancy, see Section 8.11.6), which in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.

- The participant chooses to breastfeed.
  Note: Study intervention can continue until breastfeeding is initiated.

- The participant has clinically significant confirmed viremia as defined in Section 4.2.1.1.2. Do not discontinue prior to consultation with the Sponsor when feasible.

- The participant has a new AIDS-defining opportunistic infection as listed in Appendix 9, ie, a Category C condition according to the CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults [Centers for Disease Control (CDC) 1992].Table 4

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

- A participant must be discontinued from study intervention and managed per Section 8.11.5 if any of the criteria in Table 4 are confirmed. If the investigator believes there is an alternative explanation for the result (eg, COVID-19), consultation between the investigator and Sponsor is required when evaluating the participant for discontinuation.

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

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

CD4+=cluster of differentiation 4-positive; DOR=doravirine; ISL=islatravir; N/A=not applicable; OLE=open-label extension; SoA=Schedule of Activities.

[a] Baseline is at Day 1 for all participants during the Base Study and for Group 1 participants during the OLE. Baseline is at Week 144 for Group 2 participants during the OLE (ie, last value before initiation of DOR/ISL).

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

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

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

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent or assent, when applicable, may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are

changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.1.3 Consent for Continuation of Study Intervention During Pregnancy

Upon confirming that a participant is pregnant (Section 8.3.4), the investigator or medically qualified designee and the participant will discuss the potential benefits and risks of continuing (or discontinuing) study intervention (Section 8.11.6). A separate consent is required to continue study intervention (regardless of treatment group or whether participant has been unblinded to treatment assignment) in participants who become pregnant (Section 8.11.6.1). Open-label study intervention (DOR/ISL or BIC/FTC/TAF, depending on study intervention assignment at the time of the confirmatory pregnancy test) will be provided for participants in either treatment group who consent to continue study intervention during pregnancy. Note, participants who become pregnant are not allowed to

switch study intervention at any time during the pregnancy. The investigator or medically qualified designee will explain the consent to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before continuing study intervention. A copy of the informed consent will be given to the participant.

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

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

8.1.1.5 Consent for Open-Label Extension

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history should include information pertaining to the diagnosis of HIV-1 and AIDS (if applicable) and year diagnosed. If the participant has been previously diagnosed with any

AIDS-defining conditions or CD4+ T-cell count <200 cells/mm^3, the condition as well as a corresponding medical history of AIDS must be recorded. In addition, participants' history of smoking and alcohol consumption should be obtained and recorded on the appropriate eCRF. For participants assigned female sex at birth, childbearing potential should be assessed. Menstrual history, contraceptive use, and recent sexual activity should be reviewed for POCBP to exclude potential or early, undiagnosed pregnancy prior to and on Day 1.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

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

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention will be provided per Table 2 and dispensed through the IRT system at visits indicated in the SoA (Sections 1.3.1, 1.3.4, and 1.3.5).

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

8.1.8.1 Timing of Dose Administration

From Day 1 to Week 144, participants will take 2 tablets of blinded study intervention QD at approximately the same time each day (1 tablet from each of 2 containers taken together):

(1) Bottle A: DOR/ISL or matching placebo; and
(2) Bottle B: BIC/FTC/TAF or matching placebo.

From Week 144 to 240 participants will take 1 tablet of open-label DOR/ISL QD at approximately the same time each day.

Study intervention will be taken without regard to food. If more than 1 Bottle A is dispensed, the participant is instructed to use all of the medication in 1 Bottle A before opening another Bottle A (and similarly for Bottle B).

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

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

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

For participants who become pregnant and consent to continue their assigned study intervention, see Section 8.11.6.1.

8.1.9 Discontinuation and Withdrawal

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

Participants who end study intervention while in the OLE (after Week 144 and prior to Week 240) should have a Discontinuation of Study Treatment (OLE) visit performed per the SoA (Section 1.3.5) and should be followed as outlined in the SoA and Section 8.11.3.2.

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

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

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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

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

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

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

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

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 HIV-1 RNA

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

8.2.2 Management of Participants With Viremia

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

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

- If the reflex HIV-1 RNA result is <50 copies/mL, no further action is required.

- If the reflex HIV-1 RNA result is ≥50 copies/mL or there is insufficient sample available for reflex testing, the participant will be asked to return to the clinic in 4 weeks (±1 week) for viremia confirmation (see Section 8.2.2.1 and the SoA in Section 1.3.2).

8.2.2.1 Viremia Confirmation

At the Viremia Confirmation Visit:

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

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

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

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

If it is determined that study intervention discontinuation is appropriate, Early Discontinuation of Treatment and End of Treatment Follow-up visit procedures should be completed (Sections 1.3.2 and 8.11.3) and the participant managed by the investigator per local standard of care.

8.2.2.1.2 HIV-1 Viral Drug Resistance Testing

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

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

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

Participants with confirmed HIV-1 RNA ≥50 and <200 copies/mL should continue study intervention and all regularly scheduled study visits during which HIV-1 RNA levels will be monitored per the SoA (approximately every 3 months). Additional visits may be conducted to monitor HIV-1 RNA levels more frequently than every 3 months, if appropriate, after discussion with the Sponsor.

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

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

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

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

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

Height and weight will also be measured and recorded at the visits specified in the SoA (Section 1.3). Height measurements should be taken using a stadiometer (recommended but not required). Participants should remove their shoes and stand as tall and straight as possible. Weight measurements should be taken per Section 8.3.1.1.

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

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

8.3.1.1 Weight

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

8.3.2 Vital Signs

Vital signs will be measured after approximately 5 to 10 minutes rest and will include pulse, systolic and diastolic BP, body temperature, and RR.

Note: Oral temperatures are preferred but not required.

8.3.3 Electrocardiograms

A local 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA. Results must be available prior to randomization. Sites are to use an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Clinically significant findings must be documented in the source documents and captured in the appropriate eCRF.

If an ECG is performed for any medical reason while the participant is on study intervention or during the follow-up period, any clinically significant changes compared with the baseline ECG must be appropriately reported as per requirements of safety reporting.

8.3.4 Confirmation of Contraception and Pregnancy Testing

POCBP are required to confirm heterosexual abstinence or use of contraception to prevent pregnancy during the base study, optional OLE, and for 42 days after the last dose of study intervention (base study or OLE). POCBP will be tested for pregnancy at each visit as outlined in Sections 1.3 and 5.1, Appendix 2, and Appendix 5.

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

Urine pregnancy test kits will be provided by the central laboratory to perform locally at each visit. In the event of a positive or indeterminant urine pregnancy test result, serum pregnancy testing for confirmation of the pregnancy must be performed by the central laboratory. A duplicate serum pregnancy test may be sent to a local laboratory to expedite results per investigator discretion. Positive urine pregnancy tests (except those from the screening visit), which have been confirmed by serum testing must be reported to the Sponsor using the appropriate eCRF within 24 hours of learning of the event. If a participant becomes pregnant, refer to Section 8.11.6.

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

8.3.5 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Table 18 in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

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

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

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

8.3.6 HBV Assessments

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

All eligible participants must be HBsAg-negative and HBV DNA-negative at screening. Individuals who are anti-HBc-positive and HBV DNA-positive at screening are excluded. Individuals who are anti-HBc-positive, but HBV DNA-negative at screening are eligible to enroll. All participants will have repeat hepatitis B serology and HBV DNA testing at

Weeks 48, Week 96 and Week 144 during the base study (per the SoA Section 1.3.1) and at Week 192 during the OLE (per the SoA Section 1.3.5).

For the duration of the study (base study and OLE), participants who are anti-HBc-positive should be monitored for possible HBV reactivation. Samples will be taken to monitor for HBsAg and HBV DNA per the SoA (Section 1.3). Investigators should also pay close attention to changes from baseline in ALT, AST, bilirubin, and alkaline phosphatase.

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

8.3.7 HCV Assessment

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

8.3.8 Tobacco and Alcohol Assessments

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

8.3.9 Exploratory Clinical Marker Assessments

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

- Blood for inflammatory markers (Section 8.3.9.1)
- Blood for renal function markers (Section 8.3.9.2)
- Urine for renal function markers (Section 8.3.9.2)
- Blood for fasting lipid and metabolic profiles (sample collected as part of Chemistry panel [Section 8.3.5]) (Section 8.3.9.3)
- Blood for energy and metabolism markers (Section 8.3.9.3)
- Waist and hip measurements (Section 8.3.9.4)

- DEXA (Section 8.3.9.5)

8.3.9.1 Inflammation

Blood samples will be collected to evaluate the inflammatory and thrombotic response as measured by the following laboratory markers, as indicated in the SoA (Section 1.3.1):

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

8.3.9.2 Renal Function

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

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

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

8.3.9.3 Fasting Lipid and Metabolic Profiles

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

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

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

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

8.3.9.4 Waist, Hip and BMI Measurements

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

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

8.3.9.5 DEXA Assessments

DEXA images to monitor fat distribution and BMD should be collected from all participants/sites willing and able to have the test performed and according to country law (Section 1.3.1). These participants will undergo total body DEXA scans for BMD of the spine and hip as well as peripheral and trunk fat. Participants will not be excluded from participation in the study if unwilling/unable to have DEXA images performed.

Only those participants who are confirmed eligible to be randomized will undergo DEXA images for BMD of the spine and hip as well as peripheral and trunk fat. For Day 1 (baseline), DEXA images should be performed after eligibility is confirmed and may be performed up to 45 days after randomization. The DEXA images at subsequent visits should be performed ±45 days of the scheduled visit. Only participants with valid baseline DEXA images should have DEXA images performed at subsequent visits as indicated in the SoA (Section 1.3). If DEXA scans cannot be performed within the protocol-specified time window or at a site approved by the central imaging reader, consultation is required between the investigator and the Sponsor to confirm the clinical appropriateness of performing further testing.

DEXA images will be evaluated by a central imaging reader. For clinical management of the participant, the DEXA images should be concurrently reviewed and interpreted locally by a qualified individual. Clinically significant findings noted in the local interpretation of the baseline DEXA images should be recorded in the participant's medical history. Refer to the Site Imaging Manual for additional details regarding DEXA procedures including participant preparation instructions to be considered before DEXA imaging.

DEXA should not be performed on pregnant participants.

8.3.10 Administration of Patient Questionnaires

Participants will complete 3 PRO questionnaires to be administered in the following order: EQ 5D 5L, HIVTSQ, and HIV SI/SDM, as specified in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). Participants are to complete the questionnaires on their own at the site on paper during the appropriate study visit (see SoA) prior to being seen by the investigator, discussing any medical conditions with the study personnel, or receiving any medical results. The questionnaires should not be administered to participants who are unable to complete

questionnaires unassisted or for whom native language translations of the questionnaires are unavailable.

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

PROs are not administered after Week 96.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. 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). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

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

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

This section is not applicable to the study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

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

No specific information is available on the treatment of overdose.

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma ISL

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

Investigational PK samples will be collected (except during pregnancy or when the participant has been unblinded and is known to be taking BIC/FTC/TAF) as outlined in the SoA (Section 1.3). Investigational ISL PK samples will be collected irrespective of time of last dose. The time of last dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation. Analysis of these samples will be performed by the Sponsor as needed.

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

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

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

Table 6 Collection of Population PK Samples

Study Visit	Sample Time Relative to Dose of Study Intervention[a]
Day 1	Predose
Week 4	Daytime dosing: Predose AND within 0.5 to 2 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
Week 12	Irrespective of time of last dose
Week 24	Irrespective of time of last dose
Week 48	Irrespective of time of last dose

PK=pharmacokinetic(s).
[a] Time of last dose and time of PK sample collection must be documented for all samples.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

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

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

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

documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

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

8.9 Future Biomedical Research Sample Collection

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

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

8.10 Health Economics Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening/Rescreening

8.11.1.1 Screening

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

8.11.1.2 Rescreening

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

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

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

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

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

If a participant had a baseline Day 1 DEXA scan during the original screening period and >45 days have elapsed, the Day 1 DEXA should be repeated. If ≤45 days have elapsed since the DEXA, it is not necessary to repeat the Day 1 DEXA scan during rescreening.

Participants who were previously considered screen failures because the duration of BIC/FTC/TAF was <3 consecutive months are allowed to rescreen if they have continued to receive BIC/FTC/TAF therapy with documented viral suppression (HIV-1 RNA <50 copies/mL) for ≥3 consecutive months before the rescreening visit and have no history of prior virologic treatment failure on any past or current regimen.

8.11.2 Treatment Period

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

8.11.2.1 Fasting

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

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

8.11.2.2 End of Base Study Week 144 Visit

Procedures for the blinded treatment period (base study) are to be conducted per the SoA (Section 1.3.1). Week 144 represents the end of the base study and the end of blinded treatment administration. Prior to the end of the base study/Week 144 visit, site staff should proactively discuss the potential plan for treatment to facilitate either a transition to locally available ART or DOR/ISL in the optional OLE. For participants who are entering the OLE, the Week 144 visit serves as the start of the OLE, and open-label DOR/ISL will be dispensed and participants will follow procedures outlined in SoA (Section 1.3.5).

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

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

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

8.11.2.3 Optional Open Label Extension (Week 144 to Week 240)

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

A participant entering the OLE must meet all of the following criteria:

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

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

The Week 240 Visit represents the end of treatment in the study.

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

8.11.3 Participants Who Discontinue Study Intervention

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

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

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

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

8.11.3.1 Discontinuation of Treatment

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

Early Discontinuation (Base Study)

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

Discontinuation (OLE)

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

8.11.3.2 End of Treatment Follow-up

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

8.11.4 Viremia Confirmation

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

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

To meet the protocol-defined discontinuation criteria in the base study or the OLE, participants must have a confirmed total lymphocyte count or CD4+ T-cell count that indicates a specified decrease on 2 consecutive measurements 10 to 14 weeks apart. A minimum interval of 10 weeks between consecutive tests is required to meet discontinuation criteria. The confirmation visit must occur within 10 to14 weeks after the initial decrease (or at the next scheduled visit), as specified in the SoA (Section 1.3.3) and Table 4.

Management of Participants Who Discontinue Study Intervention Due to Specified Decreases in Total Lymphocyte Count or CD4+ T-cell Count

Participants discontinued from study intervention due to specified decreases in total lymphocyte count or CD4+ T-cell count (Section 7.1 and Table 4) should undergo assessments for the Discontinuation of Treatment Visit and the End of Treatment Follow-up visit (regardless of treatment assignment) as specified in the SoA (Section 1.3.3, 1.3.5). After discontinuation from study intervention, participants will be managed for treatment of their HIV-1 infection per local standard of care. Consult with Sponsor prior to discontinuation or unblinding if the investigator believes there is an alternative explanation for the result (eg, COVID-19). No subsequent monitoring is required for participants in the BIC/FTC/TAF group who meet discontinuation criteria in Table 4.

Monitoring for Participants Receiving DOR/ISL

After completion of the Discontinuation of Treatment Visit (base study or OLE) and the End of Treatment Follow-up visit, participants who discontinued for confirmed decreases in CD4+ T-cell count or lymphocyte counts (per Table 4), should have monitoring visits every 10 to 14 weeks (Section 1.3.3). Participants should be monitored until the total lymphocyte count or CD4+T-cell count no longer meet the criteria in Table 4 at 2 consecutive visits. If

conditions that impact lymphocytes arise during the follow-up monitoring period, and are expected to persist, monitoring may be stopped.

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

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

8.11.6 Clinical Management of Participants Who Become Pregnant

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

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

Participants with a confirmed pregnancy prior to Week 144 should be unblinded by the investigator (Section 8.1.10). Upon Sponsor consultation and approval, unblinding is not required in participants who will not have a continuing pregnancy (ie, pregnancy termination or nonviable pregnancy).

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

- The appropriateness of continuing study intervention based on available data and local standard-of-care guidelines (where allowed by local regulations, health authorities, and ethics committees). For participants receiving BIC/FTC/TAF, the investigator should refer to the local product circular and local guidelines to determine if treatment may be continued. **Documented informed consent must be obtained to continue study intervention regardless of treatment assignment** (Section 8.1.1.3)

- Joining a pregnancy registry (the Antiretroviral Pregnancy Registry), which collects information about the outcome of the pregnancy, if applicable

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

- Intentions for breastfeeding (Section 8.11.6.3)
- Consenting to infant safety data collection per Sections 8.1.1.4 and 8.11.6.4

8.11.6.1 Continuing Study Intervention in Pregnancy

Participants who become pregnant and consent to continue their assigned study intervention (Section 8.1.1.3) will be transitioned to open-label study intervention (DOR/ISL or BIC/FTC/TAF) and should complete all remaining protocol-specified visits and procedures per the regular schedule in the applicable SoA (Section 1.3), with the following exceptions:

- Only participants receiving DOR/ISL will have PK samples collected (per the timing in Table 7). Participants in the BIC/FTC/TAF group will not have PK collection.
- DEXA scans will not be performed for either group.
- Participants on DOR/ISL who are pregnant at Week 144 will have the opportunity to continue into the OLE.
- Participants on BIC/FTC/TAF who are pregnant at Week 144 will continue on BIC/FTC/TAF through the postpartum visit and will then complete the study.

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

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

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

- Clinical safety laboratory assessments

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

For participants who are pregnant at the last regularly scheduled study visit (Week 144 [base study] or Week 240 [OLE]), their visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum and, as applicable, a 42-day follow-up period with an End of Treatment Follow-up visit (Section 1.3.4). After completion of the pregnancy, the participant will have completed the study after completing either the postpartum visit (if the participant chooses to breastfeed) or the End of Treatment Follow-up visit (if the participant does not choose to breastfeed and completed the 42-day follow-up period) (Section 1.3.4). Participants on DOR/ISL at the completion of the pregnancy will have continued access to DOR/ISL through the OLE, until DOR/ISL becomes commercially accessible per Section 6.7. Participants on BIC/FTC/TAF at the completion of their pregnancy will have their last dispensing of study intervention at their 3rd trimester (Pregnancy 3) visit per the SoA (Section 1.3.4).

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

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

Participants who routinely take their DOR/ISL during the day will have a predose and 2 postdose samples collected per Table 7. Participants who routinely take their DOR/ISL in the evening should continue to do so and will have only 1 sample collected at the 2nd Trimester, 3rd Trimester, and Postpartum visits, irrespective of the time of the last dose. Time of last dose and time of PK sample collection must be documented for all samples. The time of last dose of study intervention taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

Table 7 Collection of Population PK Samples During Pregnancy and Postpartum

Study Visit	Sample Time Relative to Dose of DOR/ISL[a]
1st Trimester[b]	Daytime dosing: Predose OR Evening dosing: Irrespective of time of last dose
2nd Trimester	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
3rd Trimester	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose
Postpartum[c]	Daytime dosing: Predose AND within 0.5 to 2 hours AND within 4 to 6 hours postdose OR Evening dosing: Only 1 sample irrespective of time of last dose

DOR=doravirine; ISL=islatravir; PK=pharmacokinetic(s).
[a] Time of last dose and time of PK sample collection must be documented for all samples.
[b] Collect at the scheduled 1st Trimester visit after a participant reports gravid status. (May not be collected if participant does not learn of their pregnancy until after the first trimester.)
[c] Postpartum visit ≤8 weeks after delivery.

8.11.6.2 Discontinuing Study Intervention for Pregnancy

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

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

8.11.6.3 Participants Who Choose to Breastfeed

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

8.11.6.4 Infant Safety Data Collection

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

Infant SAEs, including perinatal HIV-1 infection, will be collected as per Section 8.4.1 and should be reviewed at the participant's scheduled study visits that occur during this time. Infant safety data collection will be captured if exposure to study intervention occurs during pregnancy.

8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection

Time Point	At Birth[a]	1-Year After Birth[a,b]
Visit Name	NA	Infant Follow-up-1
Administrative and Safety Procedures		
Infant Informed Consent		X[c]
Gestational Age at Birth	X	
Apgar Score	X	
Length	X	X
Weight	X	X
Head Circumference	X	X
Directed Pediatric Examination	X	
Concomitant Medications Review[d]	X	X
Review Infant SAEs[e]	----------X----------	

HIV=human immunodeficiency virus; NA=Not applicable; SAE=serious adverse event.

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

[b] If a participant withdraws from the study, data for this time point 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 the participant's regularly scheduled study visits.

9 STATISTICAL ANALYSIS PLAN

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

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL 100 mg/0.25 mg) Once-Daily in Participants With HIV-1 Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)
Treatment Assignment	Approximately 501 participants will be randomly assigned in a 2:1 ratio to receive either DOR/ISL (Group 1) or BIC/FTC/TAF (Group 2). Clinical site personnel and participants will remain blinded to study intervention assignments through Week 144, while Sponsor personnel will remain blinded through Week 48.
Analysis Populations	Efficacy: FAS, PP, and Resistance Analysis Subset Safety: APaT
Primary Endpoints	1. Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 2. Percentage of participants who experience AEs and percentage of participants who discontinue study intervention due to AEs through Week 48
Secondary Endpoints	1. Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96 and Week 144 2. Percentage of participants with HIV-1 RNA <200 and <50 copies/mL at Week 48, Week 96 and Week 144 3. Mean change from baseline in CD4+ T-cell count at Week 48, Week 96 and Week 144 5. Viral resistance-associated substitutions 6. General safety and tolerability through Week 144

Statistical Methods for Key Efficacy Analyses	For the primary hypothesis (H1), DOR/ISL will be considered non-inferior to BIC/FTC/TAF if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the between-treatment difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 (DOR/ISL minus BIC/FTC/TAF) is less than 4 percentage points (non-inferiority margin). The CI will be based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The FDA snapshot algorithm [Food and Drug Administration (CDER) 2015] will be used to handle missing data for the analysis of the primary efficacy hypothesis.
Statistical Methods for Key Safety Analyses	For overall safety endpoints, specific AEs, and safety topics of special interest that meet predefined threshold rules, point estimates and 2-sided nominal 95% CIs for the differences between treatment groups (DOR/ISL minus BIC/FTC/TAF) in the percentages of participants with events will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
IAs	An IA will be performed when approximately 30% of participants have completed the Week 24 visit assessments. Results will be reviewed by an eDMC. All available efficacy and safety data for participants enrolled at the time of the Week 24 IA will be reviewed, and the data from the first 30% of participants who reach Week 24 will be included in the futility assessment. The nonbinding futility criterion is if the upper bound of the 2-sided 95% CI for the treatment difference (DOR/ISL minus BIC/FTC/TAF) in the percentage of participants with Week 24 HIV-1 RNA ≥200 copies/mL is greater than 8 percentage points, consideration may be given to stop the study. Additional details are provided in Section 9.7. In addition, the eDMC will periodically review efficacy and safety data (per the timelines specified in the eDMC charter).
Multiplicity	The Type 1 error rate over the multiple efficacy hypothesis tests will be controlled by a sequential testing procedure. A formal futility analysis at Week 24 is planned as described in Section 9.7, a small amount of alpha (α=0.00001) will be allocated for this IA, purely for statistical rigor. The following efficacy hypotheses will be tested sequentially at a 1-sided 2.499% Type 1 error rate in the following order: Primary efficacy hypothesis (H1) testing non-inferiority of DOR/ISL to BIC/FTC/TAF at Week 48 Primary efficacy hypothesis (H2) testing superiority DOR/ISL to BIC/FTC/TAF at Week 48 Secondary efficacy hypothesis (H3) testing superiority of DOR/ISL to BIC/FTC/TAF at Week 96 Secondary efficacy hypothesis (H4) testing superiority of DOR/ISL to BIC/FTC/TAF at Week 144 These hypotheses will be assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at the indicated time points. Testing will stop with the first of these tests failing to reach statistical significance and all subsequent tests would not be considered for statistical significance. In this way, the overall 1-sided 2.5% Type 1 error rate in testing these hypotheses is strongly controlled.

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

9.2 Responsibility for Analyses/In-house Blinding

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

Day 1 through Week 48 will be conducted as a double-blind study under in-house blinding procedures. The official, final database for Day 1 through Week 48 will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The clinical database and Sponsor personnel directly involved in the Week 48 analysis and reporting will become unblinded at the time of the Week 48 database lock, although study participants and site personnel will remain blinded until Week 144.

PK data may be unblinded early for the purpose of preparing a population PK model. A separate team from the protocol team will be unblinded for the purpose of preparing the PK model. Efficacy and safety data will not be unblinded for the purpose of preparing the PK model. Interim data or results will not be shared with the protocol team before unblinding of the Sponsor at the Week 48 database lock.

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

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

9.3 Hypotheses/Estimation

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

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

9.4 Analysis Endpoints

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

9.4.1 Efficacy/Pharmacokinetics Endpoints

9.4.1.1 Efficacy Endpoints

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

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

A PCR assay with a lower level of detection of <50 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The primary objective will be assessed based on the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48. A secondary objective will assess the percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 96 and 144.

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

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

Secondary objectives addressing the antiretroviral activity following a switch to DOR/ISL will be assessed based upon the percentage of participants with HIV-1 RNA <200 copies/mL at Weeks 48, 96 and 144, as well as the percentage of participants with HIV-1 RNA <50 copies/mL at Weeks 48, 96 and 144.

The percentage of participants with <50 copies/mL and <200 copies/mL will be summarized over time for participants who consent to the OLE.

Change From Baseline in CD4+ T-cell Count

The mean change from baseline in CD4+ T-cell count will be calculated at each time point at which CD4+ T-cell count is collected. A secondary objective will compare the mean change from baseline in CD4+ T-cell count between treatment groups at Weeks 48, 96, and 144.

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

The change from baseline in CD4+ T-cell count during the OLE will be analyzed over time for participants who consent to the OLE. The baseline for Group 2 will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

Clinically Significant Confirmed Viremia

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

Viral Resistance-associated Substitutions

Participants who meet the definition of clinically significant confirmed viremia (Section 4.2.1.1.2), or who discontinue study intervention for another reason and have HIV-1 RNA ≥200 copies/mL at the time of discontinuation, will be assessed for development of viral drug resistance. Among such participants, those with HIV-1 RNA ≥400 copies/mL will be included in the resistance analyses. In addition, anyone for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load, will also be included in the resistance analyses. The resistance analyses will count the number of participants in each treatment group who have evidence of resistance-associated substitutions. The data will be summarized with primary interest at Weeks 48, 96, 144, and during the OLE.

9.4.1.2 Pharmacokinetic Endpoints

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

9.4.2 Safety Endpoints

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

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

Adverse Events

The following clinical and laboratory AEs will be summarized: 1) participants with at least 1 AE; 2) participants with at least 1 drug-related AE; 3) participants with at least 1 SAE; 4) participants with at least 1 Grade 3 or 4 AE; 5) participants with at least 1 serious and drug-related AE; 6) participants with at least 1 AE, which is both Grade 3 or 4 and drug-related; 7) participants who discontinued study intervention due to an AE; 8) participants who discontinued study intervention due to a drug-related AE; and 9) participants with an AE leading to death.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory test results, participants must have both a baseline and a post-randomization on-treatment measurement to be included. Participants' laboratory values (based on their most abnormal laboratory test values in the direction of interest while on study intervention) will be classified as to whether they fall outside of the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3) [National Institute of Allergy and Infectious Diseases 2017].

Weight, Laboratory Markers, and Bone Mineral Density

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

Total Lymphocyte Count

The mean change from baseline in total lymphocyte count will be calculated at each time point at which lymphocyte counts are assessed. The mean change from baseline in total lymphocyte count between treatment groups will be conducted at Weeks 48, 96, and 144.

For analyses of the mean change from baseline in lymphocyte, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available.

The change from baseline in lymphocytes during the OLE will be analyzed over time for participants who consent to the OLE. The baseline for Group 2 will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

Definition of Baseline Measurements for Safety Analyses

For analyses of changes from baseline in safety parameters (eg, weight, vital signs, laboratory, and BMD), baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available.

For analyses of DEXA parameters (ie, bone density and body composition), if no Day 1 or screening values are available, the earliest measurement within 45 days after the start of study intervention will be used as baseline, when available.

The change from baseline in safety parameters during the OLE will be analyzed over time for participants who consent to the OLE. The baseline for Group 2 will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

9.4.3 Patient-reported Outcome Endpoints

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

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

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

FAS

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

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

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

PP Analysis Population

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

- Receipt of any ongoing prohibited therapies listed in Table 3
- Nonadherence to study intervention: <95% drug compliance rate (see Section 9.11)
- Pregnancy
- Unblinding for any reason (eg, due to HBV reactivation, accidental unblinding, etc)

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

The final determination of major protocol deviations, and thereby the composition of the Per-Protocol population, will be made prior to unblinding of the Sponsor at the Week 48 database lock and will be documented. A participant who deviates from the protocol at randomization (eg, violation of certain inclusion or exclusion criteria, such as the use of a prohibited prior treatment) will be excluded from the Per-Protocol population. For participants who have major deviations from the protocol during the study (eg, taking a

prohibited concomitant medication), data obtained after the deviation will be excluded from analysis. As such, the composition of the Per-Protocol population may vary by the analysis time point, based on the number of participants who satisfy the Per-Protocol criteria at that time point. Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the Per-Protocol population.

FAS for the OLE (FAS-E)

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

Resistance Analysis Subset

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

9.5.2 Safety Analysis Populations

APaT

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

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. The composition of the APaT population may vary based on the availability of baseline measurements for the relevant safety parameters of interest.

APaT-E

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

9.6 Statistical Methods

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

Definition of On-treatment Measurements for Efficacy Analyses

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

Definition of On-treatment Measurements for Safety Analyses

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

9.6.1 Statistical Methods for Efficacy Analyses

Time Windows

Definitions of time windows (day-ranges) and target days for the scheduled study visits, which will be used for all statistical analyses by time point, are shown in Table 8. The last available on-treatment measurement within a window will be used for analyses at a specific time point, unless otherwise specified. Results from additional time points beyond Week 96 may be summarized, and day-range rules for determining the analysis time windows will follow the same pattern where the ranges start and end at the midpoints between target days.

Table 8 Definitions of Study Time Points

Treatment Phase	Treatment Period	Visit	Day-Range[a]	Target Day[a]
Pretreatment	Baseline	Day 1	≤1	1
Treatment	Blinded Intervention: DOR/ISL or BIC/FTC/TAF	Week 4	≥2 and ≤56	29
		Week 12	≥57 and ≤126	85
		Week 24	≥127 and ≤210	169
		Week 36	≥211 and ≤294	253
		Week 48	≥295 and ≤378	337
		Week 60	≥379 and ≤462	421
		Week 72	≥463 and ≤546	505
		Week 84	≥547 and ≤630	589
		Week 96	≥631 and ≤714	673
		Week 108	≥715 and ≤798	757
		Week 120	≥799 and ≤882	841
		Week 132	≥883 and ≤966	925
		Week 144	Participants who do not consent to enroll in the OLE: ≥967 and ≤1051 Participants who consent to enroll in the OLE: ≥967 and ≤the last day of blinded intervention	1009
Treatment Extension[b]	Open-label Intervention: DOR/ISL	Week 148[c]	Group 1: NA Group 2: ≥first day of open-label intervention and ≤1106	Group 1: NA Group 2: 1037
		Week 168	Group 1: ≥first day of open-label intervention and ≤1260 Group 2: ≥1107 and ≤1260	Group 1 and Group 2: 1177
		Week 192	1261≥ and ≤1428	1345
		Week 216	1429≥ and ≤1596	1513
		Week 240	1597≥ and ≤1764	1681

BIC=bictegravir; DOR=doravirine; FTC=emtricitabine; ISL=islatravir; OLE=Open-label extension; TAF=tenofovir alafenamide.
[a] Day-ranges and target days are computed relative to the first day of study intervention.
[b] The treatment extension phase visits apply only to participants who consent to the OLE.
[C] The Week 148 visit applies only to participants in Group 2.

Missing Data Approaches

Three approaches will be used to handle missing HIV-1 RNA values. The primary approach for analysis of the percentage of participants with HIV-1 RNA ≥50 copies/mL is the FDA "snapshot" algorithm [Food and Drug Administration (CDER) 2015]. Using this approach, for data collected in a given analysis window (see Table 8), the last available measurement while the participant is on treatment is used to define the virologic outcome. Virologic outcome is defined according to the following categories:

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

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

  - Who have the last available on-treatment HIV-1 RNA measurement ≥50 copies/mL within the time point of interest analysis window specified in Table 8.

  - Who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window and:

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

- **No Virologic Data in Specified Analysis Time Window**: this includes participants who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window specified in Table 8 because of the following:

  - Discontinued study intervention due to AE or death: this includes participants who discontinued study intervention because of an AE or death at any time point from Day 1 through the analysis window if this resulted in no on-treatment HIV-1 RNA measurements during the specified window and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL. In addition, this category will include participants who discontinued study intervention because of an AE or death and had no on-treatment HIV-1 RNA measurements during the entirety of the study.

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

AE/death and had no on-treatment HIV-1 RNA measurements during the entirety of the study.

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

For the primary evaluation of non-inferiority as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL, the parameter for evaluation is the number of participants classified as "HIV-1 RNA ≥50 copies/mL" according to the FDA snapshot algorithm defined above, divided by the number of participants in the FAS. For the secondary endpoint involving those with HIV-1 RNA <50 copies/mL, the parameter for evaluation is the number of participants classified as "HIV-1 RNA <50 copies/mL" according to the FDA snapshot algorithm, divided by the number of participants in the FAS. The percentages of participants with HIV-1 RNA <50 copies/mL will be summarized by treatment groups at all scheduled study visit timepoints. Similar logic will also be used to define the percentage of participants with HIV-1 RNA <200 copies/mL in accordance with the relevant secondary endpoint.

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

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

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

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

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

Non-inferiority of DOR/ISL (Group 1) to BIC/FTC/TAF (Group 2) with respect to the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 will be evaluated using the unstratified method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]. For the evaluation of the primary hypothesis at Week 48, a margin of 4 percentage points is used to define the non-inferiority of a switch to DOR/ISL at Day 1 to the continuation of baseline BIC/FTC/TAF for 48 weeks; non-inferiority will be concluded if the upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL (Group 1 minus Group 2) is less than 4 percentage points. The choice of non-inferiority margin is based on the amount of virologic failure that is clinically acceptable; with an anticipated virologic failure rate of approximately 2%, a stringent margin of 4 percentage points is clinically acceptable.

Superiority of Group 1 to Group 2 with respect to the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 and 96 will also be evaluated using the unstratified method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]. For the evaluation of the efficacy superiority hypotheses, superiority will be concluded if the upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL (Group 1 minus Group 2) is less than 0 percentage points.

To summarize virologic response over time, the difference in percentages between treatment groups at each time point through Week 144 will be estimated and the associated 2-sided 95% CI will be derived in a similar fashion to that described for the primary efficacy analysis.

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

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

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

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA <200 copies/mL and the percentage of participants with HIV-1 RNA <50 copies/mL in the base study. These endpoints will be summarized by treatment group at each time point, with primary interest at Weeks 48, 96 and 144 by comparing Group 1 and Group 2. For these time points of interest, the difference in percentages between treatment groups (Group 1 minus Group 2) and the associated 2-sided 95% CI will be calculated using the unstratified Miettinen and Nieminen method [Miettinen, O. and Nurminen, M. 1985]. Supportive analyses using the M=F and OF approaches (as defined above) will also be presented.

In the OLE the percentage of participants with HIV-1 RNA <50 and <200 copies/mL will be summarized in a similar manner as for those with HIV-1 RNA ≥50 copies/mL.

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

Change From Baseline in CD4+ T-cell Count

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

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

The cLDA method assumes that data are MAR. In this study, it is expected that MAR/MCAR mechanisms will underlie most of the missingness, and the proportion of data MNAR, driven solely by unobserved values of the study endpoints, will be small. Reasons for discontinuation from the study may include lack of efficacy, death, withdrawal of consent, protocol deviations, lost to follow-up (eg, relocation), etc. Missing data caused by a participant's relocation are likely to be MCAR. Missing data caused by discontinuations due to lack of efficacy may belong to MAR because this type of discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If the assigned study intervention in large part determines the loss of data for these other reasons, the mechanism may be close to MAR, because the intervention assignment is an observed variable and included in the analysis model.

The estimates of the between-group differences in the mean change from baseline in CD4+ T-cell count will not be subject to an absolute criterion for similarity as the clinical interpretation of treatment difference is dependent upon the absolute values at baseline and the magnitude and direction of the CD4+ T-cell count changes observed in each treatment arm.

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

During the OLE, the change from baseline in CD4+ T-cell count will be summarized separately using descriptive statistics based on the DAO approach. For assessments of change from baseline in Group 2 during the OLE, the baseline measurement will be taken as the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

Clinically Significant Confirmed Viremia

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

Viral Resistance-associated Substitutions

The number of participants in the resistance analysis subset with genotypic and/or phenotypic resistance to each study intervention will be summarized for each treatment group with primary interest at Weeks 48, 96, 144, and timepoints of interest during the OLE.

Unblinding of Participants During the Base Study

Given the objective nature of the HIV-1 RNA efficacy endpoint, if a participant becomes unblinded during the base study for any reason (eg, due to a safety event, acute infection/reactivation of HBV or pregnancy that requires unblinding, or accidental unblinding), such participants will not be treated as treatment failures in the primary efficacy analyses on the FAS population due to the unblinding alone.

HBV Acute Infection/Reactivation

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

Participants Who Discontinue Due to Pregnancy or Breastfeeding

For participants who become pregnant and choose to discontinue study intervention or participants who choose to breastfeed and must discontinue study intervention in the base

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

Table 9 summarizes the key efficacy analyses of the base study.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypotheses H1 and H2				
Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48	P	M&N	FAS	Snapshot
	S	M&N	PP	OF
Secondary Hypotheses H3 and H4				
Percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 96 and 144	P	M&N	FAS	Snapshot
	S	M&N	PP	OF
Secondary Endpoints				
Percentage of participants with HIV-1 RNA <200 and <50 copies/mL at Weeks 48, 96 and 144	P	M&N	FAS	Snapshot
	S	M&N	FAS	M=F
	S	M&N	PP	OF
Mean change from baseline in CD4+ T-cell count at Weeks 48, 96 and 144	P	cLDA[b]	FAS	Model-based

cLDA=constrained longitudinal data analysis; FAS=Full Analysis Set; HIV-1=human immunodeficiency virus type 1; M=F=missing equal to failure; M&N=Miettinen and Nurminen; OF=Observed Failure; PP=Per-Protocol; RNA=ribonucleic acid.

[a] P=primary approach; S=supportive approach.

[b] The cLDA model will include terms for treatment group, time, and the interaction of time-by-treatment group.

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

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results and vital signs. For analyses of safety by time point, the same analysis windows as specified in Table 8 will be used, unless otherwise specified. Analysis windows for DEXA measurements are provided in Table 10.

Table 10 Definition of Study Time Points for DEXA Analyses

Treatment Phase	Treatment Period	Visit	Day-Range[a]	Target Day[a]
Pretreatment	Baseline	Day 1	≤45	1
Treatment	Blinded Intervention: DOR/ISL or BIC/FTC/TAF	Week 48	≥253 and ≤420	337
		Week 96	≥589 and ≤756	673
		Week 144	≥925 and ≤1092	1099

BIC=bictegravir; DEXA=dual x-ray absorptiometry; DOR=doravirine; FTC=emtricitabine; ISL=islatravir; TAF=tenofovir alafenamide.

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

9.6.2.1 Overall Safety Assessment

The overall safety evaluation in the base study will include a summary by treatment group of the number and percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 or 4 AE, with an AE that is both serious and drug-related, with an AE that is both Grade 3 or 4 and drug-related, who discontinued study intervention due to an AE, who discontinued study intervention due to a drug-related AE, and with an AE resulting in death. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with the event will be provided. The CIs for the between-group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

The number and percentage of participants with specific AEs will also be provided. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with specific AEs will be provided for AEs that occur in at least 8 participants in the DOR/ISL treatment group or at least 2 participants in the BIC/FTC/TAF group. These thresholds for the numbers of events were chosen because the 95% CI for the between-group difference in percent incidence will always include 0 when fewer participants per group have events and thus would add little to the interpretation of potentially meaningful differences. The CIs for the between-group differences will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

CIs that are not adjusted for multiplicity should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Point estimates and 2-sided 95% CIs for the differences between treatment groups (Group 1 minus Group 2) in the percentages of participants with safety parameters that meet predefined limits of change will be provided based on the same criteria used above for specific AEs.

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

For the mean change from baseline to Weeks 48, 96 and 144 in weight, the treatment difference (Group 1 minus Group 2) and corresponding 2-sided 95% CI will be estimated using ANCOVA models adjusted by baseline weight, sex at birth, race, and treatment group.

For the mean change from baseline to Weeks 48, 96, and 144 in total lymphocyte count, the treatment difference (Group 1 minus Group 2) and corresponding 2-sided 95% CI will be estimated using ANCOVA models adjusted by baseline value and treatment group.

For lipid profile analyses, participants who receive lipid-lowering therapy at baseline will be excluded from all analyses. For participants who initiate lipid-lowering therapy during the study, the last lipid measurement before initiating the lipid-lowering therapy will be carried forward. For participants who become pregnant, lipid data collected after the estimated date of conception will be excluded. Missing lipid data will not be imputed; as such, any participant with a missing value will be excluded from the analyses. The percentages of participants who initiate or modify lipid-lowering therapy prior to Weeks 48, 96 and 144 will be summarized by treatment group. Additional details will be provided in the sSAP.

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

9.6.2.2 Assessment of Safety Topics of Special Interest

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

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

9.6.2.3 Handling of Missing Data and Pregnancies in Safety Analyses

Missing safety parameters, unless otherwise specified, will not be imputed; as such, any participant with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. Baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available. If no baseline result is available for a given analysis, that participant will not be included in the analysis. Safety data for participants who consent to enter the OLE at Week 144 will be summarized from Week 144 to Week 240. For the assessment of change from baseline in Group 2 at

Week 240, baseline will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement before the switch to DOR/ISL).

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

Table 11 summarizes the analysis strategy for safety endpoints in the base study.

Table 11 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI
Overall Safety Assessment	Any AE	X	X
	Any drug-related AE	X	X
	Any SAE	X	X
	Any Grade 3 or 4 AE	X	X
	Any serious drug-related AE	X	X
	Any Grade 3 or 4 drug-related AE	X	X
	Discontinued study intervention due to an AE	X	X
	Discontinued study intervention due to a drug-related AE	X	X
	AE resulting in death	X	X
	Specific AEs	X	X[a]
	SOCs, PDLCs	X	X[a]
	Mean Change from Baseline (Laboratory, Vital Signs, Body Composition, and Lymphocyte Parameters)	X	X
Assessment of Safety Topics of Special Interest	Any Opportunistic Infection	X	X
	Specific Opportunistic Infections and Corresponding SOCs	X	X[a]

AE=adverse event; CI=confidence interval; PDLC=predefined limit of change; SAE=serious adverse event; SOC=system organ class.

[a] The between-group 95% CI will only be provided for events that occur in at least 8 participants in Group 1 or at least 2 participants in Group 2.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

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

9.7 Interim Analyses

Study enrollment is likely to be ongoing at the time of the IA. Blinding to treatment assignment will be maintained at all investigational sites until Week 144. The information regarding participants' treatment groups from IA results will not be shared with the investigators prior to week 144.

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

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

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

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

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

  Note: For such participants, if the HIV-1 RNA value of ≥200 copies/mL is not confirmed at the subsequent assessment (ie, the participant does not meet the criteria for clinically significant confirmed viremia [Section 4.2.1.1.2]), their virologic outcome will be reassessed for the primary efficacy analysis (Section 9.6.1).
- Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis visit window specified in Table 8 and

  - Discontinued study intervention prior to or in the Week 24 analysis visit window due to lack of efficacy or clinically significant confirmed viremia (Section 4.2.1.1.2), or

  - Discontinued study intervention prior to or in the Week 24 analysis visit window due to reasons other than lack of efficacy/clinically significant confirmed viremia and have their last on-treatment HIV-1 RNA measurement ≥50 copies/mL.

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

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

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

criterion. However, with 4 failures in Group 1 and 1 failure in Group 2, the treatment difference is 2% and the upper bound of the between-group 95% CI is 8.25, which meets the futility criterion. Additional details on the operational characteristics of the futility criterion are provided in Section 9.9.1.

The eDMC will review accumulating efficacy and safety data at regular intervals throughout the study duration, or at modified intervals based on the recommendation of the eDMC. The eDMC will recommend steps to ensure the safety of study participants and the integrity of the study as needed.

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

Since the hypotheses listed in Section 3 will be tested only at Week 48 or Week 96 (and not at the Week 24 IA nor any periodic review of data by the eDMC) and as there is no plan to stop the trial early for a positive efficacy finding, testing of H1, H2, H3, and H4 will not be adjusted for multiplicity on account of any eDMC reviews. The multiplicity strategy for hypothesis testing is described in Section 9.8.

While the study remains blinded to the Sponsor (ie, until the Week 48 database lock), treatment-level results from all IAs will be provided to the eDMC by the external unblinded statistician. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

The Sponsor may have a limited unblinded team not involved with day-to-day conduct of the study that will review unblinded data for internal programmatic decision-making. Participants and all field and study-site personnel will remain blinded throughout the study.

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

9.8 Multiplicity

As noted in Section 9.7, an eDMC will convene at routine intervals to monitor efficacy and safety. A formal futility analysis at Week 24 is planned as described in Section 9.7; a small among of alpha (α=0.00001) will be allocated for this IA, purely for statistical rigor.

Though the eDMC will convene at routine intervals to monitor efficacy and safety, there are no other planned for futility. The following efficacy hypotheses will be tested sequentially at a 1-sided 2.499% Type 1 error rate sequentially:

1. Primary efficacy hypothesis (H1) testing non-inferiority of Group 1 to Group 2 as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48.
2. Primary efficacy hypothesis (H2) testing superiority of Group 1 to Group 2 as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48.
3. Secondary efficacy hypothesis (H3) testing superiority of Group 1 to Group 2 as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96.
4. Secondary efficacy hypothesis (H4) testing superiority of Group 1 to Group 2 as assessed by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 144.

Testing will stop with the first of these tests failing to reach statistical significance, and all subsequent tests would not be considered for statistical significance. In this way, the overall 1-sided 2.499% Type 1 error rate in testing these hypotheses is strongly controlled.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

9.9.1.1 Evaluation of Non-inferiority and Superiority Hypotheses

This section presents power calculations for the efficacy hypotheses of demonstrating non-inferiority of DOR/ISL to BIC/FTC/TAF and demonstrating superiority of DOR/ISL to BIC/FTC/TAF. The power calculations provided in this section do not account for the futility assessment at the Week 24 IA or the sequential testing strategy described in Section 9.8.

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

Non-inferiority will be concluded if the upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48/96 (Group 1 minus Group 2) is less than 4 percentage points. The choice of non-inferiority margin is based on the amount of virologic failure that is clinically acceptable; with an anticipated virologic failure rate of approximately 1.5% to 2%, a stringent margin of 4 percentage points is clinically acceptable. The observed percentages of participants with HIV-1 RNA ≥50 copies/mL at Week 48 are based on experience with MK-8591A-017 and MK-8591A-018. They are 0.0% in DOR/ISL group and 1.5% in Baseline ART group in MK-8591A-017 and 0.6% in DOR/ISL group and 0.3% in BIC/FTC/TAF group in MK-8591A-018.

Table 12 summarizes the power to declare DOR/ISL non-inferior to BIC/FTC/TAF under various assumptions for the response rate (ie, the percentage of participants with HIV-1 RNA ≥50 copies/mL) in Group 2 and the underlying between-group difference in response rates. For example, if the true rate of participants with HIV-1 RNA ≥50 copies/mL at Week 48/96 is 1.5% in both groups, this study has approximately 93.3% power to demonstrate non-inferiority. If the true rates are 2.0% in both groups, this study has approximately 87.0% power to demonstrate non-inferiority.

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

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

ART=antiretroviral therapy; BIC=bictegravir; CI=confidence interval; DOR=doravirine; FTC=emtricitabine; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; NA=not applicable; PASS=power analysis and sample size; RNA=ribonucleic acid; TAF=tenofovir alafenamide.

334 participants in Group 1 and 167 participants in Group 2

The response rate is the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48/96.

The non-inferiority margin is 4 percentage points. To establish non-inferiority, the upper bound of the 2-sided 95% CI for the difference between groups (Group 1 minus Group 2) in the percentage of participants with HIV-1 RNA ≥50 copies/mL must be <4 percentage points. The 95% CI is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.0249. Calculations were performed using PASS 16.

The observed percentages of participants with HIV-1 RNA ≥50 copies/mL at Week 48 are based on experience with MK-8591A-017 and MK-8591A-018. They are 0.0% in DOR/ISL group and 1.5% in Baseline ART group in MK-8591A-017 and 0.6% in DOR/ISL group and 0.3% in BIC/FTC/TAF group in MK-8591A-018.

Table 13 summarizes the power to declare DOR/ISL superior to BIC/FTC/TAF with regard to the percentage of participants with HIV-1 RNA ≥50 copies/mL under various assumptions for the response rate in each treatment group. For example, if the percentage of participants

with Week 48/96 HIV-1 RNA ≥50 copies/mL is assumed to be 0.5% in Group 1 and 3% in Group 2, then this study will have approximately 64.7% power to demonstrate superiority.

Table 13 Power (%) to Establish Superiority at Week 48/96/144 Under Various Response Rate Assumptions

Group 1: True Rate of Participants with HIV-1 RNA ≥50 Copies/mL at Week 48/96/144	**Group 2: True Rate of Participants With HIV-1 RNA ≥50 Copies/mL at Week 48/96/144**	**Probability of Demonstrating Superiority at Week 48/96/144**
0.5%	0.75%	8.1%
0.5%	1%	13.0%
0.5%	1.5%	24.1%
0.5%	2%	37.8%
0.5%	3%	64.7%
0.75%	1%	6.7%
0.75%	1.5%	14.4%
0.75%	2%	25.1%
0.75%	3%	51.5%
1%	1.25%	5.8%
1%	1.5%	8.7%
1%	2%	16.7%
1%	3%	38.6%
1.5%	1.75%	4.8%
1.5%	2%	7.1%
1.5%	2.5%	13.3%
1.5%	3%	21.6%
2%	2.5%	6.3%
2%	2.75%	8.7%
2%	3%	11.2%

BIC=bictegravir; CI=confidence interval; DOR=doravirine; FTC=emtricitabine; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; RNA=ribonucleic acid; TAF=tenofovir alafenamide.

334 participants in Group 1 and 167 participants in Group 2

To establish superiority of DOR/ISL to BIC/FTC/TAF, the upper bound of the 2-sided 95% CI for the difference between groups (Group1 minus Group 2) in the percentage of participants with HIV-1 RNA ≥50 copies/mL must be <0 percentage points. The CI is based on the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.0249. Power was estimated via 10,000 simulations for each scenario. Calculations were performed in R 3.5.0.

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

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

Table 14 summarizes the probability of not meeting the futility criterion at Week 24 under various assumptions for the response rate (ie, the percentage of participants with HIV-1 RNA ≥200 copies/mL) in Group 2 and the underlying between-group difference in response rates. For example, if the true rate of participants with HIV-1 RNA ≥200 copies/mL at Week 24 among 100 participants in Group 1 and 50 participants in Group 2 is 0.75% in both groups, then the probability of not meeting the futility criterion is 0.971. If the true rates are 1.0% in both groups, then the probability of not meeting the futility criterion is 0.946. If the true rate in Group 1 is 2.0% and the true rate in Group 2 is 1.0%, then the probability of not meeting the futility criterion is 0.757.

Table 14 Probability of Not Meeting the Futility Criterion at the Week 24 Interim Analysis

True Response Rate in Group 2	**True Difference in Response Rates (Group 1 Minus Group 2)**				
	-1.0 Percentage Points	**-0.5 Percentage Points**	**0.0 Percentage Points**	**0.5 Percentage Points**	**1.0 Percentage Points**
0.50%	NA	1.000	0.989	0.935	0.839
0.75%	NA	0.999	0.971	0.900	0.797
1.0%	1	0.991	0.946	0.864	0.757
1.25%	0.999	0.976	0.917	0.827	0.720
1.5%	0.993	0.956	0.885	0.791	0.684
1.75%	0.981	0.931	0.853	0.756	0.652
2.0%	0.964	0.904	0.820	0.723	0.622
2.25%	0.943	0.875	0.789	0.692	0.595
2.5%	0.919	0.846	0.758	0.664	0.570
2.75%	0.894	0.817	0.730	0.638	0.549
3.0%	0.868	0.790	0.704	0.615	0.529

CI=confidence interval; HIV-1=human immunodeficiency virus type 1; NA=not applicable; PASS=power analysis and sample size; RNA=ribonucleic acid.

100 participants in Group 1 and 50 participants in Group 2

The response rate is the percentage of participants with HIV-1 RNA ≥200 copies/mL at Week 24.

Futility Criterion: Upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥200 copies/mL at Week 24 (Group 1 minus Group 2) is >8 percentage points.

The 95% CI is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.025. Calculations were performed using PASS 16.

The probability of not meeting the futility criterion at the Week 24 IA and the power to demonstrate non-inferiority at Week 48 under a variety of assumptions is presented in Table 15.

The power calculations shown in Table 15 incorporate the futility assessment stopping rules. Of interest is the likelihood that the study would not meet the futility criterion at Week 24 for a variety of assumed Week 24 response rates and also whether the non-inferiority criterion at Week 48 would be subsequently met (ie, the conditional power of declaring DOR/ISL non-inferior to BIC/FTC/TAF at Week 48).

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

Additional power calculations are provided in the sSAP.

Table 15 Probability of Not Meeting the Futility Criterion at the Week 24 Interim Analysis and the Conditional Power to Declare Non-inferiority at Week 48 for Various Underlying True Response Rates

Parameter	Base Case		More Conservative Base Case		Most Conservative Base Case		Low Efficacy for DOR/ISL; Low Efficacy for BIC/FTC/TAF		Low Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF		High Efficacy for DOR/ISL; Low Efficacy for BIC/FTC/TAF		High Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF		Lowest Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Assumptions[a]																
% with Week 24 HIV-1 RNA ≥200 copies/mL	0.5%	0.5%	0.75%	0.75%	1.0%	1.0%	1.5%	1.0%	1.5%	0%	0%	1.0%	0%	0%	3%	0%
% with Week 48 HIV-1 RNA ≥50 copies/mL if Week 24 HIV-1 RNA ≥200 copies/mL	95%	95%	100%	100%	100%	100%	100%	100%	100%	92%	92%	100%	92%	92%	100%	92%
% with Week 48 HIV-1 RNA ≥50 copies/mL if Week 24 HIV-1 RNA <200 copies/mL	1%	1%	1.25%	1.25%	1.5%	1.5%	3%	2%	3%	0.5%	0.5%	2%	0.5%	0.5%	3%	0.5%
% with Week 48 HIV-1 RNA ≥50 copies/mL	1.5%	1.5%	2.0%	2.0%	2.5%	2.5%	4.5%	3.0%	4.5%	0.5%	0.5%	3.0%	0.5%	0.5%	5.9%	0.5%
Study Power																
Probability of Not Meeting the Futility Criterion[b]	98.9%		97.0%		94.7%		86.5%		81.1%		~100%		~100%		42.4%	
Conditional Power to Establish Non-inferiority at Week 48[c]	93.8%		87.8%		82.4%		35.9%		2.4%		~100%		99.9%		0.2%	

Parameter	Base Case		More Conservative Base Case		Most Conservative Base Case		Low Efficacy for DOR/ISL; Low Efficacy for BIC/FTC/TAF		Low Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF		High Efficacy for DOR/ISL; Low Efficacy for BIC/FTC/TAF		High Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF		Lowest Efficacy for DOR/ISL; High Efficacy for BIC/FTC/TAF	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2

ART=antiretroviral therapy; BIC=bictegravir; CI=confidence interval; COVID-19=coronavirus disease 2019; DOR=doravirine; FTC=emtricitabine; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; RNA=ribonucleic acid; TAF=tenofovir alafenamide.

The calculations assume 100 participants in Group 1 and 50 participants in Group 2 for the assessment of futility at Week 24 and 334 participants in Group 1 and 167 participants in Group 2 for the assessment of non-inferiority at Week 48.

[a] The assumptions for calculating power are based on observed rates in the MK-8591A-017 and MK-8591A-018 switch studies and the BIC/FTC/TAF switch studies, Trials 1844 and 1878. Specifically, MK-8591A-017 showed a rate ≥50 copies/mL at Week 48 of 0.0% in the DOR/ISL arm and 1.5% in the continued baseline ART arm; MK-8591A-018 showed a rate ≥50 copies/mL at Week 48 of 0.6% in the DOR/ISL arm and 0.3% in the BIC/FTC/TAF arm. In the BIC/FTC/TAF Trials 1844 and 1878, the rates of HIV-1 RNA ≥50 copies/mL at Week 48 were 1% and 2%, respectively, in the BIC/FTC/TAF arms. For the 3 base cases, the assumed percentages of participants with HIV-1 RNA ≥50 copies/mL at Week 48 are generally higher than the rates observed across the MK-8591A-017 and MK-8591A-018 study arms and, therefore, are considered to be conservative. The conservative rates were selected in recognition that MK-8591A-017 and MK-8591A-018 were conducted during the global COVID-19 pandemic, during which time participants may have been restricted to home stay or limited travel, potentially leading to higher adherence to study intervention and subsequently lower rates of virologic failure than would be otherwise expected.

[b] Futility Criterion: Upper bound of the 2-sided 95% CI for the between-group difference in the percentage of participants with HIV-1 RNA ≥200 copies/mL at Week 24 (Group 1 minus Group 2) is greater than 8 percentage points. Values for the probability of not meeting the futility criterion were calculated via simulation.

[c] Each value was calculated via 10,000 simulations to evaluate first whether the futility criterion was met and if not, evaluate non-inferiority between groups using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The non-inferiority margin is 4 percentage points and the Type 1 error is 0.0249 (1-sided). Calculations were performed in R 3.5.0.

9.9.2 Sample Size and Power for Safety Analyses

9.9.2.1 Evaluation of Adverse Events

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

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

The point estimate and the upper bound of the corresponding 2-sided 95% CI for the underlying percentage of participants with an AE given various hypothetical observed numbers of participants with the AE within each treatment group are provided in Table 16. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 16 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs

Number of Participants in the Treatment Group	Number of Participants With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
334	0	0%	0.9%
167	0	0%	1.8%
334	1	0.3%	0.3%
167	1	0.6%	3.3%
334	2	0.6%	2.1%
167	2	1.2%	4.3%
334	5	1.5%	3.5%
167	5	3.0%	6.8%
334	10	3.0%	5.4%
167	10	6.0%	10.7%
334	15	4.5%	7.3%
167	15	9.0%	14.4%
334	20	6.0%	9.1%
167	20	12.0%	17.9%
334	25	7.5%	10.9%
167	25	15.0%	21.3%
334	30	9.0%	12.6%
167	30	18.0%	24.6%

Number of Participants in the Treatment Group	Number of Participants With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
AE=adverse event; CI=confidence interval. [a] Based on the 2-sided exact 95% CI for a binomial proportion (Clopper and Pearson method [Clopper, C. J. and Pearson, E. S. 1934]). In the 0-event case, the CI is 1-sided (α=0.05 all in the upper tail).			

Table 17 gives the difference in the incidence of an AE (Group 1 minus Group 2) that can be ruled out with different power levels and 95% confidence when there are 334 participants in Group 1 and 167 participants in Group 2. The underlying incidence of the AE is assumed to be the same for the 2 treatment groups. For example, for a reasonably common AE, which occurs in 20% of participants in both groups, the study has 80% power to declare with 95% confidence that the true difference between the treatment groups is no more than 11.7 percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 17 Difference in Incidence (Percentage Points) of AEs (Group 1 Minus Group 2) That Can Be Ruled Out With 334 Participants in Group 1 and 167 Participants in Group 2

Target Power	Underlying AE Incidence Rate						
	1%	5%	10%	20%	30%	40%	50%
80%	5.1	7.7	9.6	11.7	12.8	13.2	13.1
85%	5.5	8.3	10.3	12.5	13.7	14.1	14.0
90%	6.1	9.1	11.2	13.6	14.8	15.3	15.1
95%	7.1	10.3	12.6	15.2	16.5	17.0	16.7
AE=adverse event; CI=confidence interval. Values represent the upper bound of the 2-sided 95% CI (unstratified Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]) for the difference in AE incidences (Group 1 minus Group 2) assuming the incidences are the same.							

9.10 Subgroup Analyses

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

- Age category (<50 years of age, ≥50 years of age)
- Sex at birth (female, male)
- Gender identity (boy/man, girl/woman, transgender boy/man, transgender girl/woman, genderqueer/non-binary/gender non-conforming, other)
- Region (North America, South America, Europe, Asia, Africa, etc)

- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Chronic hepatitis C status (HCV-infected, HCV-uninfected)
- Duration of BIC/FTC/TAF therapy prior to enrollment (≥1 year, <1 year)

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

9.11 Compliance (Medication Adherence)

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

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.

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

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

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

For the secondary analysis of base study compliance, a day within the study will be considered an "On Therapy" day if the participants take at least 1 tablet from the bottle containing the active blinded study intervention. The definition of the "Number of Days Should be On Therapy" and the formula for calculating percent compliance are the same as defined above for the main analysis of compliance. This secondary compliance measure will be used to identify exclusions from the PP population (see Section 9.5.1).

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

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

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

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

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.4.3 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by a central laboratory.

  Note: In rare instances, if central laboratory use is not feasible, local laboratory tests may be used at scheduled study visits after consultation with the Sponsor. Plasma HIV-1 RNA quantification requires use of a validated PCR assay with a lower limit of detection of <50 copies/mL (see Appendix 10).

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

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

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

- The amount of blood collected from each participant over the duration of the study is provided in Table 19, Table 20, Table 21, and Table 22. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 18 Protocol-required Laboratory Assessments

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

Laboratory Assessments	Parameters
HBV DNA[c]	HBV DNA
Hepatitis C Serology	Hepatitis C antibody (if positive, perform plasma HCV quantitative test) (at screening only)
HIV-1 and HIV-2 Serology	HIV-1 and HIV-2 antibody test
Virology	HIV-1 viral RNA quantification HIV-1 viral drug resistance
PK	Plasma ISL PK
	Plasma Investigational ISL PK (Samples will be collected from all participants. Analysis of these samples will be performed by the Sponsor as needed.)
	Plasma ISL and DOR PK (Only participants on DOR/ISL who become pregnant during the study)
Renal Markers	Urine analysis: Albumin/Cr Protein B-2M/Cr RBP/Cr Serum analysis: Cystatin-C Cr Creatinine Clearance by Cockcroft-Gault equation (Appendix 8) eGFR by MDRD equation (Appendix 8)
Inflammatory Markers	IL-6 D-dimer sCD-163 hs-CRP
Energy and Metabolism Markers	Adipokines: Leptin Adiponectin

ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; AST=aspartate aminotransferase; B-2M/Cr=beta-2-microglobulin/creatinine ratio; BUN=blood urea nitrogen; CK=creatine kinase; Cr=creatinine; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; DOR=doravirine; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; HIV-1=human immune deficiency virus type 1; HIV-2=human immune deficiency virus type 2; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance; hs-CRP=high-sensitivity C-reactive protein; IL-6=interleukin-6; INR=international normalized ratio; ISL=islatravir; LDL-C=low-density lipoprotein cholesterol; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MDRD=Modification of Diet in Renal Disease; Mg=magnesium; non-HDL-C=non-high-density lipoprotein cholesterol; PK=pharmacokinetic(s); POCBP=participant(s) of childbearing potential; PT=prothrombin time; RBC=red blood cell; RBP/Cr=retinol-binding protein/creatinine ratio; RDW=red cell distribution width; RNA=ribonucleic acid; sCD-163=soluble CD-163; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TBNK=T and B Lymphocyte and Natural Killer Cell; TC=total cholesterol; TG=triglyceride; WBC=white blood cell.
Notes:
[a] The central Laboratory may reflex to manual differential to further identify atypical or immature forms of leukocytes.

Laboratory Assessments	Parameters
[b] Participants with type 1 diabetes mellitus should not fast and should not have insulin levels tested. Participants with type 2 diabetes mellitus taking medications that may result in hypoglycemia should delay their morning dose of diabetic medication while fasting and take it after the blood draw for testing. [c] All participants will be screened for HBsAg, anti-HBs, anti-HBc, and HBV DNA. Repeat serology and HBV DNA testing at Weeks 48, 96, 144, 192 and 240 is to be performed for all participants. Participants who are anti-HBc-positive but HBV DNA-negative will have HBsAg and HBV DNA monitored for the duration of the study. Pregnant participants (on DOR/ISL only) will have a sample collected once after pregnancy is confirmed or local laboratory results reported for hepatitis B serology and HBV DNA.	

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

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

Study Period	**Screen**	**Blinded Intervention (Base Study)**															**Viremia Confirm**	**Total Lymphocyte/ CD4+ T-cell Confirm**	**Early Discon of Treatment**	**Total lymphocyte /CD4+ T-cell Monitor**	**EoT Follow-up[i]**
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (fasting)		Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																				
Plasma HIV-1 RNA Quantification[a]	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6		6		6
Blood (Plasma) for HIV-1 Drug Resistance[b]		12	12	12	12	12	12	12	12	12	12	12	12	12	12		12		(12)		
Whole Blood for HIV-1 Drug Resistance		4																			
HIV-1 and HIV-2 Serology	1																				
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			6	6	6	(6)
Hepatitis B Serology and Hepatitis C (Screening only) Serology[c]	4	(4)	(4)	(4)	(4)	(4)	4	(4)	(4)	(4)	4	(4)	(4)	(4)	4						
HBV DNA[c]	6	(6)	(6)	(6)	(6)	(6)	6	(6)	(6)	(6)	6	(6)	(6)	(6)	6						
Hepatitis B Serology for Pregnant Participants (DOR/ISL only)[d]		<----------(4)---------->																			
HBV DNA for Pregnant Participants (DOR/ISL only)[c]		<----------(6)---------->																			
Plasma HCV Quantitative Test[c]	(6)																				
Chemistry (includes Serum Pregnancy Test at Screening)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6				6		
Hematology	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4			4	4	4	(4)
HbA1c		2			2		2				2				2						
Fasting Lipids		2			2		2				2				2						

Study Period	**Screen**	**Blinded Intervention (Base Study)**														**Viremia Confirm**	**Total Lymphocyte/ CD4+ T-cell Confirm**	**Early Discon of Treatment**	**Total lymphocyte /CD4+ T-cell Monitor**	**EoT Follow-up[i]**
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Fasting Insulin[e]		1			1		1				1				1					
PT/INR	3																			
Blood for Inflammatory Biomarkers		11			11		11				11				11					
Cystatin-C		2			2		2				2				2					
Blood for Energy and Metabolism Markers		6			6		6				6				6					
Blood (Plasma) for ISL PK (All Participants)		4	8	4	4		4									4		4		
Blood (Plasma) for Investigational ISL(and DOR, if applicable) PK[f]						4		4	4	4	4					4	4	4		
Blood (Plasma) for DOR and ISL PK During Pregnancy[g]			<----------(4 or 12, as indicated)---------->																	
Approximate Total Blood Volume per Visit (mL)	**42**	**76**	**52**	**48**	**72**	**48**	**72**	**48**	**48**	**48**	**72**	**44**	**44**	**44**	**68**	**22**	**14**	**38**	**10**	**16**

Study Period	**Screen**	**Blinded Intervention (Base Study)**													**Viremia Confirm**	**Total Lymphocyte/ CD4+ T-cell Confirm**	**Early Discon of Treatment**	**Total lymphocyte /CD4+ T-cell Monitor**	**EoT Follow-up[i]**
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled

anti-hBc=hepatitis B core antibody; Confirm=Confirmation; Discon=Discontinuation; DNA=deoxyribonucleic acid; DOR=doravirine; EoT=End of Treatment; HbA1c=hemoglobin A1c; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV-1=human immunodeficiency virus type 1; HIV-2=human immunodeficiency virus type 2; INR=international normalized ratio; ISL=islatravir; Monitor=Monitoring; PK=pharmacokinetic(s); PT=prothrombin time; RNA=ribonucleic acid; TBNK=T and B Lymphocyte and Natural Killer Cell.

[a] Not included in total blood volume per visit: Pregnant participants who require more frequent HIV-1 RNA testing performed per local guidelines or as determined by the investigator.

[b] Do not collect at Early Discon if collected at previous Viremia Confirm.

[c] All participants will be screened for HBsAg, anti-HBs, anti-HBc, and HBV DNA as well as hepatitis C antibody (with reflex plasma HCV quantitative test if indicated) at screening. Participants with negative hepatitis B serologic testing at screening will have repeat testing at Weeks 48, 96, 144 and 192. Only participants who are anti-HBc-positive but HBV DNA-negative will have HBsAg and HBV DNA monitored for the duration of the study.

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

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

[f] Investigational ISL PK samples will be collected from all participants. Analysis of these samples will be performed by the Sponsor as needed.

[g] Not included in total blood volume at each visit: During pregnancy, blood samples will be collected for PK sampling per Section 8.11.6.1 during the 1st trimester (4 mL), 2nd trimester (12 mL), 3rd trimester (12 mL), and Postpartum (4 mL) study visits. For participants whose pregnancy or Postpartum visit(s) extends beyond Week 96, see Table 21 and Table 22.

[h] Blood volumes collected at the Total Lymphocyte Count/CD4+ T-cell Count Monitoring visit (DOR/ISL participants only) represent single monitoring visits every 10 to 14 weeks after discontinuing study intervention.

[i] For the EoT Follow-up visit, the approximate total volume to be collected is for the assessments in Section 1.3.1 or 1.3.2 or 1.3.3 or 1.3.4 SoA, as indicated.

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

Study Period	**Screen**	**Blinded Intervention (Base Study)**														**Viremia Confirm**	**Total Lymphocyte/ CD4+ T-cell Confirm**	**Early Discon of Treatment**	**Total Lymphocyte/ CD4+ T-cell Monitor (DOR/ISL only)**	**EoT Follow-up**
Scheduled Day/Week	Screening	Day 1 (fasting)	Week 4	Week 12	Week 24 (fasting)	Week 36	Week 48 (fasting)	Week 60	Week 72	Week 84	Week 96 (fasting)	Week 108	Week 120	Week 132	Week 144 (fasting)	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																			
Blood for Genetic Analysis		9																		
Whole Blood for FBR		8			8		8				8				8	8		8		
Approximate Total Blood Volume per Visit (mL)		17			8		8				8				8	8		8		

Confirm=Confirmation; Discon=Discontinuation; DOR=doravirine; EoT=End of Treatment; FBR=future biomedical research; ISL=islatravir; Monitor=Monitoring.

Table 21 Blood Volumes (Efficacy, Safety, and PK) in the OLE

Study Period	**Optional OLE**					**Viremia Confirmation**	**Total Lymphocyte/ CD4+ T-cell Confirmation**	**Total Lymphocyte/ CD4+ T-cell Monitoring (DOR/ISL only)**	**Discontinuation of Treatment (OLE)**	**End of Treatment Follow-up (OLE)[a]**
Scheduled Day/Week	Week 148 (Group 2)	Week 168	Week 192	Week 216	Week 240	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL) a**									
Plasma HIV-1 RNA Quantification (PCR)	6	6	6	6	6	6			6	(6)
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6		6	6	6	(6)
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing	12	12	12	12	12	12			12	(12)
Hematology	2	2	2	2	2		2	2	2	(2)
Chemistry										(6)
Hepatitis B Serology HBV DNA			10		10					
HBsAg and HBV DNA (Group 2 participants with positive anti-HBc)	(10)	(10)	(10)	(10)	(10)					
Blood (Plasma) for Investigational ISL PK						4	4	4		(4)
Blood (Plasma) for DOR and ISL PK							4			
Blood (Plasma) for DOR and ISL PK (pregnant participants on DOR/ISL)						(4)			(4)	(4)
Total Blood Volume per Visit (mL)	**26**	**26**	**36**	**26**	**36**	**22**	**12**	**12**	**26**	**40**

Study Period	Optional OLE					Viremia Confirmation	Total Lymphocyte/ CD4+ T-cell Confirmation	Total Lymphocyte/ CD4+ T-cell Monitoring (DOR/ISL only)	Discontinuation of Treatment (OLE)	End of Treatment Follow-up (OLE)[a]
Scheduled Day/Week	Week 148 (Group 2)	Week 168	Week 192	Week 216	Week 240	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL) a**									

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

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

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

Visit Number	**Unscheduled**				
Scheduled Week	**Pregnancy 1[a]**	**Pregnancy 2[a]**	**Pregnancy 3[a]**	**Pregnancy 4 (Postpartum ≤8 weeks after delivery)**	**EoT Follow-up**
Blood Parameter	**Approximate Blood Volume (mL)**				
Plasma HIV-1 RNA Quantification	6	6	6	6	6
Plasma for HIV-1 Viral Drug Resistance Testing	15	15	15	15	15
TBNK Panel/CD4+ T-cell Count	6	6	6	6	6
Hepatitis B Serology and HBV DNA (DOR/ISL only)[b]	<----------(10)---------->				
Chemistry	6	6	6	6	6
Hematology	4	4	4	4	4
Blood (Plasma) for DOR and ISL PK[c]	4	12	12	4	4
Approximate Total Blood Volume per Visit (mL)	**41**	**49**	**49**	**41**	**41**

DNA=deoxyribonucleic acid; DOR=doravirine; EoT=End of Treatment; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus type 1; ISL=islatravir; PK=pharmacokinetic(s); RNA=ribonucleic acid; TBNK=T and B Lymphocyte and Natural Killer Cell.

[a] If pregnancy visit occurs at the timeframe of a scheduled OLE study visit, collection of lab samples should occur per this table. Collection of laboratory samples should not be duplicated.

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

[c] Collect PK samples during pregnancy per Section 8.11.6.1.1.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. Results in death

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

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

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

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

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer.

- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity/toxicity

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

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

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

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

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

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

    - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

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

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

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

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

    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

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

    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

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

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

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

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

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

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

- Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

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

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

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

Not applicable to this study.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile and capable of becoming pregnant 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.

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

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

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

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

- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

- Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Participants of Nonchildbearing Potential (PONCBP)

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

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

    For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.
    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency [a] Failure rate of <1% per year when used consistently and correctly.
• Progestogen-only contraceptive implant [b,c] • IUS [b,c] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) - All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent [a] Failure rate of <1% per year when used consistently and correctly.

• Combined (estrogen- and progestogen-containing) hormonal contraception [b,c]
  • Oral
  • Intravaginal
  • Transdermal
  • Injectable

• Progestogen-only hormonal contraception [b,c]
  • Oral
  • Injectable

Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly*.
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condoms should not be used together (due to risk of failure with friction)[d] [a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD [d] Vaginal/internal condom used for contraceptive purposes

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

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

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

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

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

3. Summary of Procedures for Future Biomedical Research[3, 4]

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

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

signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

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

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

4. Confidential Participant Information for Future Biomedical Research[3, 4]

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

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

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

5. Biorepository Specimen Usage[3, 4]

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

6. Withdrawal From Future Biomedical Research[3, 4]

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

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

7. Retention of Specimens[3, 4]

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

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

8. Data Security[3, 4]

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

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

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

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

10. Future Biomedical Research Study Population[3, 4]

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

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

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

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

12. Questions

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

13. References

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for Germany

Legally Acceptable Representative

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

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

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

DEXA Scans

Participants who enroll in Germany will not have DEXA scans as indicated in the SoA. This procedure will be omitted, and participants in Germany will not be included in the applicable analyses.

10.7.2 Country-specific Request for Canada

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

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

10.8 Appendix 8: Calculation of Creatinine Clearance and eGFR

10.8.1 Cockcroft-Gault Equations

- If male:

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

- If female:

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

10.8.2 MDRD Equations

eGFR estimated by MDRD-NKDEP:

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

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

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

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary

- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

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

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

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

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

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
3TC	lamivudine
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIDS	acquired immunodeficiency syndrome
albumin/Cr	albumin/creatinine ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
APaT	All-Participants-as-Treated
APaT-E	All-Participants-as-Treated in the Extension
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
B-2M/Cr	beta-2-microglobulin/creatinine ratio
BCRP	breast cancer resistance protein
BIC	bictegravir
BLOQ	below the limit of quantification
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
C_{24}	concentration after 24 hours
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
C_{max}	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
Cr	creatinine
CrCl	creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
C_{trough}	lowest concentration reached before the next dose is administered
CYP	cytochrome P450
DAIDS	Division of AIDS
DAO	data as observed

Abbreviation	Expanded Term
DDI	drug-drug interaction
DEXA	dual x-ray absorptiometry
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravirine
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EQ-5D-5L	EuroQol 5-dimensional descriptive system, 5-level version
EU	European Union
FAS	Full Analysis Set
FAS-E	Full Analysis Set-Extension
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
FSR	first site ready
FTC	emtricitabine
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIV SI/SDM	Human Immunodeficiency Virus Symptom Index (also known as the Human Immunodeficiency Virus Symptom Distress Module)
HIVTSQ	Human Immunodeficiency Virus Treatment Satisfaction Questionnaire
HIVTSQs	Human Immunodeficiency Virus Treatment Satisfaction Questionnaire status version
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance

Abbreviation	Expanded Term
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HTA	Health Technology Assessment
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
IC_{50}	inhibitory concentration required for 50% inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL-6	interleukin-6
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	interactive response technology
ISL	islatravir
ISL-TP	islatravir-triphosphate
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LDL-C	low-density lipoprotein cholesterol
M=F	missing data treated as treatment failure
MAR	missing at random
MCAR	missing completely at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing not at random
NIMP	noninvestigational medicinal product
NKDEP	National Kidney Disease Education Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
non-HDL-C	non-high-density lipoprotein cholesterol
NRTI	nucleoside/nucleotide analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OF	observed failure
OLE	open-label extension
PCR	polymerase chain reaction
PDLC	predefined limit of change
PI	protease inhibitor

Abbreviation	Expanded Term
PK	pharmacokinetic(s)
PLWH	people living with HIV
POCBP	participant(s) of childbearing potential
PONCBP	participant(s) of nonchildbearing potential
PP	Per-Protocol
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcome
PT	prothrombin time
PTs	preferred terms
QD	once-daily
QM	once-monthly
QW	once-weekly
RBC	red blood cell
RBP/Cr	retinol-binding protein/creatinine ratio
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sCD-163	soluble CD-163
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMQs	Standardized MedDRA Queries
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSARs	suspected unexpected serious adverse reactions
TAF	tenofovir alafenamide
TBNK	T and B Lymphocyte and Natural Killer Cell
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglyceride
TN	treatment-naïve
ULN	upper limit of normal
US	United States
vs	versus
VS	virologically suppressed
WBC	white blood cell
WHO	World Health Organization

11 REFERENCES

[Bailin, S. S., et al 2020]	Bailin SS, Gabriel CL, Wanjalla CN, Koethe JR. Obesity and weight gain in persons with HIV. Curr HIV/AIDS Rep. In press 2020.	[07ZG3C]
[Baker, J. V., et al 2011]	Baker JV, Neuhaus J, Duprez D, Kuller LH, Tracy R, Belloso WH, De Wit S. et al. Changes in inflammatory and coagulation biomarkers: a randomized comparison of immediate versus deferred antiretroviral therapy in patients with HIV infection. J Acquir Immune Defic Syndr. 2011 Jan 1;56(1):36-43.	[04MWL0]
[Burger, D., et al 2005]	Burger D, van der Heiden I, la Porte C, van der Ende M, Groeneveld P, Richter C, et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol. 2005;61(2):148-54.	[057GSX]
[Buzon-Martin, L. 2020]	Buzon-Martin L. Weight gain in HIV-infected individuals using distinct antiretroviral drugs. AIDS Rev. 2020;22:158-67.	[07ZG4Y]
[Cahn, P., et al 2019]	Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019 Jan 12;393:143-55.	[054KXQ]

[Carr, A., et al 1998]	Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998;12(7):F51-F58.	[03Q6RY]
[Centers for Disease Control (CDC) 1992]	Centers for Disease Control (CDC). 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(RR-17):1-17.	[03RH6J]
[Charpentier, C., et al 2014]	Charpentier C, Choquet M, Joly V, Yeni P, Visseaux B, Caseris M, et al. Virological outcome at week 48 of three recommended first-line regimens using ultrasensitive viral load and plasma drug assay. J Antimicrob Chemother. 2014 Oct;69(10):2819-25.	[04PYMQ]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[00V5VX]
[Department of HIV/AIDS 2015]	Department of HIV/AIDS. Transgender people and HIV. Geneva (Switzerland): World Health Organization (WHO); 2015 Jul. 32 p.	[05BDGP]
[European AIDS Clinical Society 2021]	European AIDS Clinical Society. Guidelines: version 11.0: October 2021. Brussels (Belgium): European AIDS Clinical Society (EACS); 2021. 149 p.	[07XP7W]
[Farahani, M., et al 2017]	Farahani M, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. Int J STD AIDS. In press 2017.	[0822J6]

[Food and Drug Administration (CDER) 2015]	Food and Drug Administration (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry [Internet]. Silver Spring, MD: U.S. Department of Health and Human Services; 2015. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf.	[04MT4V]
[Hill, A., et al 2019]	Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad. 2019;5:41-3.	[058G5N]
[Hoffmann, C., et al 2017]	Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink HJ, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017;18:56-63.	[055FBG]
[Johnson, M., et al 2019]	Johnson M, Kumar P, Molina JM, Rizzardini G, Cahn P, Bickel M, et al. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial. J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):463-72.	[05B4PY]
[Joint United Nations Programme on HIV/AIDS 2017]	Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS: progress towards the 90-90-90 targets. Slides presented at: 9th International AIDS Society (IAS) Conference on HIV Science; 2017 Jul 23-26; Paris (France).	[058SY8]
[Kenward, M. G. and Roger, J. H. 1997]	Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53:983-97.	[00V5VW]

[Knudsen, T. B., et al 2016]	Knudsen TB, Ertner G, Petersen J, Moller HJ, Moestrup SK, Eugen-Olsen J. et al. Plasma Soluble CD163 Level Independently Predicts All-Cause Mortality in HIV-1-Infected Individuals. J Infect Dis. 2016 Oct 15;214(8):1198-204.	[04MWL7]
[Liang, K-Y and Zeger, S. L. 2000]	Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankyha: The Indian Journal of Statistics 2000;62(Series B, Part 1):134-48.	[00V5V6]
[Llibre, J. M., et al 2018]	Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. 2018 Mar 3;391:839-49. Erratum in: Lancet. 2018 Feb 1.	[0528SS]
[McComsey, G. A., et al 2018]	McComsey GA, Lupo S, Parks D, Poggio MC, De Wet J, Kahl LP, et al. Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health. AIDS. 2018;32(4):477-85.	[080W84]
[Michailidis E 2014]	Michailidis E, et al. 4-Ethynyl-2-fluoro-2-deoxyadenosine (EFdA) Inhibits HIV-1 Reverse Transcriptase with Multiple Mechanisms. J Biol Chem 2014; 289(35):24533-24548.	[04PXGP]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Statist Med 1985;4:213-26.	[00W9P2]

[Molina, J. M., et al 2018]	Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018 May;5:e211-20.	[05RFGF]
[National Institute of Allergy and Infectious Diseases 2017]	National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [Internet]. Bethesda, MD: NIAID; 2017. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2.	[04R7PK]
[Norwood, J., et al 2017]	Norwood J, Turner M, Bofill C, Rebeiro P, Shepherd B, Bebawy S, et al. Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr. 2017 Dec 15;76(5):527-31.	[055F9Y]

[Orkin, C., et al 2019]	Orkin C, Squires KE, Molina JM, Sax PE, Wong WW, Sussmann O, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with Human Immunodeficiency Virus-1 Infection: week 48 results of the DRIVE-AHEAD trial. Clin Infect Dis. 2019 Feb 15;68(4):535-44.	[0580VV]
[Panel on Antiretroviral Guidelines for Adults and Adolescents 2022]	Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV: Jan 2022. Washington (DC): Department of Health and Human Services (HHS). [Last updated: 2022 Jan 20]. 460 p.	[080MHG]
[Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]	Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States: Dec 2018. Washington (DC): Department of Health and Human Services (HHS). [Last updated: 2018 Dec 7]. 365 p.	[05BXZW]
[Poteat, T., et al 2016]	Poteat T, Scheim A, Xavier J, Reisner S, Baral S. Global epidemiology of HIV infection and related syndemics affecting transgender people. J Acquir Immune Defic Syndr. 2016 Aug 15;72(suppl 3):S210-9.	[05BDHN]
[Ribaudo, H. J., et al 2013]	Ribaudo HJ, Smith KY, Robbins GK, Flexner C, Haubrich R, Chen Y, et al. Racial differences in response to antiretroviral therapy for HIV infection: an AIDS Clinical Trials Group (ACTG) study analysis. Clin Infect Dis. 2013 Dec 1;57(11):1607-17.	[057GSZ]

[Shah, S., et al 2021]	Shah S, Hindley L, Hill A. Are new antiretroviral treatments increasing the risk of weight gain? Drugs. 2021;81:299-315.	[07ZG4L]
[Taylor, E. B. 2021]	Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. Clin Sci. 2021;135:731-52.	[083NDN]
[Trickey, A., et al 2017]	Trickey A, May MT, Vehreschild JJ, Obel N, Gill MJ, Crane HM, et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV. 2017 Aug;4:e349-56.	[055HR8]
[U.S. Prescribing Information 2016]	U.S. Prescribing Information: DESCOVY (emtricitabine and tenofovir alafenamide) tablets, for oral use: Apr 2016.	[057ZP6]
[U.S. Prescribing Information 2017]	U.S. Prescribing Information: SUSTIVA (efavirenz) capsules for oral use; SUSTIVA (efavirenz) tablets for oral use: Oct 2017.	[04VGFN]
[U.S. Prescribing Information 2019]	U.S. Prescribing Information: VIREAD (tenofovir disoproxil fumarate) tablets, for oral use; VIREAD (tenofovir disoproxil fumarate) powder, for oral use: Apr 2019.	[057N3H]
[Vandenhende, M. A., et al 2015]	Vandenhende MA, Ingle S, May M, Chene G, Zangerle R, Van Sighem A, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. AIDS. 2015;29(3):373-83.	[056V0P]
[Vazquez-Carrera, M. 2016]	Vazquez-Carrera M. Unraveling the effects of PPARbeta/delta on insulin resistance and cardiovascular disease. Trends Endocrinol Metab. 2016 May;27(5):319-34.	[058MZ6]

[Wandeler, G., et al 2016]	Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr Opin HIV AIDS. 2016 Sep;11(5):492-500.	[080V4Y]
[Wang, H., et al 2016]	Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis. Medicine (Baltimore). 2016 Oct;95(41):e5146.	[04MWLQ]
[Weintrob, A. C., et al 2009]	Weintrob AC, Grandits GA, Agan BK, Ganesan A, Landrum ML, Crum-Cianflone NF, et al. Virologic response differences between African Americans and European Americans initiating highly active antiretroviral therapy with equal access to care. J Acquir Immune Defic Syndr. 2009 Dec 15;52(5):574-80.	[0576P6]
[Wong, A., et al 2019]	Wong A, Goldstein D, Mallolas J, DeJesus E, Johnson M, Molina JM, et al. Efficacy and safety of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in treatment-naive adults with HIV-1 and transmitted nonnucleoside reverse transcriptase inhibitor resistance mutations [letter]. J Acquir Immune Defic Syndr. 2019 Dec 1;82(4):e47-9.	[05FKKY]
[Wood, B. R. 2021]	Wood BR, Huhn GD. Excess weight gain with integrase inhibitors and tenofovir alafenamide: what is the mechanism and does it matter? Open Forum Infect Dis. 2021;8(12):ofab542.	[07ZG56]

[World Health Organization 2021]	World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva (Switzerland): World Health Organization (WHO); 2021 Jul. 592 p.	[080MHJ]