Official Protocol Title:	A Phase 3, Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate a Switch to Doravirine/Islatravir (DOR/ISL) Once-Daily in Participants With HIV-1 Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)
NCT number:	NCT04223791
Document Date:	20-Jan-2022

Title Page

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

Protocol Number: 018-06

Compound Number: MK-8591A

Sponsor Name:

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

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Regulatory Agency Identifying Number(s):

IND	134036
EudraCT	2019-000587-23

Approval Date: 20 January 2022

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 06	20-JAN-2022	Given the findings of decreases in CD4+ T-cell and total lymphocyte counts in clinical studies evaluating ISL, the protocol is being amended to increase the frequency of monitoring of CD4+ T-cell and total lymphocyte counts and to specify the management of participants who meet protocol-defined decreases in CD4+ T-cell and/or total lymphocyte counts.
Amendment 05	07-DEC-2021	To increase frequency of monitoring of CD4+ T-cell counts and lymphocyte counts, and to add discontinuation criteria in response to findings of decreases in CD4+ T-cell counts (in studies of participants with HIV) and lymphocytes (in studies of participants with or without HIV) in ISL clinical studies. Note: The changes made in Amendment 05 were not implemented at clinical sites. Amendment 06 supersedes Amendment 05.
Amendment 04	16-JUL-2021	As required by the Germany Health Authority (BfArM), the protocol is amended for Germany; if a participant becomes pregnant (has a positive serum pregnancy test), she must discontinue from study intervention. Additionally, Germany will not allow legally acceptable representatives to provide consent on behalf of the study participant.
Amendment 03	05-APR-2021	The protocol was amended to: (1) extend study intervention, open-label, from 96 weeks to 144 weeks for all participants, (2) add option for Group 2 to receive open-label DOR/ISL from Week 144 to Week 156 (a 12-week safety monitoring period before being offered enrollment in DOR/ISL rollover study), (3) offer the option to continue study intervention for participants who become pregnant, (4) add a discontinuation criterion if a participant chooses to breastfeed.
Amendment 02	07-MAY-2020	The protocol was amended to: (1) update the hypothesis testing strategy in the statistical analysis plan, (2) update the prohibited concomitant therapies, and (3) allow participants to rescreen one time following approval from the Sponsor.

Document	Date of Issue	Overall Rationale
Amendment 01	15-JAN-2020	At the request of Health Canada, the protocol is amended for Canada to indicate that participants who become HBsAg or HBV DNA positive after randomization must be discontinued from study intervention.
Original Protocol	24-OCT-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendments:

Given the findings of decreases in CD4+ T-cell and total lymphocyte counts in clinical studies evaluating ISL, the protocol is being amended to increase the frequency of monitoring of CD4+ T-cell and total lymphocyte counts and to specify the management of participants who meet protocol-defined decreases in CD4+ T-cell and/or total lymphocyte counts.

Summary of Changes Table:

All changes from Amendments 05 and 06 are listed below.

Note: The changes made in Amendment 05 were not implemented at clinical sites. Amendment 06 supersedes Amendment 05.

Section # and Name	Description of Change	Brief Rationale
1.3.1 (SoA) 1.3.2 (SoA) 1.3.3 (SoA) 1.3.4 (SoA) 1.3.5 (SoA)	• Expanded lymphocyte analysis to include B-cells and NK cells. • Updated laboratory procedure name CD4+ T-cell count to CD4+ T cell count/TBNK panel. • Added notes to all applicable SoAs for CD4+ T-cell count/TBNK panel testing and Hematology assessments to refer to Section 8.11.5 for participants with decreases in CD4+ T-cell and/or total lymphocyte counts.	• Given total lymphocyte count decreases seen across ISL program, to assess for changes in other subpopulations of lymphocytes in addition to T-cells. • To clarify that CD4+ T cell count is part of the TBNK panel, which measures different T-cell, B-cell, and NK cell types. • To clarify that decreases in CD4+ T-cell and/or total lymphocyte counts that meet ECI criteria must be managed according to Section 1.3.5 and Section 8.11.5.

Section # and Name	Description of Change	Brief Rationale
1.3.1 SoA (Screening Through Week 96 - Blinded Intervention)	Added CD4+ T-cell/TBNK panel testing at Weeks 72 and 84.	To allow for CD4+ T-cell, B-cell, and NK cell count monitoring at least every 12 weeks.
1.3.2 SoA (Week 108 Through Week 156 - Open-Label Intervention)	Added CD4+ T-cell/TBNK panel testing at Weeks 108, 132, 148, and 156.	To allow for CD4+ T-cell, B-cell, and NK cell count monitoring at least every 12 weeks.
1.3.3 SoA (Viremia Confirmation and End of Treatment)	Added that the EQ-5D-5L, HIV-SI/SDM, and HIVTSQ and Patient Questionnaires should not be administered after Week 96.	To clarify that the PROs should not be administered after Week 96.
1.3.5 SoA (Participants With Specified Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts)	The SoA was added (per Amendment 05) and updated (per Amendment 06) to specify visits and assessments associated with confirming and monitoring decreases in CD4+ T-cell count and/or total lymphocyte count.	To clarify timing of visits and procedures performed on participants who require monitoring for decreased CD4+ T-cell count and/or total lymphocyte count.
2.2.3 Doravirine/Islatravir	Updated results for MK-8591 011.	To provide the most current information on DOR/ISL clinical studies.

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	• Updated text based on CD4+ T-cell and lymphocyte findings. • Updated text to state that dosing of ISL (QM 60 mg) in the HIV-1 PrEP program has been stopped. • Specified DOR/ISL QD doses (100 mg/0.75 mg) used in the 2 Phase 3 studies (MK-8591A 018 and MK-8591A 017).	• To account for new safety and efficacy information from the ISL clinical development program that is relevant to the population in this study. • To provide the current status of ISL dosing in the ISL HIV-1 PrEP program. • DOR/ISL doses were specified to provide context for changes from baseline in CD4+ T-cell and/or lymphocyte counts.
6.7 Intervention After the End of the Study	Clarified management of eligible participants with regard to entering (or not entering) the rollover study.	To clarify how all participants, including those with decreases in CD4+ T-cell and/or total lymphocyte counts, will be managed with regard to entering (or not entering) the rollover study.
7.1 Discontinuation of Study Intervention	• Updated to include specific parameters around decreased CD4+ T-cell and/or total lymphocyte counts as reasons for discontinuation from study intervention. • Added a discontinuation criterion for participants with any Category C conditions included in the CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults.	• To monitor participant safety. • To minimize further immunologic suppression in participants with opportunistic infection.

Section # and Name	Description of Change	Brief Rationale
8.1.9 Discontinuation and Withdrawal	Specified that participants discontinuing for decreases in CD4+ T-cell and/or total lymphocyte counts and those who discontinued for any reason and are noted to have >10% decrease from their average baseline value in CD4+ T-cell count and/or total lymphocyte count or that meet ECI criteria at the Early Discontinuation of Treatment visit must be unblinded (if applicable) and those who received DOR/ISL require additional monitoring per Section 8.11.5.	To monitor recovery in CD4+ T-cell count and/or total lymphocyte count after discontinuation of DOR/ISL.
8.2.2.4 Viral Drug Resistance Testing	Clarified that participants with "confirmed" viremia will have viral drug resistance testing.	To correct inconsistency between Sections 8.2.2 and 8.2.2.4.
8.2.3 T- and B-Lymphocyte and Natural Killer Cell Profile (TBNK)	Updated section title to reflect TBNK panel (changed from "CD4+ T-cell Counts" to "T- and B- Lymphocyte and Natural Killer Cell Profile (TBNK)".	Revised for clarity and accuracy of laboratory test nomenclature. CD4+ T cell count is part of TBNK panel which measures different lymphocyte subpopulations – T-cell, B-cell and NK cell types. Based on the clinical laboratory findings in the ISL program, these sub-populations will be assessed within the same hematologic sample that previously enumerated the CD4+, CD8+ T-cells to study the impact of DOR/ISL on the specific lymphocyte subpopulations.
8.4.7 Events of Clinical Interest (ECIs)	Added ECI-defining criteria for decreased CD4+ T-cell counts and total lymphocyte counts.	To monitor decreases in CD4+ T-cell and total lymphocyte counts to ensure appropriate follow up per protocol.

Section # and Name	Description of Change	Brief Rationale
8.11.3 Participants Who Discontinue Study Intervention	Added guidance that additional monitoring after discontinuation is required for DOR/ISL participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts per Section 8.11.5.	Cross-reference to Section 8.11.5 added to clarify management and emphasize additional requirements to monitor decreases in CD4+ T-cell and/or total lymphocyte counts for recovery after DOR/ISL discontinuation.
8.11.3.2 End of Treatment Follow-up Visit	Updated text for clarity. Added monitoring requirements after DOR/ISL discontinuation for participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.	To refer to additional assessments required to follow for recovery of decreased CD4+ T-cell and/or total lymphocyte counts after discontinuation of DOR/ISL.
8.11.5 Management of Participants with Decreases in CD4+ T-Cell Counts and/or Total Lymphocyte Counts	Added new section for confirming and monitoring decreases in CD4+ T-cell and/or total lymphocyte counts.	To provide guidance for the management of participants with decreases in CD4+ T-cell count and/or total lymphocyte count.
8.11.6 Clinical Management of Participants Who Become Pregnant	• Section formerly numbered as Section 8.11.5; numbering updated throughout the document. • Updated to include guidance for assessment of AEs that are pregnancy-related complications.	• To accommodate new section (ie, Section 8.11.5). • To clarify the guidance for reference (within the DAIDS table) when assessing AEs that are pregnancy-related complications.
10.2 Appendix 2: Clinical Laboratory Tests	Table 16 Added details on TBNK panel.	Added for completeness; TBNK panel measures different T-cell, B-cell, and NK cell types.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Table 17 • Updated laboratory procedure name CD4+ T-cell count to CD4+ T-cell count/TBNK panel. • Added visits (confirmation and monitoring) and blood volumes for CD4+ T-cell counts and lymphocyte counts. • Added blood volumes for CD4+ T-cell counts at Weeks 72, 84, 108, and 132 and at the End of Treatment Follow-up visit. • Added blood volume for hematology at the End of Treatment Follow-up visit. • Added footnote to clarify blood collection for CD4+ T-cell count at the CD4+ T-cell Count/Lymphocyte Count Monitoring Visit.	• Added for completeness • To add confirmation and monitoring visits for CD4+ T-cell/lymphocyte counts. • To update the blood volume collected (at each visit). • Footnote “e”added for clarity.
10.2 Appendix 2: Clinical Laboratory Tests	Table 17 Removed PK collection timepoints (and accompanying footnote “f”) for the CD4+ T-cell count/lymphocyte count confirmation and monitoring visits that had been included as part of Amendment 05.	No longer applicable to Amendment 06.
Throughout as applicable	A definition was added for “average baseline” for determination of CD4+ T-cell count and lymphocyte count values.	To define the baseline timeframe used for determining CD4+ T-cell count and lymphocyte count values.

Section # and Name	Description of Change	Brief Rationale
Throughout as applicable	Minor changes made to correct typographical errors, update formatting, and add cross-referencing.	To provide consistency and/or clarity within the document.

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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) Once-Daily in Participants With HIV-1 Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)

Short Title: DOR/ISL Blinded Label Switch

Acronym: Not applicable

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

Hypotheses, Objectives, and Endpoints:

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 for ≥3 months on BIC/FTC/TAF.

Primary Objectives	Primary Endpoints
- To evaluate the antiretroviral activity following switch to DOR/ISL compared to continued treatment with 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 measured 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. If non-inferiority of HIV-1 RNA ≥50 copies/mL at Week 48 and superiority of HIV-1 RNA ≥50 copies/mL at Week 96 are met: Hypothesis (H2): DOR/ISL is superior to BIC/FTC/TAF as measured 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 switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as assessed by review of the accumulated safety data through Week 48.	- Adverse events - Adverse events leading to discontinuation of study intervention
Secondary Objectives	Secondary Endpoints
- To evaluate the antiretroviral activity following switch to DOR/ISL compared to continued treatment with 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 non-inferior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96. A margin of 4 percentage points is used to define non-inferiority. If non-inferiority of HIV-1 RNA ≥50 copies/mL at Week 48 is met: Hypothesis (H4): DOR/ISL is superior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96.	- HIV-1 RNA
- To evaluate the antiretroviral activity following switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 48, Week 96 and Week 144: - HIV-1 RNA <40 copies/mL - HIV-1 RNA <50 copies/mL	- HIV-1 RNA
- To evaluate the immunologic effect of switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as measured by 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 in participants who switch to DOR/ISL and participants who continue treatment with BIC/FTC/TAF.	- Viral resistance-associated substitutions
- To evaluate the effect of switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF on weight, as measured by the mean change from baseline to Week 48, Week 96, and Week 144. Hypothesis (H5): DOR/ISL is superior to BIC/FTC/TAF as measured by lower mean increase from baseline in body weight at Week 48. Hypothesis (H6): DOR/ISL is superior to BIC/FTC/TAF as measured by lower mean increase from baseline in body weight at Week 96.	- Weight
- To evaluate the safety and tolerability of DOR/ISL compared to BIC/FTC/TAF as assessed by review of the accumulated safety data through study duration.	- 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 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

Masking	Participant or Subject Sponsor Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3.5 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 578 participants will be randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Treatment Period	Use
Group 1	DOR/ISL	100 mg/ 0.75 mg	QD	Oral	Day 1 to Week 144	Experimental
	Placebo to BIC/FTC/ TAF	0 mg	QD	Oral	Day 1 to Week 96	Placebo
Group 2	BIC/FTC/ TAF	50 mg/200 mg/ 25 mg	QD	Oral	Day 1 to Week 144	Experimental
	Placebo to DOR/ISL	0 mg	QD	Oral	Day 1 to Week 96	Placebo
	DOR/ISL	100 mg/ 0.75 mg	QD	Oral	Week 144 to 156	Experimental

BIC=bictegravir; DOR=doravirine; FTC=emtricitabine; ISL=islatravir; QD=once-daily; TAF=tenofovir alafenamide.

Total Number	2
Duration of Participation	Each participant will participate in the 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 blinded intervention for 96 weeks and open-label intervention through Week 144 for Group 1 or 156 for Group 2. Participants who discontinue study intervention or who become pregnant will be followed as described in the protocol.

Study Governance Committees:

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

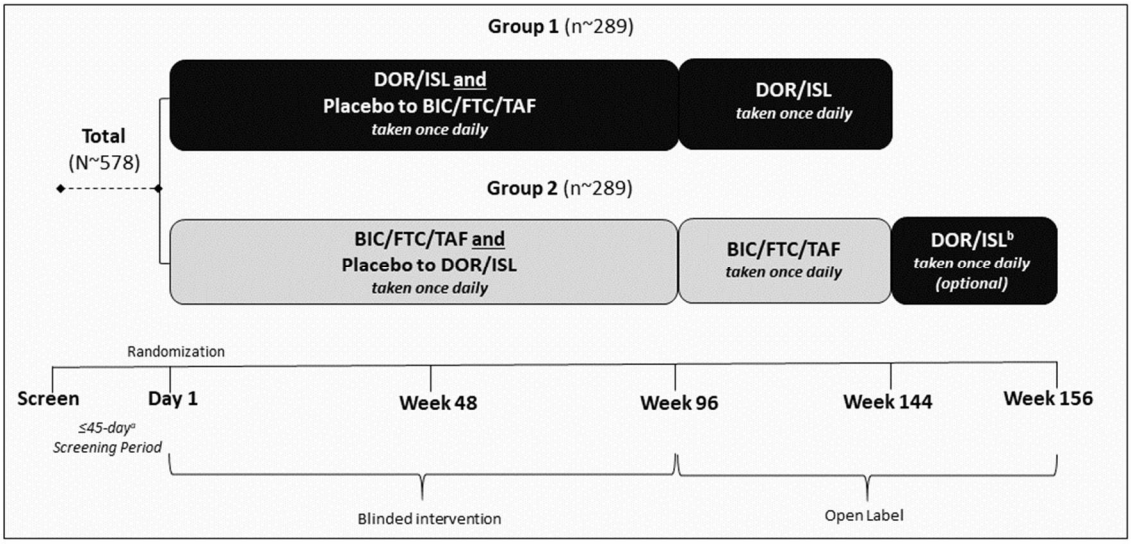
Study Accepts Healthy Volunteers: No

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema and Treatment Plan



BIC=bictegravir; DOR=doravirine; FTC=emtricitabine; ISL=islatravir; N=total number of participants in the study; n=number of participants per group; 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] At the end of Week 144 (Group 1) or Week 156 (Group 2), eligible participants will be offered the option to continue to receive open-label DOR/ISL through the rollover study (Sections 6.7 & 8.11.2.3).

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities – Screening Through Week 96 - Blinded Intervention

Study Period	**Screen**	**Intervention** (Blinded)										**Notes**
		Group 1 and Group 2										
Visit Number	1	2	3	4	5	6	7	8	9	10	11	
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)	Each visit should be calculated from date of Day 1. A visiting nurse may be utilized for visits after randomization per Section 8.11.2.2.
Visit Window	≤45 days[a]	NA	±7 days									To ensure timely study intervention resupply.
Administrative Procedures												
Informed Consent	X											
Informed Consent for Future Biomedical Research	X											
Informed Consent for Study Intervention During Pregnancy			<----------X---------->									Obtain upon confirmation of pregnancy if study intervention will be continued.
Collect and enter data from prenatal care provider in pregnant participants			<----------X---------->									The investigator (or designee) is responsible for obtaining relevant clinical and laboratory data from the obstetric care provider to monitor the safety and well-being of the mother and fetus. See 8.11.6.
Administration of EQ-5D-5L, HIV-SI/SDM, and HIVTSQ Patient Questionnaires		X	X	X			X				X	Administered prior to being seen by investigator and discussions about medical conditions or test results.
Inclusion/Exclusion Criteria	X	X										Review prior to randomization on Day 1 to confirm no changes in eligibility.
Participant Identification Card	X	X										At the time of randomization, site personnel will add the randomization number to the participant identification card.

Study Period	**Screen**	**Intervention** (Blinded)										**Notes**
		Group 1 and Group 2										
Visit Number	1	2	3	4	5	6	7	8	9	10	11	
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)	Each visit should be calculated from date of Day 1. A visiting nurse may be utilized for visits after randomization per Section 8.11.2.2.
Visit Window	≤45 days[a]	NA	±7 days									To ensure timely study intervention resupply.
Medical History	X											
Prior and Concomitant Medications Review	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	
Intervention Randomization		X										All procedures should be completed prior to dose on Day 1.
Unblind using IRT											X	
Dispense Study Intervention Using IRT		X		X	X	X	X	X	X	X	X	
Study Intervention Compliance Review			X	X	X	X	X	X	X	X	X	Reconcile doses and assess study intervention compliance.
Efficacy Procedures												
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	X	X	X	X	X	X	X	
CD4+ T-cell Count/ TBNK Panel	X	X			X		X		X	X	X	Decreases in CD4+ T-cell count that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.
Plasma for HIV Viral Drug Resistance Testing		X	X	X	X	X	X	X	X	X	X	Back-up samples, will be used if needed.

Study Period	**Screen**	**Intervention** (Blinded)										**Notes**
		Group 1 and Group 2										
Visit Number	1	2	3	4	5	6	7	8	9	10	11	
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)	Each visit should be calculated from date of Day 1. A visiting nurse may be utilized for visits after randomization per Section 8.11.2.2.
Visit Window	≤45 days[a]	NA	±7 days									To ensure timely study intervention resupply.
Safety Procedures												
Full Physical Examination	X											
Height		X										
Weight	X	X			X		X		X		X	
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	Includes pulse, blood pressure, temperature, and respiratory rate.
12-Lead ECG		X										May be performed up to 7 days prior to Day 1 after all other eligibility criteria are confirmed.
Contraceptive Use Confirmation (WOCBP Only)		X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy Test (β-hCG; WOCBP Only)	X											
Urine Pregnancy Test (WOCBP Only)		X	X	X	X	X	X	X	X	X	X	Confirm with serum test if urine test is positive. If serum positive, participants will be managed per Section 8.11.6 and safety of her infant collected per Section 8.11.6.4.1.
HIV-1 & -2 Serology	X											
Hepatitis Serology	X											Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV.

Study Period	**Screen**	**Intervention** (Blinded)										**Notes**
		Group 1 and Group 2										
Visit Number	1	2	3	4	5	6	7	8	9	10	11	
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)	Each visit should be calculated from date of Day 1. A visiting nurse may be utilized for visits after randomization per Section 8.11.2.2.
Visit Window	≤45 days[a]	NA	±7 days									To ensure timely study intervention resupply.
HBsAg	X	X	X	X	X	X	X	X	X	X	X	All participants at screening, only anti-HBc positive participants thereafter.
HBV DNA	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	Fasting is required at Day 1 and Weeks 24, 48 and 96.
Hematology	X	X	X	X	X	X	X	X	X	X	X	Decreases in total lymphocyte counts that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.
PT/INR	X											Test to be performed only in participants infected with HCV.
Urinalysis		X			X		X		X		X	
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics												
Blood (Plasma) for ISL PK		X	X	X	X		X					At Week 4, a predose and postdose sample will be taken.
Blood (Plasma) for Investigational PK						X		X	X	X	X	Analysis triggered by Sponsor as needed. Not collected for pregnant participants.
Blood (Plasma) for DOR and ISL PK in Pregnant Participants		<----------X---------->										Collected during the 1st, 2nd, and 3rd trimesters and postpartum per Section 8.11.6.1.
Biomarkers												
Blood for Genetic Analysis[b]		X										
Whole Blood for Future Biomedical Research		X			X		X				X	Optional participation; requires FBR consent.

Study Period	**Screen**	**Intervention** (Blinded)										**Notes**
		Group 1 and Group 2										
Visit Number	1	2	3	4	5	6	7	8	9	10	11	
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)	Each visit should be calculated from date of Day 1. A visiting nurse may be utilized for visits after randomization per Section 8.11.2.2.
Visit Window	≤45 days[a]	NA	±7 days									To ensure timely study intervention resupply.
DEXA Scan (Only Where Permitted by Local Law)		X					X				X	Perform after <u>all</u> eligibility criteria are confirmed and within 14 days after Day 1. At Weeks 48 and 96, scans may be performed ± 14 days of the scheduled visit. May require additional planning/scheduling. DEXA should not be performed on pregnant participants.
Waist and Hip Measurements		X					X				X	
Blood and Urine for Renal Markers		X			X		X				X	
Blood for Inflammatory Markers		X			X		X				X	

anti-HBc=hepatitis B core antibody; β-hCG=beta human chorionic gonadotropin; bp=blood pressure; DEXA=Dual X-ray Absorptiometry; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EQ-5D-5L=EuroQol five-dimensional descriptive system, five level version; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; INR=international normalized ratio; IRT=Interactive Response Technology; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic; PT=prothrombin time; RNA=ribonucleic acid; rr=respiratory rate; TBNK= T- and B- Lymphocyte and Natural Killer Cell Profile; temp=body temperature; WOCBP=a woman/women of childbearing potential.

[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, screening period of up to 45 days is allowed.

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

1.3.2 Schedule of Activities – Week 108 Through Week 156 - Open-Label Intervention

Study Period	**Intervention (Open-Label)**						**Notes**
Visit Number	12	13	14	15	16	17	Each visit should be calculated from date of Visit 2, Day 1. A visiting nurse service may be utilized for visits after randomization (if locally available and approved for use).
Scheduled Day/Week	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Week 148	Week 156	
Visit Window	±7 days						
	Group 1 and 2		Group 1	Group 2	Group 1	Group 2	Group 2 Only		
Administrative Procedures							
Prior / Concomitant Medication Review	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		Participants in Group 2 have the option to switch to open-label DOR/ISL at Week 144. IRT for P018 will be used to dispense to Group 2. Participants that are pregnant at Week 144 or Week 156 will also be dispensed study medication using IRT for this study. See Section 1.3.4.
Study Intervention Compliance Review	X	X	X	X	X	X	Reconcile doses and assess study intervention compliance.
Informed Consent for Study Intervention During Pregnancy	<----------X---------->						Obtain upon confirmation of pregnancy if study intervention will be continued.

Study Period	**Intervention (Open-Label)**						**Notes**
Visit Number	12	13	14	15	16	17	Each visit should be calculated from date of Visit 2, Day 1. A visiting nurse service may be utilized for visits after randomization (if locally available and approved for use).
Scheduled Day/Week	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Week 148	Week 156	
Visit Window	±7 days						
	Group 1 and 2		Group 1	Group 2	Group 1	Group 2	Group 2 Only	
Collect and enter data from prenatal care provider in pregnant participants	<----------X---------->						The investigator (or designee) is responsible for obtaining relevant clinical and laboratory data from the obstetric care provider to monitor the safety and well-being of the mother and fetus. See 8.11.6.
Efficacy Procedures							
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	X	X	
CD4+ T-cell Count/TBNK Panel	X	X	X	X	X	X	Decreases in CD4+ T-cell count that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.
Blood (Plasma) for HIV-1 Drug Resistance	X	X	X	X	X	X	Back-up samples, will be used if needed
Safety Procedures							
Weight		X		X			
Directed Physical Examination	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	Includes pulse, blood pressure, temperature, and respiratory rate

Study Period	**Intervention (Open-Label)**						**Notes**
Visit Number	12	13	14	15	16	17	Each visit should be calculated from date of Visit 2, Day 1. A visiting nurse service may be utilized for visits after randomization (if locally available and approved for use).
Scheduled Day/Week	Week 108	Week 120 (Fasting)	Week 132	Week 144 (Fasting)	Week 148	Week 156	
Visit Window	±7 days						
	Group 1 and 2		Group 1 / Group 2	Group 1 / Group 2	Group 2 Only		
Contraception Use Confirmation (WOCBP only)	X	X	X	X	X	X	
Urine Pregnancy Test (WOCBP only)	X	X	X	X	X	X	Confirm with serum test if urine test is positive. If serum positive, participants will be managed per Section 8.11.6 and safety of her infant collected per Section 8.11.6.4.1.
Hepatitis Serology			X				At Week 132, all Group 2 participants should be tested. Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV.
HBsAg	X	X	X	X	X	X	Participants who are anti-HBc positive at screening or at Week 132.
HBV DNA	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	Fasting is required at Week 120 and 144.
Hematology	X	X	X	X	X	X	Decreases in total lymphocyte counts should be managed according to Section 1.3.5 and Section 8.11.5.

Study Period	**Intervention (Open-Label)**								**Notes**
Visit Number	12	13	14		15		16	17	Each visit should be calculated from date of Visit 2, Day 1. A visiting nurse service may be utilized for visits after randomization (if locally available and approved for use).
Scheduled Day/Week	Week 108	Week 120 (Fasting)	Week 132		Week 144 (Fasting)		Week 148	Week 156	
Visit Window	±7 days								
	Group 1 and 2		Group 1	Group 2	Group 1	Group 2	Group 2 Only		
Urinalysis		X			X				
Review of Adverse Events	X	X	X		X		X	X	
Pharmacokinetics									
Blood (Plasma) for Investigational PK					X				Analysis triggered by Sponsor as needed. Not collected for pregnant participants
Blood (Plasma) for DOR and ISL PK in Pregnant Participants Only	<----------X---------->								Collected in participants who become pregnant. PK samples will be collected during the 1st, 2nd, and 3rd trimesters and postpartum per Section 8.11.6.1.
Biomarkers									
Whole Blood for Future Biomedical Research					X				Optional participation; requires FBR consent.
Blood for Inflammatory Markers					X				
Blood and Urine for Renal Markers					X				
Waist and Hip Measurements					X				

Study Period	**Intervention (Open-Label)**								**Notes**
Visit Number	12	13	14		15		16	17	Each visit should be calculated from date of Visit 2, Day 1. A visiting nurse service may be utilized for visits after randomization (if locally available and approved for use).
Scheduled Day/Week	Week 108	Week 120 (Fasting)	Week 132		Week 144 (Fasting)		Week 148	Week 156	
Visit Window	±7 days								
	Group 1 and 2		Group 1	Group 2	Group 1	Group 2	Group 2 Only		
DEXA Scan (only where permitted by local law)					X				At Week 144, scans may be performed ±14 days of the scheduled visit. May require additional planning/ scheduling. Participants who become pregnant will not have DEXA Scans
Administrative Procedures for the Rollover									
Begin Rollover Study Procedures					X			X	Refer to the rollover study protocol for additional information. Participants who do not consent to the roll over study will have an End of Treatment Follow-up visit and complete their study participation.
DEXA=dual-energy X-ray absorptiometry; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; IRT=interactive response technology; ISL=islatravir; NA=not applicable; PCR=polymerase chain reaction; RNA=ribonucleic acid; TBNK= T- and B- Lymphocyte and Natural Killer Cell Profile; WOCBP=woman/women of childbearing potential.									

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

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment[a]	End of Treatment Follow-up	The End of Treatment Follow-up visit should also be performed for participants who do not continue study intervention after Week 144 (Group 1 and 2) or Week 156 (Group 2 only) (ie, in the rollover study)[b]
Visit Window	Within 2 to 4 Weeks of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	
Administrative Procedures				
Prior and Concomitant Medications Review	X	X	X	
Register Study Visit in IRT	X	X		
Study Intervention Compliance Review	X	X		Reconcile doses and study intervention compliance.
Administration of EQ-5D-5L, HIV-SI/SDM, and HIVTSQ Patient Questionnaires		X		Administered prior to being seen by investigator and discussions about medical conditions or test results. Not to be collected if participant discontinues treatment after Week 96.
Efficacy Procedures				
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	
CD4+ T-cell Count/TBNK Panel		X		Participants with decreases in CD4+ T-cell count >10% from average baseline value[c] or who meet ECI criteria at the Early Discontinuation of Treatment visit should be managed per Section 8.11.5 and Section 1.3.5.

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment[a]	End of Treatment Follow-up	The End of Treatment Follow-up visit should also be performed for participants who do not continue study intervention after Week 144 (Group 1 and 2) or Week 156 (Group 2 only) (ie, in the rollover study)[b]
Visit Window	Within 2 to 4 Weeks of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	
Plasma for HIV Viral Drug Resistance Testing	X	X	X	If HIV drug resistance sample is collected at Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit. Analysis of samples collected at End of Treatment visits triggered by Sponsor as needed.
Safety Procedures				
Full Physical Examination		X	X	
Vital Signs		X	X	Includes pulse, blood pressure, temperature, and respiratory rate
Contraceptive Use Confirmation (WOCBP Only)	X	X	X	
Serum Pregnancy Test (WOCBP Only)		X	X	If serum test is positive, participants will be managed per Section 8.11.6 and safety of her infant collected per Section 8.11.6.4.1.
Chemistry		X		
Hematology		X		Participants with decreases in total lymphocyte counts >10% from average baseline value[c] or who meet ECI criteria at the Early Discontinuation of Treatment Visit should be managed per Section 8.11.5 and Section 1.3.5.
Urinalysis		X		

Study Period	**Viremia Confirmation**	**End of Treatment**		**Notes**
Visit Number	Unscheduled	Unscheduled		
Scheduled Day/Week	Viremia Confirmation	Early Discontinuation of Treatment[a]	End of Treatment Follow-up	The End of Treatment Follow-up visit should also be performed for participants who do not continue study intervention after Week 144 (Group 1 and 2) or Week 156 (Group 2 only) (ie, in the rollover study)[b]
Visit Window	Within 2 to 4 Weeks of HIV-1 Viremia (≥50 copies/mL)	NA	42 (+7) days after the end of treatment	
Review of Adverse Events	X	X	X	
Pharmacokinetics				
Blood (Plasma) for Investigational PK	X	X	X	Analysis triggered by Sponsor as needed.
Biomarkers				
Whole Blood for Future Biomedical Research	X	X		If FBR sample was collected at Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit.

bp=blood pressure; EQ-5D-5L=EuroQol five-dimensional descriptive system, five level version; FBR=future biomedical research; HIV=human immunodeficiency virus; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IRT=Interactive Response Technology; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; rr=respiratory rate; TBNK= T- and B- Lymphocyte and Natural Killer Cell Profile; temp=body temperature; WOCBP=a woman/women of childbearing potential.

[a] Early Discontinuation of Treatment visit applies to any participant who discontinues study intervention prior to Week 144.

[b] For women who become pregnant, see Section 8.11.6 for instructions on discontinuation and end of treatment follow-up.

[c] The average baseline value is defined as the average value between screening (within 45 days prior to the first dose of study medication) and Day 1.

1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 144 or 156

Visit Number	**Unscheduled**				**Notes**
Scheduled Week	**Pregnancy 1 (Week 156 or 168)**	**Pregnancy 2 (Week 168 or 180)**	**Pregnancy 3 (Week 180 or 192)**	**Pregnancy 4 (Week 192 or 204)**	For any participant who is pregnant at the last study visit and consents to continue study intervention, the visit schedule will be extended to allow assessments through each trimester and postpartum. Extension visits will only be performed through pregnancy & a single postpartum timepoint, as applicable for each participant. Each pregnancy visit will be 12 weeks apart.
Visit Window	± 7 days				
Administrative Procedures					
Prior and Concomitant Medications Review	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	
Dispense Study Intervention Using IRT	X	X	X		Study intervention dispensation will stop at the first visit postpartum.
Evaluation to Receive Continued Study Intervention	X	X	X	X	At the end of pregnancy, continued access to DOR/ISL will be offered per Section 6.7.
Study Intervention Compliance Review	X	X	X	X	Reconcile doses and study intervention compliance
Collect and enter data from prenatal care provider	<----------X---------->				Obtain relevant prenatal clinical & laboratory data to monitor the safety of the mother & fetus per Section 8.11.6
Efficacy Procedures					
Plasma HIV-1 RNA Quantification (Real Time PCR)	X	X	X	X	
CD4+ T-cell Count/TBNK Panel	X	X	X	X	Decreases in CD4+ T-cell count that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.

Visit Number	**Unscheduled**				**Notes**
Scheduled Week	**Pregnancy 1 (Week 156 or 168)**	**Pregnancy 2 (Week 168 or 180)**	**Pregnancy 3 (Week 180 or 192)**	**Pregnancy 4 (Week 192 or 204)**	For any participant who is pregnant at the last study visit and consents to continue study intervention, the visit schedule will be extended to allow assessments through each trimester and postpartum. Extension visits will only be performed through pregnancy & a single postpartum timepoint, as applicable for each participant. Each pregnancy visit will be 12 weeks apart.
Visit Window	± 7 days				
Plasma for HIV Viral Drug Resistance Testing	X	X	X	X	Back-up samples, will be used if needed
Safety Procedures					
Weight	X	X	X	X	
Directed Physical Examination	X	X	X	X	
Vital Signs	X	X	X	X	Includes pulse, blood pressure, temperature, and respiratory rate
HBsAg	X	X	X	X	Participants who are anti-HBc positive at screening or at Week 132 only
HBV DNA	X	X	X	X	
Chemistry	X	X	X	X	
Hematology	X	X	X	X	Decreases in total lymphocyte counts that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.
Urinalysis	X	X	X	X	
Review of Adverse Events	X	X	X	X	
Pharmacokinetics					
Blood (Plasma) for DOR and ISL PK	X	X	X	X	Collected during the 1st, 2nd, and 3rd trimesters and postpartum per Section 8.11.6.1.
Biomarkers					
Whole Blood for Future Biomedical Research	X	X	X	X	Optional participation; requires FBR consent

DNA=deoxyribonucleic acid; DOR=doravirine; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV=human immunodeficiency virus; IRT=Interactive Response Technology; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; TBNK= T- and B- Lymphocyte and Natural Killer Cell Profile.

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

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring DOR/ISL Only**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases to CD4+ T-cell count and/or lymphocyte count are confirmed, the participant should be discontinued from treatment and unblinded (if applicable) to determine need for additional monitoring. Only those treated with DOR/ISL require additional monitoring.
Visit Window	Within 3-4 weeks* of initial decrease **Note*: if total lymphocyte count remains ≥1 x 10^9 cells/L, confirmation of decreased lymphocytes is due in 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Every 4 weeks (±7 days)	
Administrative Procedures					
Prior and Concomitant Medications Review	X	X	X	X	
Register Study Visit in IRT	X	X		X	
Study Intervention Compliance Review		X			Reconcile doses and study intervention compliance.
Administration of EQ-5D-5L, HIV-SI/SDM, and HIVTSQ Patient Questionnaires		X			Administered prior to being seen by investigator and discussions about medical conditions or test results. Not to be collected if participant discontinues treatment after Week 96.

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring DOR/ISL Only**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases to CD4+ T-cell count and/or lymphocyte count are confirmed, the participant should be discontinued from treatment and unblinded (if applicable) to determine need for additional monitoring. Only those treated with DOR/ISL require additional monitoring.
Visit Window	Within 3-4 weeks* of initial decrease **Note*: if total lymphocyte count remains ≥1 x 10^9 cells/L, confirmation of decreased lymphocytes is due in 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Every 4 weeks (±7 days)	
Efficacy Procedures					
Plasma HIV-1 RNA Quantification (Real Time PCR)		X	X		
CD4+ T-cell Count/ TBNK Panel	X	X	X (DOR/ISL Only)	X	
Plasma for HIV Viral Drug Resistance Testing		X	X		Analysis of samples collected at End of Treatment visits will be triggered by Sponsor, as needed.
Safety Procedures					
Full Physical Examination		X	X		
Vital Signs		X	X		Includes weight, pulse, blood pressure, temperature, and respiratory rate.

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring DOR/ISL Only**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases to CD4+ T-cell count and/or lymphocyte count are confirmed, the participant should be discontinued from treatment and unblinded (if applicable) to determine need for additional monitoring. Only those treated with DOR/ISL require additional monitoring.
Visit Window	Within 3-4 weeks* of initial decrease **Note*: if total lymphocyte count remains ≥1 x 10^9 cells/L, confirmation of decreased lymphocytes is due in 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Every 4 weeks (±7 days)	
Contraceptive Use Confirmation (WOCBP Only)		X	X		
Serum Pregnancy Test (WOCBP Only)		X	X		If serum test is positive, participants will be managed per Section 8.11.6 and Section 8.11.6.2 safety of her infant collected per Section 8.11.6.4.1.
Chemistry		X			
Hematology	X	X	X (DOR/ISL Only)	X	
Urinalysis		X			
Review of Adverse Events	X	X	X	X	

Study Period	**CD4+ T-cell Count and/or Total Lymphocyte Count Confirmation**	**End of Treatment**		**CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring DOR/ISL Only**	**Notes**
Visit Number	Unscheduled	Unscheduled		Unscheduled	
Scheduled Day/Week	CD4+ T-cell and/or Total Lymphocyte Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell and/or Total Lymphocyte Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases to CD4+ T-cell count and/or lymphocyte count are confirmed, the participant should be discontinued from treatment and unblinded (if applicable) to determine need for additional monitoring. Only those treated with DOR/ISL require additional monitoring.
Visit Window	Within 3-4 weeks* of initial decrease **Note*: if total lymphocyte count remains ≥1 x 10^9 cells/L, confirmation of decreased lymphocytes is due in 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Every 4 weeks (±7 days)	
Pharmacokinetics					
Blood (Plasma) for Investigational PK		X	X		PK analysis triggered by Sponsor as needed.
Biomarkers					
Whole Blood for Future Biomedical Research		X			

bp=blood pressure; FBR=future biomedical research; HIV=human immunodeficiency virus; HIV-SI/SDM=Human Immunodeficiency Virus Symptom Index/Symptom Distress Module; HIVTSQ=Human Immunodeficiency Virus Treatment Satisfaction Questionnaire; IRT=Interactive Response Technology; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; rr=respiratory rate; TBNK= T- and B- Lymphocyte and Natural Killer Cell Profile; temp=body temperature; WOCBP=a woman/women of childbearing potential.

2 INTRODUCTION

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

2.1 Study Rationale

As treatment regimens have improved, HIV-1 infection has become a chronic, manageable condition, and those receiving effective ART regimens can expect to live near-normal lifespans [Trickey, A., et al 2017]. With anticipation of long-term treatment, 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) [AIDS info 2017] [European AIDS Clinical Society 2016] [World Health Organization 2016]. Although such regimens have become increasingly well tolerated and highly efficacious, the current paradigm of lifelong daily treatment is associated with a need for simpler and safer regimens, with reduced long-term drug exposure. Furthermore, as the population living with HIV ages, there is increasing concern for the risks of long-term toxicity and DDIs with respect to comorbid conditions (ie, neuropsychiatric, cardiovascular).

There is accumulating evidence that simplified 2-drug regimens can achieve efficacy comparable to that of 3-drug regimens, better tolerability, and improve quality of life, which can help to sustain virologic suppression [Llibre, J. M., et al 2018] [Cahn, P., et al 2019] [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]. The viability 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 agent 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) by multiple mechanisms of action, lack of food requirements, and favorable tolerability and DDI profiles observed to date.

2.2 Background

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

2.2.1 Islatravir

ISL is the first member of a new class of antiretroviral agents, known as NRTTIs, that block HIV-1 reverse transcriptase by novel mechanisms of action. It is an inactive nucleoside analogue that is converted to the pharmacologicially-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 0.75 mg QD, ISL achieves higher steady-state IQs (the ratio of drug exposure to viral susceptibility [Ctrough/IC50]) against wild-type HIV-1 than any NRTI currently approved for treatment. It also exhibits potent 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). The safety and efficacy profiles of DOR have been well characterized in Phase 3 clinical studies conducted in treatment-naïve adult participants [Orkin, C., et al 2018] [Molina, J. M., et al 2018] and in virologically suppressed adult participants switching from a stable antiretroviral regimen [CSR P024MK1439A].

2.2.3 Doravirine/Islatravir

DOR/ISL is an FDC containing DOR (100 mg) and ISL (0.75 mg), administered as a single tablet QD. DOR and ISL represent 2 distinct classes of antiretrovirals that inhibit reverse transcription by different mechanisms. Based on the profiles of each of these drugs and data available to-date, the combination DOR/ISL is expected to be well tolerated and highly efficacious, with a high barrier to resistance. The combination has demonstrated additive antiretroviral activity in vitro and has suppressed emergence of resistance at clinically relevant concentrations.

The combination of DOR and ISL (administered as single-entities, DOR + ISL) is being evaluated in an ongoing randomized Phase 2 study (MK-8591 P011) in approximately 90 treatment-naïve adult participants with HIV-1. Participants were initially assigned to receive either DOR + ISL and 3TC or an FDC of DOR, 3TC, and TDF (DOR/3TC/TDF). Participants receiving DOR + ISL + 3TC who achieved HIV-1 RNA <50 copies/mL at Week 20 (or later) discontinued 3TC at their next study visit (most were able to discontinue 3TC at Week 24) while continuing DOR + ISL. At Weeks 48 and 96, the percentage of participants with HIV-1 RNA <50 copies/mL among those who received the 2-drug regimen of DOR + ISL was comparable to those who received the 3-drug regimen of DOR/3TC/TDF. The majority of participants maintained virologic suppression through Week 144. None of the participants with protocol-defined virologic failure rebounded above the clinically relevant HIV-1 RNA >200 copies/mL cutoff. As such, no participant met the criteria for resistance testing. DOR + ISL, administered with 3TC or alone as a 2-drug regimen, had a favorable safety and tolerability profile through Week 96, comparable to that of DOR/3TC/TDF. Mean changes from baseline in CD4+ T-cell count were comparable for DOR/3TC/TDF and each dose of ISL as a 3-drug regimen (at Week 24) or a 2-drug regimen (at Weeks 48, 96, 144).

The clinical development program of DOR/ISL includes ongoing studies in treatment-naïve adults (P020), virologically suppressed adults (P017 and P018), and heavily treatment-

experienced participants (P019) and participants <18 years of age and weighing ≥35 kg (P028).

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 approved labeling for detailed information on BIC/FTC/TAF.

2.3 Benefit/Risk Assessment

Although it cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine, the totality of available nonclinical and clinical data supports continued evaluation of DOR/ISL in Phase 3 clinical studies.

The comprehensive nonclinical safety evaluations of DOR (an approved NNRTI) and ISL (an investigational NRTTI) as mono-entities have not revealed toxicities of concern for daily dosing. Nonclinical developmental and reproductive toxicity studies did not identify any clinically relevant concerns that would preclude continued dosing of DOR/ISL in participants who become pregnant during the study. Both mono-entities are differentiated by a high barrier to resistance in vitro with DOR exhibiting potent activity against the most prevalent NNRTI-resistant mutations (eg, K103N, Y181C, G190A, and E138K) and ISL against common NRTI-resistant mutations (eg, M184V and TAMs). Both may be administered without regard to food, have a low potential for DDIs, and have favorable PK and tolerability profiles.

High potency against wild-type and resistant variants of HIV-1 virus and a long half-life make ISL a suitable candidate for development for the treatment of HIV-1 infection. Across the clinical development program, ISL administered alone or with DOR was generally well tolerated. In the dose-ranging study (MK-8591 P011), ISL+DOR+3TC (as a 3-drug regimen) achieved virological suppression in most (>90%) treatment-naïve participants by Week 24. ISL+DOR (as a 2-drug regimen) maintained virologic suppression of HIV-1 RNA 24 and 48 weeks after switching from the 3-drug regimen and through Week 144. In 2 ongoing Phase 3 studies evaluating DOR/ISL for daily treatment of HIV-1 in virologically suppressed participants (MK-8591A P017 and MK-8591A P018), approximately 95% of 658 participants enrolled in the DOR/ISL arm completed 48 weeks of treatment in both studies. In P017 and P018, the percentage of participants with HIV-1 RNA ≥50 copies/mL was <1% for the DOR/ISL group and a high percentage of participants (>93% to 95%) in the DOR/ISL group maintained virologic suppression (HIV-1 RNA <50 copies/mL) comparable to baseline ART (P017) and BIC/FTC/TAF (P018) at Week 48. To date, no viral resistance to either component of DOR/ISL has been shown in the Phase 2 (P011) and Phase 3 studies (P017 and P018). At the doses administered for daily treatment, DOR/ISL has been well tolerated and associated with low rates of drug-related AEs.

Downward trends of total lymphocyte counts and CD4+ T-cell counts were observed in studies with ISL alone or in combination with other antiviral agents. In a Phase 2 study (MK-8591 P013) for once weekly HIV-1 treatment, decreases in lymphocyte and CD4+ T-cell counts from baseline were observed in the ISL 20 mg + MK-8507 treatment arms at Week 12 and Week 24. Decreases from baseline in lymphocyte count were observed in all dosing arms of ISL + MK-8507 starting at Week 8 with further decreases continuing through Week 24. Twenty of 58 participants on ISL + MK-8507 had a decrease in lymphocyte count of >30% (of whom 9 had a >50% reduction) by Week 24. These reductions were more pronounced in the 2 higher MK-8507 dose arms (200 and 400 mg), potentially indicating a dose-response relationship. Dosing of ISL+MK-8507 in P013 has been stopped.

In the Phase 2 randomized, double-blind, placebo-controlled study evaluating 60 mg and 120 mg of ISL monthly for PrEP in participants at low-risk of HIV-1 infection (MK-8591 P016), there was a 21% mean decrease in total lymphocytes observed in the 60 mg arm (the dose being evaluated in Phase 3 PrEP studies) and a 36% decrease in total lymphocytes observed in the 120 mg arm. In this population of HIV-1 uninfected participants, the mean decreases were in the normal range and there was no increase in clinical AEs related to infection. Dosing of oral ISL 60 mg QM has been stopped in PrEP clinical studies.

In an interim analysis for each of the Phase 3 studies studying DOR/ISL 100 mg/0.75 mg for HIV-1 treatment, P017 and P018, there were mean decreases from baseline in lymphocyte counts at Week 48 of 10.6% and 8.5% in the DOR/ISL groups (in P017 and P018, respectively) compared with mean increases from baseline of 2.27% and 3.46% in the comparator arms (in P017 and P018, respectively). In the same studies, DOR/ISL-treated participants had mean changes from baseline in CD4+ T-cell count of -0.7% (P017) and +0.9% (P018) compared with mean increases of 8.7% in the baseline ART group (P017) and 12.8% in the BIC/FTC/TAF group (P018). The decreases in CD4+ T-cell counts and lymphocyte counts have not been associated with an increased incidence of infection or other AEs. The clinical impact of these laboratory changes over the long term is unknown, and the Sponsor is assessing the reversibility of the reductions in CD4+ T-cell and lymphocyte counts. To mitigate the risk, increased monitoring of CD4+ T-cell and lymphocyte counts and strict stopping rules have been added to DOR/ISL studies. At this time, the data review supports continuation of the Phase 3 clinical studies for the DOR/ISL 100 mg/0.75 mg HIV-1 once-daily treatment program.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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 for ≥3 months on BIC/FTC/TAF.

Objectives	Endpoints
Primary	
• To evaluate the antiretroviral activity following switch to DOR/ISL compared to continued treatment with 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 measured 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. If non-inferiority of HIV-1 RNA ≥50 copies/mL at Week 48 and superiority of HIV-1 RNA ≥50 copies/mL at Week 96 are met: **Hypothesis (H2)**: DOR/ISL is superior to BIC/FTC/TAF as measured 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 switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as assessed by review of the accumulated safety data through Week 48.	• Adverse events • Adverse events leading to discontinuation of study intervention

Objectives	Endpoints
Secondary	
• To evaluate the antiretroviral activity following switch to DOR/ISL compared to continued treatment with 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 non-inferior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96. A margin of 4 percentage points is used to define non-inferiority. If non-inferiority of HIV-1 RNA ≥50 copies/mL at Week 48 is met: **Hypothesis (H4)**: DOR/ISL is superior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96.	• HIV-1 RNA
• To evaluate the antiretroviral activity following switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as assessed by the percentage of participants with the following at Week 48, Week 96 and Week 144: - HIV-1 RNA <40 copies/mL - HIV-1 RNA <50 copies/mL	• HIV-1 RNA
• To evaluate the immunologic effect of switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as measured by 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 in participants who switch to DOR/ISL and participants who continue treatment with BIC/FTC/TAF.	• Viral resistance-associated substitutions

Objectives	Endpoints
• To evaluate the effect of switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF on weight, as measured by the mean change from baseline to Week 48, Week 96, and Week 144. **Hypothesis (H5)**: DOR/ISL is superior to BIC/FTC/TAF as measured by lower mean increase from baseline in body weight at Week 48. **Hypothesis (H6)**: DOR/ISL is superior to BIC/FTC/TAF as measured by lower mean increase from baseline in body weight at Week 96.	• Weight
• To evaluate the safety and tolerability of DOR/ISL compared to BIC/FTC/TAF as assessed by review of the accumulated safety data through study duration.	• Adverse events • Adverse events leading to discontinuation of study intervention
Tertiary/Exploratory	
• To evaluate the effect on fasting lipid and metabolic profiles, renal function, inflammation, and body composition following switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as measured by the mean change in laboratory and radiological markers from baseline at Week 48, Week 96, and Week 144.	• Laboratory and radiological markers
• To evaluate the pharmacokinetics of ISL, when administered as a component of DOR/ISL.	• Pharmacokinetic values, such as AUC, Cmax, and C24
• To describe PROs related to HRQoL, self-reported HIV symptoms, and treatment satisfaction of switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF at Weeks 48 and 96.	• HRQoL, HIV symptom burden, and treatment satisfaction
• To explore the antiretroviral activity following switch to DOR/ISL compared to continued treatment with BIC/FTC/TAF as assessed by time to loss of virologic response at Week 48, Week 96 and Week144.	• Time to loss of virologic response

Objectives	Endpoints
• 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

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

4 STUDY DESIGN

4.1 Overall Design

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

A total of approximately 578 participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups (Figure 1):

> **Group 1** (n = approximately 289): Switch from BIC/FTC/TAF to DOR/ISL on Day 1 (taken with matching placebo to BIC/FTC/TAF through Week 96).
>
> **Group 2** (n = approximately 289): Continue BIC/FTC/TAF (taken with matching placebo to DOR/ISL through Week 96).

Clinical site personnel and participants will remain blinded through Week 96 while Sponsor personnel will remain blinded through Week 48. Safety and efficacy laboratory results, including HIV-1 RNA, will remain unmasked throughout the study. At Week 96, all participants and site personnel will be unblinded and participants will continue to receive their assigned study intervention open-label through Week 144. All participants who reach Week 144 will be considered to have completed the study. At Week 144, participants who were randomized to Group 1 will be offered to continue to receive open-label DOR/ISL in the rollover study. Participants who were randomized to Group 2 will be given the option to be switched to open-label DOR/ISL and continue to be monitored in P018 through Week 156, at which time they will be offered to continue to receive open-label DOR/ISL in the rollover study. Group 2 participants who opt out of switching to DOR/ISL will complete the study at Week 144. Participants in Group 2 who are pregnant at Week 144 will not be offered the option to switch to DOR/ISL.

Any participants with confirmed viremia, as described in Section 4.2.1.1.2, will be assessed for development of viral drug resistance and potential discontinuation from study

intervention. Viral resistance data will remain masked to the Sponsor through Week 48 and to site personnel and participants through Week 96.

Participant safety will be monitored by an independent eDMC through periodic review of safety and efficacy data (received from an unblinded independent statistician) throughout the study (Appendix 1). When 40% of target enrollment have completed Week 24, including visit assessments, an interim analysis (which will hereafter be referred to as the "Week 24 interim analysis") to assess futility based on Week 24 data is planned (Section 9.7).

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

4.2 Scientific Rationale for Study Design

The randomized active-controlled non-inferiority study design is consistent with FDA regulatory guidance [Food and Drug Administration (CBER) 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, aligned with regulatory guidance [Food and Drug Administration (CBER) 2015], the primary efficacy analysis will occur after 48 weeks of treatment with DOR/ISL or BIC/FTC/TAF. Blinded study intervention will continue through Week 96 and participants' originally assigned therapy will be continued open-label from Week 96 to Week 144 to enable a longer-term comparison between the 2 treatment groups. Participants from Group 2 will have the option of switching to DOR/ISL at Week 144 followed by a 12-week safety and tolerability monitoring period (until Week 156).

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 baseline. 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 <40 copies/mL corresponds to the lower limit of quantification of the assay being used in this study.

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:

- **Virologic Rebound**: Two consecutive (2 to 4 weeks apart) occurrences of HIV-1 RNA ≥200 copies/mL at any time during the study.

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

An HIV-1 RNA level of ≥50 copies/mL must be confirmed and requires further management as described in Section 8.2.2.

4.2.1.2 Safety Endpoints

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

4.2.1.3 Weight, Laboratory, and Radiological Markers

The study will evaluate weight, laboratory, and radiological markers as changes from baseline in the treatment arms to evaluate the impact of DOR/ISL as per the SoA (Section 1.3):

Weight

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 body weight will be compared between participants who switch to DOR/ISL and participants who continue taking BIC/FTC/TAF.

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 8.8.2).

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 8.8.3).

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 8.8.4).

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 (Section 8.8.4).

Body Composition

Decreases in BMD and lipodystrophy (peripheral and central fat redistribution) have been reported in patients with HIV-1 receiving ART [AIDS info 2017], particularly with the use of certain NRTIs. Key indicators of body composition (including DEXA assessments) will be measured (Section 8.8.6).

4.2.1.4 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoA 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 such as AUC, Cmax, and C24 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 patients' 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 is used to estimate health utility scores, which inform cost-effectiveness model analysis.

This study will include 3 self-administered PRO questionnaires. 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 HIV-SI (also known as 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 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.

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

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

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

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

4.2.1.7 Future Biomedical Research

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

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

participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

The recently approved 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 2018]. 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 2018] and the European AIDS Clinical Society[European AIDS Clinical Society 2018] 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 96.

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**: Although many ART regimens are associated with a high likelihood of achieving and maintaining undetectable HIV-1 RNA levels, globally, while 70% of all persons living with HIV 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, and/or dosing frequency 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 antiretroviral regimen even in the setting of viral suppression, before failure can occur.

  Furthermore, given the aging of the population with HIV, it is anticipated that switches will become even more common in the setting of ongoing concerns for the risks of long-term toxicity, DDIs, and comorbid conditions (ie, neuropsychiatric, cardiovascular).

- **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 are those who are already virologically suppressed. Data from the ongoing Phase 2 study (MK-8591A P011) demonstrate that after receiving at least 3 months of the 3-drug regimen of DOR + ISL + 3TC, almost all participants with HIV-1 RNA <50 copies/mL maintained virologic suppression on a 2-drug regimen of DOR + ISL through an additional 24 weeks. Based on the results of the Phase 2 study, enrollment in this study will be open to those who have demonstrated stable suppression with an HIV-1 RNA <50 copies/mL for ≥3 months.

4.2.4 Rationale for Collecting Race and Ethnicity Data

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

4.2.5 Rationale for Collecting Gender Identity Data

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

4.2.6 Rationale for Infant Safety Data Collection

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

4.2.7 Rationale for Continuing Study Intervention During Pregnancy

The US Department of Health and Human Services guidelines currently advise that women who become pregnant while receiving ART for HIV infection should continue their regimen provided it is safe, well tolerated, and effective at virologic suppression since altering the regimen could cause an increase in viral load [Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]. Nonclinical developmental and reproductive toxicology studies did not identify any teratogenicity or other clinically relevant concerns, that would preclude continued dosing of DOR/ISL in participants who become pregnant and who consent to continue study intervention (where allowed by local regulations, health authorities, and ethics committees and as appropriate based on available data/local standard-of-care guidelines) (Sections 8.1.1.4 and 8.11.6).

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

4.3 Justification for Dose

Inhibitory quotient (Ctrough/IC50) is the ratio of drug exposure to viral susceptibility. In a Phase 1b proof of concept study (MK-8591 P003), single doses as low as 0.5 mg ISL showed robust antiretroviral activity at 7 days postdose; this low single-dose provided an IQ threshold of 5 for wild-type HIV-1 virus. Simulations suggest the ISL-TP concentrations achieved after a single-dose of 0.75 mg ISL provide IQs of 21 and 4 for wild-type and M184V virus, respectively. After 7 daily doses of 0.75 mg ISL, IQs increase to 113 for wild-type virus and 23 for M184V/I virus. Antiretroviral activity against the exceedingly rare 69ins + M184I/V mutant virus (the NRTI mutant with the highest potency reduction for ISL) is expected to be achieved after 7 daily doses, with an IQ of 5. Steady-state concentrations at later timepoints will produce even higher IQs, as there is additional accumulation of ISL-TP. These simulations support the selection of 0.75 mg ISL 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 P011), 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, as demonstrated by the primary efficacy endpoint: the percentage of participants with HIV-1 RNA <50 copies/mL at both Weeks 24 and 48. Overall, no ISL dose-response for efficacy was observed. Graphical analysis of steady-state ISL-TP trough concentrations and response at Week 48 from MK-8591 P011 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. P011 also demonstrated that all doses of ISL studied, when administered with DOR + 3TC or DOR alone, had a favorable safety and tolerability profile through Week 48, comparable with that of DOR/3TC/TDF.

DOR will be administered at the approved dose of 100 mg. This dose has been studied in Phase 1 to 3 clinical studies in treatment-naïve and virologically suppressed participants with HIV-1 and was selected based upon favorable efficacy, safety, tolerability, and metabolic profiles, as confirmed in Phase 3 clinical studies [Orkin, C., et al 2018] [Molina, J. M., et al 2018] [CSR P024MK1439A]. Of note, among 32 participants in MK-1439A Protocols 024 and 030 infected with HIV-1 harboring the NNRTI resistance mutations K103N, Y181C, and/or G190A at study entry, all achieved virologic suppression following 48 weeks of treatment with DOR/3TC/TDF (24 of 32 participants had been virologically suppressed on PI or InSTI regimens and 8 had been treatment-naïve).

In summary, a 0.75-mg dose of ISL in combination with 100 mg DOR is predicted to 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 (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

Early study termination will also be considered if futility criteria are met at the Week 24 interim analysis (Section 9.7).

5 STUDY POPULATION

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

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

5.1 Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Is HIV-1 positive with plasma HIV-1 RNA <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 months prior to signing informed consent and has no history of prior virologic treatment failure on any past or current regimen.

   Note: A non-clinically significant HIV-1 RNA result above the limit of quantification (ie, transient detectable viremia) during the 3 months prior to screening is acceptable.

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

Demographics

3. Is male or female, at least 18 years of age at the time of signing the informed consent.

Contraception/Pregnancy

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

   - Is not a woman of childbearing potential (WOCBP)

   OR

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

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

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

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

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

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Has HIV-2 infection.

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

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

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

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

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

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

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

Prior/Concomitant Therapy

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

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

Prior/Concurrent Clinical Study Experience

7. Is currently participating in or has participated in a clinical study with an investigational compound or device from 45 days prior to Day 1 through the study treatment period.

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

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

Diagnostic Assessments

8. 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, M230I/L, L234I, P236L, or Y318F.

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

9. 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
Alkaline Phosphatase	>3 × ULN
AST	>5 × ULN
ALT	>5 × ULN
Hemoglobin	<9.0 g/dL (female) or <10.0 g/dL (male)
Calculated Cr_{cl}	≤30 mL/min based on the Cockcroft-Gault equation (Appendix 8).
ALT=alanine aminotransferase; AST=aspartate aminotransferase; Cr_{cl}=creatinine clearance; ULN=upper limit of normal.	

Other Exclusions

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

Note: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study intervention. Consistent with the recommendations for contraceptive use, it is recommended that all female participants refrain from egg donation for 6 weeks following their last dose of study intervention.

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

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Treatment Period	Use	IMP/ NIMP	Sourcing
Group 1	Experimental	DOR/ISL (blinded)	Drug	Tablet	100 mg/ 0.75 mg	100 mg/ 0.75 mg QD	Oral	Day 1 to Week 96	Experi-mental	IMP	Provided centrally by the Sponsor
Group 1	Experimental	Placebo to BIC/FTC/TAF (blinded)	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 96	Placebo	IMP	Provided centrally by the Sponsor
Group 2	Active Comparator	BIC/FTC/TAF (blinded)	Drug	Tablet	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg QD	Oral	Day 1 to Week 96	Experi-mental	IMP	Provided centrally by the Sponsor
Group 2	Active Comparator	Placebo to DOR/ISL (blinded)	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 96	Placebo	IMP	Provided centrally by the Sponsor
Group 1	Experimental	DOR/ISL (open-label)	Drug	Tablet	100 mg/ 0.75 mg	100 mg/ 0.75 mg QD	Oral	Week 96 to Week 144[a]	Experi-mental	IMP	Provided centrally by the Sponsor
Group 2	Active Comparator	BIC/FTC/TAF (open-label)	Drug	Tablet	50 mg/ 200 mg/ 25 mg	50 mg/ 200 mg/ 25 mg QD	Oral	Week 96 to Week 144[b]	Experi-mental	IMP	Provided centrally by the Sponsor
Group 2	Experimental	DOR/ISL (open-label)	Drug	Tablet	100 mg/ 0.75 mg	100 mg/ 0.75 mg QD	Oral	Week 144 to Week 156[c]	Experi-mental	IMP	Provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Treatment Period	Use	IMP/ NIMP	Sourcing
BIC=bictegravir; DOR=doravirine; FTC=emtricitabine; ISL=islatravir; QD=once-daily; TAF=tenofovir alafenamide. Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. [a] If a participant in Group 1 is pregnant at Week 144 they will continue to receive DOR/ISL for the duration of their pregnancy. Study intervention will be provided centrally by the Sponsor. [b] If a participant in Group 2 is pregnant at Week 144 the investigator should refer to local product circular and local guidelines to determine if BIC/FTC/TAF treatment can be continued. If the decision is made for the participant to continue to receive BIC/FTC/TAF, study intervention will be provided centrally by the Sponsor for the duration of their pregnancy. [c] If a participant in Group 2 is pregnant at Week 156 they will continue to receive DOR/ISL for the duration of their pregnancy. Study intervention will be provided centrally by the Sponsor.											

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

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to Group 1 or Group 2, 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 blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Clinical site personnel and participants will remain blinded through Week 96 while all Sponsor personnel will remain blinded through Week 48. Sponsor personnel involved in performing and reviewing results of the Week 48 analysis will be unblinded after the Week 48 database lock.

As described in Section 4, at Week 96 all clinical site personnel and participants will be unblinded and will continue to receive their assigned study intervention open-label through Week 144. At Week 144, participants in Group 1 will be offered the option of receiving open-label DOR/ISL in the rollover study. Participants in Group 2 will be offered to switch to open-label DOR/ISL for an additional 12 weeks (through Week 156) prior to entering the rollover.

To allow timely completion of population PK modeling, restricted early (before database lock) unblinding of PK data may be requested. No personnel directly associated with study conduct will be unblinded before 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 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. 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 or longer require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications 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 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 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.

Prior and concomitant therapies listed in Table 3 are not permitted from 45 days prior to Day 1 through the study treatment period. Table 3 is not comprehensive, and the investigator should use his/her medical judgement 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 DDI interactions 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.

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), study intervention should be taken either 2 hours before or 6 hours after taking any polyvalent cation containing medicine.

Table 3 Prohibited Therapies

Strong and moderate CYP3A inducers	Including, but not limited to: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Enzalutamide Rifabutin Rifampin Rifapentine Mitotane St. John's Wort Herbal remedies Modafinil Bosentan Nafcillin
Non-study ART	All non-study antiretrovirals (with the exception of baseline ART during the screening period and intrapartum treatment [eg, IV AZT] in the case of pregnancy).
Immunosuppressive therapies	Immune therapy agents, immune modulators or other systemic immunosuppressive therapy, including interferon-based treatment for hepatitis *Time-limited courses of corticosteroids (eg, for asthma exacerbation) are permitted.*
Investigational agents	All non-study investigational agents including devices
Antiarrhythmics	Dofetilide
Additional prohibited therapies based on ISL	Pentostatin
ART=antiretroviral therapy; CYP3A=cytochrome P450 3A; ISL=islatravir.	

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.

6.7 Intervention After the End of the Study

Provided development of DOR/ISL continues, there will be a rollover study for all eligible participants to continue receiving DOR/ISL without interruption until it becomes locally available. Eligible participants are those who have completed the last scheduled study visit and are considered by the investigator to derive clinical benefit from administration of DOR/ISL.

At Week 144, eligible participants in Group 1 will be given the option to continue treatment with DOR/ISL (as open-label) in the rollover study. Eligible participants in Group 2 will be given the option to switch to open-label DOR/ISL at Week 144 and continue in this study through Week 156. At Week 156, Group 2 participants will be given the option to move into the rollover study to continue to receive DOR/ISL. Participants who complete this study but who decline to participate in the rollover study should have an End of Treatment Follow Up visit (Section 1.3.3).

Participants who choose to participate in the rollover study and have decreases in CD4+ T-cell and/or total lymphocyte counts that meet ECI criteria (Section 8.4.7) at their Week 144 (Group 1) or Week 156 (Group 2) visit should have a confirmation visit in this study (per Section 8.11.5 and Section 1.3.5). The confirmatory CD4+ T-cell count and total lymphocyte count will be followed in this study and the participant will be concurrently enrolled in the rollover study.

- Upon repeat testing, if discontinuation criteria are confirmed (Section 7.1) participation in the rollover study will be stopped. The participant will be followed monthly in this study until 2 values (12 weeks apart) for the CD4+ T-cell count and total lymphocyte count are not decreased by >10% of the average baseline values (Section 8.11.5). Participants discontinuing study medication due to confirmed CD4+ T-cell count <200 cells/mm^3 will be followed monthly in this study until the CD4+ T-cell count is ≥200 cells/mm^3 on 2 visits 12 weeks apart (Section 8.11.5.3).

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

Participants receiving DOR/ISL who decline participation in the rollover study and show decreases in CD4+ T-cell count and/or lymphocyte count at the Week 144 (Group 1) or Week 156 (Group 2) should be managed per Section 8.11.5.3.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic 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 96 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 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

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

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

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

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

- The participant requests to discontinue study intervention.
- 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 has confirmed HIV-1 virologic rebound as defined in Section 4.2.1.1.2.

- Occurrence of any Category C conditions included in the CDC 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults [Centers for Disease Control (CDC) 1992].

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

- The participant chooses to breastfeed.

  Note: Study intervention can continue until breastfeeding is initiated.

A participant must be discontinued from study intervention and managed per Section 8.11.5 if any of the following criteria are met:

1) Discontinuation criteria for CD4+ T-cell count:

   a. For participants with an average baseline* CD4+ T-cell count ≥500 cells/mm^3, a ≥30% reduction from average baseline in CD4+ T-cell count AND a CD4+ T-cell count decrease to <500 cells/mm^3 on 2 consecutive measurements taken 3 to 4 weeks apart

      OR

   b. For participants with an average baseline* CD4+ T-cell count <500 cells/mm^3, a ≥30% reduction from average baseline in CD4+ T-cell count on 2 consecutive measurements taken 3 to 4 weeks apart

      OR

   c. For all participants with an average baseline* CD4+ T-cell count ≥200 cells/mm^3 (including participants with an average baseline CD4+ T-cell counts <200 cells/mm^3 who have increases in CD4+ T-cell count to ≥200 cells/mm^3 for 3 consecutive months), a CD4+ T-cell count decrease to <200 cells/mm^3 on 2 consecutive measurements taken 3 to 4 weeks apart

2) Discontinuation criteria for total lymphocyte count:

   a. For participants with an average baseline* total lymphocyte count ≥1 x 10^9 cells/L:

      i. a ≥30% reduction from average baseline* total lymphocyte count AND a decrease in total lymphocyte count to <1 x 10^9 cells/L on 2 consecutive measurements taken **3 to 4 weeks apart**

         OR

ii. a ≥30% reduction from average baseline* total lymphocyte count with total lymphocyte count remaining ≥1 x 10^9 cells/L on 2 consecutive measurements taken **10 to 14 weeks apart**.

b. For participants with an average baseline* total lymphocyte count <1 x 10^9 cells/L, a ≥30% reduction from average baseline* total lymphocyte count on 2 consecutive measurements taken 3 to 4 weeks apart.

* Average baseline is defined as the average value between screening (within 45 days prior to the first dose of study medication) and Day 1. For participants switching from BIC/FTC/TAF to DOR/ISL at Week 144 (Group 2), the baseline CD4+ T-cell count and total lymphocyte count is defined as the value from the Week 144 visit (or if not available, the last result prior to Week 144). If there are ≥2 values at Week 144, then use the most recent value.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant withdraws consent from the study.

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The amount of blood collected from each participant over the full duration of the study is provided in Table 17 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 future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent 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 trial protocol number, trial protocol title, dated signature, and /agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

- A copy of the signed and dated informed consent form should be given to the participant (or 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 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 future biomedical research consent to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

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

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

8.1.1.4 Consent for Continuation of Study Intervention During Pregnancy

Upon learning that a participant is pregnant and following unblinding, the investigator or medically qualified designee and the participant will discuss the potential benefits and risks of continuing (or discontinuing) study intervention (Section 8.11.6). A separate consent is required to continue study intervention in participants who become pregnant. The investigator or medically qualified designee will explain the consent to the participant, or the participant's legally acceptable representative, answer all of their questions, and obtain

documented informed consent before continuing study intervention. A copy of the informed consent will be given to the participant.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history should include information pertaining to the diagnosis of HIV-1 and AIDS (if applicable) and year diagnosed. If the participant has been previously diagnosed with any AIDS-defining conditions or CD4+ T-cell count <200 cells/mm^3, the condition as well as a corresponding medical history of AIDS must be reported. In addition, participants' history of smoking and alcohol consumption should be obtained and recorded on the appropriate eCRF.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

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

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

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

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

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

Study intervention should begin within 24 hours of randomization.

8.1.8.1 Timing of Dose Administration

From Day 1 to Week 96, participants will take (unsupervised at their home) 2 tablets of blinded study intervention QD at 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). 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. From Week 96 through the end of study, participants will take 1 tablet of open-label study intervention QD at the same time each day.

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.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should have an Early Discontinuation of Treatment visit performed per SoA (Section 1.3) and be encouraged to continue to be followed as outlined in Section 8.11.3.

Participants who discontinue study intervention due to decreases in CD4+ T-cell counts and/or total lymphocyte counts or who discontinue for any other reason and are found to have decreases in CD4+ T-cell count and/or total lymphocyte count of >10% of the average baseline value or that meet ECI criteria at the Early Discontinuation of Treatment Visit should be unblinded (if applicable), and those treated with DOR/ISL should be managed per Section 8.11.5 until their counts recover.

When a participant withdraws from participation in the study, all applicable activities scheduled for the Early Discontinuation of Treatment visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically

qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

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

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that 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. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.11 Calibration of Equipment

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

8.1.12 Administration of Patient Questionnaires

Participants will complete 3 PRO questionnaires at Day 1, Week 4, Week 12, Week 48, and Week 96 and/or at the Early Discontinuation of Treatment visit (if at or before Week 96). 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 will not be administered to participants if native language translations are not available for all questionnaires.

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

8.2 Efficacy Assessments

8.2.1 HIV-1 RNA

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

8.2.2 Management of Study Participants With Viremia

When viremia (HIV-1 RNA ≥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.**

8.2.2.1 Viremia Confirmation

Confirmation of viremia requires 2 consecutive plasma HIV-1 RNA results of ≥50 copies/mL (Section 4.2.1.1.2) with the second sample collected at a "Viremia Confirmation" visit at least 2 weeks, but not more than 4 weeks from the date of the initial sample. This timeframe may be extended if study intervention is interrupted for 1 of the following circumstances:

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

8.2.2.2 Participants With Clinically significant Viremia (≥200 copies/mL)

Study participants with confirmed HIV-1 RNA of ≥200 copies/mL will be assessed for development of viral drug resistance (Section 8.2.2.4) and discontinuation from study intervention (Section 7.1). Once it is determined that study intervention discontinuation is appropriate, Early Discontinuation of Treatment and End of Treatment Follow-up visit procedures should be completed (Sections 1.3.3 and 8.11.3) and the participant managed by the investigator per local standard-of-care.

8.2.2.3 Participants With Low-level Viremia (≥50 and <200 copies/mL)

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

appropriate, after discussion with the Sponsor. Participants with confirmed low-level viremia at Week 48 will not be automatically discontinued from study intervention but will be included in the virologic failure rate calculated for the purposes of the primary analyses (Section 9.6.1).

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

8.2.2.4 Viral Drug Resistance Testing

Participants with confirmed 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 drug resistance testing per SoA (Section 1.3) and used to assess resistance-associated substitutions as applicable during the study.

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

A TBNK panel, including CD4+ T-cell count, will be performed at the central laboratory (see Table 16 in Appendix 2). Refer to Section 8.11.5 for guidance on management of participants with decreased CD4+ T-cell counts and/or decreased total lymphocyte counts.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study, including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Table 17 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) as per institutional standard. The full physical examination will include examination of body systems including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system.

Height will also be measured and recorded at the visits specified in the SoA (Section 1.3.1). Height measurements should be taken using a stadiometer (recommended, but not required). Participants should remove their shoes and stand as tall and straight as possible.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. 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 1.3.1). Participants should remove their shoes and wear a single layer of clothing at each measurement.

8.3.2 Vital Signs

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

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) within 7 days prior to the Day 1 visit and prior to the first dose of study intervention as indicated in the SoA. Results must be available prior to randomization. Sites are to use an ECG machine that automatically calculates the heart rate 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 captured as AEs.

8.3.4 Confirmation of Contraception and Pregnancy Testing

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

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

Urine pregnancy test kits will be provided by the central laboratory, and routine testing will be performed by the local laboratory. In the event of a positive urine pregnancy test result, serum pregnancy testing must be performed by the central laboratory. If a participant becomes pregnant, refer to Section 8.11.6.

8.3.5 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Table 16 in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

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

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

- Management of decreases in CD4+ T-cell and/or total lymphocyte counts is described in Section 8.11.5.

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 at screening. Participants who are anti-HBc positive and HBV DNA positive at screening are excluded. Participants who are anti-HBc positive, but HBV DNA negative at screening are eligible to enroll. For the duration of the study, participants positive for anti-HBc should be monitored for possible HBV reactivation. Samples will be taken to monitor 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 (included in chemistry laboratory assessments). At Week 132, participants in Group 2 will be tested for HBsAg, HBV DNA, HBsAb and anti-HBc prior to switching to DOR/ISL at Week 144. Participants who do not meet the criteria above

will not be offered the option to switch to DOR/ISL due to the potential for HBV reactivation.

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

8.3.7 Tobacco and Alcohol Assessments

Participants' use of tobacco and alcohol will be obtained and recorded at Weeks 48, 96 and 144.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination ; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

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

This section is not applicable to the study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

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

2. A ≥30% reduction from average baseline** in CD4+ T-cell count or total lymphocyte count while on study intervention.

3. A CD4+ T-cell count of <200 cells/mm^3 while on study intervention from either (a) participants whose average baseline** CD4+ T-cell count was ≥200 cells/mm^3 or (b) participants whose CD4+ T-cell count increased to ≥200 cells/mm^3 for 3 consecutive months while on study intervention.

**Note: The average baseline value for CD4+ T-cell count and total lymphocyte count is defined as the average value between screening (within 45 days prior to the first dose of study medication) and Day 1. For participants switching from BIC/FTC/TAF to DOR/ISL at Week 144 (Group 2), the baseline is defined as the value from the Week 144 visit (or if not available, the last result prior to Week 144). If there are ≥2 values at Week 144, then use the most recent value. The first on-treatment value that reaches the above CD4+ T-cell or total lymphocyte criteria should be reported as an ECI. See Section 8.11.5 for further guidance on the management of participants meeting CD4+ T-cell and total lymphocyte criteria.

8.5 Treatment of Overdose

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

No specific information is available on the treatment of overdose.

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

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma ISL

Venous blood samples will be collected for measurement of ISL. Sample collection, storage, and shipment instructions for plasma samples will be provided in the laboratory manual. Investigational PK samples will be collected from all participants as outlined in the SoA (Section 1.3). Analysis of these samples will be triggered by the Sponsor as needed.

Population PK samples will be collected from all participants as outlined in Table 5. The time of the doses of study interventions taken prior to the sample collection will be verbally reported to study staff by the participant and recorded in the appropriate source documentation.

For participants who routinely take their study intervention during the day, a predose and postdose sample will be taken at the Week 4 visit (Table 5). Participants who routinely take their study intervention in the evening should continue to do so, and only 1 sample will be taken at the Week 4 visit irrespective of time of the last dose.

For participants who become pregnant and consent to continue DOR/ISL, PK samples will be collected to evaluate DOR and ISL concentration levels per Table 6 Section 8.11.6.1.

Table 5 Collection of Population PK Samples

Study Visit	**Time Relative to Dose**
Day 1	Predose
Week 4	Predose and within 0.5 to 2 hours postdose
Week 12	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
Week 24	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
Week 48	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
PK=pharmacokinetic.	

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

8.8.1 Planned Genetic Analysis Sample Collection

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

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.8.2 Inflammation

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

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

8.8.3 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:

- Urine: albumin, protein, beta-2-microglobulin/creatinine ratio, and retinol binding protein/creatinine ratio
- Serum: cystatin-C and creatinine clearance

8.8.4 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, TGs, TC, and non-HDL-C. HOMA-IR will be calculated.

Participants with diabetes mellitus (type 1 or type 2) or insulin resistance are not required to have the blood draw for insulin testing.

8.8.5 Waist and Hip Measurements

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

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

8.8.6 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). 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 14 days after randomization. The DEXA images at subsequent visits should be performed ± 14 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).

DEXA images will be evaluated by a central imaging reader; these analyses are not performed in real time and will not be provided to the site/participant. For clinical management of the participant, the DEXA images should be 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. Clinically significant findings noted in the local interpretation of the DEXA images during the treatment period should be recorded appropriately. 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.

8.9 Future Biomedical Research Sample Collection

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

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

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

8.10 Health Economics Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 Screening/Rescreening

Screening

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.

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 β-hCG pregnancy testing for WOCBP)
- 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 >30 days have elapsed, the Day 1 DEXA should be repeated. If <30 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 baseline ART was <3 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 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 as per SoA (Section 1.3).

8.11.2.1 Fasting

Visits at Day 1, Week 24, Week 48, Week 96, Week 120 and Week 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 are responsible to remind participants to fast prior to these visits and to confirm with participants their fasting status in the appropriate source documentation.

8.11.2.2 Optional Nurse Visits and Telephone Visits

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

For visits conducted by the visiting nurse, whole blood for FBR samples will not be collected by the visiting nurse. Participants should be instructed to return to the site within 2-4 weeks from the scheduled visit for collection of whole blood for FBR, when possible. If an unscheduled visit for collection of whole blood for FBR is not possible, the sample should be drawn at the next scheduled visit at the site.

8.11.2.3 End of Study Week 144 Visit

Week 144 represents the end of this study.

Participants who were randomized to **Group 1** will be given 2 options at the Week 144 visit:

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

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

Participants who were randomized to **Group 2** will be given 2 options at the Week 144 visit:

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

2. Continue participation in this study, which will entail switching to open-label DOR/ISL, which they will receive for 12 weeks to allow monitoring of safety and tolerability. Participants who choose this option will receive DOR/ISL through Week 156, at which time they would be given the option to continue in the rollover study. Documented consent to participate in the rollover study would be obtained at Week 156.

Participants who are pregnant at Week 144 will be managed per Section 8.11.6. Any participant in Group 2 who is pregnant at Week 144 will not be given the option to switch.

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

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

- Participants who received DOR/ISL not participating in the rollover study who have decreases in CD4+ T-cell and/or total lymphocyte counts at their Week 144 (Group 1) or Week 156 (Group 2) visit that meet ECI criteria or are decreased by >10% of their average baseline value require additional follow-up monitoring of CD4+ T-cell and lymphocyte counts per Section 6.7 and Section 8.11.5.

8.11.3 Participants Who Discontinue Study Intervention

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

When it is determined that discontinuation from study intervention is appropriate, the participant should have both an Early Discontinuation of Treatment visit (Section 8.11.3.1) 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 the treatment of HIV-1 per local standard-of-care.

- Guidance for management of participants who discontinue study intervention due to confirmed decreased CD4+ T-cell counts and/or decreased total lymphocyte counts is provided in Section 8.11.5.

- If participants receiving DOR/ISL discontinue study intervention for other reasons and the CD4+ T-cell count and/or total lymphocyte count at the Early Discontinuation of Treatment visit is decreased by >10% of their average baseline value or meets ECI criteria, additional monitoring is required per Section 8.11.5.

8.11.3.1 Early Discontinuation of Treatment

Participants who discontinue treatment early for any reason should have an Early Discontinuation of Treatment visit as outlined in Section 1.3.3. If early discontinuation occurs during the timeframe of a scheduled study visit, the assessments for the Early Discontinuation of Treatment visit should be conducted.

8.11.3.2 End of Treatment Follow-up Visit

Participants who discontinue study intervention at any time for any reason(s) will have a safety follow-up visit in-clinic 42 days (+7 days) after the last dose of study intervention. Assessments for this End of Treatment Follow-up visit are outlined in Section 1.3.3. Participants (in Group 1 who complete the Week 144 visit or in Group 2 who complete the Week 156 visit) who do not consent to participate in the rollover study or do not agree to participate in the optional 12-week switch to open-label DOR/ISL (Group 2) at the Week 144 visit should also have an End of Treatment Follow-up visit.

Participants discontinuing DOR/ISL with specified decreases in CD4+ T-cell and/or total lymphocyte counts will be followed monthly for monitoring of CD4+ T-cell and total lymphocyte counts recovery as per Section 8.11.5.

8.11.4 Viremia Confirmation

If a participant has a viral load of ≥50 copies/mL at any time during the study, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (Sections 1.3.2 and 4.2.1.1). If a scheduled visit is to occur within the timeframe that a participant would return for a viremia confirmation visit, the assessments for the scheduled visit should be conducted, and the HIV viral drug resistance sample must be collected.

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

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

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

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

**Note Exception*: Participants with an average baseline total lymphocyte count $\geq 1 \times 10^9$ cells/L and a ≥30% reduction from average baseline with the count remaining $\geq 1 \times 10^9$ cells/L, should have a confirmation visit in 10 to 14 weeks (or earlier if applicable).

Upon repeat testing at the confirmation visit (Section 1.3.5), the participant must be discontinued from study intervention if the discontinuation criteria are met (Section 7.1) and unblinded (if applicable). If receiving DOR/ISL, the participant must be managed per Section 8.11.5.2.

Upon repeat testing at the confirmation visit (Section 1.3.5), if the ECI criteria are confirmed but the values do not meet discontinuation criteria, **the Sponsor must be consulted**. Treatment may be continued with approval from Sponsor.

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

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

Participants discontinued from study intervention due to specified decreases in CD4+ T-cell and/or total lymphocyte counts should be unblinded (if applicable) and followed as noted below:

- Participants who received DOR/ISL should undergo assessments as specified under the Early Discontinuation of Treatment visit and the End of Treatment Follow-up visit (Section 1.3.5). Participants will then be monitored monthly until 2 values 12 weeks apart of CD4+ T-cell counts and total lymphocyte counts are not decreased by >10% of the average baseline value. Participants discontinued due to confirmed CD4+ T-cell count <200 cells/mm^3 need to be followed monthly until the CD4+ T-cell count is ≥200 cells/mm^3 on 2 visits 12 weeks apart.

- Participants who were receiving BIC/FTC/TAF who discontinue study intervention due to decreases in CD4+ T-cell counts or total lymphocyte counts should have an

Early Discontinuation of Treatment visit (Section 8.11.3.1) and an End of Treatment Follow-up visit (Section 8.11.3.2) and no further monitoring is needed; see also Section 1.3.3.

8.11.5.3 Participants Discontinued from Study Intervention for Other Reasons And Have Decreases in CD4+ T-cell and/or Total Lymphocyte Counts

Participants who discontinue study intervention for any other reason including participants who decline participation in the rollover study and are found to have decreases in CD4+ T-cell and/or total lymphocyte counts of >10% of the average baseline values or that meet ECI criteria at the Early Discontinuation of Treatment Visit should be unblinded (if applicable) to determine their follow-up as noted below:

- Participants who were receiving DOR/ISL should undergo assessments specified at the End of Treatment Follow-up visit at Day 42 (Section 1.3.5).
    - If the decrease(s) of >10% of average baseline or a decrease in CD4+ T-cell counts to <200 cells/mm^3 is confirmed at this visit, participants should continue to be monitored monthly until 2 values 12 weeks apart of CD4+ T-cell counts and total lymphocyte counts are not decreased by >10% of the average baseline value or the CD4+ T-cell count is ≥200 cells/mm^3, respectively.
    - If the decrease(s) of >10% of average baseline or a decrease in CD4+ T-cell counts to <200 cells/mm^3 is not confirmed at this visit, then no further follow-up for CD4+ T cell or total lymphocyte counts is required.
- Participants who were receiving BIC/FTC/TAF should have an End of Treatment Follow-up visit per Section 8.11.3.2 (and Section 1.3.3) and no further monitoring is needed.

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 her to a local provider for appropriate obstetric (prenatal) care per local standard of care. All pregnancies must be followed to completion or termination of the pregnancy by the investigator per Section 8.4.5. Severity assessment of AEs that are pregnancy-related complications should follow guidance provided as part of the DAIDS table version 2.1 “Addendum 1: Female Genital Grading Table for Use in Microbicide Studies,” particularly the section “Complications of Pregnancy.”

If a participant’s study intervention is blinded, the study intervention assignment must be unblinded by the investigator (Section 8.1.10).

The site will discuss with the participant:

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

- Consenting to infant safety data collection per Sections 8.1.1.3 and 8.11.6.4
- Her intended breastfeeding status (Section 8.11.6.3)
- Appropriateness of continuing study intervention based on available data and local standard-of care guidelines (where allowed by local regulations, health authorities, and ethics committees)

8.11.6.1 Continuing Study Intervention

Participants who become pregnant and consent to continue their assigned study intervention (Section 8.1.1.4) should complete all remaining protocol-specified visits and procedures (with the exception of DEXA scans) per the regular schedule in the SoA (Section 1.3.1 and 1.3.2). As the SoA specifies study visits at least every 12 weeks, participants will have a study visit approximately during each trimester and postpartum (ie, the first visit after delivery [~12 weeks after the 3rd trimester visit and ≤8 weeks after delivery]).

For participants receiving BIC/FTC/TAF, the investigator should refer to local product circular and local guidelines to determine if treatment may be continued. Those participants in Group 2 who consent to continue BIC/FTC/TAF and are pregnant at Week 144 will not be eligible to switch to DOR/ISL. The participant will continue with the protocol-specified visits per the SoA (with the exception of DEXA and PK collection) per the schedules in the SoA (Section 1.3) for the duration of their pregnancy.

The participant's prenatal care should be coordinated between the investigator and the local obstetric care provider. The investigator (or designee) is responsible for obtaining relevant clinical and laboratory data from the obstetric care provider to monitor the safety and well-being of the mother and fetus. Relevant data obtained by the site should be entered into the appropriate CRF and source documentation. The participant's medical records will be collected and reviewed by the study site for:

- Clinical safety laboratory assessments
- Plasma HIV-1 RNA level
- Results of Week 20 to 22 or second trimester ultrasound(s) providing gestational age and anatomic survey
- Any complications associated with the pregnancy
- Outcome of pregnancy
- Information that could indicate congenital abnormalities

For participants who are pregnant at the last regularly scheduled study visit, their visit schedule will be extended through the duration of the pregnancy to allow assessments through each trimester and postpartum (Section 1.3.4). For participants on DOR/ISL, at the

completion of the pregnancy, continued access to DOR/ISL will be offered per Section 6.7. For participants on BIC/FTC/TAF, at the completion of the pregnancy and postpartum visit, the participant will have completed the study.

For participants who continue DOR/ISL, PK samples will be collected at their scheduled visit during the 1st, 2nd, and 3rd trimesters and postpartum to evaluate DOR and ISL concentration levels per Table 6. These samples will be used to characterize the PK profile of DOR/ISL during pregnancy. Participants who do not learn of their pregnancy until the 2nd trimester will not have a 1st trimester PK sample.

Table 6 Collection of Population PK Samples During Pregnancy and Postpartum

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

PK=pharmacokinetic.
[a] Collected in the 1st trimester at a scheduled visit when a participant reports gravid status.
[b] The first visit after delivery; ~12 weeks after the 3rd trimester visit and ≤8 weeks after delivery.

8.11.6.2 Discontinuing Study Intervention for Pregnancy

Participants who become pregnant and discontinue their assigned study intervention should have an Early Discontinuation of Treatment visit per the SoA (Section 1.3.3). If the decision to discontinue study intervention occurs during the timeframe of a scheduled study visit, the assessments for the Early Discontinuation of Treatment visit should be conducted at that time. In addition, these participants will have an End of Treatment Follow-up visit in-clinic 42 days (+7 days) after the last dose of study intervention (Section 1.3.3).

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 combination ART.

8.11.6.3 Participants Who Choose to Breastfeed

If a participant chooses to breastfeed, they should 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 guidance) 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. In addition, study staff should obtain results from any ultrasounds performed per local standard-of-care.

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

8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection

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

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

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

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

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

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

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes are made to primary 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 non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan 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) Once-Daily in Participants With HIV-1 Virologically Suppressed on Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)
Treatment Assignment	This study will enroll approximately 578 evaluable participants with HIV-1 who have been virologically suppressed on BIC/FTC/TAF for ≥3 months. Participants will be randomized in a 1:1 ratio to switch to DOR/ISL on Day 1 (Group 1) or continue treatment with BIC/FTC/TAF (Group 2) with matching placebo through Week 96. Clinical site personnel and study participants will remain blinded through Week 96 while the clinical database and all Sponsor personnel will remain blinded through Week 48.
Analysis Populations	Efficacy: FAS, PP, and Resistance Analysis Subset Safety: APaT
Primary Endpoint(s)	1. Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48 2. Number of participants experiencing AEs, and discontinuing study intervention due to AEs
Key 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 <40 and <50 copies/mL at Week 48, Week 96 and Week 144 3. Change from baseline in CD4+T-cell count at Week 48, Week 96 and Week 144 4. Change from baseline in weight at Week 48, Week 96 and Week 144 5. Viral resistance-associated substitutions 6. General safety and tolerability through study duration

Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary objective and hypothesis will be assessed using a 2-sided multiplicity-adjusted 95% CI for the difference between treatment groups (Group 1 minus Group 2) in the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48. The CI will be based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method. The FAS, which is defined as all randomized participants who take at least 1 dose of study intervention, will serve as the primary analysis population for this study. The FDA 'snapshot' algorithm will be used as the primary approach to analysis; missing data at the primary timepoint will be imputed as an HIV-1 RNA result ≥50 copies/mL for those who discontinue study intervention prior to the Week 48 analysis window due to lack of efficacy, or who discontinue study intervention prior to the Week 48 analysis window due to a reason other than lack of efficacy and have the last available on-treatment HIV-1 RNA result ≥50 copies/mL.
Statistical Methods for Key Safety Analyses	Point estimates and 2-sided nominal 95% CIs will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] for the difference between treatment groups (Group 1 minus Group 2) for the following: • The percentage of participants in the broad AE categories (ie, Tier-2 events) consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 to 4 AE, with an AE that is both drug-related and serious, with an AE that is both Grade 3 to 4 and drug-related, who discontinued study intervention due to a drug-related and non-drug-related AE, and with AE(s) leading to death. • Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence ≥4 participants in either treatment group. • The percentage of participants with a cardiac SAE. Point estimates and 2-sided multiplicity-adjusted 95% CIs will be provided using ANCOVA models for the difference between treatment groups (Group 1 minus Group 2) for the change from baseline in weight at Weeks 48 and 96.
Interim Analyses	The following interim analyses and data summaries are planned. Details are provided in Section 9.7. • Week 24 interim analysis: An interim analysis to assess futility will be performed by an external unblinded statistician when 40% of participants have completed Week 24 assessments. All available efficacy and safety data for all participants enrolled by that time will be reviewed. Treatment level results will be provided by an external unblinded statistician to the eDMC. If the upper bound of the 2-sided multiplicity-adjusted 95% CI for the treatment difference (Group 1 minus Group 2) in the percentage of participants with Week 24 HIV-1 RNA ≥200 copies/mL is greater than 8 percentage points and excludes 0, consideration may be given to stop the study. • Week 48 efficacy and safety analyses (to be conducted by the Sponsor and results shared with the eDMC). • Periodic efficacy and safety reviews (eDMC reviews) to be performed every 4 to 6 months or as specified in the eDMC charter.

Multiplicity	For statistical rigor, a small amount of alpha ($\alpha = 0.00001$) will be set aside for the futility assessment and each additional eDMC evaluation. An allowance will be made such that a total of up to 5 of the unblinded eDMC reports (including the Week 24 interim analysis) may be presented prior to the evaluation of the primary efficacy hypotheses at Week 48. If further eDMC reviews occur between the evaluation of the primary efficacy hypothesis at Week 48 and the evaluation of the secondary hypotheses at Week 96, further reduction in the alpha of 0.00001 for each eDMC review will be made for the Week 96 hypotheses. The following efficacy hypotheses will be tested sequentially at a 1-sided 2.5% Type 1 error rate adjusted for the number of eDMC reports in the following order: 1) Primary efficacy hypothesis (H1) testing non-inferiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 48 2) Secondary efficacy hypothesis (H4) testing superiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 96 3) Secondary efficacy hypothesis (H2) testing superiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 48 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. The secondary safety hypotheses, (H5) testing superiority of having lower mean increase from baseline in body weight for Group 1 vs. Group 2 at Week 48 and (H6) testing superiority of having lower mean increase from baseline in body weight for Group 1 vs. Group 2 at Week 96, will be tested independently of all efficacy hypotheses. The approach for testing these safety hypotheses at a strongly controlled 1-sided 2.5% Type 1 error rate adjusted for the number of eDMC reports is described in Section 9.8.
Sample Size and Power	The planned sample size is 578 participants to be randomized in a 1:1 ratio to either Group 1 or Group 2. The primary hypothesis will be assessed based on the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48. The non-inferiority will be concluded if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL (Group 1 minus Group 2) is less than 4 percentage points. If the true rate of participants with HIV-1 RNA ≥50 copies/mL at Week 48 is 2% in both groups, this study with 289 participants per group has 85% power to demonstrate non-inferiority.

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 analysis and reporting associated with the Week 48 CSR will become unblinded at the time of the Week 48 analysis, although study participants and site personnel will remain blinded until Week 96.

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.

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

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

9.4.1 Efficacy/Pharmacokinetics Endpoints

9.4.1.1 Efficacy Endpoints

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

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

The Abbott RealTime PCR assay with a reliable lower limit of quantification of 40 copies/mL will be used to measure the HIV-1 RNA level in blood samples obtained at each visit. The primary objective will be assessed based upon 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 Week 96 and Week 144.

Percentage of Participants With HIV-1 RNA <40 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 on the basis of the percentage of participants achieving HIV-1 RNA <40 copies/mL at Week 48, Week 96 and Week 144, as well as the percentage of participants achieving HIV-1 RNA <50 copies/mL at Week 48, Week 96 and Week 144.

Change From Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be estimated at each timepoint at which CD4+ T-cell count is collected. A secondary objective will assess the change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144.

For the analysis of change from baseline in CD4+ T-cell count, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available. For assessments of change from baseline in Group 2 at Week 156, baseline will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement prior to the switch to DOR/ISL).

Clinically significant Confirmed Viremia

Participants with confirmed virologic rebound as defined in Section 4.2.1.1.2 will be identified.

Viral Resistance-associated Substitutions

Participants who meet the definition of confirmed virologic rebound (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 resistance analyses. In addition, anyone for whom available genotypic or phenotypic data show evidence of resistance, irrespective of viral load, will also be included in resistance analyses. The resistance analysis will count the number of participants who have evidence of resistance-associated with each study intervention and will be summarized with primary interest at Week 48, Week 96 and Week 144.

Time to Loss of Virologic Response

TLOVR will be assessed at Week 48, Week 96 and Week 144.

For participants who have 2 consecutive HIV-1 RNA values (measured at least 2 weeks apart) ≥50 copies/mL during the study, TLOVR is the time between Day 1 and the date of the first of the 2 consecutive HIV-1 RNA values ≥50 copies/mL.

For participants who sustain HIV-1 RNA <50 copies/mL, TLOVR is censored at the time of the last available measurement.

9.4.1.2 Pharmacokinetic Endpoint

PK samples collected from all participants as described in the SoA 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.

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 to 4 AE; 5) participants with at least 1 serious and drug-related AE; 6) participants with at least 1 AE, which is both Grade 3 to 4 and drug-related; 7) participants who discontinued study intervention due to a drug-related and non-drug-related AE; and 8) participants with AE(s) leading to death.

Predefined Limits of Change in Laboratory Parameters

For the summaries of laboratory tests, participants must have both a baseline and 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 or not they fall outside of the PDLC and are worse in grade (ie, more abnormal in the direction of interest) than at baseline. The criteria are adapted from the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017, version 2.1 (Appendix 3). A listing of the participants who meet the criteria will also be provided.

Weight, Laboratory, and Radiological Markers

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

Change from baseline in weight will be summarized at each timepoint at which weight is collected. A secondary objective will assess the change from baseline in weight at Week 48, Week 96, and Week 144.

For analyses of change from baseline in weight, laboratory, and radiological parameters, baseline measurements are defined as the Day 1 value for each participant. In the rare event when data for this visit are missing, the value obtained at the most recent screening visit will be used as baseline, when available. For assessments of change from baseline in Group 2 at Weeks 148 and 156, baseline will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement prior to the switch to DOR/ISL).

The baseline measurement for analyses of DEXA will be defined in the sSAP.

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

9.5.1.1 Full Analysis Set

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

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

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

9.5.1.2 Per-Protocol Analysis Set

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

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

- Participants who meet the exclusion criteria for receiving any ongoing prohibited therapies listed in Table 3.
- Nonadherence to study intervention: participants with <95% drug compliance rate.
- Participants who become pregnant.

Any additional criteria resulting in exclusion from the PP analysis set will be provided in the sSAP and/or CSR and will be identified prior to unblinding of the Sponsor at Week 48.

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

9.5.1.3 Resistance Analysis Subset

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

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received. Participants in Group 2 who receive at least 1 dose of open-label DOR/ISL will be included in summaries and analyses from Week 144 through Week 156.

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.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

Time Windows

Table 7 lists the definition of time windows that will be used for the purposes of the statistical analyses and the target relative day for the scheduled visits in the study, which will be used for all analyses by timepoint (with the exception of DEXA assessments). The last available on-treatment measurement within a window will be used for analyses at a specific timepoint, unless otherwise specified. Results from additional timepoints beyond Week 156 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. Analysis windows for DEXA measurements will be provided in the sSAP.

Table 7 Definitions of Study Time Points

Treatment Phase	Treatment Period	Visit	Day-Range Rules[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
	Open-label Intervention: DOR/ISL or BIC/FTC/TAF	Week 96	≥631 and ≤714	673
		Week 108	≥715 and ≤798	757
		Week 120	≥799 and ≤882	841
		Week 132	≥883 and ≤966	925
	Open-label Intervention: DOR/ISL	Week 144	Group 1 participants and Group 2 participants who do not enroll in the rollover study: ≥967 and ≤1051 Group 2 participants who enroll in the rollover study: ≥967 and ≤1022	1009
		Week 148[b]	Group 1: NA Group 2: ≥1023 and ≤1064	Group 1: NA Group 2: 1037
		Week 156[b]	Group 1: NA Group 2: ≥1065 and ≤1135	Group 1: NA Group 2: 1093

NA=not applicable.
[a] Relative days and target days are computed from the first day of study intervention.
[b] The Week 148 and Week 156 visits apply only to participants in Group 2 who consent to participate in the rollover study. The participants in Group 2 who become pregnant prior to Week 144 are not eligible to switch to DOR/ISL.

FDA Snapshot Algorithm and Missing Data Approaches

There are 3 types of missing values:

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

Three approaches will be used to handle missing values. The primary approach for analysis of the percentage of participants with HIV-1 RNA ≥50 copies/mL is the FDA "snapshot" algorithm [Food and Drug Administration (CBER) 2015]. Virologic outcome will be defined according to the following categories:

- **HIV-1 RNA <50 copies/mL**: participants who have the last available on-treatment HIV-1 RNA measurement <50 copies/mL within the time point of interest analysis window specified in Table 7.
- **HIV-1 RNA ≥50 copies/mL**: this includes participants
    1) 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 7.
    2) Who do not have on-treatment HIV-1 RNA data in the time point of interest analysis window and
        a) Who discontinue study intervention prior to or in the time point of interest analysis window due to lack of efficacy, or
        b) 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 because of the following:

1) Discontinued study intervention due to AE or death: this includes participants who discontinued study intervention because of an AE or death at any time point from Day 1 through the analysis window if this resulted in no on-treatment 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.

2) Discontinued study intervention for other reasons: this includes participants who discontinued study intervention prior to or in the time point of interest analysis window due to reasons other than lack of efficacy or AE/death (ie, lost to follow-up, non-compliance 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 or AE/death and had no on-treatment HIV-1 RNA measurements during the entirety of the study.

3) On study intervention but missing data in window: only data in the predefined analysis window can be used for the statistical analysis at a given time point for participants remaining on study intervention. Participants with HIV-1 RNA results outside 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 based on 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 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 snapshot algorithm, divided by the number of participants in the FAS. Similar logic will also be used to define the percentage of participants with HIV-1 RNA <40 copies/mL in accordance with the relevant secondary endpoints.

A second approach, the missing data treated as treatment failure (M=F) approach, will be performed as a sensitivity analysis for the percentage of participants achieving HIV-1 RNA <50 copies/mL. Under this approach, participants who 1) have at least 1 on-treatment HIV-1 RNA measurement within the timepoint of interest analysis window specified in Table 7 and have the last available on-treatment measurement within the window <50 copies/mL, OR 2) are on study intervention and have no HIV-1 RNA measurements within the timepoint of interest analysis window specified in Table 7 and have both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements <50 copies/mL, will be classified as a virologic "success" at the timepoint of interest. Participants with other reasons for missing data will be classified as a virologic failure at the timepoint of interest.

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

The same supportive approaches as described above will similarly be used for the analysis of the percentage of participants achieving HIV-1 RNA <40 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. The full categorization of virologic outcome at a timepoint by the snapshot approach includes 1) HIV-1 RNA <50 copies/mL, 2) HIV-1 RNA ≥50 copies/mL, and 3) no virologic data in window for reasons of a) discontinued study intervention due to an AE/death, b) discontinued study intervention for other reasons (includes withdrawal of consent, loss to follow-up, move, etc.), or c) on study intervention, but missing data in window.

Non-inferiority of Group 1 compared to Group 2 with respect to the percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 48 and 96 will be calculated using the unstratified method of Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]. For the evaluation of the primary hypothesis at Week 48 and the secondary hypothesis at Week 96, a margin of 4 percentage points is used to define the non-inferiority of a switch to DOR/ISL at Day 1 compared to the continuation of baseline BIC/FTC/TAF for 48 weeks and 96 weeks, as appropriate; non-inferiority will be concluded if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the 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 driven by 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 compared to Group 2 with respect to the percentage of participants with HIV-1 RNA ≥50 copies/mL at Weeks 48 and 96 will also be calculated 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 multiplicity-adjusted 95% CI for the difference in the percentage of participants with HIV-1 RNA ≥50 copies/mL (Group 1 minus Group 2) is less than 0 percentage points.

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

Percentage of Participants With HIV-1 RNA <40 copies/mL and Percentage of Participants With HIV-1 RNA <50 copies/mL

The percentage of participants achieving HIV-1 RNA <40 copies/mL and the percentage of participants with HIV-1 RNA <50 copies/mL will be summarized by treatment group at each timepoint, with primary interest at Week 48,Week 96, and Week 144 by comparing Group 1 and Group 2. For each timepoint of interest, the difference in percentages between treatment groups and the associated 2-sided nominal 95% CI will be calculated using the unstratified Miettinen and Nieminen method [Miettinen, O. and Nurminen, M. 1985]. The supportive analyses using the M=F and OF approaches (as defined above) will also be presented.

Change From Baseline in CD4+ T-cell Count

Change from baseline in CD4+ T-cell count will be summarized by treatment group at each timepoint at which CD4+ T-cell count is collected, with primary interest at Week 48, Week 96, and Week 144. The treatment difference in changes from baseline in CD4+ T-cell count at each timepoint will be estimated using the ANCOVA model adjusted by baseline CD4+ T-cell count and treatment group through Week 144. However, these estimates will not be subject to an absolute criterion for similarity. The clinical interpretation of treatment difference is dependent upon the absolute value at baseline and the magnitude and direction of the CD4+ T-cell count changes observed in each treatment arm. The DAO approach will be used to handle missing data for these analyses. Under the DAO approach, participants must have both a baseline measurement and at least 1 post-baseline measurement within the timepoint of interest analysis window specified in Table 7 to be included in the analyses of the mean change from baseline in CD4+ T-cell count. Supportive analyses will also be provided using the LOCF and BOCF methods to account for missing data.

Clinically significant Confirmed Viremia

The number of participants with confirmed virologic rebound, 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 and 144.

Unblinding of Participants During the Study

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

If the unblinding is due to HBV acute infection/reactivation that requires discontinuation of study intervention or if the clinical management of the HBV requires the addition of a concomitant therapy that is also active against HIV-1, efficacy assessments in these participants will be censored from that point forward and will be handled in the primary efficacy analyses following the FDA snapshot algorithm classification rules.

In the event of a pregnancy that necessitates unblinding of the treatment regimen to allow appropriate clinical management, such participants will not be treated as treatment failures in the primary efficacy analyses on the FAS population due to the unblinding alone. Efficacy assessments in participants who become pregnant and require discontinuation of study intervention or choose to breastfeed will be censored from that point forward and will be handled in the primary efficacy analyses following the FDA snapshot algorithm classification rules. Results for participants whose pregnancy extends beyond Week 144 (for participants in Group 2 who become pregnant prior to Week 144 and are thus not eligible to switch to DOR/ISL or participants in Group 1 who do not consent to continue treatment beyond Week 144) or beyond Week 156 (for participants in Group 1 who consent to continue treatment beyond Week 144) will be reported separately. Additional details will be provided in the sSAP and/or CSR.

Table 8 summarizes the key efficacy analyses of the study.

Table 8 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis				
Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 48	P	M&N	FAS	Snapshot[a]
Secondary Objectives				
Percentage of participants with HIV-1 RNA <40 and <50 copies/mL at Week 48	P	M&N	FAS	Snapshot[a]
	S	M&N	FAS	M=F
	S	M&N	PP	OF
Percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96	P	M&N	FAS	Snapshot[a]
Percentage of participants with HIV-1 RNA <40 and <50 copies/mL at Week 96 and Week 144	P	M&N	FAS	Snapshot[a]
	S	M&N	FAS	M=F
	S	M&N	PP	OF
Change from baseline in CD4+ T-cell counts at Study Weeks 48, Week 96, and Week 144	P	ANCOVA	FAS	DAO
	S	ANCOVA	FAS	LOCF
	S	ANCOVA	FAS	BOCF

BOCF=Baseline Observation Carried Forward; DAO=Data-As-Observed; FAS=Full Analysis Set; HIV=human immunodeficiency virus; LOCF=Last Observation Carried Forward; M=F=missing equal to failure; M&N=Miettinen and Nurminen; OF=Observed Failure; P=Primary approach; PP=Per Protocol; RNA=ribonucleic acid; S=Supportive approach; vs=versus.

[a] Number of participants who meet the endpoint clinical response criteria over total FAS population.

9.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 9) at Weeks 48, 96 and 144. The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change in

laboratory and vital signs are either prespecified as “Tier 1” endpoint or will be classified as belonging to “Tier 2” or “Tier 3”, based on the number of events observed.

Safety parameters or adverse events of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as there are no a priori clinical events of concern that have been identified for this study.

Tier 2 parameters will be assessed via point estimates and 2-sided nominal 95% CIs provided for between treatment differences (Group 1 minus Group 2) in the percentage of participants with Tier 2 events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus, would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between group differences in AEs and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad categories consisting of the percentage of participants with any AE, with a drug-related AE, with an SAE, with a Grade 3 to 4 AE, with an AE that is both drug-related and serious, with an AE that is both Grade 3 to 4 and drug-related, who discontinued study intervention due to a drug-related and non-drug-related AE, and with AE(s) leading to death will be considered Tier 2 endpoints. The percentage of participants with a cardiac SAE will also be considered a Tier 2 endpoint.

The mean change from baseline to Weeks 48, 96 and 144 in body weight will be considered Tier 2 events. For the evaluation of the secondary hypotheses of the effect on weight of a switch to DOR/ISL at Day 1 compared to the continuation of baseline BIC/FTC/TAF at Weeks 48 and 96, the treatment difference in the change from baseline will be estimated between treatment groups using ANCOVA models adjusted by baseline weight, sex at birth, race, and treatment group. Superiority of having lower mean increase from baseline will be concluded if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the estimate of the treatment group difference (Group 1 minus Group 2) is less than 0. P-values for the comparisons at Week 48 and Week 96 will also be provided. For participants who become pregnant during the study, weight measured after the estimated date of conception will be excluded from the analyses. The APaT population will be used for this analysis, and the DAO approach will be used to handle missing data. The same statistical model will be used to evaluate the between group difference in the change from baseline to Week 144 in body weight.

Safety endpoints that are not Tier 2 events are considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters.

For continuous measures such as change from baseline in laboratory and vital signs parameters that are not prespecified as Tier 2 endpoints, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For the lipid profile analyses, participants who receive lipid-lowering therapy at baseline will be excluded from all lipid-related analyses. Missing lipid data will be handled using the DAO approach, that is, any participant with a missing value will be excluded from the analysis. 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. The percentages of participants who initiate or modify lipid-lowering therapy prior to Week 48, Week 96, and Week 144 will be summarized by treatment group.

Missing safety parameters, unless otherwise specified, will be handled using the DAO approach, that is, any participant with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. In the rare event when Day 1 data are missing, the value obtained at the most recent screening visit will be used as baseline, when available. If no baseline result is available, that participant will not be included in the summary.

Safety data for participants in Group 2 who consent to switch to DOR/ISL at Week 144 will be summarized from Week 144 to Week 156. For the assessment of change from baseline in Group 2 at Week 156, baseline will be the Week 144 measurement (or, if the Week 144 measurement is not available, the last measurement prior to the switch to DOR/ISL).

For participants who become pregnant during the study, safety parameters assessed during the pregnancy period (estimated date of conception to-date of conclusion of the pregnancy) may be summarized separately from the primary and secondary safety analyses. For continuous measures that are considered to be Tier 2 events, data collected after the estimated date of conception will be excluded from the analyses. Data collected for participants whose pregnancy or postpartum visit(s) extend beyond Week 144 or 156 will be reported separately. Infant safety data will be reported separately. Additional details on how pregnancy and infant data will be handled in safety analyses will be provided in the sSAP and/or CSR.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Difference	Descriptive Statistics
Tier 2	• The percentage of participants with an AE in each of the following categories: 1 or more AE(s); drug-related AE(s), serious AE(s), Grade 3 to 4 AE(s), AE(s), which are both drug-related and serious, AE(s), which are both Grade 3 to 4 and drug-related, AE(s) [drug-related and non-drug-related] leading to discontinuation of study intervention, and AE(s) leading to death • Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence ≥4 participants in either treatment group • The percentage of participants with a cardiac SAE • Change from baseline to Weeks 48, 96 and 144 in body weight[ab] • Change from baseline in select laboratory, and radiological markers of fasting lipid profiles, renal function, inflammation, and body composition[b]	X	X
Tier 3	• Specific AEs (preferred terms), SOCs, or PDLCs occurring with an incidence <4 participants in both treatment groups • Change from baseline in body weight, laboratory measurements and vital signs[c]		X

AE=adverse event; CI=confidence interval; PDLC=predefined limit of change; SOC=System Organ Class.
[a] Though classified as a Tier 2 event, p-values will be provided for change from baseline to Week 48 and Week 96 in body weight to support the evaluation of the corresponding secondary hypotheses.
[b] For participants who become pregnant, data collected after the estimated date of conception will be excluded.
[c] Includes only those endpoints not already prespecified as Tier-2 endpoints.

9.6.3 Summaries of Baseline Characteristics, Demographic, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, gender, 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 interim analyses. Blinding to treatment assignment will be maintained at all investigational sites until Week 96.

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

Treatment level results from all interim analyses will be provided to the eDMC by the external unblinded statistician. The external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts.

Once 40% of target enrollment (n = 232 participants) have completed Week 24, including visit assessments, the Week 24 interim analysis will be conducted by an external unblinded statistician to assess futility. This analysis will be reviewed by the eDMC.

Futility Criteria: If the upper bound of the 2-sided multiplicity-adjusted 95% CI for the difference in the percentage of participants with HIV-1 RNA ≥200 copies/mL (Group 1 minus Group 2) is greater than 8 percentage points and the 95% CI excludes 0, consideration may be given to stop the study.

The futility analysis will include all participants in the first 40% of target enrollment. For the purpose of the Week 24 interim analysis, those classified as HIV-1 RNA ≥200 copies/mL includes participants:

1) Who have the last available on-treatment HIV-1 RNA measurement ≥200 copies/mL at the Week 24 visit window specified in Table 7.

   If participants do not have confirmed viremia (Section 4.2.1.1.2) at the subsequent visit, their virologic outcome will be reassessed for the primary analyses (Section 9.6.1).

2) Who do not have on-treatment HIV-1 RNA data at Week 24

   - Who discontinue study intervention prior to the Week 24 visit due to lack of efficacy or confirmed viremia (Section 4.2.1.1.2), or

   - Who discontinued study intervention prior to the Week 24 visit due to reasons other than lack of efficacy and have their last on-treatment HIV-1 RNA measurement ≥50 copies/mL

   Those participants will be included in the virologic failure rate calculated for the purposes of the primary analyses (Section 9.6.1).

A possibility exists that unblinded data from this interim analysis may ultimately be submitted to regulatory authorities prior to Week 48, when the Sponsor becomes unblinded. In that event, to preserve the blinding integrity of the trial, an unblinded team at the Sponsor will be identified and those working with these unblinded data, working on the submission, and responding to regulatory questions would be firewalled from those blinded Sponsor personnel still working on the study. A separate data integrity/management plan will be developed to further define the roles and access for those on the unblinded and blinded teams at the Sponsor.

In addition, the eDMC will review accumulating safety and efficacy data at regular intervals throughout the study duration, or 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 trial.

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 also be provided to the eDMC.

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. There is no intention of stopping the study due to positive efficacy at any of these reviews. Nevertheless, since unblinded summaries of HIV-1 RNA values may be included in these reviews, a small amount of alpha (α=0.00001) will be allocated for each of these looks, purely for statistical rigor. An allowance will be made such that a total of up to 5 of these unblinded eDMC reports (including the futility assessment once 40% of participants have reached Week 24) may be presented prior to the evaluation of the primary non-inferiority efficacy hypothesis at Week 48. If further eDMC reviews occur between the evaluation of the primary non-inferiority efficacy hypothesis at Week 48 and the evaluation of the efficacy hypotheses tested at Week 96 (ie, (H4) and (H2)), further reduction in the alpha of 0.00001 for each eDMC review will be made for the hypotheses tested at Week 96.

The following efficacy hypotheses will be tested sequentially at a 1-sided 2.5% Type 1 error rate adjusted for the number of eDMC reports in the following order:

1) Primary efficacy hypothesis (H1) testing non-inferiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 48.

2) Secondary efficacy hypothesis (H4) testing superiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 96.

3) Primary efficacy hypothesis (H2) testing superiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 48.

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.

It is noted that the last sequential hypothesis to be evaluated concerns efficacy at Week 48 although it would not be evaluated until the Week 96 analyses are conducted as the second sequential hypothesis involves a Week 96 endpoint.

The secondary efficacy hypothesis (H3) testing non-inferiority of HIV-1 RNA ≥50 copies/mL between Group 1 and Group 2 at Week 96 will be tested independently of the efficacy hierarchy described above. This hypothesis will be tested at a 1-sided 2.5% Type 1 error rate adjusted for the number of eDMC reports from Day 1 to Week 96.

The secondary safety hypotheses, (H5) testing superiority of having lower mean increase from baseline in body weight for Group 1 vs. Group 2 at Week 48 and (H6) testing superiority of having lower mean increase from baseline in body weight for Group 1 vs. Group 2 at Week 96, will be tested independently of all aforementioned efficacy hypotheses. These hypotheses will be tested using the following rules:

(1) (H5) will be tested at a 1-sided 0.25% Type 1 error rate adjusted for the number of eDMC reports from Day 1 to Week 48, denoted by α_1^*.

(2a) If (H5) is retained (ie, the null hypothesis is not rejected) at Week 48, (H6) will be tested at Week 96 at a 1-sided 2.25% Type 1 error rate adjusted for the number of eDMC reports from Week 48 to Week 96, denoted by α_2^*.

(2b) If (H5) is rejected at Week 48, (H6) will be tested at Week 96 at a 1-sided Type 1 error rate of $\alpha_1^* + \alpha_2^*$.

(3) If (H5) is retained at Week 48 and (H6) is rejected at Week 96, (H5) will be retested at Week 96 at a 1-sided Type 1 error rate of α_2^*.

This approach strongly controls the overall 1-sided Type 1 error rate for the safety hypotheses (H5) and (H6) to be less than or equal to $\alpha_1^* + \alpha_2^* \leq 0.25\% + 2.25\% = 2.5\%$ [Maurer, W., et al 2011].

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

9.9.1.1 Futility Criteria

The probability of passing the Week 24 interim analysis and the overall study power to demonstrate non-inferiority at Week 48 under a variety of assumptions is presented in Table 10.

The power calculations shown in Table 10 incorporate the Week 24 interim analysis stopping rules. The interim analysis for futility will be conducted when 40% of the study enrollment (approximately 116 participants per arm) have reached Week 24. The study may stop if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the difference in the percentage of participants with HIV-1 RNA ≥200 copies/mL (Group 1 minus Group 2) is greater than 8 percentage points and the 95% CI excludes 0. Of interest is the likelihood that the study would meet the stopping criteria at Week 24 for a variety of assumed Week 24 response rates and also whether the non-inferiority criteria at Week 48 would be met.

Table 10 Probability of Passing the Interim Analysis and the Overall Study Power for Various Underlying True Response Rates Assuming Futility Assessed at 40% Enrollment

Group 1: True Rate for Week 24 | True Rate for Week 48	Group 2: True Rate for Week 24 | True Rate for Week 48	Probability of Passing Interim Analysis (40% of Enrollment at Week 24)	Probability of Demonstrating Non-Inferiority at Week 48 (Overall Study Power)
0.75% | 1.5%	1% | 2%	99.6%	95.4%
1% | 2%	1% | 2%	99.0%	82.8%
1.25% | 2.5%	1% | 2%	97.9%	64.0%
1.5% | 3%	1% | 2%	96.7%	42.2%
1.75% | 3.5%	1% | 2%	95.1%	25.6%
2% | 4%	1% | 2%	93.1%	13.5%
2.5% | 5%	1% | 2%	88.4%	2.8%

HIV=human immunodeficiency virus.
Rate for Week 24 is the percentage of participants at Week 24 with HIV-1 RNA ≥200 copies/mL. Rate for Week 48 is the percentage of participants at Week 48 with HIV-1 RNA ≥50 copies/mL.

For example, if the true rate of participants at Week 24 with HIV-1 RNA ≥200 copies/mL is 1% in both groups, and the true rate of participants at Week 48 with HIV-1 RNA ≥50 copies/mL is 2% in both groups, there is a 99.0% chance of not meeting the futility criteria at Week 24. The overall study power for that scenario is 82.8%.

9.9.1.2 Evaluation of Non-inferiority and Superiority Hypotheses

This section presents a fuller description of the power calculations for the primary analysis of non-inferiority at Week 48. In contrast to the power shown in Table 10, the power calculations shown here do not account for the futility analysis and instead assume the futility criteria are not met and the study continues through Week 48.

As described in Section 9.8, the alpha level used in the final analysis (corresponding to the multiplicity-adjusted 95% CI) will account for the actual number of eDMC evaluations conducted in the study. For the purposes of the power calculations, 5 eDMC evaluations are

assumed, leaving α=0.02495 (1-sided) available for the final analysis. Non-inferiority will be concluded if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the 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 driven by 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 power calculations are simulated based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985] and were carried out using SAS version 9.4.

Table 11 summarizes the power for the primary comparison under various assumptions for the control response rate and underlying difference in response rate (the percentage of participants with HIV-1 RNA ≥50 copies/mL). For example, if the true rates are 1.5% in both groups, this study has approximately 91% power to demonstrate non-inferiority. If the true rates are 2.0% in both groups, this study has approximately 85% power to demonstrate the primary hypothesis that Group 1 is non-inferior to Group 2 at Week 48.

Note that Table 11 can also be used to approximate the power to declare Group 1 non-inferior to Group 2 with respect to the percentage of participants with HIV-1 RNA ≥50 copies/mL at Week 96. The estimated power values at Week 96 would differ slightly from the Week 48 values presented in Table 11 due to the additional adjustment to the 1-sided Type 1 error that would be made for the number of eDMC reports that occur between Week 48 and Week 96.

Table 11 Power (%) to Establish Non-Inferiority at Week 48/96 Under Various Response Rate Assumptions (289 Participants per Group)

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**
1.5%	100	98	91	77	59
2.0%	99	95	85	71	54
2.5%	97	91	80	65	49
3.0%	94	87	74	59	45
3.5%	91	82	69	54	41

CI=confidence interval; eDMC=external Data Monitoring Committee; NI=non-inferiority.

Note: Non-inferiority margin=4%. To establish NI: upper bound of the 2-sided multiplicity-adjusted 95% CI must be <4 percentage points for Group 1 minus Group 2. The 95% CI is based on the Miettinen & Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.02495, which adjusts for an assumed 5 eDMC reports between Day 1 and Week 48. If additional eDMC reports occur between Week 48 and Week 96, the 1-sided Type 1 error rate would be further adjusted for the assessment of non-inferiority at Week 96. Power was assessed via 10,000 simulations for each scenario.

Table 12 summarizes the power to declare Group 1 superior to Group 2 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 0.3% in Group 1 and 2% in Group 2, then this study will have approximately 51% power to demonstrate superiority.

Table 12 Power (%) to Establish Superiority at Week 48/96 Under Various Response Rate Assumptions (Assuming All Prior Hypothesis Tests Reach Statistical Significance) (289 Participants per Group)

Group 1: True Rate for Week 48/96	Group 2: True Rate for Week 48/96	Probability of Demonstrating Superiority at Week 48/96
0%	2%	83%
0.3%	2%	51%
0.6%	2%	31%
1%	2%	14%

CI=confidence interval; eDMC=external Data Monitoring Committee.

Note: Values are computed assuming that all prior hypotheses in the testing hierarchy (see Section 9.8) reach statistical significance.

Note: To establish superiority: upper bound of the 2-sided multiplicity-adjusted 95% CI must be <0 percentage points for Group 1 minus Group 2. The 95% CI is based on the Miettinen & Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.02495, which adjusts for an assumed 5 eDMC reports between Day 1 and Week 48. If additional eDMC reports occur between Week 48 and Week 96, the 1-sided Type 1 error rate would be further adjusted for the assessment of superiority at Week 96. Power was estimated via 10,000 simulations for each scenario.

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 94.5% chance of observing at least 1 AE among 289 participants in a treatment group. If no AE of that type is observed among the 289 participants in a treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <1.27% (1 out of every 78 participants).

The estimate of, and the upper bound of the 2-sided nominal 95% CI for, the underlying percentage of participants with an AE given various hypothetical observed number of participants with the AE within each treatment group are provided in Table 13. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 13 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs (289 Participants per Group)

Hypothetical Number of Participants With Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
0	0.0%	1.0%
5	1.7%	4.0%
10	3.5%	6.3%
15	5.2%	8.4%
20	6.9%	10.5%
25	8.7%	12.5%
30	10.4%	14.5%

AE=adverse event; CI=confidence interval.

[a] Based on the 2-tailed exact CI for a binomial proportion (Clopper and Pearson method[Clopper, C. J. and Pearson, E. S. 1934]). In the 0 event case, the 95% CI is 1-sided (α=0.05 all in the upper tail).

Table 14 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 289 participants in each group. 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 10.1 percentage points. The calculations are based on an asymptotic method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985].

Table 14 Difference in Incidence of AEs (Group 1 minus Group 2) That Can Be Ruled Out With 289 Participants in Each Group.

Target Power	Underlying AE Incidence Rate						
	1%	5%	10%	20%	30%	40%	50%
80%	4.0	6.4	8.1	10.1	11.1	11.6	11.6
85%	4.4	6.9	8.7	10.8	11.9	12.4	12.3
90%	4.9	7.6	9.5	11.8	12.9	13.4	13.3
95%	5.8	8.7	10.8	13.2	14.4	14.9	14.8

AE=adverse event; CI=confidence interval.

Note: The upper bound of the 2-sided nominal 95% CI (unstratified Miettinen and Nurminen[Miettinen, O. and Nurminen, M. 1985]) for the difference in AE incidences (Group 1 minus Group 2) assuming the incidences are the same.

9.9.2.2 Evaluation of Change in Weight

Table 15 gives the hypothetical minimal treatment differences in the change from baseline in weight that can be detected between Group 1 and Group 2 with given power at Weeks 48 and 96 assuming varying values of the underlying standard deviation and accounting for potential participant dropout. The calculations incorporate the testing strategy specified in Section 9.8, which allows for the transfer of alpha back and forth between the Week 48 and Week 96 hypotheses based on whether hypotheses (H5) and (H6) are retained (ie, the null hypothesis is not rejected) or rejected. Calculations are performed conditionally, that is, the probability that the Week 48 and Week 96 hypotheses are retained or rejected are not estimated or accounted for in the power calculations. For example, if the standard deviation of change in weight from baseline in both treatment groups at Week 96 is 8 kg and the number of participants in each treatment group at Week 96 is 243, then this study will provide 90% power to detect a difference at least as large as 2.39 kg at Week 96 assuming that the Week 48 hypothesis (H5) was retained.

Table 15 Hypothetical Minimal Treatment Differences in the Change From Baseline in Body Weight That can Be Detected With Given Power at Weeks 48 and 96

Week 48 Hypothesis (H5) is Tested at $\alpha_1^* = 0.00245$			
Power	n = 260 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	4 kg	5 kg	6 kg
80%	1.29	1.61	1.93
85%	1.36	1.69	2.03
90%	1.44	1.80	2.16
If Week 48 Hypothesis (H5) is Rejected, Week 96 Hypothesis (H6) is Tested at $\alpha_1^*+\alpha_2^* = 0.02493$			
Power	n = 243 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	8 kg	10 kg	12 kg
80%	2.04	2.55	3.06
85%	2.18	2.72	3.27
90%	2.36	2.95	3.54

If Week 48 Hypothesis (H5) is Retained, Week 96 Hypothesis (H6) is Tested at $\alpha_2^* = 0.02248$			
Power	n = 243 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	8 kg	10 kg	12 kg
80%	2.07	2.59	3.11
85%	2.21	2.77	3.32
90%	2.39	2.99	3.59
If Week 48 Hypothesis (H5) is Retained and Week 96 Hypothesis (H6) is Rejected, Week 48 Hypothesis (H5) is Retested at $\alpha_2^* = 0.02248$			
Power	n = 260 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	4 kg	5 kg	6 kg
80%	1.00	1.25	1.50
85%	1.07	1.34	1.60
90%	1.16	1.44	1.73

3TC=lamivudine; DOR=doravirine; eDMC=external Data Monitoring Committee; ISL=islatravir; TDF=tenofovir disoproxil fumarate.

[a] The calculations account for potential participant dropout prior to the Week 48 and Week 96 time points. A dropout rate of 10% at Week 48 and 16% at Week 96 was assumed in the calculations based on data from MK-1439A-024. As such, the number of participants per group is assumed to be 260 at Week 48 and 243 at Week 96.

[b] Values of the standard deviation of change in weight from baseline are based on experience with MK-8591 P011. In this study, the standard deviation of change in weight from Day 1 through Week 48 ranged from approximately 4.1 kg (DOR/3TC/TDF treatment group) to 5.9 kg (ISL[0.75 mg]+DOR+3TC treatment group). Assuming the change in weight from Week 48 through Week 96 would be consistent with the observed change in weight from Day 1 through Week 48, the 96-week weight change standard deviations range from approximately 8 kg to 12 kg.

α_1^*=0.25% 1-sided Type 1 error for the Week 48 weight hypothesis (H5) adjusted for an assumed 5 eDMC reports between Day 1 and Week 48.

α_2^*=2.25% 1-sided Type 1 error for the Week 96 weight hypothesis (H6) adjusted for an assumed 2 eDMC reports between Week 48 and Week 96.

Note: “Retained” means the corresponding null hypothesis is not rejected.

Note: Calculations are performed conditionally (ie, the probability that the Week 48 and Week 96 hypotheses are retained or rejected are not estimated or accounted for in the power calculations).

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between group treatment effect (with a nominal 95% Miettinen and Nurminen CI) for the primary endpoint and the key secondary endpoints (HIV-1 RNA <50 copies/mL and HIV-1 RNA <40 copies/mL endpoint to aid in the EU review) will be calculated for the following classification variables:

- Age category (<50 years of age, ≥50 years of age)
- Sex at birth
- Gender identity
- 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 in the study intervention CRF page, the number of tablets remaining in study packaging will be counted and reviewed at regular intervals. These results will be used to calculate participant compliance.

For the 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.

For participants in Group 1 and Group 2 (prior to the potential switch to DOR/ISL at Week 144), the "Number of Days Should be on Therapy" is the total number of days from Day 1 to the date of the last dose of study intervention for each participant. As such, the "Number of Days Should be on Therapy" will be the number of days from Day 1 to the timepoint of interest (ie. Week 48, Week 96, or Week 144) for those participants who are on study intervention for the entire study period of interest. For participants who discontinue study intervention prior to or within the study period of interest, the "Number of Days Should be on Therapy" will be the number of days from Day 1 to the date of discontinuation of study intervention.

For participants in Group 2 who consent to switch to DOR/ISL at Week 144, the "Number of Days Should be on Therapy" is the total number of days from the DOR/ISL treatment start date to the date of the last dose of DOR/ISL for each participant. The "Number of Days Should be on Therapy" will be the number of days from the DOR/ISL treatment start date to the Week 156 timepoint for those participants who are on DOR/ISL for the entire study period from Week 144 through Week 156. For participants who discontinue DOR/ISL prior to Week 156, the "Number of Days Should be on Therapy" will be the number of days from the DOR/ISL treatment start date to the date of discontinuation of DOR/ISL.

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

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

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

9.12 Extent of Exposure

The extent of exposure to study intervention for all randomized and treated participants will be summarized. The number of participants exposed to various doses (actual total daily dose) for defined periods of time will be listed, 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 and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.4.3 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 input with respect to 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 International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

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

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 16 Protocol-required Laboratory Assessments

<table>
<tr><td>Laboratory Assessments</td><td colspan="3">Parameters</td></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet Count</td><td rowspan="4">RBC Indices:
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
MCH concentration
Red Cell Distribution Width (RDW)</td><td rowspan="4">White Blood Cell (WBC) count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>Red Blood Cell (RBC) Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td>CD4+ T-cell count/TBNK Panel</td><td colspan="3">T-cell, B-cell, and Natural Killer cell profile that includes:
CD3+ Percent
CD3+ Value/Absolute Count
CD3+CD4+ Percent
CD3+CD4+ Value/Absolute Count
CD3+CD8+ Percent
CD3+CD8+ Value/Absolute Count
CD3-CD19+ Percent
CD3-CD19+ Value/Absolute Count
CD16+CD56+ Percent
CD16+CD56+ Value/Absolute Count
CD3+CD4+CD8+ Percent
CD3+CD4+CD8+ Value/Absolute Count
CD4/CD8 Ratio</td></tr>
</table>

Laboratory Assessments	Parameters			
Coagulation	Prothrombin time / international normalized ratio (INR)			
Chemistry (non-fasting)	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin • Direct bilirubin • Indirect bilirubin
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Total Protein
	Glucose [non-fasting]	Calcium	Alkaline phosphatase	Creatinine Clearance
	Creatine kinase	Lipase	Amylase	Magnesium
Additional chemistry at fasting visits (fasting for at least 8h)	Glucose [fasting] High-density lipoprotein (HDL-C) Low-density lipoprotein (LDL-C) Triglycerides (TGs) Total Cholesterol (TC) Non-HDL-C Insulin[a] Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (calculation)			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes			
Pregnancy testing	Serum and urine β human chorionic gonadotropin (β hCG) pregnancy test (for a woman/women of childbearing potential [WOCBP])			
Urinary analytes	Albumin Protein Beta-2-microglobulin/creatinine ratio (B-2 M/Cr) Retinol binding protein/creatinine ratio (RBP/Cr)			
Renal function	Estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) equation			
Hepatitis screening and monitoring[b]	Hepatitis B virus surface antigen (HBsAg) Hepatitis B virus (HBV) surface antibody Anti-HBc (hepatitis B core antibody) HBV DNA Hepatitis C antibody (if positive perform plasma hepatitis C virus quantitative test) (at screening only)			
Human immunodeficiency virus-1 (HIV-1) serology	HIV 1/2 antibody test			
Virology	HIV-1 viral ribonucleic acid (RNA) quantification (Real time polymerase chain reaction [PCR]) HIV-1 viral resistance			

Laboratory Assessments	Parameters
Inflammatory Markers	D-dimer Interleukin-6 (IL-6) Soluble CD-163 (sCD-163) High-sensitivity C-reactive protein (hs-CRP)
Blood for Renal Biomarkers	Cystatin-C
Pharmacokinetics (PK)	Islatravir (ISL) PK
	Investigational PK samples will be collected from all participants. Analysis of these samples will be triggered by the Sponsor as needed.
	ISL and DOR PK (Only participants on DOR/ISL who are pregnant)
[a] Participants with diabetes mellitus (type 1 or type 2) or insulin resistance are not required to have the blood draw for insulin testing. [b] All participants will be screened for HBsAg, HBV surface antibody, anti-HBc and HBV DNA. Participants who are anti-HBc positive, but HBV DNA negative will have HBsAg and HBV DNA monitored for the duration of the study.	

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

Table 17 Blood Volumes

Study Period	**Screening**	**Group 1 and 2**														**Group 2 only**		Viremia Confirmation	CD4+ T-cell/ Lymphocyte Confirmation	Early Discon of Treatment	CD4+ T-cell/ Lymphocyte Monitoring[e]	EoT Follow-Up
Scheduled Day/Week	Screening	Day 1	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 148[c]	Week 156[c]	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																					
Plasma HIV-1 RNA Quantification (Real Time PCR)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6		6
CD4+ T-cell Count/TBNK Panel	6	6			6		6		6	6	6	6	6	6	6		6		6	6	6	6
Blood (Plasma) for HIV-1 Drug Resistance Testing		12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		12		12
HIV-1 & -2 and Hepatitis Screen[a]	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4					
HIV Confirmation Geenius	1																					
HBV DNA[a]	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6					
Chemistry (Includes Serum Pregnancy at Screening and Early Discontinuation)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			6		
Hematology	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2
Fasting Lipids		2			2		2				2		2		2							
Fasting Insulin		1			1		1				1		1		1							

Study Period	**Screening**	**Group 1 and 2**														**Group 2 only**		Viremia Confirmation	CD4+ T-cell/ Lymphocyte Confirmation	Early Discon of Treatment	CD4+ T-cell/ Lymphocyte Monitoring[e]	EoT Follow-Up
Scheduled Day/Week	Screening	Day 1	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 148[c]	Week 156[c]	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter	**Approximate Blood Volume (mL)**																					
PT/INR	2.7																					
Blood for Inflammatory Biomarkers		10.7			10.7		10.7				10.7				10.7							
Cystatin-C		2			2		2				2				2							
PK Blood Sample Collection (All Participants)		4	8	4	4		4															
Blood (Plasma) for Investigational PK[b]						4		4	4	4	4				4			4		4		4
Blood (Plasma) for DOR and ISL PK During Pregnancy[d]			<----------X[d]---------->																			
Blood for Genetic Analysis		8.5																				
Whole Blood for FBR		8			8		8				8				8			8		8		
Total Blood Volume per Visit (mL)	33.7	78.2	44	40	63.7	40	69.7	40	46	46	69.7	46	49	46	69.7	40	46	30	8	44	8	30

anti-HBc=hepatitis B core antibody; DNA=deoxyribonucleic acid; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus-1; INR=international normalized ratio; PCR=polymerase chain reaction; PK=pharmacokinetic(s) PT=prothrombin time; RNA=ribonucleic acid.

[a] All participants will be screened for HBsAg, HBV surface antibody, anti-HBc and HBV DNA. Participants who are anti-HBc positive, but HBV DNA negative, will have HBsAg and HBV DNA monitored for the duration of the study. Testing will be repeated at Week 132 for all participants in preparation for potential switch.

[b] Investigational PK samples will be collected from all participants. Analysis of these samples will be triggered by the Sponsor as needed.

[c.] Study visit only applies for Group 2 participants who switch to DOR/ISL at Week 144.

[d] PK samples collected during pregnancy will be collected per Section 8.11.6.1. During the 1st trimester and postpartum study visits, 4 mL of blood will be collected for PK sampling. During the 2nd and 3rd trimester study visits, 12 mL of blood will be collected for PK sampling.

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

Table 18 Blood Volumes: Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 144 or 156

The assessments in Table 18 are for any participant who is pregnant at the last scheduled study visit (ie, Week 144) and whose visit schedule will be extended through the duration of the pregnancy, to allow assessments through each trimester and postpartum.

Visit Number	**Unscheduled**			
Scheduled Week	**Pregnancy 1 (Week 156 or 168)**	**Pregnancy 2 (Week 168 or 180)**	**Pregnancy 3 (Week 180 or 192)**	**Pregnancy 4 (Week 192 or 204)**
Blood Parameter	**Approximate Blood Volume (mL)**			
Plasma HIV-1 RNA Quantification (Real Time PCR)	6	6	6	6
CD4+ T-cell Count	6	6	6	6
Plasma for HIV Viral Drug Resistance Testing	15	15	15	15
HBsAg and DNA	6	6	6	6
Chemistry	6	6	6	6
Hematology	2	2	2	2
Blood (Plasma) for DOR and ISL PK	----------X[a]----------			
Whole Blood for FBR	8	8	8	8
Approximate Blood Volume per Visit (mL)[a]	61	61	61	61

DNA=deoxyribonucleic acid; DOR=doravirine; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus Type 1; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic(s); RNA=ribonucleic acid.; mL=milliliter.

[a] PK samples collected during pregnancy will be collected per Section 8.11.6.1. During the 1st trimester and postpartum study visits, 4 mL of blood will be collected for PK sampling. During the 2nd and 3rd trimester study visits, 12 mL of blood will be collected for PK sampling.

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

10.3.1 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

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

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

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

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

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

d. **Results in persistent or significant disability/incapacity**

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

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

e. **Is a congenital anomaly/birth defect**

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

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

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

Assessment of intensity/toxicity

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

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

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

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

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

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

  - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

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

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

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

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

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

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

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

- Transgender women (assigned male gender at birth and transitioning toward femaleness).
- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

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

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

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

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

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

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

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c] · IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] • Oral • Intravaginal • Transdermal • Injectable
• Progestogen-only hormonal contraception[c] • Oral • Injectable
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[e]
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. d. IUS is a progestin releasing IUD. e. A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research

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

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally

identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for Germany

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.

In Germany, if a participant becomes pregnant (has a positive serum pregnancy test), she must discontinue from study intervention, and the participant's HIV-1 infection and treatment should be managed per local standard of care. All reported pregnancies must be followed to completion or termination so that the outcome of the pregnancy is reported. Additionally, pregnant women who discontinue study intervention are encouraged, but not required, to consent to postnatal infant safety data collection.

The following protocol sections related to pregnancy remain applicable in Germany:

- Section 8.1.1.3 Consent for Postnatal Infant Safety Data Collection Through One Year of Age
- Sections 8.4.5 Pregnancy and Exposure During Breastfeeding
- Section 8.11.6 Clinical Management of Participants Who Become Pregnant
- Section 8.11.6.2 Discontinuing Study Intervention for Pregnancy
- 8.11.6.4 Infant Safety Data Collection
- 8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection

The following sections are not applicable in Germany:

- Section 1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visits Extend Beyond Week 144 or 156
- Section 4.2.7 Rationale for Continuing Study Intervention During Pregnancy
- Section 8.1.1.4 Consent for Continuation of Study Intervention During Pregnancy
- Section 8.11.6.1 Continuing Study Intervention
- Section 8.11.6.3 Participants Who Choose to Breastfeed

In addition, consent must be obtained directly from the participant in Germany; the use of a legally acceptable representative to obtain consent is not permitted. Participants who cannot directly provide informed consent cannot participate in this study.

10.7.2 Country-specific Request for Canada

Participants who become HBsAg or HBV DNA positive after randomization must be discontinued from study intervention. This was included in a country-specific amendment (MK-8591A-018-01).

10.7.3 Country-specific Request for Japan

Changes to the protocol-required per Japanese local regulation are documented in the translated version of the protocol that is filed locally.

10.8 Appendix 8: Calculation of Creatinine Clearance

Cockcroft-Gault equations:

- If male:

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

- If female:

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

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
β-hCG	Beta human chorionic gonadotropin
3TC	lamivudine
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
APaT	All Participants as Treated
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
BIC	bictegravir
BMD	bone mineral density
BMI	body mass index
BOCF	baseline observation carried forward
C24	concentration after 24 hours
CD4+	CD4-positive
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
Cmax	maximum (peak) observed drug plasma concentration
CNS	central nervous system
Cr_{cl}	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
Ctrough	lowest concentration reached by a drug before the next dose is administered
DAIDS	The Division of AIDS
DAO	Data-As-Observed
DDI	drug-drug interaction
DEXA	Dual X-ray Absorptiometry
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
EFV	efavirenz
eDMC	external Data Monitoring Committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EQ-5D-5L	EuroQol five-dimensional descriptive system, five level version
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed dose combination
FSH	follicle stimulating hormone

Abbreviation	Expanded Term
FTC	emtricitabine
GCP	Good Clinical Practice
H	hypothesis
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HIV SDM	Human Immunodeficiency Virus Symptom Distress Module
HIV-SI	Human Immunodeficiency Virus Symptom Index
HIVTSQ	Human Immunodeficiency Virus Treatment Satisfaction Questionnaire
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HRQoL	health-related quality of life
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HTA	Health Technology Assessment
IA	Interim Analysis(ses)
IB	Investigator's Brochure
IC50	concentration of drug needed to inhibit 50% of viral growth
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-6	interleukin-6
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
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
M=F	missing data treated as treatment failure
MSD	Merck Sharp & Dohme, Corp.
NK	natural killer
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OF	Observed Failure
PCL	Protocol Clarification Letter
PCR	polymerase chain reaction
PDLC	predefined limit of change
PI	protease inhibitor
PK	pharmacokinetic
PP	Per Protocol
PrEP	preexposure prophylaxis
PRO	patient-reported outcome
QD	once-daily
RNA	ribonucleic acid

Abbreviation	Expanded Term
SAC	Scientific Advisory Committee
SAE	serious adverse event
sCD-163	soluble CD-163
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TAMS	thymidine analogue mutations
TBNK	T- and B- Lymphocyte and Natural Killer Cell Profile
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglyceride
TLOVR	Time to Loss of Virologic Response
TP	triphosphate
US	United States
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

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