Official Protocol Title:	Phase 3 Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/ Islatravir Once-Daily in HIV-1 Infected Treatment-Naïve Participants
NCT Number:	NCT04233879
Document Date:	26-Mar-2024

Title Page

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

Protocol Title: A Phase 3 Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/Islatravir Once-Daily in HIV-1 Infected Treatment-Naïve Participants

Protocol Number: 020-06

Compound Number: MK-8591A

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	134,036
EudraCT	2019-000590-23

Approval Date: 26 March 2024

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 06	26-MAR-2024	The protocol was amended to revise the post-treatment management of participants with specific decreases in CD4+ T-cell or total lymphocyte counts. The recovery criteria were revised to account for normal physiologic variability in CD4+ T-cell or total lymphocyte counts and the frequency of monitoring was updated to minimize the burden on study participants.
Amendment 05	12-OCT-2022	This protocol was amended to allow participants who continue to benefit (as determined by the Investigator) from their assigned study intervention, to continue their assigned study intervention through a study extension after Week 144. This extension will continue for up to 24 additional weeks (up to maximum Week 168) or until the participant has the option to enroll in a DOR/ISL 100 mg/0.25 mg study; whichever is sooner. Participants choosing not to enroll in a DOR/ISL 100 mg/0.25 mg study, will transition to commercially available ART as soon as possible.
Amendment 04	26-JAN-2022	The protocol was amended to: (1) 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, given the findings of decreases in CD4+ T-cell and total lymphocyte counts in clinical studies evaluating ISL and (2) to update the timing of when the Sponsor will be unblinded to individual participants' treatment assignments.

Document	Date of Issue	Overall Rationale
Protocol Amendment 03	09-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 03 were not implemented at clinical sites. Amendment 04 supersedes amendment 03.
Protocol Amendment 02	28-MAY-2021	The protocol was amended to: (1) extend study intervention (open-label) from 96 weeks to 144 weeks for all participants; (2) provide an option for Group 2 to receive open-label DOR/ISL from Week 144 to Week 156; (3) offer the option to continue study intervention for participants who become pregnant; and (4) add a discontinuation criterion if a participant chooses to breastfeed.
Protocol Amendment 01	11-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.
Original Protocol	05-NOV-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendment:

The protocol was amended to revise the post-treatment management of participants with specific decreases in CD4+ T-cell or total lymphocyte counts. The recovery criteria were revised to account for normal physiologic variability in CD4+ T-cell or total lymphocyte counts and the frequency of monitoring was updated to minimize the burden on study participants.

Summary of Changes Table:

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 8.11.5.2, Participants Discontinued from Study Intervention Due to Decreased CD4+ T-cell Count and/or Total Lymphocyte Count	Revised the post-treatment management of participants by reducing the post-treatment lymphocyte monitoring frequency (from monthly to approximately every 10 to 14 weeks) and by updating the criteria to stop monitoring for Group 1 participants who discontinued DOR/ISL.	This amendment provides an update to the strategy for posttreatment monitoring. CD4+ T-cell and total lymphocyte counts exhibit significant normal physiologic variability independent of ISL, such that the original criteria to stop monitoring are challenging to satisfy even long after DOR/ISL is stopped. Given this information, the frequency of monitoring may be decreased to minimize participant burden and it is no longer required to continue monitoring until CD4+ T-cell and total lymphocyte values are within 10% of baseline.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3.5, Schedule of Activities for Participants With Specified Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts	Reduced the posttreatment lymphocyte monitoring frequency from monthly to approximately every 10 to 14 weeks.	Refer to Section 8.11.5.2 rationale.

Section Number and Name	Description of Change	Brief Rationale
Section 8.11.3.2, End of Treatment Follow-up Visit	Removed the requirement for monthly monitoring.	Refer to Section 8.11.5.2 rationale.
Section 8.11.5.3, Participants Discontinued from Study Intervention for Other Reasons and Have Decreases in CD4+ T-cell and/or Total Lymphocyte Counts	Removed monitoring details to refer to Section 8.11.5.2.	Refer to Section 8.11.5.2 rationale.
Section 10.2, Appendix 2: Clinical Laboratory Tests	Removed frequency of monitoring visits from footnote e in Table 17.	Refer to Section 8.11.5.2 rationale.
Section 10.10, Appendix 10: Summary of Protocol Clarification Letters	Added Appendix 10.	To incorporate a summary of protocol clarification letters that were implemented at sites. No text was incorporated into this protocol amendment because it is not relevant to study conduct at this time.

Table of Contents

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **5**
1 PROTOCOL SUMMARY **16**
1.1 Synopsis **16**
1.2 Schema **21**
1.3 Schedule of Activities (SoA) **22**
1.3.1 Schedule of Activities – Screening Through Week 96 (Blinded Intervention) 22
1.3.2 Schedule of Activities – Week 108 Through Week 168 Open-label Intervention, Including Study Extension 29
1.3.3 Schedule of Activities – Viremia Confirmation and End of Treatment (End of Treatment for all Participants Except Those with Specified Decreases in CD4+ T-cell/Total Lymphocyte Counts) 34
1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 168 37
1.3.5 Schedule of Activities for Participants With Specified Decreases in CD4+ T-cell Counts and/or Total Lymphocyte Counts 39
2 INTRODUCTION **43**
2.1 Study Rationale **43**
2.2 Background **43**
2.2.1 Pharmaceutical and Therapeutic Background 43
2.2.2 Information on Other Study-related Therapy 45
2.3 Benefit/Risk Assessment **45**
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS **47**
4 STUDY DESIGN **51**
4.1 Overall Design **51**
4.2 Scientific Rationale for Study Design **52**
4.2.1 Rationale for Endpoints 53
4.2.1.1 Efficacy Endpoints 53
4.2.1.1.1 HIV-1 RNA Measurement 53
4.2.1.1.2 Definition of Clinically Significant Confirmed Viremia 53
4.2.1.2 Safety Endpoints 54
4.2.1.3 Weight, Laboratory, and Radiological Markers 54
4.2.1.4 Pharmacokinetic Endpoints 55
4.2.1.5 Patient-Reported Outcomes 55
4.2.1.6 Planned Exploratory Biomarker Research 55

4.2.1.6.1 Planned Genetic Analysis 55
4.2.1.7 Future Biomedical Research 56
4.2.2 Rationale for the Use of Comparator/Placebo 56
4.2.3 Rationale for the Selected Participant Population 56
4.2.4 Rationale for Collecting Race and Ethnicity 57
4.2.5 Rationale for Collecting Gender Identity Data 57
4.2.6 Rationale for Infant Safety Data Collection....57
4.2.7 Rationale for Continuing Study Intervention During Pregnancy 57
4.3 Justification for Dose 58
4.4 Beginning and End of Study Definition 59
4.4.1 Clinical Criteria for Early Study Termination 59
5 STUDY POPULATION 59
5.1 Inclusion Criteria 60
5.2 Exclusion Criteria 61
5.3 Lifestyle Considerations 63
5.4 Screen Failures 64
5.5 Participant Replacement Strategy....64
6 STUDY INTERVENTION....64
6.1 Study Intervention(s) Administered....64
6.2 Preparation/Handling/Storage/Accountability 66
6.2.1 Dose Preparation....66
6.2.2 Handling, Storage, and Accountability....66
6.3 Measures to Minimize Bias: Randomization and Blinding....67
6.3.1 Intervention Assignment....67
6.3.2 Stratification....67
6.3.3 Blinding....67
6.4 Study Intervention Compliance....68
6.5 Concomitant Therapy....68
6.5.1 Rescue Medications and Supportive Care 69
6.6 Dose Modification (Escalation/Titration/Other)....69
6.7 Intervention After the End of the Study....70
6.8 Clinical Supplies Disclosure....70
6.9 Standard Policies....70
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL....71
7.1 Discontinuation of Study Intervention....71
7.2 Participant Withdrawal From the Study....73
7.3 Lost to Follow-up 73

8 STUDY ASSESSMENTS AND PROCEDURES 73
8.1 Administrative and General Procedures 74
8.1.1 Informed Consent 74
8.1.1.1 General Informed Consent 74
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 75
8.1.1.3 Consent for Postnatal Infant Safety Data Collection Through One Year of Age 75
8.1.1.4 Consent for Continuation of Study Intervention During Pregnancy 75
8.1.1.5 Consent to Participate in the Study Extension 75
8.1.2 Inclusion/Exclusion Criteria 75
8.1.3 Participant Identification Card 75
8.1.4 Medical History 76
8.1.5 Prior and Concomitant Medications Review 76
8.1.5.1 Prior Medications 76
8.1.5.2 Concomitant Medications 76
8.1.6 Assignment of Screening Number 76
8.1.7 Assignment of Treatment/Randomization Number 76
8.1.8 Study Intervention Administration 77
8.1.8.1 Timing of Dose Administration 77
8.1.9 Discontinuation and Withdrawal 77
8.1.9.1 Withdrawal From Future Biomedical Research 78
8.1.10 Participant Blinding/Unblinding 78
8.1.11 Calibration of Equipment 79
8.1.12 Administration of Participant Questionnaires 79
8.2 Efficacy Assessments 79
8.2.1 HIV-1 RNA 79
8.2.2 Management of Study Participants with Viremia 79
8.2.2.1 Viremia Confirmation 80
8.2.2.2 Participants with Clinically Significant Viremia (≥200 copies/mL) 80
8.2.2.3 Participants with Low-level Viremia (≥50 and <200 copies/mL) 80
8.2.2.4 Viral Drug Resistance Testing 81
8.2.3 T- and B-Lymphocyte and Natural Killer Cell Profile (TBNK) 81
8.3 Safety Assessments 81
8.3.1 Physical Examinations 81
8.3.1.1 Weight 82
8.3.2 Vital Signs 82

8.3.3 Electrocardiograms 82
8.3.4 Confirmation of Contraception and Pregnancy Testing 82
8.3.5 Clinical Safety Laboratory Assessments 83
8.3.6 HBV Assessments....83
8.3.7 Tobacco and Alcohol Assessments....84
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events 84
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 84
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events....86
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information...86
8.4.4 Regulatory Reporting Requirements for SAE 86
8.4.5 Pregnancy and Exposure During Breastfeeding 86
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs 87
8.4.7 Events of Clinical Interest (ECIs) 87
8.5 Treatment of Overdose....88
8.6 Pharmacokinetics....88
8.6.1 Blood Collection for Plasma ISL 88
8.7 Pharmacodynamics....89
8.8 Biomarkers 89
8.8.1 Planned Genetic Analysis Sample Collection....89
8.8.2 Inflammation....89
8.8.3 Renal Function 89
8.8.4 Fasting Lipid and Metabolic Profiles....89
8.8.5 Waist and Hip Measurements 90
8.8.6 DEXA Assessments 90
8.9 Future Biomedical Research Sample Collection 91
8.10 Health Economics Medical Resource Utilization and Health Economics....91
8.11 Visit Requirements....91
8.11.1 Screening/Rescreening....91
8.11.2 Treatment Period....92
8.11.2.1 Fasting....92
8.11.2.2 Optional Nurse Visits and Telephone Visits....92
8.11.2.3 Week 144 Visit 93
8.11.3 Participants Who Discontinue Study Intervention....93
8.11.3.1 Early Discontinuation of Treatment....93
8.11.3.2 End of Treatment Follow-up Visit....94

8.11.4 Viremia Confirmation 94
8.11.5 Management of Participants with Specified Decreases in CD4+ T-cell Count and/or Total Lymphocyte Count 94
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 94
8.11.5.2 Participants Discontinued from Study Intervention Due to Decreased CD4+ T-cell Count and/or Total Lymphocyte Count 95
8.11.5.3 Participants Discontinued from Study Intervention for Other Reasons And Have Decreases in CD4+ T-cell and/or Total Lymphocyte Counts 96
8.11.6 Clinical Management of Participants Who Become Pregnant 96
8.11.6.1 Continuing Study Intervention 97
8.11.6.2 Discontinuing Study Intervention for Pregnancy 98
8.11.6.3 Participants Who Choose to Breastfeed 98
8.11.6.4 Infant Safety Data Collection 99
8.11.6.4.1 Schedule of Activities: Infant Safety Data Collection 99
9 STATISTICAL ANALYSIS PLAN 99
9.1 Statistical Analysis Plan Summary 100
9.2 Responsibility for Analyses/In-house Blinding 102
9.3 Hypotheses/Estimation 102
9.4 Analysis Endpoints 102
9.4.1 Efficacy/Pharmacokinetics Endpoints 102
9.4.1.1 Efficacy Endpoints 102
9.4.1.2 Pharmacokinetics Endpoints 104
9.4.2 Safety Endpoints 104
9.4.3 Patient-reported Outcome Endpoints 105
9.5 Analysis Populations 105
9.5.1 Efficacy Analysis Populations 105
9.5.1.1 Sentinel Cohort 105
9.5.1.2 Full Analysis Set 105
9.5.1.3 Per-Protocol Analysis Set 106
9.5.1.4 Resistance Analysis Subset 106
9.5.2 Safety Analysis Population 106
9.6 Statistical Methods 106
9.6.1 Statistical Methods for Efficacy Analyses 107
9.6.2 Statistical Methods for Safety Analyses 113
9.6.3 Summaries of Baseline Characteristics, Demographic, and Other Analyses 116

9.6.3.1 Demographic and Baseline Characteristics 116
9.7 Interim Analyses 116
9.8 Multiplicity 118
9.9 Sample Size and Power Calculations 120
9.9.1 Sample Size and Power Calculations for Efficacy Analyses....120
9.9.2 Sample Size and Power for Safety Analyses 126
9.9.2.1 Evaluation of Adverse Events....126
9.9.2.2 Evaluation of Change in Weight....128
9.10 Subgroup Analyses....130
9.11 Compliance (Medication Adherence)....130
9.12 Extent of Exposure....131
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 132
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 132
10.1.1 Code of Conduct for Clinical Trials....132
10.1.2 Financial Disclosure....134
10.1.3 Data Protection....135
10.1.3.1 Confidentiality of Data 135
10.1.3.2 Confidentiality of Participant Records....135
10.1.3.3 Confidentiality of IRB/IEC Information....135
10.1.4 Committees Structure....136
10.1.4.1 Executive Oversight Committee 136
10.1.4.2 External Data Monitoring Committee 136
10.1.4.3 Scientific Advisory Committee (SAC) 136
10.1.5 Publication Policy 136
10.1.6 Compliance with Study Registration and Results Posting Requirements .137
10.1.7 Compliance with Law, Audit, and Debarment 137
10.1.8 Data Quality Assurance 138
10.1.9 Source Documents 138
10.1.10 Study and Site Closure....139
10.2 Appendix 2: Clinical Laboratory Tests....140
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....148
10.3.1 Definitions of Medication Error, Misuse, and Abuse....148
10.3.2 Definition of AE 148
10.3.3 Definition of SAE 149
10.3.4 Additional Events Reported....151
10.3.5 Recording AE and SAE 151

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor 155
10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation 156
10.5 Appendix 5: Contraceptive Guidance 157
10.5.1 Definitions 157
10.5.2 Contraception Requirements 159
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research 160
10.7 Appendix 7: Country-specific Requirements 165
10.7.1 Country-specific Request for Germany 165
10.7.2 Country-specific Request for Japan 165
10.8 Appendix 8: Calculation of Creatinine Clearance and eGFR 166
10.9 Appendix 9: Abbreviations 167
10.10 Appendix 10: Summary of Protocol Clarification Letters 170
11 REFERENCES 171

LIST OF TABLES

Table 1 Laboratory Exclusion Criteria....63
Table 2 Study Interventions....65
Table 3 Prohibited Therapies....69
Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events....85
Table 5 Collection of Population PK Samples....88
Table 6 Collection of Population PK Samples During Pregnancy and Postpartum....98
Table 7 Definitions of Study Time Points....107
Table 8 Analysis Strategy for Key Efficacy Variables....113
Table 9 Analysis Strategy for Safety Parameters....116
Table 10 Summary of Assumptions and Overall Study Power Assuming 60 Participants in the Sentinel Cohort and 680 Participants Overall....121
Table 11 Power to Establish Superiority at Week 48/96 Under Various Response Rate Assumptions (Assuming All Prior Hypothesis Tests Reach Statistical Significance) (340 Participants Per Group)....125
Table 12 Power to Establish Noninferiority at Week 96 Under Various Response Rate Assumptions (340 Participants per Group)....126
Table 13 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based on Hypothetical Numbers of Participants with AEs (340 Participants Per Group)....127
Table 14 Difference in Incidence of AEs (Group 1 Minus Group 2) That Can Be Ruled Out with 340 Participants in Each Group....127
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....128
Table 16 Protocol-required Laboratory Assessments....140
Table 17 Blood Volumes....144
Table 18 Blood Volumes: Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 168....147

LIST OF FIGURES

Figure 1 Study Schema and Treatment Plan 21
Figure 2 Estimated Power to Declare Noninferiority of DOR/ISL to BIC/FTC/TAF at Week 48 Assuming 30 Enrolled and Evaluable Participants in Group 1 in the Sentinel Cohort and 680 Participants Overall.....123

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Active-Controlled, Double-Blind Clinical Study to Evaluate the Antiretroviral Activity, Safety, and Tolerability of Doravirine/Islatravir Once-Daily in HIV-1 Infected Treatment-Naïve Participants

Short Title: Randomized, double-blind, safety, efficacy Doravirine/Islatravir in Tx naïve

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 who are infected with HIV-1 and naïve to antiretroviral therapy.

Primary Objectives	Primary Endpoints
- To evaluate the antiretroviral activity of DOR/ISL compared to 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 noninferior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48. A margin of 10 percentage points is used to define noninferiority. - 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 DOR/ISL compared to 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 of DOR/ISL compared to 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 noninferior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 96. A margin of 10 percentage points is used to define noninferiority. 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 of DOR/ISL compared to 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 <200 copies/mL	- HIV-1 RNA
- To evaluate the immunologic effect of DOR/ISL as measured by the 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 in participants who receive DOR/ISL and in those who receive BIC/FTC/TAF	- Viral resistance-associated substitutions

- To evaluate the effect of DOR/ISL compared to 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-1 infection
Population	Participants ≥18 years of age with HIV-1 who are naïve to antiretroviral therapy
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo with active control
Study Blinding	Double-blind
Masking	Sponsor (through Week 48) Investigator (through Week 96) Participants or Subjects (through Week 96)
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 680 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administration</th><th>Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="2">Group 1</td><td>DOR/ISL</td><td>100 mg/0.75 mg</td><td>QD</td><td>Oral</td><td>Day 1 to Week 168[a]</td><td>Test Product</td></tr>
<tr><td>Placebo to BIC/FTC/TAF</td><td>0 mg</td><td>QD</td><td>Oral</td><td>Day 1 to Week 96</td><td>Placebo</td></tr>
<tr><td rowspan="2">Group 2[a]</td><td>BIC/FTC/TAF</td><td>50/ 200/ 25 mg</td><td>QD</td><td>Oral</td><td>Day 1 to Week 168[a]</td><td>Comparator</td></tr>
<tr><td>Placebo to DOR/ISL</td><td>0 mg</td><td>QD</td><td>Oral</td><td>Day 1 to Week 96</td><td>Placebo</td></tr>
<tr><td colspan="7">BIC=bictegravir; DOR/ISL=fixed dose combination of doravirine and islatravir, also known as MK-8591A; FTC=emtricitabine; QD=once-daily; TAF=tenofovir alafenamide.
a. Participants who consent to the study extension beginning after Week 144 may continue their assigned study intervention up to Week 168, if needed.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Participants will participate in the study for approximately 3.5 years from the time the participant provides documented informed consent through the final contact. After a screening period of up to 45 days, each participant will receive assigned blinded intervention for approximately 96 weeks and open-label intervention through Week 144. Participants may then participate in an open-label 24-week extension (up to Week 168). Participants who discontinue study intervention or who become pregnant will be followed as described in the protocol.</td></tr>
</table>

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.	

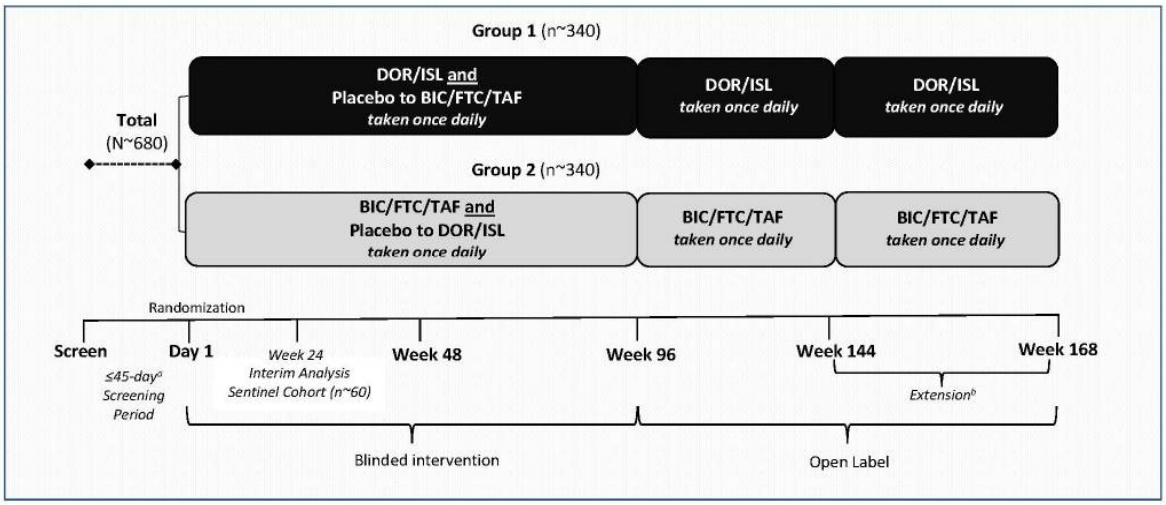
Study Accepts Healthy Volunteers: No

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/ISL=fixed dose combination of doravirine and islatravir, also known as MK-8591A; FTC=emtricitabine; N=total number of participants in the study; n=number of participants per group; TAF=tenofovir alafenamide.

Note: Randomization will occur at Day 1.

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, eligible participants will be offered the option to continue their assigned study intervention for up to 24 additional weeks (up to Week 168) during the open-label extension (Section 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**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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										
	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
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 for 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 Section 8.11.6.

Study Period	**Screen**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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										
	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
Administration of EQ-5D-5L and HIV-SI Participant Questionnaires		X	X		X			X				X	Administer before being seen by investigator and discussing 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 time of randomization, site personnel will add randomization number to participant identification card.
Medical History	X												
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X	X	X	X	X	X	X	
Intervention Randomization		X											All procedures should be completed prior to dose on Day 1.
Dispense Study Intervention Using IRT		X	X	X	X	X	X	X	X	X	X	X	At Week 96 open-label study intervention will be dispensed.

Study Period	**Screen**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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										
	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
Study Intervention Compliance Review			X	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	X	
CD4+ T-cell Count/TBNK Panel	X	X		X	X	X	X	X	X	X	X	X	Decreases in CD4+ T-cell count that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.
Blood (Plasma) for HIV-1 Drug Resistance	X												
Blood (Plasma) for HIV-1 Drug Resistance – Backup	X	X	X	X	X	X	X	X	X	X	X	X	Backup samples will be used if needed.
Safety Procedures													
Full Physical Examination	X												
Height		X											
Weight	X	X				X		X		X		X	

Study Period	**Screen**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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										
	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse, blood pressure, body temperature, and respiratory rate.
12-Lead ECG		X											May be performed up to 7 days prior to dose on Day 1 after all other eligibility criteria are confirmed.
Contraception Use Confirmation (WOCBP only)		X	X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy Test (hCG; WOCBP only)	X												
Urine Pregnancy Test (WOCBP only)		X	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 and HIV-2 Serology	X												

Study Period	**Screen**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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).
			Week										
Scheduled Day/Week	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
Hepatitis Serology	X												Participants who do not demonstrate immunity to HBV should be encouraged to be vaccinated against HBV.
HBV DNA	X												
Chemistry	X	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	X	Decreases in total lymphocyte count that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.
PT/INR	X												
Urinalysis		X				X		X		X		X	
Review of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics													
Blood (Plasma) for ISL PK		X	X	X	X	X		X					At Week 4, a predose and postdose sample will be taken.
Blood (Plasma) for Investigational ISL PK							X		X	X	X	X	Analysis will be triggered by Sponsor as needed.

Study Period	**Screen**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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).
			Week										
Scheduled Day/Week	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
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. Only applicable for women receiving DOR/ISL.
Biomarkers													
Blood for Genetic Analysis[b]		X											
Whole Blood for Future Biomedical Research		X				X		X				X	Requires FBR consent.
Blood for Inflammatory Markers		X				X		X				X	
Blood and Urine for Renal Markers		X				X		X				X	
Waist and Hip Measurements		X						X				X	

Study Period	**Screen**	**Blinded Intervention**											**Notes**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	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).
			Week										
Scheduled Day/Week	Screening	Day 1 (Fasting)	4	8	16	24 (Fasting)	36	48 (Fasting)	60	72	84	96 (Fasting)	
Visit Window	≤45 days[a]	NA	±7 days										
			Group 1 and Group 2										
DEXA Scan (only where permitted by local law)		X						X				X	Perform after all eligibility criteria are confirmed and up to 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 scans should not be performed on pregnant participants.

CD4+=CD4 positive; DEXA=dual-energy x-ray absorptiometry; DNA=deoxyribonucleic acid; DOR= doravirine; ECG=electrocardiogram; EQ-5D-5L=EuroQol Five-Dimensional Descriptive System, Five Level Version; HBV=hepatitis B virus; hCG= human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; HIV-2= human immunodeficiency virus type 2; HIV-SI=Human Immunodeficiency Virus Symptom Index; INR=international normalized ratio; IRT=interactive response technology; ISL=islatravir; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic; PT=prothrombin time; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells; WOCBP=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, a 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 (or their legally acceptable representative) provides documented informed consent for future biomedical research. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

1.3.2 Schedule of Activities – Week 108 Through Week 168 Open-label Intervention, Including Study Extension

Study Period	**Open-label Intervention**						**Notes**
Visit Number	13	14	15	16	17	18	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 Week	108	120 (Fasting)	132	144 (Fasting)	Week 156*	Week 168* (Fasting)	*Week 156 and Week 168 are part of the study extension
Visit Window	±7 days						
	Group 1 and Group 2						
Administrative Procedures							
Prior / Concomitant Medication Review	X	X	X	X	X	X	
Register Study Visit in IRT	X	X	X	X	X	X	
Informed Consent for Study Extension	<----------X---------->						Participants who do not consent to the study extension will have an End of Treatment Follow-up Visit in 42 (+) 7 days and complete their study participation.
Dispense Study Intervention Using IRT	X	X	X	X	X		Study intervention should only be dispensed at Week 144 and Week 156 if the participant consents to the 24-week study extension or is pregnant and consents to continue study intervention during pregnancy. See Section 1.3.4 for pregnant participants continuing treatment beyond Week 168.

Study Period	**Open-label Intervention**						**Notes**
Visit Number	13	14	15	16	17	18	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 Week	108	120 (Fasting)	132	144 (Fasting)	Week 156*	Week 168* (Fasting)	*Week 156 and Week 168 are part of the study extension
Visit Window	±7 days						
	Group 1 and Group 2						
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.
Collect and enter data from prenatal care provider for 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 Section 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.

Study Period	Open-label Intervention						Notes
Visit Number	13	14	15	16	17	18	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 Week	108	120 (Fasting)	132	144 (Fasting)	Week 156*	Week 168* (Fasting)	*Week 156 and Week 168 are part of the study extension
Visit Window	±7 days						
	Group 1 and Group 2						
Blood (Plasma) for HIV-1 Drug Resistance	X	X	X	X	X	X	Backup samples will be used if needed.
Safety Procedures							
Directed Physical Examination	X	X	X	X	X	X	
Weight		X		X	X	X	
Vital Signs	X	X	X	X	X	X	Includes pulse, blood pressure, body temperature, and respiratory rate.
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 infant collected per Section 8.11.6.4.1.
Chemistry	X	X	X	X	X	X	Fasting is required at Week 120, Week 144, and Week 168.
Hematology	X	X	X	X	X	X	Decreases in total lymphocyte count that meet ECI criteria should be managed per Section 1.3.5 and Section 8.11.5.

Study Period	Open-label Intervention						Notes
Visit Number	13	14	15	16	17	18	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 Week	108	120 (Fasting)	132	144 (Fasting)	Week 156*	Week 168* (Fasting)	*Week 156 and Week 168 are part of the study extension
Visit Window	±7 days						
	Group 1 and Group 2						
Urinalysis		X		X		X	
Review of Adverse Events	X	X	X	X	X	X	
Pharmacokinetics							
Blood (Plasma) for Investigational ISL PK				X			**Group 1 (DOR/ISL) only.** Analysis triggered by Sponsor as needed
Blood (Plasma) for DOR and ISL PK in Pregnant Participants Only	<----------X---------->						**Group 1 (DOR/ISL) only.** 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			Requires FBR consent.
Blood for Inflammatory Markers				X			
Blood and Urine for Renal Markers				X			
Waist and Hip Measurements				X			

Study Period	Open-label Intervention						Notes
Visit Number	13	14	15	16	17	18	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 Week	108	120 (Fasting)	132	144 (Fasting)	Week 156*	Week 168* (Fasting)	*Week 156 and Week 168 are part of the study extension
Visit Window	±7 days						
	Group 1 and Group 2						
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. DEXA should not be performed on pregnant participants.

anti-HBc=hepatitis B core antibody; CD4+=CD4 positive; DEXA=dual-energy x-ray absorptiometry; DNA=deoxyribonucleic acid; DOR=doravirine; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; IRT=interactive response technology; ISL=islatravir; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells; WOCBP=woman/women of childbearing potential.

1.3.3 Schedule of Activities – Viremia Confirmation and End of Treatment (End of Treatment for 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 all participants except those continuing DOR/ISL in a new 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 assess study intervention compliance.
Administration of EQ-5D-5L and HIV-SI Participant Questionnaires		X		Administer before being seen by investigator and discussing medical conditions or test results. Not to be collected if participant discontinues study intervention 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 the average baseline value[c] or who meet relevant ECI criteria at the Early Discontinuation of Treatment visit should be managed per Section 1.3.5 and Section 8.11.5.

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 all participants except those continuing DOR/ISL in a new 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	
Blood (Plasma) for HIV-1 Drug Resistance	X	X	X	If HIV-1 Drug Resistance sample is collected at the Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit. Analysis of samples collected at Viremia Confirmation and End of Treatment Follow-up Visits will be triggered by Sponsor as needed.
Safety Procedures				
Full Physical Examination		X	X	
Weight		X	X	
Vital Signs		X	X	Includes pulse, blood pressure, body temperature, respiratory rate.
Contraception Use Confirmation (WOCBP only)	X	X	X	
Serum Pregnancy Test (WOCBP only)		X	X	If serum test is positive, participant will be managed per Section 8.11.6 and safety of infant collected per Section 8.11.6.4.1.
Chemistry		X		
Hematology		X		Participants with decreases in total lymphocyte count >10% from the average baseline value[c] at the Early Discontinuation of Treatment visit should be managed per Section 1.3.5 and Section 8.11.5
Urinalysis		X		
Review of Adverse Events	X	X	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 all participants except those continuing DOR/ISL in a new 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	
Pharmacokinetics				
Blood (Plasma) for Investigational ISL PK	X	X	X	Analysis will be triggered by Sponsor as needed. Do not collect if participant is known to be in Group 2 (BIC/FTC/TAF) at time of visit.
Biomarkers				
Whole Blood for Future Biomedical Research	X	X		If FBR sample is collected at the Viremia Confirmation visit, it is not necessary to collect another sample at Early Discontinuation of Treatment visit.

CD4+=CD4 positive; EQ-5D-5L=EuroQol Five-Dimensional Descriptive System, Five Level Version; FBR=future biomedical research; HIV= human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; HIV-SI=Human Immunodeficiency Virus Symptom Index; IRT=interactive response technology; ISL= islatravir; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells; WOCBP=woman/women of childbearing potential.

[a] Early Discontinuation of Treatment visit applies to any participant who discontinues study intervention prior to Week 144 or prior to Week 168 for those participants who continue in the study extension.

[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 for CD4+ T-cell count and total lymphocyte count is defined as the average of the screening (within 45 days prior to the first dose of study intervention) and Day 1 values through Week 48. After Week 48, the baseline resets to the Week 48 value only if the Week 48 value is greater than the average baseline value. If there are ≥2 values at Week 48, then use the most recent value.

1.3.4 Schedule of Activities for Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 168

Visit Number	**Unscheduled**				**Notes**
Scheduled Week	**Pregnancy 1 (Week 180)**	**Pregnancy 2 (Week 192)**	**Pregnancy 3 (204)**	**Pregnancy 4 (Week 216)**	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. The End of Treatment Follow-up Visit should also be performed approximately 42 days (+7 days) after the last dose of study intervention (See Section 1.3.3).
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	Following pregnancy completion, options for future treatment are managed 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.
Plasma for HIV-1 Viral Drug Resistance Testing	X	X	X	X	Backup samples, will be used if needed

Visit Number	**Unscheduled**				**Notes**
Scheduled Week	**Pregnancy 1 (Week 180)**	**Pregnancy 2 (Week 192)**	**Pregnancy 3 (204)**	**Pregnancy 4 (Week 216)**	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. The End of Treatment Follow-up Visit should also be performed approximately 42 days (+7 days) after the last dose of study intervention (See Section 1.3.3).
Visit Window	± 7 days				
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.
Chemistry	X	X	X	X	
Hematology	X	X	X	X	Decreases in total lymphocyte count 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. Only applicable for women receiving DOR/ISL
Biomarkers					
Whole Blood for Future Biomedical Research	X	X	X	X	Optional participation; requires FBR consent

anti-HBc=hepatitis B core antibody; CD4+=CD4 positive; DNA=deoxyribonucleic acid; DOR=doravirine; FBR=future biomedical research; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HIV=human immunodeficiency virus; HIV-1= human immunodeficiency virus type 1; IRT=Interactive Response Technology; ISL=islatravir; PCR=polymerase chain reaction; PK=pharmacokinetic; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells.

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 Count and/or Total Lymphocyte Count Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases in CD4+ T-cell counts and/or total lymphocyte counts are confirmed, then the participant should be unblinded (if applicable) to determine the need for additional monitoring. Only those receiving 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 within 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Approximately every 10-14 weeks	
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.

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 Count and/or Total Lymphocyte Count Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases in CD4+ T-cell counts and/or total lymphocyte counts are confirmed, then the participant should be unblinded (if applicable) to determine the need for additional monitoring. Only those receiving 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 within 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Approximately every 10-14 weeks	
Administration of EQ-5D-5L and HIV-SI 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 study intervention after Week 96.
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	
Blood (Plasma) for HIV-1 Viral Drug Resistance Testing		X	X		Analysis of samples collected at End of Treatment Follow-up Visits triggered by Sponsor as needed.

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 Count and/or Total Lymphocyte Count Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases in CD4+ T-cell counts and/or total lymphocyte counts are confirmed, then the participant should be unblinded (if applicable) to determine the need for additional monitoring. Only those receiving 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 within 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Approximately every 10-14 weeks	
Safety Procedures					
Full Physical Examination		X	X		
Vital Signs		X	X		Includes weight, pulse, blood pressure, temperature, and respiratory rate.
Contraception 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 safety of her infant collected per Section 8.11.6.4.1.
Chemistry		X			
Hematology	X	X	X (DOR/ISL Only)	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 Count and/or Total Lymphocyte Count Confirmation	Early Discontinuation of Treatment	End of Treatment Follow-up	CD4+ T-cell Count and/or Total Lymphocyte Count Monitoring	**See Sections 8.1.9 and 8.11.5 for details regarding discontinuation and monitoring.** If specified decreases in CD4+ T-cell counts and/or total lymphocyte counts are confirmed, then the participant should be unblinded (if applicable) to determine the need for additional monitoring. Only those receiving 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 within 10 to 14 weeks (ie, at the next routine study visit).	NA	42 (+7) days after discontinuing study intervention	Approximately every 10-14 weeks	
Urinalysis		X			
Review of Adverse Events	X	X	X	X	
Pharmacokinetics					
Blood (Plasma) for Investigational ISL PK		X	X		PK analysis triggered by Sponsor as needed. No PK sampling after Week 144 visit. PK sampling not needed if participant is known to be in Group 2 (BIC/FTC/TAF).
Biomarkers					
Whole Blood for Future Biomedical Research		X			

CD4+=CD4 positive; EQ-5D-5L=EuroQol Five-Dimensional descriptive system, five level version; FBR=future biomedical research; HIV=human immunodeficiency virus; HIV-SI=Human Immunodeficiency Virus Symptom Index; IRT=Interactive Response Technology; NA=not applicable; PCR=polymerase chain reaction; PK=pharmacokinetics; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells; WOCBP=woman/women of childbearing potential.

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 lifelong treatment, the 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 an 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 one of the components having a relatively high barrier to resistance.

DOR/ISL has the potential for use in the treatment of HIV-1 infection in TN patients 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 Pharmaceutical and Therapeutic Background

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. ISL is an inactive nucleoside analogue that is converted to the pharmacologically active triphosphate (ISL-TP) form via endogenous intracellular kinases. It acts through multiple mechanisms, including immediate

chain termination by blocking translocation and delayed chain termination by preventing nucleotide excision [Michailidis E 2014].

ISL is differentiated from other HIV-1 antiretrovirals by its high potency, long intracellular half-life, and favorable drug resistance profile. ISL (at the proposed dose of 0.75 mg QD) achieves higher steady-state IQs (the ratio of drug exposure to viral susceptibility [C_{trough}/IC_{50}]) against wild-type HIV-1 than any NRTI currently approved for treatment. It also exhibits potent activity against the most prevalent NRTI resistance-associated substitutions, including M184V and TAMs.

Doravirine

DOR, a potent NNRTI with demonstrated efficacy and good tolerability, was first approved for the treatment of HIV-1 infection by the FDA and the EMA in 2018. DOR is differentiated from other NNRTIs by its distinct resistance profile, low likelihood of selection for viral resistance in vivo, and low potential for DDIs. DOR 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 TN adult participants [Orkin, C., et al 2018] [Molina, J. M., et al 2018] and in virologically suppressed adult participants switching from a stable antiretroviral regimen (MK-1439A Protocol 024).

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) was evaluated in a randomized Phase 2 study (MK-8591 Protocol 011) in ~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). Three doses of ISL were tested: 0.25 mg, 0.75 mg, and 2.25 mg. 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 in all dose groups 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 tolerability profile through Week 96, comparable to that of DOR/3TC/TDF.

The 0.75 mg dose of ISL (in combination with DOR 100 mg) was initially selected for further development for the daily treatment program. The clinical development program of DOR/ISL 100 mg/0.75 mg included 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).

Due to findings of decreases in CD4+ T-cell and lymphocyte counts in the ISL 0.75 mg development program, a post hoc analysis was conducted of P011 data (see IB for details). Dose-dependent changes from baseline in total lymphocyte and CD4+ T-cell counts were observed for the different ISL dose groups. Lymphocytes, CD4+ T-cells, CD8+ T-cells, B-cells, and NK cells in ISL 0.25 mg + DOR 100 mg QD (±3TC) participants increased (as would be expected in a treatment-naïve population) and were comparable to results in those receiving DOR/3TC/TDF.

Based on this Phase 2 data and PK modeling, the ISL 0.25 mg dose is expected to maintain treatment efficacy against HIV-1 without lowering CD4+ T-cell and total lymphocyte counts. Where available, participants currently enrolled in this study may be given the option to join a new DOR/ISL 100 mg/0.25 mg study.

2.2.2 Information on Other Study-related Therapy

BIC/FTC/TAF is approved for the treatment of HIV-1 infection in patients naïve to ART. 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-resistance-associated substitutions (eg, K103N, Y181C, G190A, and E138K) and ISL against common NRTI-resistance-associated substitutions (eg, M184V and TAMs). Both may be administered without regard to food, have a low potential for DDIs, and have favorable PK, safety, 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. In the dose-ranging study (MK-8591 Protocol 011), ISL+DOR+3TC (as a 3-drug regimen) achieved virological suppression in most (>90%) of treatment-naïve participants by Week 24.

ISL+DOR (as a 2-drug regimen) maintained virologic suppression of HIV-1 RNA at all doses tested 24 and 48 weeks after switching from the 3-drug regimen and through Week 144. In 2 ongoing Phase 3 studies evaluating DOR/ISL 100 mg/0.75 mg for daily treatment of HIV-1 in virologically suppressed participants (MK-8591A Protocol 017 and MK-8591A Protocol 018), approximately 95% of 658 participants enrolled in the DOR/ISL arm completed 48 weeks of treatment in both studies. In Protocol 017 and Protocol 018, the percentage of participants with HIV-1 RNA ≥50 copies/mL was <1% for the DOR/ISL group and a high percentage of participants (>93% to 95%) in the DOR/ISL group maintained virologic suppression (HIV-1 RNA <50 copies/mL) comparable to baseline ART and BIC/FTC/TAF groups, respectively, at Week 48. To date, no viral resistance to either component of DOR/ISL has been shown in the Phase 2 (Protocol 011) and Phase 3 studies involving approximately 1096 treatment-naïve and switch participants with HIV-1 treated with DOR/ISL. At the doses administered for daily treatment (ie, 100 mg DOR + 0.25, 0.75, or 2.25 mg ISL), DOR/ISL has been well tolerated and associated with low rates of drug-related AEs.

Exposure-dependent decreases in total lymphocyte counts and lymphocyte subsets including CD4+ T-cell counts were observed in studies with ISL alone or in combination with other antiviral agents. In a Phase 2 study (MK-8591 Protocol 013) for once weekly HIV-1 treatment, decreases in total lymphocyte, CD4+ T-cell, CD8+ T-cell, and B-cell counts from baseline were observed in the ISL 20 mg + MK-8507 treatment arms at Week 12 and Week 24. Decreases from baseline in total lymphocyte counts were observed in all dosing arms of ISL + MK-8507 QW starting at Week 8 with further decreases continuing through Week 24. Twenty of 58 participants on ISL + MK-8507 had a decrease in total lymphocyte counts of >30% (of whom 9 had a >50% reduction) by Week 24. These reductions were more pronounced in the 2 higher MK-8507 dose arms (200 and 400 mg), potentially indicating a dose-response relationship. Dosing of ISL + MK-8507 in Protocol 013 has been discontinued.

In the Phase 2 randomized, double-blind, placebo-controlled study evaluating 60 mg and 120 mg of ISL monthly for PrEP in participants at low-risk of HIV-1 infection (MK-8591 Protocol 016), there was a 21% mean decrease in total lymphocyte counts observed in the 60 mg arm (the dose being evaluated in Phase 3 PrEP studies) and a 36% decrease in total lymphocyte counts 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. Lymphocyte subsets were not measured in Protocol 016. Dosing of oral ISL 60 mg QM has been discontinued in PrEP clinical studies.

Interim analyses of Protocol 017 and Protocol 018 studying DOR/ISL 100 mg/0.75 mg daily for HIV-1 treatment in a virologically suppressed population indicates that mean total lymphocyte count decreases in the DOR/ISL group reached a nadir at Week 48 and then stabilized through Week 84 (see IB for details). After a switch from various baseline ART regimens, including BIC/FTC/TAF, the mean decreases from baseline in lymphocyte counts at Week 48 were 10.6% and 8.5%, respectively, in the DOR/ISL groups compared with mean increases of 2.3% and 3.5% in the comparator arms. In the same studies, DOR/ISL treated participants had a mean change in CD4+ T-cell counts of -0.7% and 0.9%, compared with an

increase of 8.7% in the baseline ART group and 12.8% in the BIC/FTC/TAF group. These decreases in CD4+ T-cell and lymphocyte counts have not been associated with an increased incidence of infection or other AEs.

Overall, the evaluation of data from across the ISL clinical programs to date suggests that the decrease in mean total lymphocyte and lymphocyte subset counts is ISL dose-dependent with lower doses less likely to cause decreases. In the dose-ranging phase of P011 (Part 1 and Part 2 through Week 72), the 0.25 mg dose of ISL with DOR ± 3TC achieved and maintained high rates of virologic suppression. Participants who received ISL 0.25 mg QD had changes in total lymphocyte and CD4+ T-cell counts comparable to those observed for participants in the DOR/3TC/TDF comparator group. The results of modeling analyses of ISL exposure-effect predict no meaningful decreases in total lymphocyte or CD4+ T-cell counts with the 0.25 mg daily dose (see Section 4.3). For these reasons, the Sponsor is initiating new studies of DOR/ISL 100 mg/0.25 mg for daily treatment of HIV-1.

The Sponsor is assessing the reversibility of the reductions in CD4+ T-cell and total lymphocyte counts. A return toward baseline in lymphocyte and lymphocyte subset counts has been observed across the ISL clinical development program. The most robust data on recovery of the lymphocyte counts available at this point is from the studies involving administration of ISL QW (20 mg) and QM (60 mg and 120 mg) for PrEP where a full recovery was not observed by 24 weeks after stopping 60 mg ISL monthly.

To mitigate the risk of decreases in total lymphocyte and CD4+ T-cell counts, increased monitoring of CD4+ T-cell and total lymphocyte counts and strict study intervention discontinuation rules were added to DOR/ISL studies. As these rules requiring treatment discontinuation for specified decreases in total lymphocyte counts and/or CD4+ T-cell counts went into effect more recently, data on recovery to baseline following discontinuation of DOR/ISL 100 mg/0.75 mg QD in virologically suppressed adults (Protocol 017 and Protocol 018) is not yet available. At this time, the data review supports continuation of DOR/ISL 100 mg/0.75 mg in participants who continue to receive benefit and have not met discontinuation criteria until they can be enrolled in a DOR/ISL 100 mg/0.25 mg study (where available) or transitioned to commercially available ART. 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 who are infected with HIV-1 and naïve to antiretroviral therapy.

Objectives	Endpoints
Primary	
• To evaluate the antiretroviral activity of DOR/ISL compared to 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 noninferior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48. A margin of 10 percentage points is used to define noninferiority. **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 DOR/ISL compared to 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	
• To evaluate the antiretroviral activity of DOR/ISL compared to 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 noninferior to BIC/FTC/TAF as measured by the percentage of participants with HIV-1 RNA <50 copies/mL at Week 96. A margin of 10 percentage points is used to define noninferiority. **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

Objectives	Endpoints
• To evaluate the antiretroviral activity of DOR/ISL compared to 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 <200 copies/mL	• HIV-1 RNA
• To evaluate the immunologic effect of DOR/ISL as measured by the 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 in participants who receive DOR/ISL and in those who receive BIC/FTC/TAF	• Viral resistance-associated substitutions
• To evaluate the effect of DOR/ISL compared to 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

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate the effect of DOR/ISL compared to BIC/FTC/TAF on fasting lipid and metabolic profiles, renal function, inflammation, and body composition, as measured by the mean change from baseline to Week 48, Week 96, and Week 144 in laboratory and radiological markers	• Weight and laboratory and radiological markers
• To evaluate the pharmacokinetics of ISL when administered as a component of DOR/ISL	• Pharmacokinetic values, such as area under the curve, maximum (peak) observed drug plasma concentration, and concentration after 24 hours
• To describe patient-reported outcomes related to health-related quality of life and self-reported HIV symptoms for participants who receive DOR/ISL compared to BIC/FTC/TAF at Weeks 48 and 96	• EQ-5D-5L and HIV-SI
• To explore the antiretroviral activity of DOR/ISL compared to BIC/FTC/TAF as assessed by time to loss of virologic response at Week 48, Week 96, and Week 144	• Time to loss of virologic response
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanism of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study	• Germline genetic variation and association to clinical data collection in this study

Success of this study is predicated only upon establishing noninferiority 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, multisite, double-blind, double-dummy clinical study to evaluate the antiretroviral activity, safety, and tolerability of DOR/ISL QD in TN participants with HIV-1. The active control selected for this study is the 3-drug combination of BIC/FTC/TAF QD with demonstrated antiretroviral activity against HIV-1 in TN patients.

A total of approximately 680 participants will be randomized (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) in a 1:1 ratio into 1 of 2 treatment groups (Figure 1):

Group 1 (n = approximately 340): DOR/ISL (taken with matching placebo to BIC/FTC/TAF) on Day 1 through Week 96 (double-blind period); and DOR/ISL (taken without matching placebo to BIC/FTC/TAF) from Week 96 through Week 144 (open-label period).

Group 2 (n = approximately 340): BIC/FTC/TAF (taken with matching placebo to DOR/ISL) on Day 1 through Week 96 (double-blind period); BIC/FTC/TAF (taken without matching placebo to DOR/ISL) from Week 96 through Week 144 (open-label period).

Participants will receive blinded oral therapy for 96 weeks. The participant and the clinical site personnel will be unblinded to the participant's study intervention assignment at the Week 96 visit. Sponsor personnel will be unblinded to each participant's study intervention assignment at the earlier of the Week 96 visit or the Week 48 database lock. Safety and efficacy laboratory results, including HIV-1 RNA, will remain unmasked throughout the study. Viral resistance data will remain masked to the Sponsor until the Week 48 database lock.

All participants who reach Week 144 will be considered to have completed the base study. At Week 144, participants may be offered the option to continue study intervention up to Week 168 in the study extension.

Participants receiving assigned study intervention may be eligible to enroll in a DOR/ISL 100 mg/0.25 mg study (when and where available) or to transition to commercially available ART (see Section 6.7).

The first 60 participants enrolled and evaluable at the Week 24 time point will be identified as the Sentinel Cohort. An interim analysis (which will hereafter be referred to as the "Sentinel Cohort Week 24 interim analysis") will be conducted by an external unblinded statistician once the Sentinel Cohort completes the Week 24 visit; all available efficacy and safety data for all participants enrolled by that time will be submitted to an independent eDMC for review. A futility assessment will also be conducted at this interim analysis using Week 24 data from the 30 participants in the Sentinel Cohort that received DOR/ISL (Section 9.7). Decisions regarding study continuation will be made based on the eDMC

review of the Sentinel Cohort Week 24 interim analysis results, and in consultation with the Sponsor.

Enrollment will be capped at a total of 180 participants prior to the availability of the Sentinel Cohort Week 24 interim analysis results. All participants enrolled prior to the availability of these results must have screening HIV-1 RNA level ≤100,000 copies/mL. Following the Sentinel Cohort Week 24 interim analysis, participants with HIV-1 RNA level >100,000 copies/mL may be enrolled.

In addition to the Sentinel Cohort Week 24 interim analysis, the eDMC will also review accumulating efficacy and safety data at regular intervals throughout the study duration and when either of the following occur (as assessed by the external unblinded statistician):

- In the Sentinel Cohort (prior to completion of the Sentinel Cohort Week 24 interim analysis):
  >3 participants in the DOR/ISL treatment group meet the definition for confirmed virologic rebound or incomplete virologic response (Section 4.2.1.1.2).

- Overall (following enrollment of the Sentinel Cohort):
  >10% of participants in the DOR/ISL treatment group meet the definition for confirmed virologic rebound or incomplete virologic response (Section 4.2.1.1.2).

The eDMC will recommend steps to ensure the safety of study participants and the integrity of the study (see Appendix 1).

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.

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, noninferiority study design is consistent with regulatory guidance [Food and Drug Administration (CDER) 2015] and is considered appropriate for a study population with HIV-1 who are naïve to antiretroviral therapy. Inconsistencies in virologic efficacy, emergence of resistance, and loss of tolerability or safety may be detected in TN patients prior to 48 weeks, particularly for therapies with largely comparable characteristics. Thus, aligned with regulatory guidance [Food and Drug Administration (CDER) 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, reduce participant pill burden, and study simplification. The study extension allows participants who continue to benefit from study intervention (as determined by the investigator) to continue their

assigned treatment for up to 24 additional weeks when needed until the participant is able to enroll in a DOR/ISL 100 mg/0.25 mg study (where available, see Section 6.7) or transition to commercially available ART.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 HIV-1 RNA Measurement

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

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 after achieving HIV-1 RNA <50 copies/mL at any time during the study,

  or as

- **Incomplete Virologic Response**: Two consecutive (2 to 4 weeks apart) occurrences of HIV-1 RNA ≥200 copies/mL at or after Week 24 in the absence of previous suppression of HIV-1 RNA to <50 copies/mL

There is currently no global standard for definition of patients with low-level viremia (viral load ≥50 and <200 copies/mL), and the predictive implication of such low-level viremia is uncertain [Vandenhende, M. A., et al 2015] [Charpentier, C., et al 2014]. The US DHHS guidelines currently define virologic failure as confirmed HIV RNA ≥200 copies/mL and do not recommend that low-level viremia (detectable HIV RNA <200 copies/mL) automatically results in treatment modification or more frequent virologic monitoring [Panel on Antiretroviral Guidelines for Adults and Adolescents 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 following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression to <50 copies/mL 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 (hematology, chemistry, and urinalysis) performed per the SoA in 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 changes from baseline in weight, laboratory, and radiological markers between DOR/ISL and BIC/FTC/TAF to evaluate the impact of DOR/ISL as per the SoA on the following:

Weight

Compared with other antiretrovirals, use of integrase inhibitors in patients with HIV-1 has been associated with greater increases in body weight [Hill, A., et al 2019]. Thus, the mean change in weight will be measured (Section 8.8.5).

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 (Sections 8.8.5 and 8.8.6).

4.2.1.4 Pharmacokinetic Endpoints

PK samples collected from all participants as described in the SoA (Section 1.3) and Section 8.6 will be used to evaluate PK concentrations of ISL, and as appropriate, PK-efficacy, PK-pharmacodynamic, and PK-AE relationships of ISL. PK values such as AUC, C_{max}, 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 patient's perspective as some domains are difficult to observe or are subjective and best collected through patient report. HIV infection and its treatment can impair HRQOL. Symptom burden associated with HIV treatment has decreased with improvements in ART regimens, but persists despite viral suppression and immunologic recovery. In conjunction with efficacy and safety, PRO data may help clinicians and patients in informed decision-making on appropriate ART regimens. HTA authorities in many countries recommend patient perspective 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.

The study will include 2 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.

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 for use in TN patients and is recommended by DHHS guidelines as a preferred first-line treatment for HIV-1 infection in most TN adults [Panel on Antiretroviral Guidelines for Adults and Adolescents 2018].

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:

- **Antiretroviral TN Participants**: The current paradigm of lifelong treatment for HIV creates the desire for safe, simple regimens. While the standard of care has been a 3-drug regimen for the treatment of HIV, there is growing interest in 2-drug regimens for a TN population. This study is designed to evaluate the antiretroviral efficacy and safety of DOR/ISL QD compared to the 3-drug regimen of BIC/FTC/TAF QD in TN participants using a randomized, double-blind, active-controlled noninferiority design. The combination of DOR+ISL is being studied in HIV-1 infected antiretroviral TN adult participants in a randomized Phase 2 multicenter study (MK-8591 Protocol 011). At Week 24, all ISL treatment groups demonstrated potent antiretroviral activity comparable

to DOR/3TC/TDF as demonstrated by the primary efficacy endpoint, the proportion of participants with HIV-1 RNA <50 copies/mL.

4.2.4 Rationale for Collecting Race and Ethnicity

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

4.2.5 Rationale for Collecting Gender Identity Data

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

4.2.6 Rationale for Infant Safety Data Collection

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

4.2.7 Rationale for Continuing Study Intervention During Pregnancy

The US Department of Health and Human Services guidelines currently advise that women who become pregnant while receiving ART for HIV should continue their regimen provided it is safe, well tolerated, and effective at virologic suppression since altering the regimen could cause an increase in viral load [Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]. Nonclinical developmental and reproductive toxicology studies did

not identify any teratogenicity or other clinically relevant concerns that would preclude continued dosing of DOR/ISL in participants who become pregnant and consent to continue study intervention (where allowed by local regulations, health authorities, and ethics committees and as appropriate based on available data/local standard of care guidelines) (Sections 8.1.1.4 and 8.11.6). For participants who become pregnant on BIC/FTC/TAF see Section 8.11.6.

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

4.3 Justification for Dose

IQ (C_{trough}/IC_{50}) is the ratio of drug exposure to viral susceptibility. In a Phase 1b proof of concept study (MK-8591 Protocol 003), single doses as low as 0.5 mg ISL showed robust antiretroviral activity at 7 days postdose; this low single-dose provided an IQ threshold of 5 for wild-type HIV-1 virus. Simulations suggest the ISL-TP concentrations achieved 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 time points 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 in TN participants with HIV-1.

In a Phase 2 clinical study (MK-8591 Protocol 011), 3 daily doses of ISL (0.25, 0.75, and 2.25 mg) were evaluated in combination with DOR (100 mg) +3TC for 24 weeks and subsequently with DOR alone through Week 48. All 3 doses of ISL with DOR±3TC demonstrated potent antiretroviral activity comparable with the comparator, DOR/3TC/TDF, as demonstrated by the primary efficacy endpoint: the proportion 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 Protocol 011 showed no trends in exposure-response. The totality of these efficacy data supports the conclusion that the dose range studied (0.25 to 2.25 mg daily) is on the plateau of the dose-response curve. MK-8591 Protocol 011 also demonstrated that all doses of ISL studied, when administered with DOR+3TC or DOR alone, had a favorable safety and tolerability profile through Week 48, comparable with that of DOR/3TC/TDF.

DOR will be administered at the approved dose of 100 mg. This dose has been studied in Phase 1 to 3 clinical studies in TN and virologically suppressed participants with HIV-1 and was selected based upon favorable efficacy, safety, tolerability, and metabolic profiles as confirmed in the Phase 3 clinical studies ([Orkin, C., et al 2018] [Molina, J. M., et al 2018] and MK-1439A Protocol 024). Participants harboring NNRTI resistance-associated substitutions RT K103N or G190A were evaluated in MK-8591 Protocol 030, a Phase 2 trial evaluating TN participants with transmitted NNRTI drug resistance. Of the 8 participants treated with DOR/3TC/TDF who completed Week 48, all had HIV-1 RNA <50 copies/mL at

Week 48. In MK-8591 Protocol 024, a Phase 3 trial in virologically suppressed adults, 24 participants had NNRTI resistance-associated substitutions RT K103N, Y181C, and/or G190A. All 24 participants maintained virologic suppression after switching to DOR/3TC/TDF.

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 HIV-1 virus and most common NRTI- and NNRTI-resistant variants.

4.4 Beginning and End of Study Definition

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3 ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

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

Early study termination may also be considered if the Sentinel Cohort meets the futility criteria as assessed at the Sentinel Cohort Week 24 interim analysis or after review of accumulating efficacy and safety data by the eDMC (Section 9.7).

5 STUDY POPULATION

Participants with HIV-1 ≥18 years of age who are naïve to ART will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant is eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Is HIV-1 positive with plasma HIV-1 RNA ≥500 copies/mL at screening.
   Note: A single repeat of the plasma HIV-1 RNA screening test by the central laboratory will be allowed, provided results are available within the 45-day screening window.

   Note: Participants enrolled prior to the availability of the Sentinel Cohort Week 24 interim analysis results must have HIV-1 RNA ≤100,000 copies/mL at screening.

2. Is naïve to ART defined as having received ≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection including prevention of mother-to-child transmission up to 1 month prior to screening.

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

Demographics

3. Is male or female ≥18 years of age inclusive at the time of signing 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 infection (defined as HBsAg-positive or HBV DNA positive).

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

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

   Note: Chronic HCV infection (detectable HCV RNA) and treatment with direct-acting antiviral therapies are not exclusionary, provided the participant has stable liver function tests and no significant hepatic synthetic dysfunction 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. Has been treated for a viral infection other than HIV-1, such as hepatitis B, with an agent that is active against HIV-1, including, but not limited to, the following: adefovir, TDF, TAF, FTC, or 3TC.

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

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

Prior/Concurrent Clinical Study Experience

8. 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 intervention 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 noninterventional studies may be permitted and should be discussed with the Sponsor prior to enrollment and through the study duration.

Diagnostic Assessments

9. Has a documented or known virologic resistance to any approved HIV-1 reverse transcriptase inhibitor, or any study intervention, as demonstrated by any of the following resistance substitutions (according to the 2017 IAS-USA drug resistance mutations list) [Wensing, A. M., et al 2017]:

   a. FTC: K65R/E/N or M184I/V

   b. TAF: K65R/E/N or K70E

   c. Multi-NRTI resistance substitutions: T69insert, Q151M, or 3 or more of thymidine analogue-associated mutations (M41L, D67N, K70R, L210W, T215F/Y, K219E/Q).

d. DOR resistance substitutions: V106A/M, V108I, Y188L, H221Y, P225H, F227C/L, M230I/L, L234I, P236L, or Y318F.

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

Note: Resistance testing will be performed by the central laboratory as part of the screening assessments. However, if resistance testing results obtained from a local laboratory ≤90 days prior to the screening visit date are available prior to the availability of the central laboratory screening resistance results, the local results can be used to determine participant eligibility.

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

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 CrCL	≤30 mL/min based on the Cockcroft-Gault equation (Appendix 8)
ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCL=creatinine clearance; ULN=upper limit of normal.	

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

Other Exclusions

11. Is female and is expecting to conceive or donate eggs at any time during the study.
Note: Investigators should provide appropriate guidance to female participants regarding egg donation after completion of the study 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 from the study will not be replaced.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2. Country-specific differences are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP/	Sourcing
Group 1	Experimental	DOR/ISL	Drug	Tablet	100 mg/ 0.75 mg	100 mg/ 0.75 mg QD	Oral	Day 1 to Week 168 [a,c]	Test Product	IMP	Provided centrally by the Sponsor
Group 1	Experimental	Placebo to BIC/FTC/TAF	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	Drug	Tablet	50/200/25 mg	50/200/ 25 mg QD	Oral	Day 1 to Week 168 [b,c]	Comparator	IMP	Provided centrally by the Sponsor
Group 2	Active Comparator	Placebo to DOR/ISL	Drug	Tablet	0 mg	0 mg QD	Oral	Day 1 to Week 96	Placebo	IMP	Provided centrally by the Sponsor

BIC=bictegravir; DOR/ISL=fixed dose combination of doravirine and islatravir, also known as MK-8591 A; FTC=emtricitabine; QD=once-daily; TAF=tenofovir alafenamide.

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

[a.] If a participant in Group 1 is pregnant at their last routine study visit 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 their last routine study visit 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.] Participants who consent to the study extension at Week 144 may continue their assigned study intervention up to Week 168, if needed.

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 (DOR/ISL and placebo to BIC/FTC/TAF) and Group 2 (BIC/FTC/TAF and placebo to DOR/ISL), respectively.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

- Screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 copies/mL)
- Screening CD4+ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3)

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.

Sponsor personnel involved in performing and reviewing results of the Week 48 analysis will be unblinded to all participants' study intervention assignments at the time of the Week 48 database lock. However, it is noted that participants who reach Week 96 (and are dispensed open-label study intervention) prior to the Week 48 database lock will have already been unblinded to the Sponsor.

As described in Section 4, at Week 96 all clinical site personnel and participants will be unblinded and participants will continue to receive their assigned study intervention open-label through Week 144 (and up to Week 168 if participating in the study extension).

The investigator and participant may become unblinded by the Sponsor (after the Week 48 database lock) to facilitate decisions regarding the option to enroll the participant in a DOR/ISL 100 mg/0.25 mg study (where available) or transition to commercially available ART.

To allow timely completion of population PK modeling, restricted early (before database lock) unblinding of PK data may be requested. Before granting select study 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. 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 intervention period. Table 3 is not comprehensive, and the investigator should use his/her medical judgment when assessing a participant's prior and concomitant therapy(ies). The Sponsor's Clinical Director or designee should be contacted if there are any questions about a therapy not listed or regarding potential DDIs with a specific treatment that the participant may plan to receive.

In instances where the local product circular for DOR or BIC/FTC/TAF is more restrictive with regards to prohibited (ie, contraindicated or not recommended) therapies, the local product circular supersedes this section. Concomitant medications will be monitored for the duration of the study and once a participant is unblinded, local product circular should be followed for participants on BIC/FTC/TAF.

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
Nonstudy ART	All nonstudy antiretrovirals (with the exception of 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 nonstudy 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

The following options are available upon study completion:

Group 1 participants (DOR ISL 100 mg/0.75 mg) may be eligible to enroll in an open-label study of DOR/ISL 100 mg/0.25 mg, where available. Participants who are not eligible or do not consent to continued participation in the DOR/ISL investigational program should be transitioned to commercially available ART. Group 1 participants receiving DOR/ISL 100 mg/0.75 mg with decreases in CD4+ T-cell count and/or lymphocyte count should be managed per Section 8.11.5.3.

Group 2 participants (BIC/FTC/TAF) may be eligible to enroll in a randomized study of a switch to DOR/ISL 100 mg/0.25 mg, where available. Participants who are not eligible or do not consent to continued participation in the DOR/ISL investigational program should be transitioned to commercially available ART.

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 product to provide the following advice:

“You have participated in a study conducted by the Sponsor. This letter is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug BIKTARVY 50/200/25 mg (BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) as much as possible. You did not receive the active drug 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 chooses to breastfeed.
  Note: Study intervention can continue until breastfeeding is initiated.
- The participant has confirmed HIV-1 virologic rebound or incomplete virologic response as defined in Section 4.2.1.1.2.
- 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.
- 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].

A participant must be discontinued from study intervention for any of the following reasons (those receiving DOR/ISL must continue to be monitored per Section 8.11.5):

- CD4+ T-cell count:
  - 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

  - 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

  - For all participants with an average baseline* CD4+ T-cell count ≥200 cells/mm^3 (as well as participants with an average baseline CD4+ T-cell count <200 cells/mm^3 who have increases in CD4+ T-cell count to ≥200 cells/mm^3 for 2 consecutive measurements approximately 12 weeks apart), a CD4+ T-cell count decrease to <200 cells/mm^3 on 2 consecutive measurements taken 3 to 4 weeks apart.

- Total lymphocyte count:
  - For participants with an average baseline* total lymphocyte count ≥1×10^9 cells/L
    - A ≥30% reduction from average baseline* total lymphocyte count AND a decrease in total lymphocyte count to <1×10^9 cells/L on 2 consecutive measurements taken 3 to 4 weeks apart

      OR

    - A ≥30% reduction from average baseline* total lymphocyte count on 2 consecutive measurements taken 10 to 14 weeks apart.
  - For participants with an average baseline* total lymphocyte count <1×10^9 cells/L, a ≥30% reduction from average baseline* total lymphocyte count on 2 consecutive measurements taken 3 to 4 weeks apart.

    **Note: The average baseline value for CD4+ T-cell count and total lymphocyte count is defined as the average of the screening (within 45 days prior to the first dose of study intervention) and Day 1 values through Week 48. After Week 48, the baseline resets to the Week 48 value only if the Week 48 value is greater than the average baseline value. If there are ≥2 values at Week 48, 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 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 his/her 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 their legally acceptable representative, answer all questions, and obtain documented informed consent before continuing study intervention. A copy of the informed consent will be given to the participant.

8.1.1.5 Consent to Participate in the Study Extension

The investigator or medically qualified designee will explain the consent to participate in the study extension to the participant, or the participant's legally acceptable representative, answer all questions, and obtain documented informed consent before participating in the study extension. 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 the first dose of study intervention. All prior HIV medication use, regardless of timing, including PrEP, must be recorded.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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 (Section 6.1) and dispensed through the IRT system at visits indicated in the SoA (Section 1.3).

8.1.8.1 Timing of Dose Administration

The first dose of study intervention will be administered at the study site on Day 1. Following Day 1, all study interventions will be taken together QD by the participant (ie, unsupervised at their home) at approximately the same time each day without regard to food. Participants will take 2 tablets of blinded study intervention (1 tablet from each of 2 containers: [1] Bottle A: DOR/ISL or placebo to DOR/ISL, and [2] Bottle B: BIC/FTC/TAF or placebo to BIC/FTC/TAF). If more than 1 Bottle A is dispensed at a time, the participant is instructed to use all of the study intervention in 1 Bottle A before opening another Bottle A.

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 visit performed per SoA (Section 1.3) and be encouraged to continue to be followed as outlined in Section 8.11.3.

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.

Participants who discontinue study intervention due to decreases in CD4+ T-cell count and/or total lymphocyte counts, or those who discontinue for any other reason and have decreases in CD4+ T-cell and/or total lymphocyte counts >10% of the average baseline values or that meet ECI criteria at the Early Discontinuation of Treatment visit should be managed per Section 8.11.5.

8.1.9.1 Withdrawal From Future Biomedical Research

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

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

8.1.10 Participant Blinding/Unblinding

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

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

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

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

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 Participant Questionnaires

Participants will complete 2 PRO questionnaires at Day 1, Week 4, Week 16, Week 48, Week 96, and/or the Early Discontinuation of Treatment visit. Participants are to complete the questionnaires on their own at the site on paper during the appropriate study visit (per SoA in Section 1.3) prior to being seen by the investigator, discussing any medical conditions with the study personnel, or receiving any medical results. The questionnaires should not be administered to participants who are illiterate, who are unable to complete questionnaires unassisted, or for whom native language translations of the questionnaires are unavailable.

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

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) following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression to <50 copies/mL, the investigator should query the participant regarding adherence to study intervention, intercurrent illness, or recent immunization. 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 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 (following suppression to <50 copies/mL or at or after Week 24 in the absence of previous suppression to <50 copies/mL) will be assessed for development of viral drug resistance (Section 8.2.2.4) and discontinuation from study intervention (Section 7.1). Once it is determined that study intervention discontinuation is appropriate, "Early Discontinuation of Treatment" and "End of Treatment Follow-up" Visit procedures should be completed (Sections 1.3.2 and 8.11.3) and the participant managed by the investigator per local standard of care.

8.2.2.3 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 the SoA (approximately every 3 months). Additional visits may be conducted to monitor HIV-1 RNA levels more frequently than every 3 months, if appropriate, after discussion with the Sponsor. 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 virologic rebound or incomplete virologic response (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. Samples with HIV-1 RNA ≥200 copies/mL that were collected either to confirm viremia or at discontinuation will be sent for genotypic and phenotypic resistance testing.

Samples will be collected for genotypic and phenotypic HIV-1 Drug Resistance testing per the 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 (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 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). 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). 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 first dose of study intervention on Day 1 as outlined in the SoA (see Section 1.3.1). 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 the SoA to verbally confirm their use of contraception since the prior visit, according to the Contraceptive Guidance in Appendix 5. Confirmation should be noted in the source documents for each visit.

Urine pregnancy test kits will be provided by the central laboratory, and routine testing will be performed by the local laboratory. In the event of a positive urine pregnancy test result, serum pregnancy testing must be performed by the central laboratory. If a participant becomes pregnant, refer to Section 7.1. 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 Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

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

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

Note: Decreases in CD4+ T-cell and/or total lymphocyte counts should be managed per 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. Investigators should pay close attention to changes from baseline in ALT, AST, bilirubin, and alkaline phosphatase (included in chemistry laboratory assessments).

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

Information on tobacco and alcohol use by participants will be collected 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 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.

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 occurring (including perinatal HIV-1 infection) 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 2 consecutive measurements approximately 12 weeks apart while on study intervention.

   **Note: The average baseline value for CD4+ T-cell count and total lymphocyte count is defined as the average of the screening (within 45 days prior to the first dose of study intervention) and Day 1 values through Week 48. After Week 48, the baseline resets to the Week 48 value only if the Week 48 value is greater than the average baseline value. If there are ≥2 values at Week 48, then use the most recent value.

See Section 8.11.5 for further details on the management of participants with specified decreases in CD4+ T-cell and/or total lymphocyte counts.

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 operations/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 that routinely take their study intervention during the day, a predose and postdose sample will be taken at the Week 4 visit (Table 5). Participants that 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 in 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 8	Sample collected irrespective of time of dose (time of last dose and time of PK sample collection must be documented)
Week 16	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 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 (Appendix 7, 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 BICR; 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 prior to DEXA imaging.

DEXA scans 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 FBR

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

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

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

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

If the informed consent form has been updated, participants should be reconsented prior to rescreening. If no updates have been made, documented informed consent obtained 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.

8.11.2 Treatment Period

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

8.11.2.1 Fasting

Visits at Day 1, Week 24, Week 48, Week 96, Week 120, Week 144, and Week 168 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 to 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 Week 144 Visit

Week 144 represents the end of the base study.

Participants will be given the following options at the Week 144 visit:

1. End participation in the clinical study and resume commercial treatment of their choice. These participants should have an End of Treatment Follow-up Visit approximately 42 days (+7 days) after the last dose of study intervention.

2. Provide documented consent to participate in the study extension to continue assigned study intervention for a maximum of 24 additional weeks.

3. Enroll in a new study of DOR/ISL 100 mg/0.25 mg (where available).

Participants who are pregnant at Week 144 will be managed per Section 8.11.6.

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.

- 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 due to other reasons and the CD4+ T-cell count and/or total lymphocyte count at the Early Discontinuation of Treatment visit is >10% lower than the average baseline value or meets ECI criteria, then additional monitoring is required per Section 8.11.5.

8.11.3.1 Early Discontinuation of Treatment

Participants who discontinue study intervention 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 reasons(s) will have a safety follow-up visit in-clinic approximately 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 ending study intervention should have an End of Treatment Follow-up Visit unless enrolling in a new study within the DOR/ISL 100 mg/0.25 mg program.

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

8.11.4 Viremia Confirmation

If a participant has a viral load of ≥50 copies/mL following suppression of HIV-1 RNA to <50 copies/mL at any time during the study or at or after Week 24 in the absence of previous suppression, a Viremia Confirmation visit must be conducted within 2 to 4 weeks of the initial HIV-1 viremia (see Section 1.3.3 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 Specified Decreases in CD4+ T-cell Count and/or Total Lymphocyte Count

Management of participants with specified 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 meet ECI criteria (Section 8.4.7) must have a confirmation visit in 3 to 4 weeks. Participants whose decreases in total lymphocytes meet ECI criteria should have a confirmation visit in 3 to 4 weeks, except for those with an average baseline* total lymphocyte count $\geq 1\times10^9$ cells/L that does not decline to $<1\times10^9$ cells/L, in which case the confirmation visit should be conducted in 10 to 14 weeks.

* The average baseline value for CD4+ T-cell count and total lymphocyte count is defined as the average of the screening (within 45 days prior to the first dose of study intervention) and Day 1 values through Week 48. After Week 48, the baseline resets to the Week 48 value only if the Week 48 value is greater than the average baseline value. If there are ≥2 values at Week 48, then use the most recent value.

If the discontinuation criteria are met (Section 7.1), the participant must be discontinued from study intervention 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 the 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 due to specified decreases in CD4+ T-cell and/or total lymphocyte counts should be unblinded (if applicable) and managed 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). CD4+ T-cell counts and total lymphocyte counts will be monitored until 2 values approximately 10 to 14 weeks apart are within 30% of the average baseline value. If additional test results are available within this timeframe, no more than 1 value should show a decrease of ≥30% of average baseline.

Participants who have previously met the above recovery criterion after discontinuing DOR/ISL no longer require monitoring regardless of test results from the most recent visit.

If after ≥24 months following discontinuation of DOR/ISL, a participant has not met the above recovery criterion, and their CD4+ T-cell count or total lymphocyte values have increased since discontinuation, then the Sponsor may be consulted to discuss whether monitoring may be stopped (based on the participant's clinical status and the trajectory of laboratory test results).

Participants who were receiving BIC/FTC/TAF who discontinue study intervention due to decreases in CD4+ T-cell count or total lymphocyte count will be managed per Section 8.11.3 and will not require further monitoring after their End of Treatment Follow-up visit (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 who are found to have decreases in CD4+ T-cell and/or total lymphocyte counts >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 (Section 1.3.5).
    - If the decrease(s) of >10% of average baseline and/or a decrease in CD4+ T-cell count to <200 cells/mm^3 is confirmed at this visit, participants should continue to be monitored according to the criteria specified in Section 8.11.5.2.
    - If the decrease(s) of >10% of average baseline and/or a decrease in CD4+ T-cell count 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 their End of Treatment Follow-up Visit after study intervention is discontinued (Section 1.3.3) and no further monitoring is needed.
- Participants who are enrolling directly into a DOR/ISL 100 mg/0.25 mg study will be managed per their study's guidelines.

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. 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). Their End of Treatment Follow-up Visit should be performed approximately 42 days (+7 days) after the last dose of study intervention (Section 1.3.4). Following pregnancy completion, options for future treatment are managed per Section 6.7.

For participants who continue DOR/ISL, PK samples will be collected at their scheduled visit during the 1st, 2nd, and 3rd trimesters and postpartum to evaluate DOR and ISL concentration

levels per Table 6. These samples will be used to characterize the PK profile of DOR/ISL during pregnancy. 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[a]**	
	If participant routinely takes study intervention during the day, collect:	**If participant routinely takes study intervention in the evening, collect:**
1st Trimester[b]	Predose	Irrespective of time of last dose
2nd Trimester	Predose AND 0.5 to 2 hours AND 4 to 6 hours postdose	Only 1 sample, irrespective of time of last dose
3rd Trimester	Predose AND 0.5 to 2 hours AND 4 to 6 hours postdose	Only 1 sample, irrespective of time of last dose
Postpartum[c]	Predose	Irrespective of time of last dose

PK=pharmacokinetic.

[a] Time of last dose and time of PK sample collection must be documented for all samples.

[b] Collected in the 1st trimester at a scheduled visit when a participant reports gravid status. May not be collected if a participant does not learn of their pregnancy until after the 1st trimester.

[c] 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 approximately 42 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; N/A=not applicable; 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 nonconfirmatory analyses made after the protocol has been finalized, but prior to final

database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the 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 the Antiretroviral Activity, Safety, and Tolerability of DOR/ISL Once-Daily in HIV-1 Infected Treatment-Naïve Participants.
Treatment Assignment	This study will enroll approximately 680 TN participants with HIV-1 infection. Participants will be randomized (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) in a 1:1 ratio to DOR/ISL QD (Group 1) or the 3-drug combination of BIC/FTC/TAF QD (Group 2). Clinical site personnel and participants will remain blinded through Week 96, while 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 <200 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. Viral resistance-associated substitutions 5. Change from baseline in weight at Week 48, Week 96, and Week 144 6. General safety and tolerability through study duration
Statistical Methods for Key Efficacy Analyses	The primary objective and hypothesis will be assessed using a 2-sided multiplicity-adjusted 95% CI for the difference between treatment groups (DOR/ISL minus BIC/FTC/TAF) in the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48. The CI will be based on the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with Cochran-Mantel-Haenszel weights (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]). Noninferiority at Week 48 will be concluded if the lower bound of the CI is greater than -10 percentage points.

Statistical Methods for Key Safety Analyses	Point estimates and 2-sided nominal 95% CIs will be provided using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] for the difference between treatment groups (DOR/ISL minus BIC/FTC/TAF) 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 nondrug-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 (DOR/ISL minus BIC/FTC/TAF) 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. • Interim analysis once the Sentinel Cohort completes Week 24: An interim analysis (hereafter referred to as the "Sentinel Cohort Week 24 interim analysis") will be performed once the Sentinel Cohort has completed the 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. Additionally, a futility assessment will be conducted based on the Sentinel Cohort data. If 7 or more participants in Group 1 (out of 30 enrolled and evaluable participants) fail to achieve HIV-1 RNA <200 copies/mL at Week 24, the eDMC may recommend the study be stopped; the eDMC will review the totality of the available data at the time of the Sentinel Cohort Week 24 interim analysis before making such a recommendation. • Primary efficacy and safety analyses conducted at the Week 48 interim time point (will be conducted by the Sponsor and results shared with the eDMC). • Continuous safety and efficacy monitoring throughout the study: The eDMC will review accumulating safety and efficacy data at regular intervals throughout the study duration.
Multiplicity	For statistical rigor, a small amount of alpha (α=0.00001) will be set aside for the Sentinel Cohort Week 24 interim analysis and each additional eDMC evaluation. An allowance will be made such that a total of up to 5 of these unblinded eDMC reports may be presented prior to the evaluation of the primary noninferiority efficacy hypothesis at Week 48. A subset of the efficacy hypotheses listed in Section 3 will be tested in a sequential order specified in Section 9.8 at a 1-sided 2.5% Type 1 error rate adjusted for the number of eDMC reports. Testing will stop with the first of these tests failing to reach statistical significance; in this way, the overall 1-sided 2.5% Type 1 error rate is strongly controlled among these hypotheses. Additional details are provided in Section 9.8. 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 680 participants to be randomized in a 1:1 ratio to Group 1 or Group 2. The rate of participants in Group 1 in the Sentinel Cohort with Week 24 HIV-1 RNA <200 copies/mL is assumed to be 90%, and the rate of participants in both Group 1 and Group 2 with Week 48 HIV-1 RNA <50 copies/mL is assumed to be 82%. Under these assumptions, there is a 97.7% chance of continuing the study after the futility assessment on the Sentinel Cohort Week 24 data and a 90% chance of declaring noninferiority between groups at Week 48.

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.

The Week 48 database lock will occur once all participants have completed the Week 48 visit assessments, and data from Day 1 through Week 48 will be analyzed. The database lock will not occur until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. Sponsor personnel directly involved in the analysis and reporting associated with the Week 48 CSR will be unblinded to each participant's study intervention assignment at the earlier of the Week 96 visit or the time of the Week 48 database lock.

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

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

Blinding issues related to the planned 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, Percentage of Participants with HIV-1 RNA <40 copies/mL, and Percentage of Participants with HIV-1 RNA <200 copies/mL at Week 48

The Abbott Real-Time 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 <40 copies/mL and the percentage of participants with HIV-1 RNA <200 copies/mL at Week 48.

Percentage of Participants with HIV-1 RNA <50 copies/mL, Percentage of Participants with HIV-1 RNA <40 copies/mL, and Percentage of Participants with HIV-1 RNA <200 copies/mL at Week 96 and Week 144

Secondary objectives will assess the percentage of participants with HIV-1 RNA <50 copies/mL, the percentage of participants with HIV-1 RNA <40 copies/mL, and the percentage of participants with HIV-1 RNA <200 copies/mL at 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 time point 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.

Clinically Significant Confirmed Viremia

Participants with confirmed virologic rebound or incomplete virologic response 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 or incomplete virologic response (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 achieve HIV-1 RNA <50 copies/mL and subsequently have 2 consecutive HIV-1 RNA values (measured at least 2 weeks apart) ≥50 copies/mL, TLOVR is the time between the date of the initial HIV-1 RNA suppression to <50 copies/mL and the date of the first of the 2 consecutive HIV-1 RNA values ≥50 copies/mL.

For participants who achieve and sustain HIV-1 RNA <50 copies/mL, TLOVR is censored at the time of the last available measurement. For participants who do not achieve an HIV-1 RNA value <50 copies/mL, TLOVR is 0 weeks.

9.4.1.2 Pharmacokinetics Endpoints

PK samples collected from all participants as described in the SoA (Section 1.3) and Section 8.6 will be used to evaluate PK concentrations of ISL, and 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 time point 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.

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.

Patient-reported outcomes from each questionnaire at Day 1 and Weeks 4, 16, 48, and 96 will be summarized for each treatment group.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

9.5.1.1 Sentinel Cohort

The first 30 participants enrolled and evaluable at the Week 24 time point in each treatment group will be identified as the Sentinel Cohort (60 total). To be considered "enrolled and evaluable" at Week 24, participants must be randomized in the study and 1) have at least one on-treatment HIV-1 RNA measurement in the Week 24 analysis window (Table 7) or 2) discontinue study intervention prior to or within the Week 24 analysis window due to lack of efficacy. Participants who do not meet these criteria will not be eligible for inclusion in the Sentinel Cohort population. The external unblinded statistician will monitor participant status throughout the trial to identify the first 30 participants in each treatment group (by date of study intervention discontinuation due to lack of efficacy or the date of clinically significant confirmed viremia/date of the Week 24 HIV-1 RNA measurement) who meet the requirements for inclusion in the Sentinel Cohort.

9.5.1.2 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.

9.5.1.3 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 (Section 6.5).
- 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 the Week 48 database lock.

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

9.5.1.4 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.

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 (QP2). 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 time point (with the exception of DEXA assessments). The last available on-treatment measurement within a window will be used for analyses at a specific time point, unless otherwise specified. Results from additional time points beyond Week 144 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 ≤42	29
		Week 8	≥43 and ≤84	57
		Week 16	≥85 and ≤140	113
		Week 24	≥141 and ≤210	169
		Week 36	≥211 and ≤294	253
		Week 48	≥295 and ≤378	337
		Week 60	≥379 and ≤462	421
		Week 72	≥463 and ≤546	505
		Week 84	≥547 and ≤630	589
		Week 96	≥631 and ≤714	673
	Open-Label Intervention: DOR/ISL or BIC/FTC/TAF	Week 108	≥715 and ≤798	757
		Week 120	≥799 and ≤882	841
		Week 132	≥883 and ≤966	925
		Week 144	≥967 and ≤1050	1009
Treatment Extension[b]	Open-Label Intervention: DOR/ISL or BIC/FTC/TAF	Week 156	≥1051 and ≤1134	1093
		Week 168	≥1135 and ≤1218	1177

[a] Relative days and target days are computed from the first day of study intervention.
[b] The treatment extension phase visits apply only to participants who consent to the 24-week study extension.

FDA Snapshot Algorithm and Missing Data Approaches

There are 3 types of missing values:

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

Three approaches will be used to handle missing values. The primary approach for analysis of the percentage of participants with HIV-1 RNA <50 copies/mL is the FDA "snapshot" algorithm [Food and Drug Administration (CDER) 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 AE/death 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.

  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 and AE/death (ie, lost to follow-up, noncompliance with study intervention, physician decision, protocol deviation, withdrawal by participant, etc.) and have the last available on-treatment HIV-1 RNA measurement <50 copies/mL.

  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 noninferiority 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. Similar logic will also be used to define the percentage of participants with HIV-1 RNA <40 copies/mL and the percentage of participants with HIV-1 RNA <200 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 time point 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 time point of interest analysis window specified in Table 7 and have both the immediately preceding and immediately subsequent on-treatment HIV-1 RNA measurements <50 copies/mL, will be classified as a virologic "success" (HIV-1 RNA <50 copies/mL) at the time point of interest. Participants with other reasons for missing data will be classified as a virologic failure (HIV-1 RNA ≥50 copies/mL) at the time point of interest.

A third approach, the OF approach, will also be performed as a sensitivity analysis for the percentage of participants achieving HIV-1 RNA <50 copies/mL. Under this approach, participants with nonintermittent missing data who prematurely discontinue study intervention due to lack of efficacy or who discontinue study intervention for other reasons and are failures (HIV-1 RNA ≥50 copies/mL) at the time of study intervention

discontinuation are considered as failures at time points thereafter. Participants who discontinue study intervention for reasons other than lack of efficacy and who are not failures at the time of study intervention discontinuation will be excluded from the analyses at subsequent time points. Participants with intermittent missing data will be considered as successes (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 and the percentage of participants achieving HIV-1 RNA <200 copies/mL.

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

The snapshot approach will be used as the primary approach to analysis with respect to the percentage of participants with HIV-1 RNA <50 copies/mL. The full categorization of virologic outcome at a time point 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 i) discontinued study intervention due to an AE or death, ii) discontinued study intervention for other reasons (includes withdrawal of consent, loss to follow-up, move, etc.), or iii) on study intervention but missing data in window.

Noninferiority of DOR/ISL compared to BIC/FTC/TAF with respect to the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48 and at Week 96 will be calculated using the stratified Miettinen and Nurminen method with CMH weights (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) [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 10 percentage points is used to define the noninferiority of DOR/ISL compared to BIC/FTC/TAF; noninferiority will be concluded if the lower bound of the 2-sided multiplicity-adjusted 95% CI for the difference in the percentage of participants with HIV-1 RNA <50 copies/mL (DOR/ISL minus BIC/FTC/TAF) is greater than -10 percentage points. A noninferiority margin of 10 percentage points is clinically reasonable because it preserves a large portion of the treatment effect, which is expected to be >80%. The supportive analyses using the M=F and OF approaches (as defined above) will also be presented.

Superiority of DOR/ISL compared to BIC/FTC/TAF 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 stratified Miettinen and Nurminen method with CMH weights [Miettinen, O. and Nurminen, M. 1985]. For the evaluation of the efficacy superiority hypotheses at Weeks 48 and 96, superiority will be concluded if the lower bound of the 2-sided multiplicity-adjusted 95% CI for the difference in the percentage of participants with HIV-1 RNA <50 copies/mL (DOR/ISL minus BIC/FTC/TAF) is greater than 0 percentage points.

For the summary of virologic response over time, the difference in percentages between treatment groups at each time point 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 <200 copies/mL

The percentage of participants achieving HIV-1 RNA <40 copies/mL and the percentage of participants achieving HIV-1 RNA <200 copies/mL will be summarized by treatment group at each time point, with primary interest at Week 48, Week 96, and Week 144 by comparing Group 1 and Group 2. For each time point of interest, the difference in percentages between treatment groups and the associated 2-sided nominal 95% CI will be calculated using the stratified Miettinen and Nurminen method with CMH weights (stratified by screening HIV-1 RNA level [≤100,000 copies/mL, >100,000 copies/mL] and screening CD4+ T-cell count [<200 cells/mm^3, ≥200 cells/mm^3]) [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 time point 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 time point through Week 144 will be estimated using an ANCOVA model adjusted by baseline CD4+ T-cell count, stratum, and treatment group. 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 postbaseline measurement within the analysis window specified in Table 7 for the time point of interest to be included in the analyses of the mean change from baseline in CD4+ T-cell count by time point. Supportive analyses will also be provided using the BOCF and LOCF methods to account for missing data.

Clinically Significant Confirmed Viremia

The number of participants with confirmed virologic rebound or incomplete virologic response, as defined in Section 4.2.1.1.2, 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 Week 48, Week 96, and Week 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 not related to efficacy (eg, due to a safety event, acute infection/reactivation of HBV or pregnancy that requires unblinding, or accidental unblinding), such participants will not be treated as treatment failures in the primary efficacy analyses on the FAS population due to the unblinding alone.

If the unblinding is due to 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 according to 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 who choose to breastfeed will be censored from the time of study intervention discontinuation forward and will be handled in the primary efficacy analyses according to the FDA snapshot algorithm classification rules. Results for participants whose pregnancy extends 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[a]	Analysis Population	Missing Data Approach
Primary Hypothesis				
Percentage of participants with HIV-1 RNA <50 copies/mL at Week 48	P	M&N with CMH weights	FAS	Snapshot[b]
	S	M&N with CMH weights	FAS	M=F
	S	M&N with CMH weights	PP	OF
Secondary Objectives				
Percentage of participants with HIV-1 RNA <50 copies/mL at Week 96 and Week 144	P	M&N with CMH weights	FAS	Snapshot[b]
	S	M&N with CMH weights	FAS	M=F
	S	M&N with CMH weights	PP	OF
Percentage of participants with HIV-1 RNA <40 copies/mL and percentage of participants with HIV-1 RNA <200 copies/mL at Week 48, Week 96, and Week 144	P	M&N with CMH weights	FAS	Snapshot[b]
	S	M&N with CMH weights	FAS	M=F
	S	M&N with CMH weights	PP	OF
Change from baseline in CD4+ T-cell count at Week 48, Week 96, and Week 144	P	ANCOVA	FAS	DAO
	S	ANCOVA	FAS	BOCF
	S	ANCOVA	FAS	LOCF

ANCOVA=analysis of covariance; BOCF=Baseline Observation Carried Forward; CMH=Cochran-Mantel-Haenszel; 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.

[a] The Miettinen and Nurminen method with CMH weights will be stratified by screening HIV-1 RNA level (≤100,000 copies/mL, >100,000 copies/mL) and screening CD4+ T-cell count (<200 cells/mm^3, ≥200 cells/mm^3) [Miettinen, O. and Nurminen, M. 1985].

[b] 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. For analyses of safety by time point, the same analysis windows as specified in Table 7 will be used, unless otherwise specified.

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. Adverse events (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” endpoints 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 with 2-sided nominal 95% confidence intervals provided for between-treatment differences in the percentage of participants with

events via the unstratified 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 nondrug-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 of DOR/ISL on weight compared to that of BIC/FTC/TAF at Weeks 48 and 96, the treatment difference in the change from baseline will be estimated between the treatment groups using ANCOVA models adjusted by baseline weight, sex at birth, race, stratum, and treatment group. Superiority of DOR/ISL to BIC/FTC/TAF will be concluded if the upper bound of the 2-sided multiplicity-adjusted 95% CI for the estimate of the treatment group difference (DOR/ISL minus BIC/FTC/TAF) 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 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters. Safety endpoints collected after Week 144 for participants who choose to continue their assigned study intervention during the open-label study extension (up to Week 168) are considered Tier 3 events.

For continuous measures such as change from baseline in laboratory and vital signs parameters that are not pre-specified 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 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.

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: one or more AE(s); drug-related AE(s), serious AE(s), Grade 3 to 4 AE(s), AE(s) which are both drug-related and serious, AE(s) which are both Grade 3 to 4 and drug-related, AE(s) [drug-related and nondrug-related] leading to discontinuation of study intervention, and AE(s) leading to death • 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 in select laboratory and radiological markers of fasting lipid profiles, renal function, inflammation, and body composition[a] • Change from baseline to Weeks 48, 96, and 144 in body weight[a,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; SAE=serious adverse event; SOC=System Organ Class.

[a] For participants who become pregnant, data collected after the estimated date of conception will be excluded.

[b] 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.

[c] Includes only those endpoints not already pre-specified 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 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 any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites until Week 96.

An external Data Monitoring Committee 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 interim analyses will be documented by the external unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Once participants in the Sentinel Cohort (defined in Section 9.5.1.1) have completed the Week 24 visit, an interim analysis (referred to as the "Sentinel Cohort Week 24 interim analysis") will be conducted by the external unblinded statistician and reviewed by the eDMC. All available efficacy and safety data for all participants enrolled by that time will be reviewed at this interim analysis. Additionally, a futility assessment will be performed based on the Sentinel Cohort data. Due to potential differences in the viral decline profiles of the compounds under study, the futility assessment will be based only on participants who receive DOR/ISL. If 7 or more participants (out of 30 enrolled and evaluable Group 1 participants in the Sentinel Cohort) fail to achieve HIV-1 RNA <200 copies/mL at Week 24, the eDMC may recommend the study be stopped; the eDMC will review the totality of the available data at the time of the Sentinel Cohort Week 24 interim analysis before making such a recommendation.

The endpoint of <200 copies/mL for the futility assessment was selected in recognition that the time profile for viral suppression to <50 copies/mL may differ between the treatment groups and that participants with high viral loads at baseline (eg, >50,000 copies/mL) may be enrolled in the study. Such participants may not be able to achieve suppression to <50 copies/mL (the primary efficacy endpoint) by the Week 24 time point, but achieving an HIV-1 RNA level <200 copies/mL by Week 24 is clinically meaningful as it indicates that participants have declining viral loads.

A possibility exists that unblinded data from the Sentinel Cohort Week 24 interim analysis may ultimately be submitted to regulatory authorities prior to the Week 48 database lock when the Sponsor becomes unblinded to all participants' study intervention assignments. In that event, 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 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 team at the Sponsor.

The eDMC will also be convened in the event that the listed efficacy criteria for either the Sentinel Cohort prior to completion of the Sentinel Cohort Week 24 interim analysis or for the complete study population after enrollment of the Sentinel Cohort are met, as assessed by the external unblinded statistician (see Section 4.1 for the listed efficacy criteria).

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 interim data summary may be conducted to support any potential marketing authorization application of DOR/ISL. In such an event, efficacy and/or safety summaries will be prepared by the Sponsor.

An analysis will be conducted to test the primary noninferiority efficacy hypothesis once all participants have completed the Week 48 visit assessments. This will be the formal evaluation of the primary noninferiority efficacy hypothesis, and the Sponsor will become unblinded to all participants' study intervention assignments 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.

Treatment-level results from all unblinded 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 deviations, or data validation efforts.

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 Sentinel Cohort Week 24 interim analysis data) may be presented prior to the evaluation of the primary noninferiority efficacy hypothesis at Week 48. If further eDMC reviews occur between the evaluation of the primary noninferiority 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 noninferiority 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 noninferiority 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 1% 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 1.5% 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 $\alpha_1^* + \alpha_2^* \leq 1\% + 1.5\% = 2.5\%$ [Maurer, W., et al 2011].

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power Calculations for Efficacy Analyses

The probability of passing the futility assessment based on the Week 24 Sentinel Cohort data and the overall study power to demonstrate noninferiority at Week 48 under a variety of assumptions is presented in Table 10.

The power calculations shown in Table 10 incorporate the futility assessment stopping rule based on a continuation of the study if at least 24 participants (out of 30 enrolled and evaluable Group 1 participants in the Sentinel Cohort) achieve HIV-1 RNA <200 copies/mL at Week 24. Given the threshold of 24 out of 30, there is a high probability the study will continue if the rate of HIV-1 RNA <200 copies/mL at Week 24 is high (eg, with a rate of 90%, the estimated probability of continuing the study is 97.7%—see "Baseline Case" in Table 10). Conversely, if the rate of HIV-1 RNA <200 copies/mL at Week 24 is low, then the probability of continuing the study is low given the threshold of 24 out of 30 participants (eg, with a rate of 70%, the estimated probability of continuing the study is 15.6%—see "Low Efficacy Case" in Table 10).

The "Baseline Case" summarized in Table 10 is the most likely scenario. In this case, the rate of participants in Group 1 in the Sentinel Cohort with Week 24 HIV-1 RNA <200 copies/mL is assumed to be 90%, and the rate of participants in both Group 1 and Group 2 with Week 48 HIV-1 RNA <50 copies/mL is assumed to be 82%. Under these assumptions, there is a 97.7% chance of continuing the study after the futility assessment and a 90% chance of declaring noninferiority between groups at Week 48.

Table 10 Summary of Assumptions and Overall Study Power Assuming 60 Participants in the Sentinel Cohort and 680 Participants Overall

Parameter	Baseline Case	More Conservative Case	Less Conservative Case	Low Efficacy Case	High Efficacy Case
Assumptions[a]					
% with Week 24 HIV-1 RNA <200 copies/mL	90%	88%	93%	70%	93%
% with Week 48 HIV-1 RNA <50 copies/mL if Week 24 HIV-1 RNA <200 copies/mL	90%	90%	93%	90%	93%
% with Week 48 HIV-1 RNA <50 copies/mL if Week 24 HIV-1 RNA ≥200 copies/mL	10%	6.67%	7.29%	66.67%	50.14%
% with Week 48 HIV-1 RNA <50 copies/mL (Group 1)	82%	80%	87%	83%	90%
% with Week 48 HIV-1 RNA <50 copies/mL (Group 2)	82%	80%	87%	83%	90%
Study Power					
Probability of Passing Futility Assessment[b]	97.73%	94.32%	99.72%	15.55%	99.72%
Overall Study Power to Establish Noninferiority at Week 48[c]	90.01%	84.99%	96.91%	14.69%	98.73%

HIV=human immunodeficiency virus; RNA=ribonucleic acid.

[a] Assumptions for calculating power are based on experience with MK-1439A Protocol 018 and Protocol 020 and MK-8591 Protocol 011. Specifically, pooled results for MK-1439A in a TN population showed a rate <200 copies/mL at Week 24 of 90.6%, a rate <50 copies/mL at Week 48 among those with <200 copies/mL at Week 24 of 92%, a rate <50 copies/mL at Week 48 among those with ≥200 copies/mL at Week 24 of 7.1%, and an overall rate of <50 copies/mL at Week 48 of 84.1%.

[b] The cutoff for futility is 7 participants, ie, if 7 or more participants (out of 30 enrolled and evaluable Group 1 participants in the Sentinel Cohort) are observed to have HIV-1 RNA ≥200 copies/mL at Week 24, the study may be stopped. Values presented are based on simulation. The corresponding exact values based on the binomial distribution are 97.42%, 93.94%, 99.60%, 15.95%, and 99.60% for the Baseline Case, More Conservative Case, Less Conservative Case, Low Efficacy Case, and High Efficacy Case, respectively.

[c] Calculated via simulation to evaluate first whether the futility criteria were met and if not, evaluate noninferiority between groups using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. Noninferiority margin was 10 percentage points and Type 1 error was 0.02495 (1-sided).

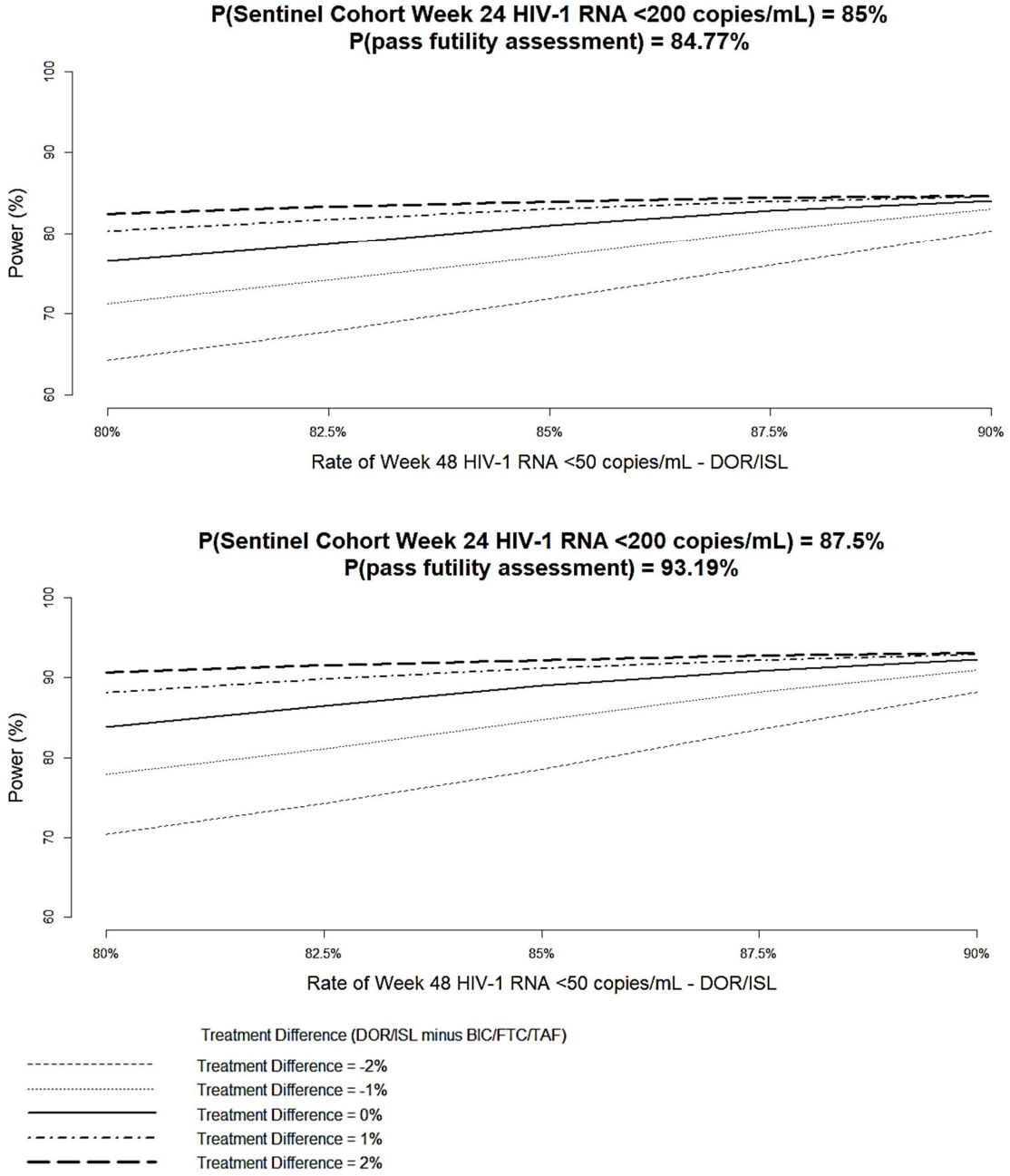
To supplement the cases presented in Table 10, Figure 2 displays the estimated power to declare noninferiority of DOR/ISL to BIC/FTC/TAF at Week 48 under a broader range of potential scenarios. All scenarios in Figure 2 assume 30 enrolled and evaluable participants in Group 1 in the Sentinel Cohort with a cutoff for futility of 7 (ie, the underlying simulation assumes that the study is stopped at the Sentinel Cohort Week 24 interim analysis if 7 or more participants in Group 1 in the Sentinel Cohort fail to achieve HIV-1 RNA <200 copies/mL at Week 24), 340 participants each in Group 1 and Group 2, a 1-sided Type 1 error of 0.02495, and a noninferiority margin of 10%. The power achieved for each scenario was estimated using 10,000 simulations.

To generate the graphs, the percentage of participants with Week 48 HIV-1 RNA <50 copies/mL in the DOR/ISL group was assumed to be 80%, 82.5%, 85%, 87.5%, or 90%, as indicated on the x-axis. For each of these quantities, the corresponding percentage of participants with Week 48 HIV-1 RNA <50 copies/mL in the BIC/FTC/TAF group ranges between ±2% the value assumed in the DOR/ISL group (in increments of 1%). For example, when the percentage of participants with Week 48 HIV-1 RNA <50 copies/mL in the DOR/ISL group is assumed to be 80%, power is estimated for the 5 cases in which the percentage of participants with Week 48 HIV-1 RNA <50 copies/mL in the BIC/FTC/TAF group is 78%, 79%, 80%, 81%, and 82%. Additionally, for each scenario the rate of HIV-1 RNA <50 copies/mL at Week 48 in Group 1 for participants who achieved HIV-1 RNA <200 copies/mL at Week 24 is assumed to be 5 percent greater than the overall rate of HIV-1 RNA <50 copies/mL at Week 48 in Group 1 (ie, for Group 1, P[<50 copies/mL at Week 48|<200 copies/mL at Week 24] = P[<50 copies/mL at Week 48] + 0.05). The value of 5 percent was selected for illustrative purposes only and, as such, is not representative of all possible cases that could be produced via the simulation. Each of the 4 graphs in Figure 2 assumes a distinct value for the percentage of participants in Group 1 in the Sentinel Cohort with HIV-1 RNA <200 copies/mL at Week 24 (values displayed are for 85%, 87.5%, 90%, and 92.5%), as indicated in the panel titles; these percentages correspond to estimated probabilities of passing the futility assessment of 84.77%, 93.19%, 97.73%, and 99.56%, respectively.

The legend at the bottom of Figure 2 indicates the difference in the percentage of participants with Week 48 HIV-1 RNA <50 copies/mL in terms of DOR/ISL minus BIC/FTC/TAF (eg, a treatment difference of 2% in the legend indicates that the percentage of participants with Week 48 HIV-1 RNA <50 copies/mL is 2% higher in the DOR/ISL group than the BIC/FTC/TAF group).

To illustrate the use of Figure 2, consider the first panel where the probability of having HIV-1 RNA <200 copies/mL at Week 24 in Group 1 in the Sentinel Cohort is 85%. When the probability of HIV-1 RNA <50 copies/mL at Week 48 in the DOR/ISL group is 90% and the probability of HIV-1 RNA <50 copies/mL at Week 48 in the BIC/FTC/TAF group is 88% (corresponding to a treatment difference of DOR/ISL minus BIC/FTC/TAF equal to 2%), the estimated power to declare DOR/ISL noninferior to BIC/FTC/TAF is approximately 84.7%; this value is comprised of 1) an 84.77% chance of passing the futility assessment as a result of the assumption that 85% of participants in Group 1 in the Sentinel Cohort would have Week 24 HIV-1 RNA <200 copies/mL, and 2) a 99.93% chance that, having passed the futility assessment, noninferiority would be concluded at Week 48, driven by the assumed 2% treatment difference [DOR/ISL=90% minus BIC/FTC/TAF=88%] in the percentage of participants with Week 48 HIV-1 RNA <50 copies/mL.

Figure 2 Estimated Power to Declare Noninferiority of DOR/ISL to BIC/FTC/TAF at Week 48 Assuming 30 Enrolled and Evaluable Participants in Group 1 in the Sentinel Cohort and 680 Participants Overall



(Figure Continued on Next Page)

Figure 2 Continued Estimated Power to Declare Noninferiority of DOR/ISL to BIC/FTC/TAF at Week 48 Assuming 30 Enrolled and Evaluable Participants in Group 1 in the Sentinel Cohort and 680 Participants Overall

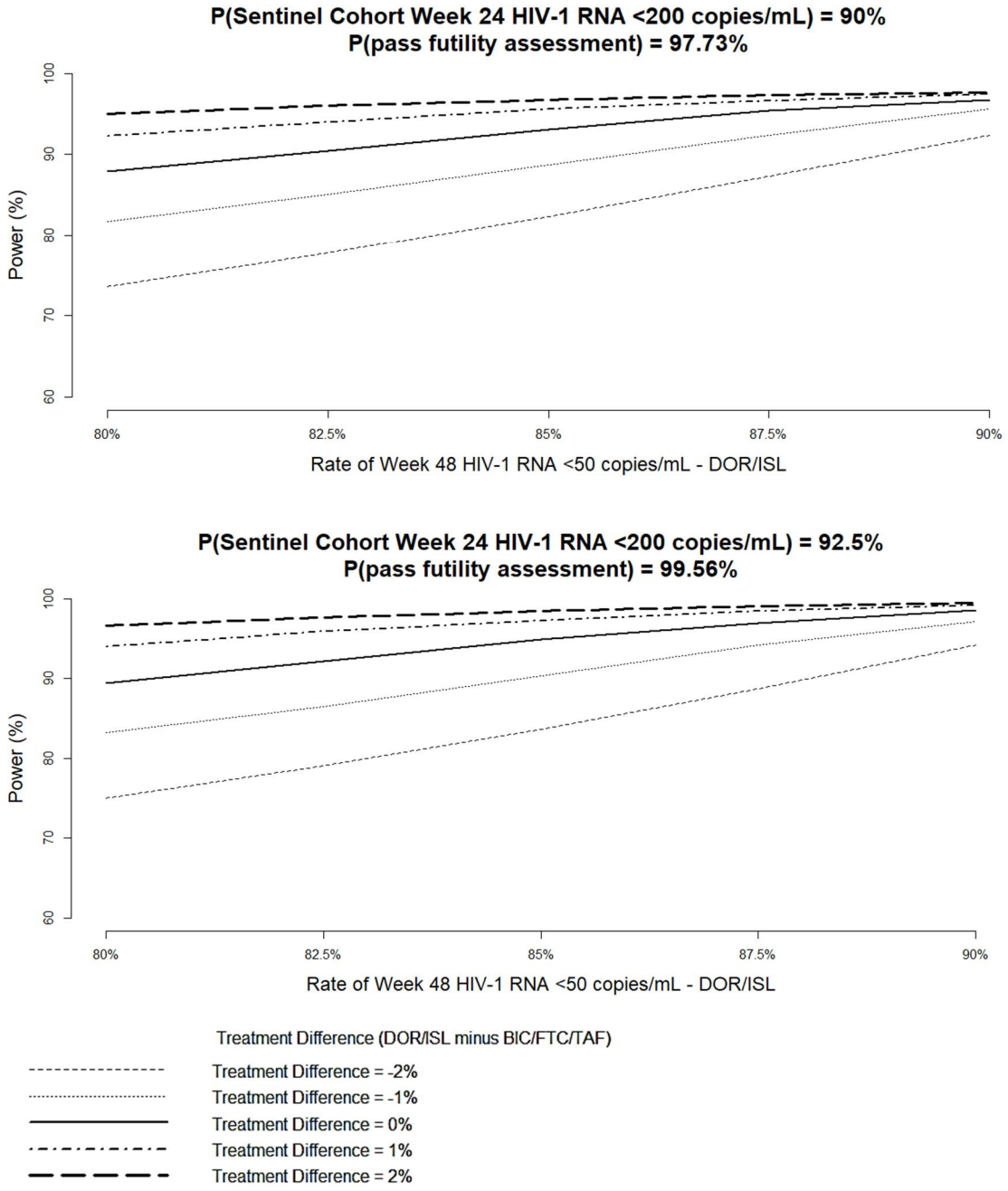


Table 11 summarizes the power to declare DOR/ISL superior to BIC/FTC/TAF with regard to the percentage of participants with HIV-1 RNA <50 copies/mL at Week 48/96 under various assumptions for the response rate in each treatment group. For example, if the

percentage of participants with Week 48/96 HIV-1 RNA <50 copies/mL is assumed to be 96% in the DOR/ISL group and 90% in the BIC/FTC/TAF group, then this study will have approximately 88.5% power to declare DOR/ISL superior to BIC/FTC/TAF at Week 48/96.

Table 11 Power to Establish Superiority at Week 48/96 Under Various Response Rate Assumptions (Assuming All Prior Hypothesis Tests Reach Statistical Significance) (340 Participants Per Group)

Group 1: True Rate of HIV-1 RNA <50 copies/mL at Week 48/96	Group 2: True Rate of HIV-1 RNA <50 copies/mL at Week 48/96	Probability of Demonstrating Superiority at Week 48/96
92%	90%	14.56%
94%	90%	49.21%
96%	90%	88.45%
87%	85%	11.17%
90%	85%	50.98%
93%	85%	92.54%

CI=confidence interval; eDMC=external Data Monitoring Committee; HIV=human immunodeficiency virus.

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

Note: To establish superiority, the lower bound of the 2-sided multiplicity-adjusted 95% CI must be greater than 0 percentage points for Group 1 minus Group 2. The 95% CI used for the power calculations is based on the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], and power was estimated via 10,000 simulations for each scenario. 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.

Table 12 summarizes the power to declare DOR/ISL noninferior to BIC/FTC/TAF with regard to the percentage of participants with HIV-1 RNA <50 copies/mL at Week 96 under various assumptions for the response rate in Group 2 and the underlying difference in response rates between treatment groups. For example, if the true rate of HIV-1 RNA <50 copies/mL in the BIC/FTC/TAF group at Week 96 is 90% and the true rate in the DOR/ISL group is 91% (ie, a true difference in response rates of 1%), then this study has approximately 99.8% power to declare DOR/ISL noninferior to BIC/FTC/TAF at Week 96. If the true rate of HIV-1 RNA <50 copies/mL at Week 96 is 80% in both treatment groups, then this study has approximately 90.1% power to declare DOR/ISL noninferior to BIC/FTC/TAF at Week 96.

Table 12 Power to Establish Noninferiority at Week 96 Under Various Response Rate Assumptions (340 Participants per Group)

Group 2: True Rate of HIV-1 RNA <50 copies/mL at Week 96	True Difference in Week 96 Response Rates (Group 1 Minus Group 2)				
	2%	1%	0%	-1%	-2%
90%	99.97%	99.76%	99.05%	96.54%	90.50%
85%	99.38%	98.04%	95.09%	89.09%	80.63%
80%	97.90%	94.87%	90.12%	82.25%	72.45%
75%	95.41%	91.16%	85.16%	76.55%	66.15%
70%	92.83%	88.35%	81.32%	72.13%	61.44%

CI=confidence interval; eDMC=external Data Monitoring Committee; HIV=human immunodeficiency virus.

Note: Noninferiority margin=10%. To establish noninferiority, the lower bound of the 2-sided multiplicity-adjusted 95% CI must be greater than -10 percentage points for Group 1 minus Group 2. The 95% CI used for the power calculations is based on the unstratified Miettinen & Nurminen method [Miettinen, O. and Nurminen, M. 1985]. The 1-sided Type 1 error is 0.02493, which adjusts for an assumed 7 eDMC reports between Day 1 and Week 96 (5 reports assumed between Day 1 and Week 48 and 2 reports assumed between Week 48 and Week 96). Power was assessed 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 96.7% chance of observing at least 1 AE among 340 participants in a treatment group. If no AE of that type is observed among the 340 participants in a treatment group, this study will provide 97.5% confidence that the underlying percentage of participants with that particular AE is <1.08% (1 out of every 92 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 numbers 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 (340 Participants Per Group)

Hypothetical Number of Participants with Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
0	0.0%	0.9%
5	1.5%	3.4%
10	2.9%	5.3%
15	4.4%	7.2%
20	5.9%	8.9%
25	7.4%	10.7%
30	8.8%	12.4%

AE=adverse event; CI=confidence interval.

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

Table 14 gives the difference in the incidence of an AE (DOR/ISL minus BIC/FTC/TAF) that can be ruled out with different power levels and 95% confidence when there are 340 participants in each group. The underlying incidence of the AE is assumed to be the same for the two 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 9.2 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 340 Participants in Each Group

Target Power	Underlying AE Incidence Rate						
	1%	5%	10%	20%	30%	40%	50%
80%	3.5	5.8	7.4	9.2	10.2	10.7	10.7
85%	3.9	6.3	7.9	9.9	11.0	11.4	11.4
90%	4.3	6.9	8.7	10.8	11.9	12.4	12.3
95%	5.1	7.8	9.8	12.1	13.3	13.7	13.6

AE=adverse event; CI=confidence interval.

Note: Values represent 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 the DOR/ISL and BIC/FTC/TAF treatment groups 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 272, then this study will provide 90% power to detect a difference at least as large as 2.37 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 $\alpha_1^* = 0.00995$			
Power	n = 295 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	4 kg	5 kg	6 kg
80%	1.05	1.31	1.57
85%	1.11	1.39	1.67
90%	1.19	1.49	1.79
If Week 48 Hypothesis (H5) is Rejected, Week 96 Hypothesis (H6) is Tested at $\alpha_1^*+\alpha_2^* = 0.02493$			
Power	n = 272 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	8 kg	10 kg	12 kg
80%	1.93	2.41	2.89
85%	2.06	2.57	3.09
90%	2.23	2.79	3.34

If Week 48 Hypothesis (H5) is Retained, Week 96 Hypothesis (H6) is Tested at $\alpha_2^* = 0.01498$			
Power	n = 272 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%	2.20	2.76	3.31
90%	2.37	2.97	3.56
If Week 48 Hypothesis (H5) is Retained and Week 96 Hypothesis (H6) is Rejected, Week 48 Hypothesis (H5) is Retested at $\alpha_2^* = 0.01498$			
Power	n = 295 Participants per Group[a]		
	Standard Deviation of Change in Weight From Baseline[b]		
	4 kg	5 kg	6 kg
80%	0.99	1.24	1.49
85%	1.06	1.32	1.59
90%	1.14	1.42	1.71

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 13% at Week 48 and 20% at Week 96 was assumed in the calculations based on data from MK-1439A-021. As such, the number of participants per group is assumed to be 295 at Week 48 and 272 at Week 96.

[b] Values of the standard deviation of change in weight from baseline are based on experience with MK-8591 Protocol 011. 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^*=1% 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^*=1.5% 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 unadjusted for stratification factors) for the primary endpoint of HIV-1 RNA <50 copies/mL and the secondary endpoint of HIV-1 RNA <40 copies/mL (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)
- Baseline CD4+ T-cell count category (<200 cells/mm^3, ≥200 cells/mm^3)
- Screening HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL)
- Baseline HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL)
- Baseline HIV-1 RNA (≤500,000 copies/mL, >500,000 copies/mL)
- HIV-1 subtype

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.

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

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

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and 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 and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. 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, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

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.
- Any laboratory tests related to study endpoints (eg, HIV-1 RNA and CD4+ T-cell enumeration) must be performed by the central laboratory.
- 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

Laboratory Assessments	**Parameters**
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit RBC Indices: • MCV • MCH • MCH Concentration • Red Cell Distribution Width (RDW) WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils

Laboratory Assessments	Parameters
CD4+ T-cell count/TBNK panel	T-cell, B-cell, and natural killer cell profile that includes but is not limited to the following: CD3+ Percent CD3+ Value/Absolute Count CD3+CD4+ Percent CD3+CD4+ Value/Absolute Count CD3+CD8+ Percent CD3+CD8+ Value/Absolute Count CD3-CD19+ Percent CD3-CD19+ Value/Absolute Count CD16+CD56+ Percent CD16+CD56+ Value/Absolute Count CD3+CD4+CD8+ Percent CD3+CD4+CD8+ Value/Absolute Count CD4/CD8 Ratio
Coagulation	Prothrombin Time/INR
Chemistry (nonfasting)	Alanine Aminotransferase (ALT) Albumin Alkaline Phosphatase Amylase Aspartate Aminotransferase (AST) Bicarbonate Blood Urea Nitrogen (BUN) Calcium Chloride Creatine Kinase Creatinine Creatinine Clearance eGFR (by MDRD calculation) Glucose (nonfasting) Lipase Magnesium Phosphorous Potassium Sodium Total Bilirubin • Direct Bilirubin • Indirect Bilirubin Total Protein

Laboratory Assessments	Parameters
Additional Chemistry at Fasting Visits (fasting for at least 8 hours)	Glucose (fasting) High-Density Lipoprotein Cholesterol (HDL-C) Low-Density Lipoprotein Cholesterol (LDL-C) Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Total Cholesterol (TC) Triglycerides (TGs) Insulin a HOMA-IR (calculation)
Routine Urinalysis	Blood Bilirubin Glucose Ketones Leukocytes Nitrite pH Protein Specific Gravity Urobilinogen
Pregnancy Testing	Serum human chorionic gonadotropin (hCG) test (as needed for WOCBP) Urine human chorionic gonadotropin (hCG) test (as needed for WOCBP)
Blood for Renal Biomarkers	Cystatin – C
Urine for Renal Biomarkers	Albumin Protein Beta-2-microglobulin/creatinine ratio (B-2 M/Cr) Retinol Binding Protein/creatinine ratio (RBP/Cr)
Hepatitis Serology	Hepatitis B Virus Surface Antigen Hepatitis B Virus Surface Antibody Anti-HBc HBV DNA Hepatitis C Antibody (if positive perform plasma Hepatitis C Virus quantitative test)
HIV-1 and HIV-2 Serology	HIV-1 and HIV-2 Antibody Test HIV Confirmation
Virology	HIV-1 Viral RNA Quantification (Real-time PCR) HIV-1 Drug Resistance
Inflammatory Markers	D-dimer hs-CRP IL-6 Soluble CD163

Laboratory Assessments	Parameters
PK	ISL PK
Blood for Genetic Analysis	
Whole Blood for FBR	
Blood (plasma) for backup HIV-1 Drug Resistance testing as needed	
Blood (plasma) for investigational ISL PK testing as needed	
[a] Participants with diabetes mellitus (type 1 or type 2) or insulin resistance are not required to have the blood draw for insulin testing.	

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

Table 17 summarizes the blood volumes collected for laboratory assessments.

Table 17 Blood Volumes

Study Period	**Screening**	**Group 1 and Group 2**																	**Viremia Confir-mation**	**CD4+ T-cell /Lymphocyte Confirmation**	**Early Discon of Treatment**	**CD4+ T-cell /Lymphocyte Monitoring[e]**	**End of Treatment Follow-up**
Scheduled Day/Week	Screening	Day 1	Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	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		6
CD4+ T-cell Count/TBNK Panel	6	6		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		6	6	6	6[f]
Blood (Plasma) for HIV-1 Drug Resistance	6																		12		12[c]		12
Blood (Plasma) for HIV-1 Drug Resistance – Backup	6	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12		12		12
HIV Serology and Hepatitis Serology[a]	6																						
HIV Confirmation	1																						
HBV DNA	6																						
Plasma Hepatitis C Virus PCR Quantitative Test (only performed if antibody positive)	6																						

Study Period	**Screening**	**Group 1 and Group 2**																	**Viremia Confir-mation**	**CD4+ T-cell /Lymphocyte Confirmation**	**Early Discon of Treatment**	**CD4+ T-cell /Lymphocyte Monitoring[e]**	**End of Treatment Follow-up**
Scheduled Day/Week	Screening	Day 1	Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter			**Approximate Blood Volume (mL)**																				
Serum Pregnancy (hCG; WOCBP only)																					2		2
Chemistry (includes Serum Pregnancy at Screening)	6	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	2[g]
PT/INR	2.7																						
Blood (Plasma) for ISL PK		4	8	4	4	4		4															
Blood (Plasma) for Investigational ISL PK							4		4	4	4	4				4			4		4		4
Blood (Plasma) for DOR and ISL PK in Pregnant Women Only			<----------X[b]---------->																				
Blood for Genetic Analysis		8.5																					
Whole Blood for FBR		8				8		8				8				8			8		8[c]		
Inflammatory Markers		7.7				7.7		7.7				7.7				7.7							
Cystatin-C		2				2		2				2				2							

Study Period	**Screening**	**Group 1 and Group 2**																	**Viremia Confir-mation**	**CD4+ T-cell /Lymphocyte Confirmation**	**Early Discon of Treatment**	**CD4+ T-cell /Lymphocyte Monitoring[e]**	**End of Treatment Follow-up**
Scheduled Day/Week	Screening	Day 1	Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Unscheduled	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Blood Parameter		**Approximate Blood Volume (mL)**																					
Fasting Insulin[d]		1				1		1				1		1		1							
Total Blood Volume per Visit	53.7	63.2	34	36	36	54.7	36	54.7	36	36	36	54.7	36	37	36	58.7	36	36	42	8	58	12	44

hCG=human chorionic gonadotropin; FBR=future biomedical research; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV-1=human immunodeficiency virus; HIV-1=human immunodeficiency virus type 1; INR=international normalized ratio; PCR=polymerase chain reaction; PK=pharmacokinetic; PT=prothrombin time; RNA=ribonucleic acid; TBNK=T and B lymphocyte and natural killer cells; WOCBP= woman/women of childbearing potential.

[a] At screening visit, HIV-1 and HIV-2 screen, and HBV and HCV testing are performed from same 6 mL sample, with the exception of HBV DNA testing, which requires a separate sample. Plasma hepatitis C virus PCR quantitative test (performed if hepatitis C virus antibody is positive) requires 6 mL of whole blood.

[b] 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.

[c] If sample is collected at Viremia Confirmation visit, it is not necessary to collect another sample at the Early Discontinuation of Treatment visit.

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

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

[f] CD4+ T-cell count and hematology samples to be collected only for participants with specified decreases in CD4+ T-cell counts and/or absolute lymphocyte counts per Section 1.3.5.

The assessments in Table 18 are for any participant who is pregnant at the last scheduled study visit (ie, Week 168) and whose visit schedule will be extended through the duration of the pregnancy, to allow assessments through each trimester and postpartum.

Table 18 Blood Volumes: Participants Whose Pregnancy or Postpartum Visit(s) Extends Beyond Week 168

Visit Number	**Unscheduled**			
Scheduled Week	**Pregnancy 1 (Week 180)**	**Pregnancy 2 (Week 192)**	**Pregnancy 3 (Week 204)**	**Pregnancy 4 (Week 216)**
Blood Parameter	**Approximate Blood Volume (mL)**			
Plasma HIV-1 RNA Quantification (Real-Time PCR)	6	6	6	6
CD4+ T-cell Count/TBNK Panel	6	6	6	6
Plasma for HIV Viral Drug Resistance Testing	15	15	15	15
Chemistry	6	6	6	6
Hematology	2	2	2	2
Blood (Plasma) for DOR and ISL PK	----------X[a]----------			
Whole Blood for FBR	8	8	8	8
Approximate Blood Volume per Visit (mL)[a]	55	55	55	55

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; TBNK=T and B lymphocyte and natural killer cells.

[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 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

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

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

- NOTE: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, 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.

10.3.3 Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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.

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

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

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

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

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

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

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

    - Grade 5 Death: Deaths related to an AE.

Assessment of causality

- Did the study intervention cause the AE?

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

- **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:

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

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

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

- **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

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

- Rechallenge: Was the participant re-exposed to the study intervention in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

- The assessment of relationship will be reported on the 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the 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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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,d] • IUS[c, d, e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - 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[3, 4]

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

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

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

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

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link 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[3, 4]

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[3, 4]

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

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

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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[3, 4]

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

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

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

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

10. Future Biomedical Research Study Population[3, 4]

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

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Request for Germany

Participants that enroll in Germany will not have DEXA scans as indicated in the SoA. This procedure will be omitted, and participants in Germany will not be included in the applicable analyses.

10.7.2 Country-specific Request for Japan

BIC/FTC/TAF taken by participants in Group 2 is not categorized as “product(s) used in the clinical trial” in Japan.

10.8 Appendix 8: Calculation of Creatinine Clearance and eGFR

Cockcroft-Gault equations

- If male:

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

- If female:

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

Modification of Diet in Renal Disease Study (MDRD) equation

$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ [if female] x 1.212 [if African American]

- Note:eGFR = estimated glomerular filtration rate
- SCr = standardized serum creatinine
- age = years

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
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
BICR	blinded independent central review
BMD	bone mineral density
BMI	body mass index
BOCF	baseline observation carried forward
bp	blood pressure
C_{24}	concentration after 24 hours
CD4+	CD4-positive
cART	combination antiretroviral therapy
CI	confidence interval
C_{max}	maximum (peak) observed drug concentration
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CrCL	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
C_{trough}	lowest concentration reached by a drug before the next dose is administered
CYP3A	CYP3A=cytochrome P450 3A
DAIDS	The Division of AIDS
DAO	Data-As-Observed
DDI	drug-drug interaction
DEXA	dual-energy X-ray absorptiometry
DHHS	Department of Health and Human Services
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	doravirine
DTG	dolutegravir
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EQ-5D-5L	EuroQol Five-Dimensional descriptive system, five level version
EU	European Union

Abbreviation	Expanded Term
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
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
hCG	human chorionic gonadotropin
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV SDM	Human Immunodeficiency Virus Symptom Distress Module
HIV-SI	Human Immunodeficiency Virus Symptom Index
HOMA-IR	homeostatic model assessment-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
IC_{50}	concentration of drug needed to inhibit 50% of viral growth
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL-6	interleukin-6
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
InSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISL	islatravir
IUD	intrauterine device
LDL-C	low-density lipoprotein cholesterol
LNG/EE	levonorgestrel/ethinyl estradiol
LOCF	last observation carried forward
M=F	missing equal to failure
M&N	Miettinen and Nurminen
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
NA	not applicable
NIMP	Non-Investigational Medicinal Product
NK	Natural killer
NNRTI	non-nucleoside reverse transcriptase inhibitor

Abbreviation	Expanded Term
Non-HDL-C	non-high-density lipoprotein cholesterol
NRTI	nucleoside analog reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
OF	Observed Failure
P	primary approach
PCL	protocol clarification letter
PCR	polymerase chain reaction
PDLC	predefined limit of change
PEP	postexposure prophylaxis
PI	protease inhibitor
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per-Protocol
PrEP	pre-exposure prophylaxis
PRO	patient-reported outcomes
PT	prothrombin time
QD	once-daily
QM	once-monthly
QW	once-weekly
RAP	Resistance Analysis Population
RNA	ribonucleic acid
rr	respiratory rate
S	supportive approach
SAC	Scientific Advisory Committee
SAE	serious adverse event
sCD-163	soluble CD-163
SCr	standardized serum creatinine
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 cells
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
temp	body temperature
TG	triglycerides
TLOVR	Time to Loss of Virologic Response
TN	treatment-naïve
TP	triphosphate
ULN	upper limit of normal
US	United States
WOCBP	woman/women of childbearing potential
WONCBP	Woman/women of nonchildbearing potential

10.10 Appendix 10: Summary of Protocol Clarification Letters

Protocol	PCL date	Correction not implemented in a subsequent amendment	Impact
P020	16-JUN-2021	Added a reference to Appendix 3: DAIDS criteria for the assessment of AEs that are pregnancy-related complications. DAIDS table version 2.1 "Addendum 1: Female Genital Grading Table for Use in Microbicide Studies", particularly the section "Complications of Pregnancy" (found on pages 11-12 of the Addendum): https://rsc.niaid.nih.gov/sites/default/files/addendum-1-female-genital-grading-table-v1-nov-2007.pdf	Study conduct, assessment of AEs, 1 pregnant participant with a due date that occurred prior to the approval of the protocol amendment
P020	05-DEC-2022	Japan Specific: Removed text in Section 10.7.2 Country-specific Request for Japan: BIC/FTC/TAF taken by participants in Group 2 was not categorized as "product(s) used in the clinical trial" in Japan.	None
P020	22-FEB-2023[a]	Transition 0.75 to 0.25 PCL, Transition from 0.75 to 0.25 mg: Informed sites that additional guidance documents will be provided to assist in transitioning participants to either the new studies or discontinuation from the current study.	Study conduct

AE=adverse event; BIC/FTC/TAF=bictegravir/emtricitabine/tenofovir alafenamide; DAIDS=Division of Acquired Immunodeficiency Syndrome; PCL=protocol clarification letter.

[a] Not issued as a PCL but as a memo to sites.

11 REFERENCES

[AIDS info 2017]	AIDS info. Guidelines for the use of antiretroviral agents in HIV-1-Infected adults and adolescents [Internet]. Rockville, MD: AIDS info; 2017. Available from: http://aidsinfo.nih.gov/guidelines.	[04LV4N]
[Baker, J. V., et al 2011]	Baker JV, Neuhaus J, Duprez D, Kuller LH, Tracy R, Belloso WH, De Wit S. et al. Changes in inflammatory and coagulation biomarkers: a randomized comparison of immediate versus deferred antiretroviral therapy in patients with HIV infection. J Acquir Immune Defic Syndr. 2011 Jan 1;56(1):36-43.	[04MWL0]
[Burger, D., et al 2005]	Burger D, van der Heiden I, la Porte C, van der Ende M, Groeneveld P, Richter C, et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol. 2005;61(2):148-54.	[057GSX]
[Cahn, P., et al 2019]	Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019 Jan 12;393:143-55.	[054KXQ]
[Carr, A., et al 1998]	Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998;12(7):F51-F58.	[03Q6RY]
[Centers for Disease Control (CDC) 1992]	Centers for Disease Control (CDC). 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(RR-17):1-17.	[03RH6J]

[Centers for Disease Control and Prevention 2019]	Centers for Disease Control and Prevention. HIV and transgender communities. Atlanta (GA): U.S. Department of Health and Human Services (HHS); 2019 Apr; 4 p.	[05BCMG]
[Charpentier, C., et al 2014]	Charpentier C, Choquet M, Joly V, Yeni P, Visseaux B, Caseris M, et al. Virological outcome at week 48 of three recommended first-line regimens using ultrasensitive viral load and plasma drug assay. J Antimicrob Chemother. 2014 Oct;69(10):2819-25.	[04PYMQ]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[00V5VX]
[Department of HIV/AIDS 2015]	Department of HIV/AIDS. Transgender people and HIV. Geneva (Switzerland): World Health Organization (WHO); 2015 Jul. 32 p.	[05BDGP]
[European AIDS Clinical Society 2016]	European AIDS Clinical Society (EACS). Guidelines - Version 8.1 October 2016 [Internet]. Brussels, Belgium; 2016. Available from: http://www.eacsociety.org/files/guidelines_8.1-english.pdf.	[04MN4Z]
[Food and Drug Administration (CDER) 2015]	Food and Drug Administration (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry [Internet]. Silver Spring, MD: U.S. Department of Health and Human Services; 2015. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf.	[04MT4V]
[Hill, A., et al 2019]	Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad. 2019;5:41-3.	[058G5N]

[Knudsen, T. B., et al 2016]	Knudsen TB, Ertner G, Petersen J, Moller HJ, Moestrup SK, Eugen-Olsen J. et al. Plasma Soluble CD163 Level Independently Predicts All-Cause Mortality in HIV-1-Infected Individuals. J Infect Dis. 2016 Oct 15;214(8):1198-204.	[04MWL7]
[Llibre, J. M., et al 2018]	Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. 2018 Mar 3;391:839-49. Erratum in: Lancet. 2018 Feb 1.	[0528SS]
[Maurer, W., et al 2011]	Maurer W, Glimm E, Bretz F. Multiple and repeated testing of primary, coprimary, and secondary hypotheses. Stat Biopharm Res. 2011;3(2):336-52.	[045MYM]
[Michailidis E 2014]	Michailidis E, et al. 4-Ethynyl-2-fluoro-2-deoxyadenosine (EFdA) Inhibits HIV-1 Reverse Transcriptase with Multiple Mechanisms. J Biol Chem 2014; 289(35):24533-24548.	[04PXGP]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Statist Med 1985;4:213-26.	[00W9P2]
[Molina, J. M., et al 2018]	Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV. In press 2018.	[04WHL3]

[Orkin, C., et al 2018]	Orkin C, Squires KE, Molina JM, Sax PE, Wong WW, Sussmann O, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. Clin Infect Dis. In press 2018.	[050SC7]
[Panel on Antiretroviral Guidelines for Adults and Adolescents 2018]	Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV: Oct 2018. Washington (DC): U.S. Department of Health and Human Services (HHS); [last updated: 2018 Oct 25]. 331 p.	[053CRN]
[Panel on Treatment of Pregnant Women with HIV Infection and Prev 2018]	Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States: Dec 2018. Washington (DC): Department of Health and Human Services (HHS). [Last updated: 2018 Dec 7]. 365 p.	[05BXZW]
[Poteat, T., et al 2016]	Poteat T, Scheim A, Xavier J, Reisner S, Baral S. Global epidemiology of HIV infection and related syndemics affecting transgender people. J Acquir Immune Defic Syndr. 2016 Aug 15;72(suppl 3):S210-9.	[05BDHN]
[Ribaudo, H. J., et al 2013]	Ribaudo HJ, Smith KY, Robbins GK, Flexner C, Haubrich R, Chen Y, et al. Racial differences in response to antiretroviral therapy for HIV infection: an AIDS Clinical Trials Group (ACTG) study analysis. Clin Infect Dis. 2013 Dec 1;57(11):1607-17.	[057GSZ]

[Trickey, A., et al 2017]	Trickey A, May MT, Vehreschild JJ, Obel N, Gill MJ, Crane HM, et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV. 2017 Aug;4:e349-56.	[055HR8]
[U.S. Prescribing Information 2017]	U.S. Prescribing Information: SUSTIVA (efavirenz) capsules for oral use; SUSTIVA (efavirenz) tablets for oral use: Oct 2017.	[04VGFN]
[U.S. Prescribing Information 2019]	U.S. Prescribing Information: VIREAD (tenofovir disoproxil fumarate) tablets, for oral use; VIREAD (tenofovir disoproxil fumarate) powder, for oral use: Apr 2019.	[057N3H]
[Vandenhende, M. A., et al 2015]	Vandenhende MA, Ingle S, May M, Chene G, Zangerle R, Van Sighem A, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. AIDS. 2015;29(3):373-83.	[056V0P]
[Vazquez-Carrera, M. 2016]	Vazquez-Carrera M. Unraveling the effects of PPARbeta/delta on insulin resistance and cardiovascular disease. Trends Endocrinol Metab. 2016 May;27(5):319-34.	[058MZ6]
[Wang, H., et al 2016]	Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis. Medicine (Baltimore). 2016 Oct;95(41):e5146.	[04MWLQ]
[Weintrob, A. C., et al 2009]	Weintrob AC, Grandits GA, Agan BK, Ganesan A, Landrum ML, Crum-Cianflone NF, et al. Virologic response differences between African Americans and European Americans initiating highly active antiretroviral therapy with equal access to care. J Acquir Immune Defic Syndr. 2009 Dec 15;52(5):574-80.	[0576P6]
[Wensing, A. M., et al 2017]	Wensing AM, Calvez V, Gunthard HF, Johnson VA, Paredes R, Pillay D, et al. 2017 update of the drug resistance mutations in HIV-1. Top Antivir Med. 2017 Dec/Jan;24(4):132-41.	[04Q6MZ]

[World Health Organization 2016] World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection 2016: recommendations for a public health approach, second edition 2016 [Internet]. Geneva, Switzerland: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. [04MN5R]