# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Title:** | A Phase 2 Randomized, Open-Label, Active-Controlled Study Evaluating the Safety and Efficacy of an Oral Weekly Regimen of Islatravir in Combination with Lenacapavir in Virologically Suppressed People with HIV |
| **Name of Test Drug:** | Islatravir + Lenacapavir |
| **Study Number:** | GS-US-563-6041 |
| **Protocol Version (Date):** | Amendment 4 (21 February 2024) |
| **Analysis Type:** | Interim Week 48 Analysis |
| **Analysis Plan Version:** | Version 1.0 |
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| **Analysis Plan Author(s):** | PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CK | creatine kinase |
| CRF | case report form |
| CSR | clinical study report |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| ET | early termination |
| FAS | Full Analysis Set |
| Hb | hemoglobin |
| HLT | high-level term |
| ICH | International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use) |
| IRT | interactive response technology |
| LLT | lowest-level term |
| LOQ | limit of quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OL | open-label |
| PT | preferred term |
| Q1, Q3 | first quartile, third quartile |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | system organ class |
| TA | therapeutic area |
| TEAE | treatment-emergent adverse event |
| TFLs | tables, figures, and listings |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# PHARMACOKINETIC ABBREVIATIONS

| | |
|---|---|
| AUC | area under the concentration versus time curve |
| $AUC_{last}$ | area under the concentration versus time curve from time zero to the last quantifiable concentration |
| $AUC_{tau}$ | area under the concentration versus time curve over the dosing interval |
| CL/F | apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$ , where "Dose" is the dose of the drug |
| $C_{last}$ | last observed quantifiable concentration of the drug |
| $C_{max}$ | maximum observed concentration of drug |
| $C_{min}$ | minimum observed concentration of drug |
| $CL_{ss}/F$ | apparent oral clearance at steady-state |
| $C_{tau}$ | observed drug concentration at the end of the dosing interval |
| $t_{1/2}$ | estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant ($\lambda_z$) |
| $T_{last}$ | time (observed time point) of $C_{last}$ |
| $T_{max}$ | time (observed time point) of $C_{max}$ |
| $\lambda z$ | terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve |

# 1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of an interim analysis for Study GS-US-563-6041. A formal interim analysis for efficacy will be performed when all participants have completed Week 48 assessment or prematurely discontinued from the study. The purpose of this interim analysis is to support the planning of Phase 3 studies.

This SAP is based on Study GS-US-563-6041 Protocol Amendment 4 dated 21 February 2024 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the interim analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

Enrollment and dosing in Cohort 1 evaluating the safety and efficacy of Islatravir (ISL, MK-8591) 20 mg + Lenacapavir (LEN, GS-6207) 300 mg oral weekly were stopped prematurely by the sponsor in December 2021 due to observations of decreases in total lymphocytes and CD4+ T-cell counts in some participants receiving ISL in clinical studies. Cohort 1 data will not be summarized at interim analyses due to low sample size and only few participants reached Week 12 visit but will be listed at final analysis. Only data collected in Cohort 2 evaluating the safety and efficacy of ISL 2 mg + LEN 300 mg oral weekly will be summarized.

## 1.1. Study Objectives and Endpoints

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| • To evaluate the efficacy of oral weekly islatravir (ISL, MK-8591) in combination with lenacapavir (LEN, GS-6207) in virologically suppressed people with HIV (PWH) at Week 24 | • The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US Food and Drug Administration (FDA)-defined snapshot algorithm |
| **Secondary Objectives** | **Secondary Endpoints** |
| • To evaluate the efficacy of oral weekly ISL in combination with LEN in virologically suppressed PWH at Weeks 12, 24, and 48<br>• To evaluate the safety and tolerability of oral weekly ISL in combination with LEN<br>• To evaluate the pharmacokinetics (PK) of ISL and LEN administered as an oral weekly combination regimen | • The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 48 as determined by the US FDA-defined snapshot algorithm<br>• The proportions of participants with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm<br>• The change from baseline in CD4+ T-cell count at Weeks 12, 24, and 48<br>• The incidence of treatment-emergent adverse events (AEs) leading to study drug discontinuation<br>• ISL and LEN PK parameters ($C_{max}$, $T_{max}$, $C_{tau}$, $AUC_{tau}$, and $t_{1/2}$, as applicable) |

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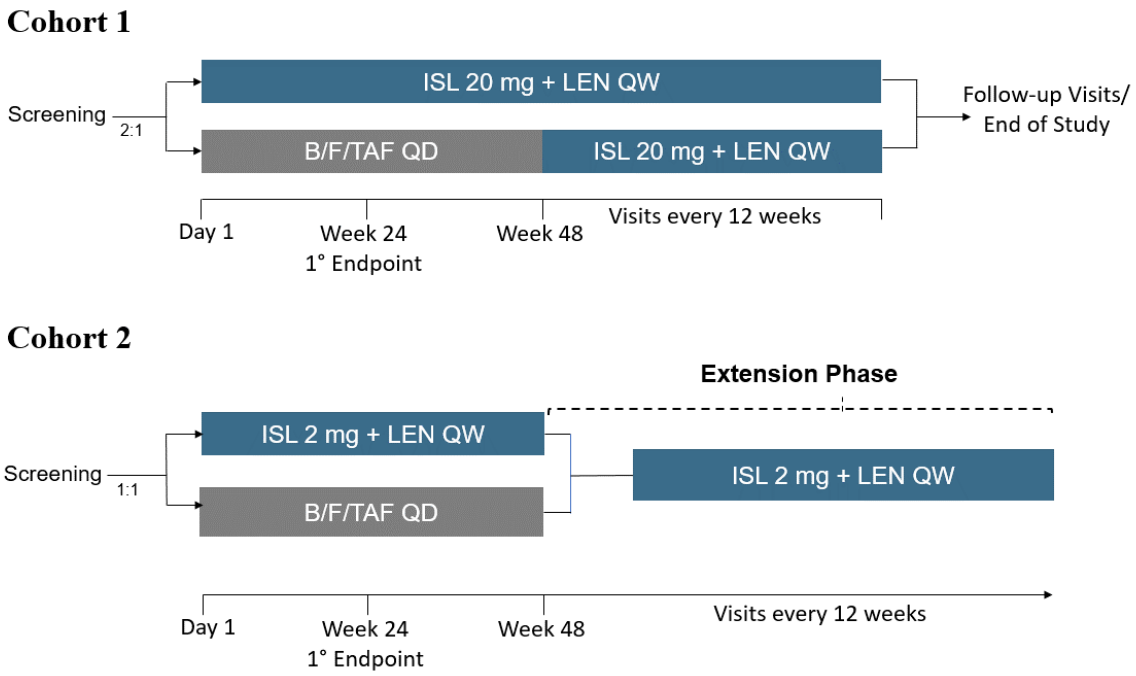
## 1.2. Study Design

**Study Design:**

This is a Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate the safety, efficacy, and PK of ISL+LEN.

A schematic diagram of the study is provided in Figure 1.

**Figure 1. Study Schema**




1°=primary; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); ISL = islatravir; LEN = lenacapavir; QD = once daily; QW = once weekly
The randomized treatment period is at least 48 weeks. At the Week 48 visit, all participants will be given the option to take ISL+LEN in an Extension Phase until drug is commercially available or until Gilead elects to discontinue the development of ISL+LEN, whichever occurs first.

**Cohort 1:**

Virologically suppressed PWH who meet all eligibility criteria will be randomized in a 2:1 ratio to 1 of 2 treatment groups. Enrollment and dosing in Cohort 1 were stopped prematurely by the sponsor.

**Treatment Group 1 (n = 50 planned)**

Oral ISL 40 mg and LEN 600 mg loading on Days 1 and 2

Oral weekly ISL 20 mg administered with LEN 300 mg (ISL+LEN)

**Treatment Group 2 (n = 25 planned)**

Oral daily bictegravir/emtricitabine/tenofovir alafenamide (1 × 50/200/25 mg tablet) (B/F/TAF).

Participants in Cohort 1 will receive randomized study drugs for 48 weeks. Prior to the sponsor discontinuation of Cohort 1, it was planned that following completion of the Week 48 visit, participants receiving ISL+LEN in Treatment Group 1 were to continue ISL+LEN and attend visits every 12 weeks. Participants in Treatment Group 2 were to switch from B/F/TAF to the ISL+LEN regimen (starting with the loading doses over 2 days) and continue the study. Participants in Treatment Group 2 who did not switch from B/F/TAF to ISL+LEN at Week 48 were to be discontinued from the study.

After Week 48, participants taking ISL+LEN were to attend visits every 12 weeks until the product became accessible to participants commercially or Gilead Sciences (Gilead) elected to discontinue the study.

**Cohort 2:**

Virologically suppressed PWH who meet all eligibility criteria will be randomized in a 1:1 ratio to 1 of 2 treatment groups:

**Treatment Group 3 (n = 50 planned)**

Day 1: LEN oral 600 mg (2 × 300 mg) and ISL 2 mg (2 × 1 mg)

Day 2: LEN oral 600 mg (2 × 300 mg)

Day 8 and weekly thereafter (ie, every 7 days): LEN oral 300 mg (1 × 300 mg) and ISL 2 mg (2 × 1 mg)

**Treatment Group 4 (n = 50 planned)**

Oral daily B/F/TAF (1 × 50/200/25 mg tablet)

Randomization will be stratified by CD4+ T-cell count (350 to 499 [inclusive] cells/$mm^3$ or ≥ 500 cells/$mm^3$) at screening.

Participants in Cohort 2 will receive study drugs for at least 48 weeks during the Randomized Phase. At the Week 48 visit, all participants will be given an option to participate in an Extension Phase to receive ISL+LEN. Participants in Treatment Group 3 may continue to receive ISL+LEN, while participants in Treatment Group 4 may switch from B/F/TAF to ISL+LEN, starting with the loading doses of LEN over 2 days. Participants who do not wish to participate in the Extension Phase will be discontinued from the study. Participants in the Extension Phase will attend visits every 12 weeks until the product becomes accessible to participants commercially or Gilead elects to discontinue the study, whichever occurs first.

**Number of Participants Planned:**

Cohort 1: Approximately 75 virologically suppressed PWH will be enrolled in this cohort. Fifty participants may be enrolled in Treatment Group 1 and 25 participants may be enrolled in Treatment Group 2. Cohort 1 enrollment was stopped prior to reaching the target.

Cohort 2: Approximately 100 virologically suppressed PWH will be enrolled in this cohort. Fifty participants may be enrolled in each of Treatment Groups 3 and 4.

**Target Population:** Virologically suppressed PWH ≥ 18 years of age.

**Duration of Treatment:** Duration of treatment in the Randomized Phase is 48 weeks.

**Diagnosis and Main Eligibility Criteria:** Virologically suppressed PWH who meet the following criteria:

- Aged ≥ 18 years at screening
- Plasma HIV-1 RNA < 50 copies/mL for ≥ 24 weeks before and at screening
- Received B/F/TAF for ≥ 24 weeks prior to screening
- No nonnucleoside reverse transcriptase inhibitor (NNRTI) or nucleos(t)ide reverse transcriptase inhibitor (NRTI) resistance, including M184V/I (Cohort 2)
- CD4+ T-cells ≥ 200 cells/$mm^3$ (Cohort 1)
- CD4+ T-cells ≥ 350 cells/$mm^3$ (Cohort 2).

**Study Procedures/Frequency:**

**Cohort 1:**

The schedule of study procedures is presented in the Protocol.

After screening, participants will have onsite visits on Day 1; at Weeks 4, 8, and 12; and then every 12 weeks thereafter. Participants in the PK substudy will have an additional onsite visit on Day 2. Participants in Treatment Group 1 will have telephone visits on Day 2 and at Week 2.

**Cohort 2:**

The schedule of study procedures is presented in Appendix Table 1.

After screening, participants will have onsite visits on Day 1; at Weeks 4, 8, and 12; and then every 6 weeks thereafter through Week 48 of the Randomized Phase. Participants in the PK substudy will have an additional onsite visit on Day 2 of the Randomized Phase. Participants in Treatment Group 3 and 4 will have a telephone visit at Day 2 and Week 2 of the Randomized Phase.

Participants in the Extension Phase will have onsite visits every 12 weeks. Participants in Treatment Group 4 who switch to ISL+LEN in the Extension Phase will receive telephone calls to confirm adherence to the second day of the LEN loading dose and the second ISL+LEN weekly dose.

**Statistical Methods:** The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm. The 95% CI of the difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 between the ISL+LEN group and the B/F/TAF group within each cohort will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 48 and the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm will be analyzed using the same methods as for the primary efficacy endpoint.

Changes from baseline in CD4+ T-cell count at Weeks 12, 24, and 48 will be summarized by treatment group within each cohort using descriptive statistics. The differences in changes from baseline in CD4+ T-cell count between the ISL+LEN group and the B/F/TAF group within each cohort and the associated 95% CIs will be constructed using analysis of covariance (ANCOVA) models, including baseline CD4+ T-cell count as a covariate and treatment (ISL+LEN vs B/F/TAF) as a fixed-effect in the models.

Incidence of treatment-emergent AEs, AEs leading to discontinuation of study drugs, and treatment-emergent laboratory abnormalities will be summarized using descriptive statistics by treatment group within each cohort.

For the general PK analyses, the PK of ISL and LEN may be evaluated using descriptive statistics or population analysis approaches. For the intensive PK substudy, plasma concentrations of ISL and LEN will be summarized by nominal sampling time. Pharmacokinetic parameters ($C_{max}$, $T_{max}$, $C_{tau}$, $AUC_{tau}$, and $t_{1/2}$, as appropriate) will be listed and summarized using descriptive statistics.

## 1.3. Sample Size and Power

A sample size of 50 participants in the ISL+LEN treatment group was chosen to estimate the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm to allow for the planning of Phase 3 studies. This study is not formally powered.

**Cohort 1**

Assuming no failure (0%) in Treatment Group 2 (B/F/TAF) at Week 24, the number of failures in Treatment Group 1 (ISL+LEN) at Week 24 would need to be ≥ 8 (16%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. Similarly, assuming 1 failure (4%) in Treatment Group 2 at Week 24, the number of failures in Treatment Group 1 at Week 24 would need to be ≥ 12 (24%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. The 95% CI is calculated based on an exact unconditional method {Chan 1999}.

If the underlying incidence of a specific AE is 5%, there is a 92.3% chance of observing at least 1 AE among 50 participants in Treatment Group 1 and a 72.3% chance of observing at least 1 AE among 25 participants in Treatment Group 2.

**Cohort 2**

Assuming no failure (0%) in Treatment Group 4 (B/F/TAF) at Week 24, the number of failures in Treatment Group 3 (ISL+LEN) at Week 24 would need to be ≥ 4 (8%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. Similarly, assuming 1 failure (2%) in Treatment Group 4 at Week 24, the number of failures in Treatment Group 3 at Week 24 would need to be ≥ 7 (14%) for the 95% CI for the between-treatment difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL to exclude 0. The 95% CI is calculated based on an exact unconditional method {Chan 1999}.

If the underlying incidence of a specific AE is 5%, there is a 92.3% chance of observing at least 1 AE among 50 participants in Treatment Groups 3 and 4.

# 2. TYPE OF PLANNED ANALYSIS

All interim analyses will be based on Cohort 2 data. Cohort 1 data will be listed only in Final Analysis.

## 2.1. Interim Analyses

Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

### 2.1.1. Planned Interim Analysis

2.1.1.1. Week 48 Interim Analysis

The Week 48 analysis will be conducted after all participants in Cohort 2 either complete their Week 48 visit or prematurely discontinue from the study drug, outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis. All data collected from the randomized and the extension phases of the study will be included in data listings. Only data from the randomized phase of the study will be summarized by treatment group in the randomized phase, unless specified otherwise.

This SAP describes the analysis plan for the Week 48 interim analysis.

2.1.1.2. Extension Phase Week 24 Analysis

The Extension Phase Week 24 analysis will be conducted after all the participants in Treatment Group 3 complete their Week 72 visit, and all the participants in Treatment Group 4 complete their Extension Week 24 visit, or prematurely discontinue from the study drug, outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis.

### 2.1.2. Data Monitoring Committee Analyses

Three external multidisciplinary Data Monitoring Committee (DMC) analyses will be conducted after all participants in Cohort 2 have completed their Week 12, 24, and 48 visits, or prematurely discontinued from study drug during the Randomized Phase, all outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis.

No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of AEs associated with a study treatment warrant the early termination of the study in the best interest of the participants.

No alpha penalty will be applied for the primary analysis of the primary efficacy endpoint given that the study is not adequately powered for a formal efficacy evaluation. The purpose of the interim analysis was to provide the DMC with a statistical report for review. More details are documented in the DMC charter.

## 2.2. Primary (Week 24) Analysis

The Week 24 interim analysis was conducted after all participants in Cohort 2 had completed Week 24 visit or had prematurely discontinued the study drug, outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis. This was the primary analysis of this study.

## 2.3. Final Analysis

The final analysis will be performed after all participants in Cohort 2 have completed the study or have prematurely discontinued the study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. All data that are collected in the study (ie, Cohort 1 and Cohort 2) will be included and listed in Final Analysis.

# 3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by participant ID number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

Cohort 1 data will not be included due to low sample size and only few participants reached Week 12 visit. Only data collected in Cohort 2 evaluating the safety and efficacy of ISL 2 mg + LEN 300 mg oral weekly will be included in this analysis.

## 3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion as well as the number and percentage of participants who were excluded and the reasons for their exclusion will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by participant.

### 3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were randomized in the study.

This is the primary analysis set for by-participant listings.

### 3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

### 3.1.3. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

### 3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized participants who took at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

### 3.1.5. Pharmacokinetic Substudy Analysis Set

The Pharmacokinetic (PK) Substudy Analysis Set will include all randomized participants who receive at least 1 dose of study drug, participated in the PK substudy, and have at least 1 nonmissing postdose concentration. This is the primary analysis set for detailed PK analysis of intensive PK sampling.

## 3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set or the FAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set, participants will be grouped according to the actual treatment they received.

## 3.3. Strata and Covariates

Participants will be randomly assigned to treatment groups via the interactive response technology (IRT) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- CD4+ T-cell count (350 to 499 [inclusive] cells/$mm^3$ or ≥ 500 cells/$mm^3$) at screening

If there are discrepancies in stratification factor values between the IRT and the clinical database, the values recorded in the clinical database will be used for analyses. Additionally, stratification discrepancies will be reviewed and assessed. Based on the assessment of stratification discrepancies, a sensitivity analysis of the primary endpoint may be performed.

## 3.4. Examination of Participant Subgroups

### 3.4.1. Participant Subgroups for Efficacy Analyses

The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be analyzed for the following participant subgroups based on FAS:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack

### 3.4.2. Participant Subgroups for Safety Analyses

Incidence of all treatment-emergent AEs (TEAEs) will be analyzed based on Safety Analysis Set for the following participant subgroups:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack

## 3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this Phase 2, non-confirmatory study

## 3.6. Missing Data and Outliers

### 3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2. The handling of missing or incomplete dates for AE start is described in Section 7.1.6.2, and for prior and concomitant medications in Section 7.4.

### 3.6.2. Outliers

Outliers of non-PK data will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

## 3.7. Data Handling Conventions and Transformations

Only year of birth is collected on the CRF; "01July" will be imputed as the day and month of birth.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization [enrollment] date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at start date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters in intensive PK samples. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose and postdose time points for summary purposes. The number of samples will be summarized to reflect the actual number of samples assessed at that time point.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the participants have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of order statistics for postdose time points:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

Concentration related PK parameters (eg, $C_{last}$, $C_{max}$, and $C_{tau}$) that are BLQ will be excluded before log transformation or statistical model fitting and displayed as described above.

## 3.8. Analysis Visit Windows

### 3.8.1. Definition of Key Dates and Study Day

**Study Day 1 (Randomized Phase**) is defined as the day when the first dose of study drug was taken, as recorded on the Study Drug Administration eCRF. For participants in Treatment Groups 3, the earliest of the first dose dates of any component (ie, ISL or LEN) is considered as the first dose date of the study drug.

**Study Day 1 (Extension Phase)** is defined as the day when the first dose of extension phase study drug was taken, as recorded on the "Post Week 48 Treatment/Extension Phase" Study Drug Administration eCRF. The earliest of the first dose dates of any component (ie, ISL or LEN) is considered as the first dose date of the study drug. This day will only be available for participants who received at least 1 dose of ISL or LEN in the extension phase.

**Study Days** are calculated as follows:

- For postdose study days: Assessment Date – First Dose Date + 1
- For days prior to the first dose: Assessment Date – First Dose Date

All study days will be calculated from randomized phase Study Day 1 including observations collected from the extension phase of the study.

**Last Dose Date (Randomized Phase)** is the latest of the randomized study drug (including B/F/TAF, ISL or LEN) end dates, as recorded on the "Treatment Phase" Study Drug Administration eCRF.

**Last Dose Date (Extension Phase)** is defined for participants who prematurely discontinued or completed study drug according to the "Extension Phase" Study Drug Completion eCRF as the latest of the extension phase study drug (including ISL or LEN) end dates recorded on the "Post Week 48 Treatment/Extension Phase" Study Drug Administration eCRF.

**Last Dose Date** is defined for participants who prematurely discontinued study drug (at either phase) or who completed study drug, as the latest of the study drug (including B/F/TAF, ISL or LEN) end dates recorded on Study Drug Administration eCRF.

**Last Study Date** is the latest of the randomized or extension phase (if available) study drug start dates and end dates, the clinic visit dates, the laboratory visit dates, and/or latest AE onset date and end date, whichever is latest, including any follow-up visit date, for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF.

**Baseline Value** is defined as the last value obtained on or prior to the first dose of study drug except for average baseline used for safety monitoring (Section 7.2.1).

### 3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. Observations collected from the extension phase of the study (ie, extension phase data), defined as any data after when the first dose of extension phase study drug was taken, will be not be assigned to an analysis window and will be included in listings with derived visit marked as "Extension". For participants who prematurely discontinued study drug during the randomized phase, or who completed study drug in the randomized phase and did not enter the extension phase, any data obtained later than the randomized last dose date + 60 days for participants who received ISL+LEN, or later than the randomized last dose date + 30 days for participants who received B/F/TAF, will not be assigned to an analysis window.

The analysis windows for HIV-1 RNA, CD4+ T-cell count, CD4%, TBNK, Hematology, Chemistry, Urinalysis, Urine Chemistry, Vital Signs, and Weight are provided in Table 3-1.

**Table 3-1. Analysis Visit Windows for HIV-1 RNA, CD4+ T-Cell Count, CD4%, Hematology, Chemistry, Urinalysis, Urine Chemistry, Vital Signs, and Weight**

| Visit | Study Day | Visit Window Study Day | |
|---|---|---|---|
| | | Lower Limit | Upper Limit |
| Baseline | 1 | (none) | 1 |
| Week 4 | 28 | 2 | 42 |
| Week 8 | 56 | 43 | 70 |
| Week 12 | 84 | 71 | 105 |
| Week 18 | 126 | 106 | 147 |
| Week 24 | 168 | 148 | 189 |
| Week 30 | 210 | 190 | 231 |
| Week 36 | 252 | 232 | 273 |
| Week 42 | 294 | 274 | 315 |
| Week 48 | 336 | 316 | 378 |

### 3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dose date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data (except for HIV-1 RNA, see below), or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram ECG findings) for categorical data.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected with the exception of HIV-1 RNA in which the latest record will be selected (see below).
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both HIV test results ("HIV RNA Cobas 6800" or "HIV RNA Taqman 2.0") and repeated HIV test results ("HIV RNA Cobas6800RPT" or "HIV RNA Taqman 2.0 Repeat", ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the repeated HIV tests ("HIV RNA Cobas6800RPT" or "HIV RNA Taqman 2.0 Repeat ) will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Cobas 6800" or "HIV RNA Taqman 2.0" records with the same collection time, the geometric mean will be taken for analysis purposes.

# 4. PARTICIPANT DISPOSITION

## 4.1. Participant Enrollment and Disposition

Key study dates (ie, first participant screened, first participant randomized, last participant randomized, last participant last visit for the primary endpoint, and last participant last visit/lab for the Week 48 Interim Analysis) will be provided.

A summary of participant enrollment will be provided by treatment group for each country, investigator within a country or region, and overall. The summary will present the number and percentage of participants randomized. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of participants in the stratum will be the total number of randomized participants. If there are discrepancies in the value used for stratification assignment between the IRT and the clinical database, the value collected in the clinical database will be used for the summary. A listing of participants with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided. If there are differences between randomization stratum using screening CD4+ T-cell count value and baseline CD4+ T-cell count value, a listing of the differences will also be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of participant disposition will be provided by treatment group and study phase. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not randomized with reasons participants not randomized, the number of participants randomized, and the number of participants in each of the categories listed below for each study phase:

- Safety Analysis Set
- Full Analysis Set (FAS)
- Completed study drug in the randomized phase
- Did not complete study drug with reasons for premature discontinuation of study drug in the randomized phase (if applicable)
- Completed study drug in the randomized phase and not entering the extension phase
- Completed study drug in the randomized phase and entered the extension phase
- Continuing study drug in the extension phase

- Completed study drug in the extension phase
- Did not complete study drug with reasons for premature discontinuation of study drug in the extension phase (if applicable)
- Continuing study
- Completed study
- Did not complete the study with reasons for premature discontinuation of study (if applicable)

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column in that study phase (if applicable). No inferential statistics will be generated.

In addition, the total number of participants who were randomized, and the number of participants in each of the disposition categories listed above will be displayed in a flowchart.

The following by-participant listings will be provided by participant identification (ID) number in ascending order to support the above summary tables:

- Participant disposition, including treatment, date of randomization, first dose date, last dose date and day, end of study date and day, study drug discontinuation in the Randomized/Extension Phase, study discontinuation, and reasons for study drug or study discontinuation.
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Lot number and kit ID
- Participant profile, including treatment, date of randomization, first dose date, last dose date and day, last visit date and day, last lab date and day, last study date and day.

## 4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

### 4.2.1. Duration of Exposure to Study Drug

Duration of exposure to randomized study drug will be calculated regardless of temporary interruptions in study drug administration as the following.

a) For participants who prematurely discontinued study drug during the randomized phase, or who completed study drug in the randomized phase and did not enter the extension phase: (the randomized last dose date – the randomized first dose date + dosing interval)

b) For participants who received at least 1 dose of ISL or LEN in the extension phase extension phase: minimal (the randomized last dose date + dosing interval, Study Day 1 (Extension Phase)) - the randomized first dose date

The dosing interval is 7 days for participants who receive ISL+LEN and 1 day for participants who receive B/F/TAF, respectively, during the randomized phase. Duration will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Duration of exposure to randomized study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of participants exposed for specified periods, eg, ≥ 1 day, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 18 weeks (126 days), ≥ 24 weeks (168 days), ≥ 30 weeks (210 days), ≥ 36 weeks (252 days), ≥ 42 weeks (294 days), and ≥ 48 weeks (336 days).

Summaries will be provided by treatment group for participants in the Safety Analysis Set. No inferential statistics will be provided.

### 4.2.2. Adherence to Study Drug

During the randomized phase of the study, study drug regimen adherence will be computed based on pill counts for active randomized drug (eg, randomized study drug regimen in Treatment Group 3 includes 2 study drugs: *once weekly (QW) ISL and LEN*. Randomized study drug regimen in Treatment Group 4 includes 1 study drug: *once daily (QD) B/F/TAF*), excluding Day 1 ISL and LEN and Day 2 LEN where ISL or LEN is used for loading. The numbers of pills of study drug dispensed and returned are captured on the Study Drug Accountability eCRF.

Adherence (%) of randomized study drug(s) will be calculated as follows:

$$\text{Adherence (\%)} = 100 \times \frac{Total \ \text{No. of pills taken}}{\text{Total No. of pills prescribed}}$$

$$= 100 \times \frac{\sum\sum \text{No. of pills taken at each dispensing period for each study drug}^{[1]}}{\sum\sum \text{No. of pills prescribed at each dispensing period for each study drug}^{[2]}}$$

[1] Number of pills taken at a distinct dispensing period for study drug(s) will be calculated based on each dispensing period and summed together from all evaluable dispensing periods.

[2] Number of pills prescribed at a distinct dispensing period for QW ISL or LEN will be calculated as the duration of treatment divide by 7, while for B/F/TAF will be calculated as the duration of treatment, respectively, at the dispensing period of the same dispensing date. Total number of pills prescribed is determined by summing the number of pills prescribed from all evaluable dispensing periods for all study drug(s).

The number of pills taken at each dispensing period will be calculated follows:

a) For LEN and B/F/TAF: as the number of pills dispensed minus the number of pills returned,

b) For ISL: as the number of pills dispensed minus the number of pills returned, and divided this number by 2.

Total number of pills taken is determined by summing the number of pills taken from all evaluable dispensing periods for all study drug(s). If total number of pills taken is greater than total number of pills prescribed (ie, total duration of treatment of QW ISL or LEN divided by 7, or total duration of treatment of B/F/TAF), then the total number of pills prescribed will be used as numerator instead.

The duration of treatment of study drug(s) at each dispensing period will be calculated as the following:

a) the last returned date of the study drug at a dispensing period, or

b) the date of premature discontinuation of the study drug + dosing frequency (1 for QD study drug and 7 for QW study drug), or

c) next pill dispensing date of the study drug, minus dispensing date of the study.

The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date. For a record where the number of pills returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of pills returned was zero. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation.

Overall adherence will be calculated for participant in ISL + LEN group by taking the average adherence of ISL and LEN.

Adherence will be calculated for each participant for the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinued study drug, or using all available data up to the earliest of (1) data cut date or (2) Study Day 1 (Extension Phase), for participants ongoing on study drug.

Descriptive statistics for adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for participants who return at least 1 bottle of randomized QD study drug, and who have calculable adherence in the Safety Analysis Set. No inferential statistics will be provided.

A by-participant listing of study drug administration and drug accountability will be provided separately by participant ID number (in ascending order) and visit (in chronological order).

## 4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with at least 1 important protocol deviation will be summarized by treatment group and by deviation category for the All Randomized Analysis Set for the randomized phase. Additionally, the number and percentage of participants with at least 1, 1, 2, or 3 or more important protocol deviations will be summarized. The total number of important protocol deviations will be summarized by deviation category. A by-participant listing will be provided for those participants with important protocol deviations, including all important protocol deviations occurred during the study, and a flag indicating if the deviation occurred during randomized phase.

# 5. BASELINE CHARACTERISTICS

## 5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, sex, gender identity, sexual orientation, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in $kg/m^2$]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set. Missing values will not be included in the denominator when calculating percentages.

Statistical comparison between the 2 treatment groups will be performed. For categorical data, the CochranMantelHaenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

## 5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4+ T-cell counts (/uL)
- CD4+ T-cell count categories (/μL): (a) < 350, (b) ≥ 350 to < 500, and (c) ≥ 500
- CD4+ T-cell percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- Lymphocyte count (x10^3/uL)

The summary of these baseline disease characteristics will be provided for the Safety Analysis Set. Statistical comparison between the 2 treatment groups will be conducted similarly as described for the demographic and baseline characteristics.

A by-participant listing of other baseline characteristics will be provided by participant ID number in ascending order.

## 5.3. Medical History

Medical history will be collected at screening for HIV-1 disease related events and general conditions (ie, conditions not specific to the disease being studied). Medical history will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

General medical history data will be listed.

# 6. EFFICACY ANALYSES

## 6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The proportions are expressed as percentages for presentation purposes.

The statistical analysis methods for the primary efficacy endpoint were described in the Week 24 SAP and the analysis was performed in the Week 24 analyses.

## 6.2. Secondary Efficacy Endpoints

### 6.2.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 48 as determined by the US FDA-defined snapshot algorithm
- The proportions of participants with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ T-cell count at Weeks 12, 24, and 48

The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 12, and with HIV-1 RNA < 50 copies/mL at Weeks 12 and 24 as determined by the US FDA-defined snapshot algorithm has been performed in the Week 12 DMC and Week 24 analyses and will not be repeated here. The proportion of participants with HIV-1 RNA ≥ 50 copies/mL and with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm will be analyzed based on the FAS.

### 6.2.2. US FDA-defined Snapshot Algorithm

The analysis window at Week 48 is defined as from Study Day 316 to Study Day 378, inclusive. All HIV1 RNA data collected on-treatment (ie, data collected up to 14 days or 1 day after the last dose date for participants who receive ISL+LEN or B/T/TAF, respectively) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- HIV-1 RNA < 50 copies/mL: this includes participants who have the last available ontreatment HIV-1 RNA < 50 copies/mL in the Week 48 analysis window

- HIV-1 RNA ≥ 50 copies/mL: this includes participants
  - Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or
  - Who do not have ontreatment HIV1 RNA data in the Week 48 analysis window and
    - Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or
    - Who discontinue study drug prior to or in the Week 48 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or
    - Who discontinue study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
- No Virologic Data in the Week 48 analysis window: this includes participants who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:
  - Discontinuation of study drug prior to or in the Week 48 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
  - Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
  - Missing data during the window but on study drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in Section 12 (Appendix 2).

### 6.2.3. Primary Analysis for the Secondary Endpoints

The point estimate of treatment difference (ISL+LEN group – B/F/TAF group) in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL and with HIV-1 RNA < 50 copies/mL, and the associated 2-sided 95% CI will be constructed based on an unconditional exact method using 2 inverted 1-sided tests {Chan 1999}.

The number and percentage of participants with HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Week 48 will be summarized.

The FAS will be used for the secondary efficacy endpoint analysis.

### 6.2.4. Secondary Analysis for the Secondary Endpoints

The change and percentage change from baseline in CD4+ T-cell counts will be based on the FAS and summarized up to the visits with available data in randomized phase using descriptive statistics. The differences in changes from baseline in CD4+ T-cell count between the two treatment groups (ISL+LEN vs B/F/TAF) and the associated p-values and 95% CIs will be constructed using analysis of covariance (ANCOVA) models, including baseline CD4+ T-cell count as a covariate and treatment (ISL+LEN versus B/F/TAF) as a fixed-effect in the models.

Mean ± 95% CI and median (Q1, Q3) of the change from baseline in CD4+ T-cell counts will be plotted by visit.

## 6.3. Other Efficacy Endpoints

### 6.3.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL by Missing = Failure and Missing = Excluded Analyses

Number and percentage of participants with HIV-1 RNA < 50 copies/mL by visit will be analyzed using the following 2 analyses:

- Missing = Failure (M = F):

In this approach, missing data will be treated as virologic failure and summarized into the "missing" category (see list of HIV-RNA categories below). Results will be summarized by treatment group for all visits up to Week 48.

- Missing = Excluded (M = E):

In this approach, missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit.

For both M = F and M = E analyses, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized based on the FAS:

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL Not Detectable
    - < 20 copies/mL Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL

- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL
- Missing (only applicable to M = F analysis)

The proportion of participants with HIV-1 RNA < 50 copies/mL as defined by the 2 different missing data imputation methods will be analyzed using the same statistical method applied to the primary analysis of the primary efficacy endpoint. In addition, the 95% CI of the proportion of participants with HIV-1 RNA < 50 copies/mL within each treatment group will be provided using the Clopper-Pearson Exact method.

For the M = F and M = E analyses, the proportion of participants with HIV-1 RNA < 50 copies/mL will be plotted by treatment group for all visits up to Week 48 and all available visits in randomized phase, respectively, using the FAS.

### 6.3.2. Efficacy Subgroup Analysis

Subgroups defined in Section 3.4.1 will be performed for the proportion of participants with HIV1 RNA < 50 copies/mL at Week 48 as determined by the US FDA defined snapshot algorithm. Subgroup analysis will be performed on participants who have reached Week 48 at the time for the Week 48 analysis in the FAS. Results will be descriptive and the associated 95% CIs will be constructed using Exact method.

## 6.4. Changes from Protocol-Specified Efficacy Analysis

No change from protocol-specified efficacy analysis is planned.

# 7. SAFETY ANALYSES

Safety data will be summarized for the participants in the Safety Analysis Set. All safety data collected up to

a) For participants who prematurely discontinued study drug during the randomized phase, or who completed study drug in the randomized phase and did not enter the extension phase: 60 days after the randomized last dose date for participants who received ISL+LEN, or up to 30 days for participants who received B/F/TAF, or

b) For participants who received at least 1 dose of ISL or LEN in the extension phase: all available data up Study Day 1 (Extension Phase)

will be included in the table summary, unless specified otherwise. All collected data will be included in data listings.

## 7.1. Adverse Events and Deaths

### 7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT) will be provided in the AE dataset.

### 7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

### 7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE CRF to the question of “Related to Study Treatment.” Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

### 7.1.4. Relationship of Adverse Events to Study Procedures

Study procedure related AEs are those for which the investigator selected “Yes” on the AE case report form (CRF) to the question of “Related to Study Procedures.” Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationships to study procedure will be considered related to study procedure for summary purposes. However, by-participant data listings will show the relationship as missing.

### 7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety (GLPS) Department before data finalization.

### 7.1.6. Treatment-Emergent Adverse Events

#### 7.1.6.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and, for participants who completed or prematurely discontinued study drug, no later than 60 days for participants who received ISL+LEN, or no later than 30 days for participants who received B/F/TAF, after the last dose date

- Any AEs leading to premature discontinuation of study drug.

TEAEs with an onset date during the time period specified in the beginning of Section 7 will be summarized. In AE listings, TEAEs with an onset date during or after this time period will be flagged differently to specify if the TEAE occurred in Randomized or Extension Phase.

#### 7.1.6.2. Incomplete Dates

If the start date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of start determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE start date is the same as or after the month and year (or year) of the first dosing date of study drug, and

- The AE start date is the same as or before the month and year (or year) of the date corresponding to 60 days or 30 days after the date of the last dose of study drug for participants who receive ISL+LEN or B/F/TAF, respectively

An AE with completely missing start and stop dates, or with the start date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the start date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

### 7.1.7. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

#### 7.1.7.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group as follows:

- TEAEs

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to premature discontinuation of study
- TEAEs leading to death (by SOC and PT only)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the worst severity grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only unless otherwise specified, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs leading to premature discontinuation of study drug
- All AEs leading to premature discontinuation of study

For each listing, whether the event is treatment emergent will be indicated.

#### 7.1.7.2. Summaries of AE Incidence by Severity

A brief, high-level summary of the number of percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group.

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs (by severity)
- TE treatment-related AEs (by severity)
- TEAEs with Grade 3 or higher (by severity)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the worst severity will be used for those AEs that occurred more than once in a given participant in during the study.

In addition, data listings will be provided for the following:

- All AEs with severity of Grade 3 or higher
- All AEs with severity of Grade 2 or higher

## 7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected during the time period specified in the beginning of Section 7.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher will be flagged in the data listings, as appropriate.

A by-participant listing for participant with the percentage change in CD4+ T-cell or lymphocyte declined >=30% at 2 consecutive visits that are at least 10 weeks apart will be provided separately.

No formal statistical testing is planned unless specified otherwise.

### 7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory tests as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

**Lymphocyte and TBNK Panel**

For lymphocyte and TBNK panel (ie, CD4+ T-cell count, CD8, CD16, CD19, CD4%, CD8%, and CD4/CD8), descriptive statistics will be provided by treatment group as follows:

- Baseline values
- Values at each postbaseline visit
- Change and percentage change from baseline at each postbaseline
- Categorical Percentage Change as < -50%, -50% to <-30%, -30% to < 0, 'No Change or No Decline' categories at each postbaseline visit (for CD4+ T-cell count and lymphocyte only)

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the change from baseline values for these selected laboratory tests will be plotted using a line plot by treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Statistical comparison between treatment groups will be performed for lymphocyte and TBNK panel only. The differences in changes from baseline between the ISL+LEN group and the B/F/TAF group, p-values, and the associated 95% CIs will be constructed using analysis of covariance (ANCOVA) models, including baseline value as a covariate and treatment (ISL+LEN versus B/F/TAF) as a fixed-effect in the models.

Categorical percentage change will be summarized for CD4+ T-cell count and lymphocyte only. Number and percentage of participants at each category (< -50%, -50% to -30%, -30% to < 0, and 'No Change or No Decline') will be analyzed by visit and treatment group. P-values will be derived from CMH test to compare the 2 treatment groups.

A by-participant listing for TBNK panel and lymphocyte will be provided individually. For CD4+ T-cell count and lymphocyte, a by-participant listing will be provided with absolute values, change, and percentage change.

The following criteria are used for safety monitoring:

- If the average baseline CD4+ T-cell count is ≥ 500 cells/mm$^3$, then select the participants with absolute CD4 decline to < 350 cells/mm$^3$ confirmed by a repeat measure that are at least 10 weeks apart
- If the average baseline CD4+ T-cell count is ≥ 350 and ≤ 499 cells/mm$^3$ (inclusive), then select the participants with absolute CD4 decline to < 200 cells/mm$^3$ at confirmed by a repeat measure that are at least 10 weeks apart
- Select participants with Grade 2 or above absolute lymphocyte count confirmed by a repeat measure that are at least 10 weeks apart
- Percentage decline ≥ 30% in CD4+ T-cell count or absolute lymphocyte count that is confirmed by a repeat measure at least 10 weeks apart

A by-participant listing for CD4+ T-cell count and lymphocyte will be provided for participants who met any of the criterion. Absolute values, change, percentage change, toxicity grade (lymphocyte only), and average baseline will be included in the listing.

### 7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

#### 7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point during the time period specified in Section 7.2. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

#### 7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values during the time period specified in Section 7.2.

A by-participant listing of treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades and abnormal flags displayed.

## 7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

## 7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

### 7.4.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug ARV medications are defined as any ARV medications taken prior to, during, or after the study (if collected). All nonstudy drug ARV medications will be listed. No inferential statistics will be provided.

### 7.4.2. Concomitant Medications

Concomitant medications are defined as non-ARV medications taken while a participant took study drug. Use of concomitant medications during the time period specified in the beginning of Section 7 will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each treatment group. A participant reporting the same medication more than once within each ATC drug class will be counted only once when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after 60 days or 30 days after last dose date for participants who receive ISL+LEN or B/F/TAF, respectively
- The month and year of stop of the medication is before the first dose date of study drug

If the start and stop date of non-ARV medications are complete, the start date is not after the last dose date and the stop date is not before the first dose date, or the non-ARV medications are marked as ongoing and start date is on or before the last dose date, the non-ARV medications are concomitant.

Summaries of non-ARV concomitant medications will be based on the Safety Analysis Set. No formal statistical testing is planned.

All non-ARV prior and concomitant medications will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order. In this listing, a medication will be flagged differently to specify if it is concomitant to study drug in Randomized Phase, concomitant to study drug in Extension phase, concomitant to study drug in both phases, or not concomitant to study drug.

### 7.5. Electrocardiogram Results

The investigators' assessment of ECG results (normal; abnormal, not clinically significant; abnormal, clinically significant) are collected at screening only. A by-participant listing for ECG assessment results will be provided by participant ID number.

### 7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy and participants using/misusing any substances (eg, illicit drug) during the study, respectively. Physical examination was not collected in the eCRF. Therefore, it will not be included in the analysis.

### 7.7. Participant Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.2 using the Safety Analysis set. No formal statistical testing is planned.

### 7.8. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

# 8. PHARMACOKINETIC (PK) ANALYSES

## 8.1. PK Sample Collection

### 8.1.1. Single Anytime Plasma PK Sampling

Single anytime plasma PK sampling for ISL and LEN will occur in Treatment Group 3 participants at each onsite visit through Week 72 except Day 1 for Treatment Group 3. Day 1 PK sample will be collected 1 hour (± 30 minutes) postdose after onsite drug administration for Treatment Group 3. The date and time of ISL and LEN dosing on Day 1 and previous ISL and LEN dosing for subsequent visits will be recorded. PK collections after Week 48 will be stored and analyzed only if deemed necessary by sponsor.

### 8.1.2. Pharmacokinetics Substudy

A PK substudy will be conducted approximately 15 participants in Treatment Group 3 who provide consent. Samples will be collected on Day 1, Day 2, and Week 12 at the time points presented in Table 8-1 Study drugs will be administered during the onsite visits on Day 1, Day 2, and Week 12. For Day 2, only LEN samples will be collected; both ISL and LEN samples will be collected for Day 1 and Week 12. Week 12 PK substudy sample collection may be performed at Week 18 if the participant took the Week 12 study drugs prior to the clinic visit instead of administered onsite.

Additional single anytime PK sampling will not be collected for participants in the substudy during PK substudy visits (Day 1, Week 12, or Week 18).

**Table 8-1. PK Substudy Sample Collection Time Points**

| Visit[a] | Sampling Time Points |
|---|---|
| Day 1 | predose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, and 8 hours postdose |
| Day 2 [b] | predose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, and 8 hours postdose |
| Week 12[c, d] | predose (within 30 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 72, 120, and 168 hours postdose |

LEN = lenacapavir; PK = pharmacokinetics
a The study drugs will be administered at the site during the study visit.
b For Day 2, only LEN samples will be collected after LEN only (2 x 300 mg) administration onsite.
c Week 12 PK substudy sample collection may be performed at Week 18 if the participant took the Week 12 study drugs prior to the clinic visit instead of administered onsite.
d 168-hour sample must be collected prior to next dose to capture trough concentration.

## 8.2. PK Analyses Related to Intensive PK Sampling

### 8.2.1. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up log down rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as $AUC_{tau}$, $\lambda_z$ and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

### 8.2.2. PK Parameters

PK parameters will be generated for all participants in the PK substudy Analysis Set from Treatment Group 3. The analytes presented in Table 8-2 will be evaluated if data are available.

**Table 8-2. Study Treatments and Associated Analytes**

| Treatment Group | Analyte |
|---|---|
| Treatment Group 3 | ISL, LEN |

The analytes and parameters presented in Table 8-2 and Table 8-3 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

**Table 8-3. PK Parameters for Each Analyte**

| Analyte | Parameters |
|---|---|
| ISL | $C_{max}$, $T_{max}$, $C_{tau,}$ $AUC_{tau,}$ partial AUC ($AUC_{0-8}$, $AUC_{0-24}$), and $t_{1/2}$, as applicable |
| LEN | $C_{max}$, $T_{max}$, $C_{tau,}$ $AUC_{tau,}$ partial AUC ($AUC_{0-8}$, $AUC_{0-24}$), and $t_{1/2}$, as applicable |

## 8.3. PK Analyses Related to PK Sampling

Individual participant concentration data and individual participant PK parameters will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual participant concentration data by time point and individual participant PK parameters by treatment. Moreover, the geometric mean, % GCV, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. Time elapsed from last dose taken when the PK sample was drawn will be added to individual concentration data listings but will not be summarized. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and postdose time points.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter.

The following tables will be provided for each analyte based on PK Analysis Set and PK Substudy Analysis Set:

- Individual participant concentration data and summary statistics
- Individual participant plasma PK parameters and summary statistics

The following figures may be provided for each analyte based on PK Analysis Set and PK Substudy Analysis Set:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are ≤ LOQ will not be displayed in the figures and remaining points connected.

PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

### 8.4. Sensitivity Analyses Sampling

Sensitivity analysis may be conducted for the key PK analyses if the PK scientist identifies PK data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK parameter(s) data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

### 8.5. Changes From Protocol-Specified PK Analyses

There are no deviations from the protocol-specified PK analyses.

# 9. REFERENCES

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55 (4):1202-9.

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

# 10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

Phoenix WinNonlin® 7.0 Pharsigh Corporation, Princeton, NJ, USA.

# 11. SAP REVISION

| Revision Date (DD MMM YYYY) | Section | Summary of Revision | Reason for Revision |
|---|---|---|---|
| | | | |

# 12. APPENDICES

## Appendix 1. Schedule of Assessments

### Appendix Table 1. Study Procedures for Cohort 2

| | | Randomized Phase | | | | | | | | | Extension Phase | | ESDD[f] | Post-Study Drug Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Week | | | | | | | Week | | | | | |
| **Study Procedures** | **Screening[a]** | **Day 1[b]** | **Day 2[c]** | **2[d]** | **4, 8** | **12** | **18** | **24** | **30, 36, 42** | **48[e]** | **Week 60 and every 12 weeks thereafter** | **Week 96 and every 48 weeks thereafter** | **Within 3 Days of Last Dose** | **30-Day Follow-up[g]** | **60-Day Follow-up[g]** | **100-Day and 200-Day Follow-up[h]** |
| **Visit Window (Days)** | **Within 35 Days Prior to Day 1** | | | **± 1 day** | **± 7 days** | | | | | | **± 14 days** | | **+ 1 day** | **± 7 days** | | |
| Written informed consent | X | | | | | | | | | | | | | | | |
| Obtain demographic information | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| AEs | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | |
| HIVDQoL[i] | | X | | | | | | X | | X | | | | | | |
| HIVTSQs12[i] | | X | | | X[i] | | | X | | X | | | | | | |
| HIVTSQc12[i] | | | | | | | | | | X | | | | | | |
| EQ-5D-5L[i] | | X | | | X[i] | | | X | | X | | | | | | |
| HIV Patient Perspective of Regimen (PP-R)[j] | | X | | | X | X | | X | X[j] | X | X | | | | | |
| HIV Patient Perspective of Regimen Change (PP-RC)[k] | | | | | X | X | | X | X[k] | X | X | | | | | |

| | | Randomized Phase | | | | | | | | | Extension Phase | | ESDD[f] | Post-Study Drug Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Week | | | | | | | Week | | | | | |
| **Study Procedures** | **Screening[a]** | **Day 1[b]** | **Day 2[c]** | **2[d]** | **4, 8** | **12** | **18** | **24** | **30, 36, 42** | **48[e]** | **Week 60 and every 12 weeks thereafter** | **Week 96 and every 48 weeks thereafter** | **Within 3 Days of Last Dose** | **30-Day Follow-up[g]** | **60-Day Follow-up[g]** | **100-Day and 200-Day Follow-up[h]** |
| **Visit Window (Days)** | **Within 35 Days Prior to Day 1** | | | **± 1 day** | **± 7 days** | | | | | | **± 14 days** | | **+ 1 day** | **± 7 days** | | |
| Vital signs[l] (including weight) | X | X | | | X | X | X | X | X | X | X | | X | X | X | |
| Height | X | | | | | | | | | | | | | | | |
| Complete physical examination[m] | X | X | | | | | | | | | | | X | | | |
| Symptom-directed physical examination | | | | | X | X | X | X | X | X | X | | | X | X | |
| 12-lead ECG (supine) | X | | | | | | | | | | | | | | | |
| Hematology, chemistry, urinalysis and urine chemistry, CD4+ T-cell count/TBNK panel[n] | X | X | | | X | X | X | X | X | X | X | | X | X | X | X |
| Serum pregnancy test[o] | X | | | | | | | | | | | | | | | |
| Serum FSH[p] | X | | | | | | | | | | | | | | | |
| Urine pregnancy test[o] | | X | | | | X | | X | Week 36 only | X | X | | X | | | |
| HBV, HCV tests[q] | X | | | | | | | | | X | | X | | | | |
| Plasma HIV-1 RNAs | X | X | | | X | X | X | X | X | X | X | | X | X | X | |
| Plasma storage sample[r] | X | X | | | X | X | X | X | X | X | X | | X | X | X | |
| HIV-1 proviral genotype[s] | X | | | | | | | | | | | | | | | |
| Whole blood storage sample[t] | | X | | | | | | X | | X | X[t] | | | | | |

| | | Randomized Phase | | | | | | | | | Extension Phase | | ESDD[f] | Post-Study Drug Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Week | | | | | | | Week | | | | | |
| **Study Procedures** | **Screening[a]** | **Day 1[b]** | **Day 2[c]** | **2[d]** | **4, 8** | **12** | **18** | **24** | **30, 36, 42** | **48[e]** | **Week 60 and every 12 weeks thereafter** | **Week 96 and every 48 weeks thereafter** | **Within 3 Days of Last Dose** | **30-Day Follow-up[g]** | **60-Day Follow-up[g]** | **100-Day and 200-Day Follow-up[h]** |
| **Visit Window (Days)** | **Within 35 Days Prior to Day 1** | | | **± 1 day** | **± 7 days** | | | | | | **± 14 days** | | **+ 1 day** | **± 7 days** | | |
| PK plasma collection[u] | | X | | | X | X | X | X | X | X | X | | | | | |
| CCI | | | | | | | | | | | | | | | | |
| Randomization[w] | | X | | | | | | | | | | | | | | |
| Oral ISL+LEN dispensation | | X | | | X | X | X | X | X | X | X | | | | | |
| B/F/TAF dispensation (Treatment Group 4)[x] | | X | | | X | X | X | X | X | | | | | | | |
| Telephone visit | | | X[c] | X[d] | | | | | | | | | | | | |
| Study drug accountability | | | | | X | X | X | X | X | X | X | | X | | | |

AE = adverse event; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CD4 = clusters of differentiation 4; CPK = creatine phosphokinase; ECG = electrocardiogram; EQ-5D-5L = 5-level EuroQoL (5 dimensions); ESDD = early study drug discontinuation; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIVDQoL = HIV Dependent Quality of Life; HIVTSQs12 = HIV Treatment Satisfaction Questionnaire 12 status version; HIVTSQc12 = HIV Treatment Satisfaction Questionnaire change version; ICF = informed consent form; ISL = islatravir; LEN = lenacapavir; PK = pharmacokinetic(s); PP-R = Patient Perspective of Regimen; PP-RC = Patient Perspective of Regimen Change; PRO = patient-reported outcome; TBNK = T, B, and natural killer cells

a Screening evaluations must be completed within 35 days prior to Day 1. Conditions for participant rescreening are outlined in Section 6.2.. Participants in Treatment Group 3 must stop their B/F/TAF treatment on Day −1.

b Day 1 tests and procedures must be completed prior to administration of the dose of study drugs. Participants in Treatment Group 3 must begin dosing on Day 1 and will take their dose of study drug on site.

c Participants in the PK substudy will come to the site for a study visit on Day 2 and will take their dose of study drug at the site. All other participants in Treatment Group 3 will receive a telephone call to confirm adherence to the Day 2 LEN dose.

d Participants in Treatment Groups 3 and 4 will have a telephone visit at Week 2 to assess AEs and concomitant medications and, for Treatment Group 3 only, to confirm adherence to weekly ISL+LEN dosing.

e At the Week 48 visit, all participants will be given the option to take ISL+LEN in an Extension Phase until drug is commercially available or until Gilead elects to discontinue the development of ISL+LEN, whichever occurs first. Participants in Cohort 2 who complete the study through the Week 48 visit and do not wish to participate in the Extension Phase will be required to return to the clinic after the Week 48 visit for a 30-day follow-up visit, and participants in Treatment Group 3 will also return for a 60-day follow-up visit. Then the participants will be considered to have completed the study. Participants in Treatment Group 4 who switch to ISL+LEN in the Extension Phase will receive telephone calls to confirm adherence to the second day of the LEN loading dose and the second ISL+LEN weekly dose.

f Visit should occur within 3 days (+1 day) of permanently discontinuing study drugs. Participant should be counseled regarding the importance of resuming a complete ARV therapy in accordance with standard-of-care and referred to an appropriate HIV treatment facility.

g Participants who received ISL+LEN and discontinue study drugs are required to return to the clinic for follow-up visits 30 and 60 days after the last ISL+LEN dose. Participants who received only B/F/TAF (ie, did not switch to ISL+LEN) and discontinue study drugs will be required to return to the clinic for a follow-up visit 30 days after the last on-study B/F/TAF dose. Details are provided in Section 6.4.

h Participants in Treatment Group 3 or any Cohort 2 participant in the Extension Phase who were discontinued on ISL+LEN due to decrease in CD4 or lymphocytes. Day 200 follow-up visit to be completed only as needed.

i Participants will complete the questionnaires at the specified visits before completion of other study procedures. Questionnaires are to be completed at Week 4 and not completed at Week 8.

j The PP-R will be completed by participants in Treatment Groups 3 and 4 on Day 1, Weeks 4, 8, 12, 24, 36, 48, 60, and every 12 weeks thereafter.

k The PP-RC will be completed at Weeks 4, 8, 12, 24, 36, 48, 60, and every 12 weeks thereafter. Participants in Treatment Group 4 will complete the PP-RC every 12 weeks after switching to ISL+LEN in the Extension Phase.

l Vital signs include blood pressure, pulse, temperature, and weight.

m Complete physical examination is required at the screening, Day 1, and ESDD visits.

n Analyses to be performed by the central laboratory.

o Women of childbearing potential will have a serum pregnancy test at screening and urine pregnancy test at Day 1, Weeks 12, 24, 36, 48, and Post Week 48-Every 12 Weeks in Randomized Phase, in Extension Phase every 12 weeks and at ESDD. If any pregnancy test is positive, study drugs should be immediately discontinued, and participant should come to the site for serum pregnancy test.

p FSH test is required for women who are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

q HBcAb, HBsAg, HBsAb, HBV DNA, HCV RNA.

r For additional safety and virology testing (HIV-1 genotype and phenotype).

s Whole blood sample collected at screening visit for proviral genotype analysis of archived resistance.

t Whole blood sample storage to test for archived resistance. Sampling will occur at the Day 1, Week 24, and Week 48 visits, and every 24 weeks thereafter.

u PK collection: For Treatment Group 3, single anytime plasma PK sampling for ISL and LEN will occur at each onsite visit through Week 72 except at Day 1. Day 1 PK sample will be collected 1 hour (± 30 minutes) postdose after onsite study drug administration. The date and time of the previous dose of ISL+LEN will be recorded. PK samples collected at Week 60 and 72 will be stored and analyzed only if deemed necessary by the sponsor.

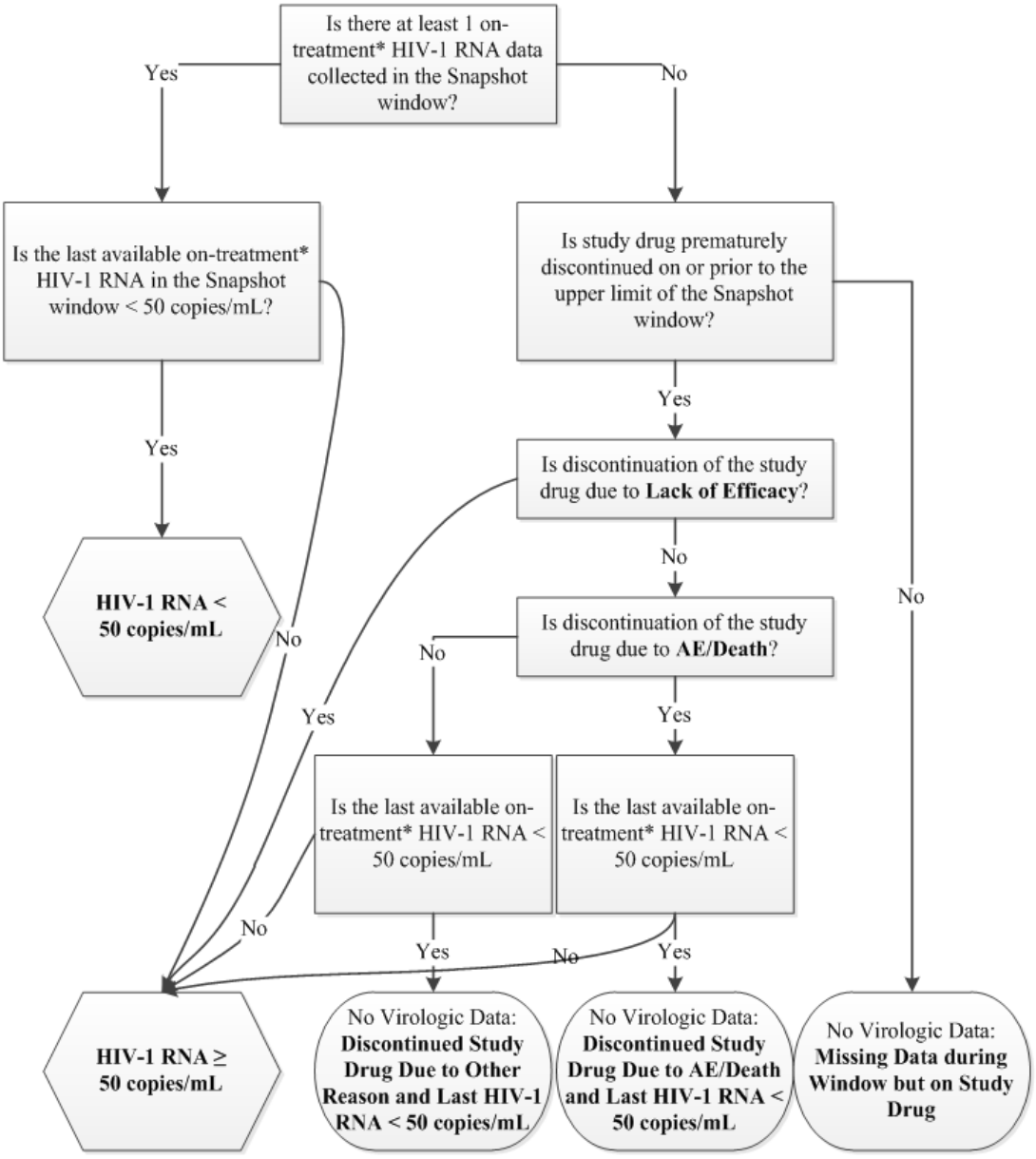
v CCI [redacted]

w Participants will be randomized to 1 of the 2 treatment groups in Cohort 2 on Day 1 after the ICF has been signed, all screening and eligibility tests and assessments have been performed, and study eligibility has been confirmed. Participants in Treatment Group 3 will stop B/F/TAF on Day −1.

x B/F/TAF dispensation applies only to participants randomized to Treatment Group 4.

# Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Switched Trial)

**Appendix Figure 1. The following flowchart for US FDA-defined snapshot algorithm is based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment {U. S. Department of Health and Human Services 2015}**




* On-Treatment HIV-1 RNA data include all HIV-1 RNA data for subjects who are on-going and HIV-1 RNA data up to 1 day after the last dose date of study drug for subjects who prematurely discontinue or complete study drug.

## Appendix 3. Programming Specification

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

b) Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

c) Divide the result in (b) by 12,

AGE = the integer of the result in (c),

Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened participants refer to all participants who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same participant is counted only once.

3) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the participant is randomized (ie, participant with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset.

4) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if participant took at least 1 dose of study drug and assigned as blank if the participant was never dosed.

5) In the disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

6) Body mass index (BMI)

BMI will be calculated only at baseline as follows:

— BMI = (weight [kg]) / (height [meters]$^2$)

Baseline height and weight will be used for this calculation if available.

7) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

a) CMH test for nominal variable (Y), the p-value from general association test should be used for nominal variable:

```
proc freq order=adsl;
   tables trtgrp * Y /cmh /*general association test*/
run;
```

b) CMH test for ordinal variable (Y), the p-value from row mean score test should be used for ordinal variable:

```
proc freq order=adsl;
   tables trtgrp * Y / cmh2 ; /*row mean score test*/
run;
```

c) Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variable:

```
proc npar1way wilcoxon data=adsl;
   class trtgrp;
   var Y;
run;
```

d) For race and ethnicity, “Not Permitted”, or “Missing” will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis (eg, CMH test or Wilcoxon rank sum test).

8) Study Day 1, Last Dose Date, and Last Study Date

a) All the key dates were defined in Section 3.8.1.

b) **Study Day 1 (Randomized Phase)** is defined as the earliest of the dose start dates from any Study Drug Administration eCRF (ie, EX).

c) **Study Day 1 (Extension Phase)** is defined as the earliest of the dose start dates in extension phase from Study Drug Administration eCRF (ie, EX.PHASE=’Post Week 48 Treatment/Extension Phase’).

d) **Last Dose Date (Randomized Phase)** is the latest of the randomized study drug (including B/F/TAF, ISL or LEN) end dates, as recorded on the “Treatment Phase” Study Drug Administration eCRF (ie, EX.PHASE=’Treatment’).

e) **Last Dose Date (Extension Phase)** is defined for participants who prematurely discontinued or completed study drug according to the “Extension Phase” Study Drug Completion eCRF as the latest of the extension phase study drug (including ISL or LEN) end dates recorded on the “Post Week 48 Treatment/Extension Phase” Study Drug Administration eCRF (ie, EX.PHASE=’Post Week 48 Treatment/Extension Phase’).

f) **Last Dose Date** is defined for participants who prematurely discontinued study drug (at either phase) or who completed study drug, as the latest of the study drug (including B/F/TAF, ISL or LEN) end dates recorded on Study Drug Administration eCRF.

g) For participants who prematurely discontinued study drug with a partial or missing study drug end date, the **Last Dose Date** (for the phase from which the participant discontinued treatment, and for the sutdy) will be imputed as following,

- If only year of last dose date is known or completely missing due to lost to follow-up, the latest of the study drug nonmissing start dates and stop dates, the clinical visit dates (excluding the follow-up after ESDD/ET) and the laboratory visit dates will be used to impute the last dose.
- If month and year of last dose are known, the latest of the dispensing dates of study drug, study drug start dates and stop dates, and the imputed last dose date (day imputed as 15) will be used as the final imputed last dose date. However, if dispensing date's month is after last dose date's month, data query is needed.
- If participant died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

h) **Last Dose Date** (of extension phase and for the study) is not applicable for participants still on study drug (of extension phase) at the time of Week 48 Interim Analysis. The data cut date will be used for last dose date in calculations. If the date cut date is earlier than the Study Day 1 (of extension phase), then the Study Day 1 (of extension phse) will be used as last dose date for calculation propose only for participants still on study drug.

i) **Last Study Date** is the latest of the study drug start dates and stop dates, the clinic visit dates (including the date of follow-up visits), the laboratory visit dates, and/or latest AE onset date and end date, whichever is latest, for participants who prematurely discontinued study, or who completed the study for randomized phase. If study drug start date or stop date is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis. If participant died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

j) Last study date is not applicable for participants still on study. However, for programing purposes, the data finalization date will be used to impute the last study date for participants still on study.

9) Efficacy and Safety Analysis comparison

a) For categorical efficacy response (eg, Participants with HIV-1 RNA < 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between ISL+LEN group and the B/F/TAF group and its 95% CIs are calculated using an unconditional exact method using 2 invert 1-sided tests {Chan 1999} with an alpha level at 0.05.

```
proc freq data = example;
table trt*outcome /riskdiff(CL=(exact)) alpha=0.05;
exact barnard RISKDIFF(METHOD=SCORE);
output out=ciexact (keep=_RDIF1_ XL_RDIF1 XU_RDIF1) riskdiff;
run;
```

b) All the ANCOVA model for continuous efficacy variable or safety variable (eg, CD4+, lymphocyte): The differences in changes from baseline between treatment groups and the associated 95% CI will be constructed using an ANCOVA, including baseline absolute value *base*, and treatment *trtgrp* as fixed effects in the model,

```
proc glm data=adeff;
      class trtgrp;
      model CD4_chg=base trtgrp;
      lsmeans trtgrp /alpha=0.05 cl pdiff;
run;
```

10) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken on or after first dose date) will be flagged in “Antiviral Medication” listings.

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## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
|---|---|---|
| PPD | | |