STATISTICAL ANALYSIS PLAN

Study Title:	Phase 3 Double-Blind Multicenter Randomized Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide) in Virologically Suppressed People with HIV-1
Name of Test Drug:	Bictegravir/Lenacapavir (BIC/LEN)
Study Number:	GS-US-621-6290
Protocol Version (Date):	Amendment 2 (03 April 2025)
Analysis Type:	Week 48 Primary Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	20 November 2025
Analysis Plan Author(s):	PPD .

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 4
LIST OF IN-TEXT FIGURES 4
LIST OF ABBREVIATIONS 5
1. INTRODUCTION 7
1.1. Study Objectives and Endpoints 7
1.2. Study Design 8
1.3. Sample Size and Power 9
1.3.1. Rationale for Non-Inferiority Margin 9
2. TYPE OF PLANNED ANALYSES 10
2.1. Interim Analyses 10
2.1.1. Data Monitoring Committee Analyses 10
2.1.2. Week 96 Interim Analysis 11
2.2. Week 48 Primary Analysis 11
2.3. Final Analysis 11
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 12
3.1. Analysis Sets 12
3.1.1. All Randomized Analysis Set 12
3.1.2. Full Analysis Set 12
3.1.3. Per-Protocol Analysis Set 13
3.1.4. Safety Analysis Set 13
3.1.5. Pharmacokinetic Analysis Set 14
3.2. Participant Grouping 14
3.3. Strata and Covariates 14
3.4. Examination of Participant Subgroups 14
3.5. Multiple Comparisons 15
3.6. Missing Data and Outliers 15
3.6.1. Missing Data 15
3.6.2. Outliers 15
3.7. Data Handling Conventions and Transformations 15
3.8. Analysis Visit Windows 17
3.8.1. Definition of Study Day 17
3.8.2. Analysis Visit Windows 18
3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window 20
4. PARTICIPANT DISPOSITION 22
4.1. Participant Enrollment and Disposition 22
4.2. Extent of Study Drug Exposure and Adherence 23
4.2.1. Duration of Exposure to Study Drug 23
4.2.2. Adherence to Study Drug 24
4.3. Protocol Deviations 25
5. BASELINE CHARACTERISTICS 26
5.1. Demographics and Baseline Characteristics 26

5.2. Other Baseline Characteristics 26
5.3. Medical History 27
6. EFFICACY ANALYSES 28
6.1. US FDA-Defined Snapshot Algorithm 28
6.2. Estimand 29
6.3. Primary Efficacy Endpoint 30
6.3.1. Definition of the Primary Efficacy Endpoint 30
6.3.2. Statistical Hypothesis for the Primary Efficacy Endpoint 30
6.3.3. Primary Analysis of the Primary Efficacy Endpoint 30
6.3.4. Sensitivity and Supportive Analysis of the Primary Efficacy Endpoint 31
6.3.5. Subgroup Analysis of the Primary Efficacy Endpoint 32
6.4. Secondary Efficacy Endpoints at Week 48 32
6.4.1. Definition of Secondary Efficacy Endpoints at Week 48 32
6.4.2. Primary Analysis of Secondary Efficacy Endpoints at Week 48 32
6.4.3. Sensitivity and Supportive Analysis of Secondary Efficacy Endpoints 33
6.4.4. Subgroup Analysis of the Secondary Efficacy Endpoints 33
6.5. Other Efficacy Evaluations 34
6.5.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL by Visit 34
6.5.2. Change from Baseline in HIV-1 RNA Values by Visit 35
6.5.3. Change from Baseline in CD4 Cell Count by Visit 35
7. SAFETY ANALYSES 36
7.1. Adverse Events and Deaths 36
7.1.1. Adverse Event Dictionary 36
7.1.2. Adverse Event Severity 36
7.1.3. Relationship of Adverse Events to Study Drug 36
7.1.4. Relationship of Adverse Events to Study Procedure 36
7.1.5. Serious Adverse Events 37
7.1.6. Treatment-Emergent Adverse Events 37
7.1.7. Summaries of Adverse Events and Deaths 37
7.2. Laboratory Evaluations 39
7.2.1. Summaries of Numeric Laboratory Results 40
7.2.2. Graded Laboratory Values 40
7.2.3. Liver-related Laboratory Evaluations 41
7.3. Body Weight and Vital Signs 42
7.4. Prior and Concomitant Medications 42
7.4.1. Antiretroviral Medications 43
7.4.2. General Medications (Non-Antiretroviral) 43
7.5. Other Safety Measures 44
7.6. Changes From Protocol-Specified Safety Analyses 44
8. PHARMACOKINETIC ANALYSES 45
8.1. PK Sample Collection 45
8.2. PK Analysis Related to Sparse PK Sampling 45
8.3. Changes from Protocol-Specified PK Analyses 46
9. REFERENCES 47
10. SOFTWARE 48
11. SAP REVISION 49
12. APPENDICES 50
12.1. Schedule of Assessments 50

12.2. US FDA-Defined Snapshot Algorithm 55
12.3. Stratified Mantel-Haenszel Method with the Sato Variance Estimator 56
12.4. Programming Codes for Multiple Imputation 57
12.5. Handling of Laboratory Values 58

LIST OF IN-TEXT TABLES

Table 3-1. Participants Excluded from Week 48 Per-Protocol Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 48 Analysis Window 13
Table 3-2. Analysis Visit Windows for Plasma HIV-1 RNA, CD4 Cell Count, Chemistry, Hematology, Weight and Vital Signs 19
Table 3-3. Analysis Visit Windows for Urinalysis Assessments 19
Table 3-4. Analysis Visit Windows for Metabolic Assessments 20
Table 3-5. Analysis Visit Windows for Hemoglobin A1c 20
Table 6-1. Estimand and Handling for Intercurrent Events for Virologic Outcomes 29
Table 8-1. Study Treatments and Associated Analytes 45
Table 12-1. Study Procedures Table 50

LIST OF IN-TEXT FIGURES

Figure 1-1. Study Schema 8
Figure 12-1. Flowchart of US FDA-Defined Snapshot Algorithm 55

LIST OF ABBREVIATIONS

%CV	percentage coefficient of variation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BIC	bictegravir
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
DMC	data monitoring committee
ECG	electrocardiogram
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EBT	end of blinded treatment
ESDD	early study drug discontinuation
ET	early termination
EU	Europe
FAS	Full Analysis Set
FDC	fixed-dose combination
HDL	high-density lipoprotein
HLGT	high-level group term
HLT	high-level term
ID	identification
INSTI	integrase strand-transfer inhibitor
IRT	Interactive Response Technology
IXRS	interactive voice or web response system
LEN	lenacapavir
LDL	low-density lipoprotein
LLT	lower-level term
LOQ	limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model with repeated measures

NI	noninferiority
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitors
OL	open-label
PI	protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
PWH	people with HIV-1
Q1	first quartile
Q3	third quartile
QD	once daily
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TELA	treatment-emergent laboratory abnormality
TFLs	tables, figures, and listings
UK	United Kingdom
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the primary analysis at Week 48 of Study GS-US-621-6290. The analysis will be performed after all participants enrolled complete their Week 48 visit or prematurely discontinue from the study drug.

This SAP is based on the study protocol amendment 2 dated 03 April 2025 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the primary analysis. Any changes made after the finalization of the SAP will be documented in the Interim Week 48 clinical study report (CSR).

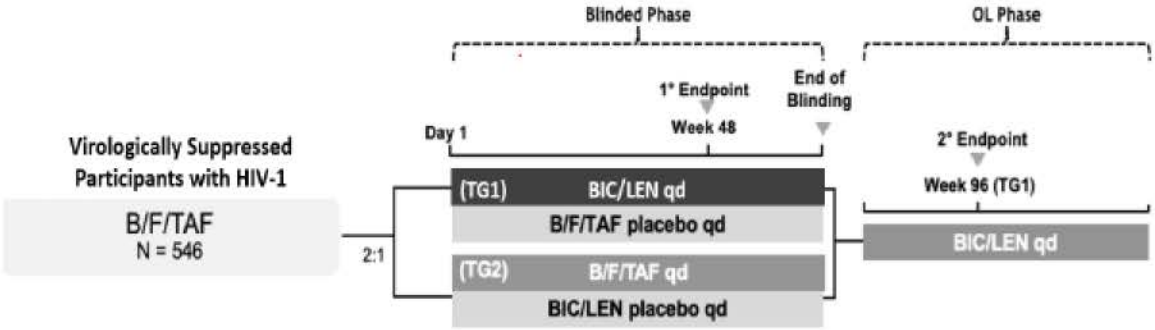
1.1. Study Objectives and Endpoints

Primary Objective	Primary Endpoint
• To evaluate the efficacy of switching to bictegravir/lenacapavir (BIC/LEN) (75/50 mg) fixed-dose combination (FDC) tablets versus continuing on bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) (50/200/25 mg) FDC tablets in virologically suppressed people with HIV-1	• 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
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of study drug(s) for the 2 treatment groups in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count	• Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA–defined snapshot algorithm • Change from baseline in CD4 cell count at Week 48
• To evaluate the long-term efficacy of BIC/LEN in participants from Treatment Group 1 as determined by viral load suppression rate and CD4 cell count	• Proportion of participants from Treatment Group 1 with HIV-1 RNA ≥ 50 copies/mL at Week 96 (96 weeks on BIC/LEN including blinded and open-label [OL] phases) as determined by US FDA–defined snapshot algorithm • Proportion of participants from Treatment Group 1 with HIV-1 RNA < 50 copies/mL at Week 96 (96 weeks on BIC/LEN including blinded and OL phases) as determined by US FDA–defined snapshot algorithm • Change from baseline in CD4 cell count at Week 96 for participants from Treatment Group 1 (96 weeks on BIC/LEN including blinded and OL phases)
• To evaluate the safety and tolerability of the study drug(s) for the 2 treatment groups	• Proportion of participants experiencing treatment-emergent adverse events (AEs) through Week 48
• To evaluate the long-term safety and tolerability of BIC/LEN in participants from Treatment Group 1	• Proportion of participants from Treatment Group 1 experiencing treatment-emergent AEs through Week 96 (96 weeks on BIC/LEN including blinded and OL phases)

1.2. Study Design

This study is a Phase 3 double-blind, multicenter, randomized, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus B/F/TAF in virologically suppressed people with HIV-1 on B/F/TAF for at least 6 months prior to screening.

Figure 1-1. Study Schema



1° = primary; 2° = secondary; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC/LEN = bictegravir/lenacapavir; OL = open label; qd = once daily; TG1 = Treatment Group 1: TG2 = Treatment Group 2
Week 96 is 96 weeks treatment duration including the blinded and OL phase up to OL Week 48.

Participants were randomized in a 2:1 ratio to one of the following treatment groups during the blinded phase:

- **Treatment Group 1 (n = 364):** Participants switched from B/F/TAF (50/200/25 mg) FDC tablets to BIC/LEN (75/50 mg) FDC tablets + placebo-to-match (PTM) B/F/TAF tablets administered orally, once daily, without regard to food. Participants received a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN tablets on Day 1 and on Day 2, without regard to food), in addition to the daily doses of BIC/LEN FDC tablet starting on Day 1.

- **Treatment Group 2 (n = 182):** Participants continue with B/F/TAF (50/200/25 mg) FDC tablets and start PTM BIC/LEN tablets on Day 1 administered orally, once daily, without regard to food. Participants received PTM LEN tablets for 2 days (2 PTM LEN tablets on Day 1 and on Day 2, without regard to food).

Randomization was stratified by geographic region.

Participants will be treated for at least 48 weeks during the blinded phase; participants from Treatment Group 1 will be treated with BIC/LEN FDC tablets for at least 96 weeks, including the blinded and open-label (OL) phases, up to OL Week 48. After blinded Week 48, all participants will continue to take their blinded study drug, and attend visits every 12 weeks. Once the last participant completes the Week 48 visit and the analysis of safety and efficacy data of BIC/LEN FDC compared with B/F/TAF FDC is completed, all participants will attend an end of blinded treatment (EBT) visit at the next in-clinic visit (preferably within 12 weeks). At the EBT visit, participants in Treatment Group 1 will enter the OL phase and will continue to receive BIC/LEN FDC tablets through at least OL Week 48. At the OL Week 48 visit, participants in

Treatment Group 1 will be given option to continue to receive BIC/LEN FDC tablets. At the EBT visit, participants from Treatment Group 2 will be given the option to enter the OL phase to receive BIC/LEN FDC tablets and continue in the study.

Following the Day 1 visit, participants will be required to return for study visits on Day 2 (option to conduct this as a virtual visit will be available, as appropriate), Weeks 4, 12, 24, 36, and 48. After the Week 48 visit and until the EBT visit, all participants will be required to return for visits every 12 weeks.

All participants enrolled in the OL phase will return for clinic visits every 12 weeks and will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the end of the OL phase. Participants from Treatment Group 1 will continue the BIC/LEN FDC tablets in the OL phase without any oral loading doses of LEN. Participants from Treatment Group 2 who enter the OL phase will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily BIC/LEN FDC tablet starting on Day 1 of the OL phase. Following the Day 1 visit, participants will be required to return for the study visit on Day 2 (option to conduct this as a virtual visit will be available, as appropriate) and will attend a Week 4 visit during the OL phase.

Additional details regarding study assessment can be found in Table 12-1.

1.3. Sample Size and Power

Sample size calculations are based on the historical Gilead Genvoya® and B/F/TAF studies. Assuming that the virologic failure rate is 2% for both treatment groups, and a noninferiority margin of 4%, a total of approximately 546 participants, with 2:1 randomization ratio of BIC/LEN versus B/F/TAF, will provide approximately 90% power to show noninferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/mL) at Week 48 at a 1-sided significance level of 0.025.

1.3.1. Rationale for Non-Inferiority Margin

According to the FDA's 2015 guidance document {U. S. Department of Health and Human Services 2015}, the margin for switch trials is driven by the largest clinically tolerable virologic failure rate. Per the FDA guidance, a margin of 4% for the primary endpoint of virologic failure rate (HIV-1 RNA ≥ 50 copies/mL) is considered clinically tolerable, with typical observed rates of virological failure seen in switch studies range from 1% to 3%.

2. TYPE OF PLANNED ANALYSES

This SAP describes the analyses for the primary and secondary endpoints planned for the Week 48 primary analysis of this study.

2.1. Interim Analyses

Prior to the final analysis, at least 2 analyses will be conducted to evaluate primary and secondary objectives of the protocol, one after all participants complete their visits at Week 48, and the other after all participants in Treatment Group 1 complete their visits at Week 96. The Week 48 analysis will serve as the primary analysis. Additional interim analyses may be conducted as necessary after Week 96 in order to support regulatory submission and/or publication(s).

No interim analysis will be conducted prior to Week 48 primary analysis.

2.1.1. Data Monitoring Committee Analyses

An external multidisciplinary Data Monitoring Committee (DMC) reviews the progress of the study and performs interim reviews of the safety data in order to protect participant welfare and preserve study integrity. To ensure the best interests of the participants, the DMC makes recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

There were 2 planned DMC analyses conducted. The Week 12 DMC analysis was conducted after approximately the first 50% of participants enrolled completed their Week 12 visit or prematurely discontinued the study drug. The Week 24 DMC analysis was conducted after all participants enrolled completed their Week 24 visit or prematurely discontinued the study drug.

The DMC's role and responsibilities and the scope of analyses to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

The study will not be stopped early for positive efficacy findings. Conservatively, an alpha penalty of 0.00001 will be applied for each DMC efficacy evaluation performed prior to the analysis of the primary efficacy endpoint.

No formal interim efficacy analysis, which may lead to early termination for efficacy or futility, is planned.

2.1.2. Week 96 Interim Analysis

Week 96 interim analysis will be conducted after all participants enrolled in Treatment Group 1 either complete 96 weeks of study intervention starting from Day 1 or prematurely discontinue from the study drug, outstanding data queries are resolved or adjudicated as unresolvable, and the data are cleaned and finalized for the analysis.

2.2. Week 48 Primary Analysis

The primary analysis for the primary endpoint of proportion of participants with HIV-1 RNA $\geq$ 50 copies/mL as determined by the US FDA-defined snapshot algorithm will be conducted at Week 48. The Week 48 primary analysis will be conducted after all participants enrolled either complete their Week 48 visit or prematurely discontinue from the study drug, outstanding data queries are resolved or adjudicated as unresolvable, and the data are cleaned and finalized for the analysis. This analysis of the primary endpoint will serve as the final analysis for this endpoint and will be used to evaluate the efficacy of BIC/LEN FDC.

2.3. Final Analysis

The final analysis will be performed after all participants complete the study or prematurely discontinue from the study, outstanding data queries are resolved or adjudicated as unresolvable, and the data are cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The Week 48 primary analysis will include all data collected from the blinded phase of the study. No participant will be enrolled into the OL phase before the completion of the Week 48 primary analysis.

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.

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 are 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

The **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. Per-Protocol Analysis Set

The **Week 48 Per-Protocol (PP) Analysis Set** includes all participants in the FAS excluding participants meeting any of the following criteria:

- Do not have on-treatment HIV-1 RNA data in the Week 48 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation in the randomized treatment period on Study Drug Completion eCRF form). See Table 3-1.

Table 3-1. Participants Excluded from Week 48 Per-Protocol Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 48 Analysis Window

Discontinuation from Study Drug prior to or on the Upper Bound of Week 48 Analysis Window		On-Treatment HIV-1 RNA Data Available in Week 48 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Reasons Other Than Lack of Efficacy	+	-
No		+	-

"+" = Inclusion of participants in Week 48 Per-Protocol analysis set; "-" = Exclusion of participants in Week 48 Per-Protocol analysis set.

- Non-adherence to study drug: adherence rate below the 2.5th percentile for study drug up to Week 48.

- Did not have at least one documented plasma HIV-1 RNA level measured between 6 and 12 months (± 2 months) prior to screening, or not all available plasma HIV-1 RNA measurements in the 6 months prior to screening or between 6 and 12 months (± 2 months) prior to screening were < 50 copies/mL (inclusion criteria 4 and 5 in the protocol).

- Did not meet the exclusion of documented or suspected resistance to BIC (inclusion criterion 7 in the protocol).

The Week 48 PP Analysis Set is the secondary analysis set for the efficacy analyses.

3.1.4. Safety Analysis Set

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

3.1.5. Pharmacokinetic Analysis Set

The **Pharmacokinetic (PK) Analysis Set** includes participants who were randomized and took at least 1 dose of study drug BIC/LEN FDC, and have at least 1 nonmissing concentration value reported by the PK laboratory. This is the analysis set for general/sparse PK analyses.

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 PP Analysis Set, Safety Analysis Set, and PK 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.

3.3. Strata and Covariates

Participants were randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 2:1 ratio using a stratified randomization schedule. Stratification was based on the geographic region as below.

- Europe (EU): France, Italy, Spain, Germany, United Kingdom (UK)
- Asia: South Korea, Taiwan, Japan
- Oceania: Australia
- Africa: South Africa
- Central and South America: Dominican Republic, Argentina
- North America (NA): United States (US, including Puerto Rico), Canada, Mexico

No participants were enrolled in France, South Africa, and Dominican Republic as initially planned. If there are discrepancies in stratification factor values between the IXRS 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.

Efficacy endpoints will be evaluated using stratification factor as covariate or stratification variable for analyses, as specified in Section 6.

3.4. Examination of Participant Subgroups

The primary and key secondary efficacy endpoints will be examined using the following subgroups based on FAS:

- Age (< 55 years and ≥ 55 years)

- Sex (male and female)
- Race (white, non-white, and not permitted)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not permitted)
- Region (US [including US and Puerto Rico] and Ex-US)

If there is an imbalance between treatment groups in the presumed prognostic baseline characteristics that are not prespecified, subgroupings based on these imbalanced baseline characteristics may also be explored for analysis of efficacy endpoints.

3.5. Multiple Comparisons

For the study, noninferiority evaluation of the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by US FDA-defined snapshot algorithm is the prespecified primary comparison.

There were 2 interim DMC analyses performed prior to the analysis for the primary endpoint. Conservatively, an alpha penalty of 0.00001 will be applied for each interim DMC analysis on efficacy. Therefore, the alpha level for the primary endpoint (ie, the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA–defined snapshot algorithm) will be adjusted to 0.04998 (corresponding to 95.002% CI) to control the overall Type I error rate.

No alpha level adjustment will be applied other than for the primary endpoint listed above.

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 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for prior and concomitant medications is 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

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age on 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 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 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 (except HIV-1 RNA 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).

HIV-1 RNA data will be applied by logarithm (base 10) transformation for analysis of change from baseline in HIV-1 RNA. HIV-1 RNA reported results of "No HIV-1 RNA detected" and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes. HBV DNA reported results of "No HBV DNA Detected" and "<10 IU/mL HBV DNA Detected" will be imputed as 9 IU/mL for analysis purposes.

Pharmacokinetic 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. Values that are BLQ will be treated as 0 at all predose and postdose time points for summary purposes.

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 PK concentrations:

- 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".

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day will be calculated from the first dosing date of study drug and derived as follows:

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

The earliest of the first dosing date of any component is considered as the first dose date of the study drug.

Study Day 1 is the day of first dose of study drug administration (ie, LEN oral loading or placebo, BIC/LEN or placebo, B/F/TAF or placebo).

Last Dose Date in the blinded phase is the latest of the blinded study drug stop dates recorded on the Study Drug Administration eCRF form for participants who prematurely discontinue or complete study drug in the blinded phase.

If the last dose date is incomplete (ie, only year of last dose date is known) or missing, the latest date among the study drug nonmissing start date and stop date, the clinic visit dates (excluding the follow-up dates after early study drug discontinuation [ESDD]), and the laboratory sample collection dates (excluding the follow-up dates after ESDD) will be used for participants who prematurely discontinue study drug in the blinded phase, or the date cut date will be used for participants who are still on treatment at the time of an interim analysis.

If only the month and year of the last dose are known, the latest date among the study drug dispensing date, study drug start date and stop date, and the imputed last dose date (day imputed as 15) will be used as the last dose date.

If a participant dies, the death date is complete and before the imputed last dose date by above rules, the complete death date should be used as the imputed last dose date.

Last Study Date in the blinded phase is the latest date among the study drug start date and stop date, the clinic visit date (including the 30-day and 60-day follow-up visit dates), and the laboratory sample collection date, for participants who prematurely discontinue study, or who complete the study.

Baseline value is defined as the last value obtained on or prior to Study Day 1 in the blinded phase for all assessments, unless otherwise specified.

3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations collected from the blinded phase visits will be assigned to analysis windows.

Analysis windows for the blinded phase analysis are derived relative to Study Day 1 in the blinded phase.

The analysis windows for efficacy endpoints, vital signs, weight and chemistry/hematology laboratory data are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for Plasma HIV-1 RNA, CD4 Cell Count, Chemistry, Hematology, Weight and Vital Signs

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week X* (Every 12 weeks post-Week 48, X > 48)	7*X	7*X - 41	7*X + 42

* After Week 48, visits will be conducted every 12 weeks until end of blinded treatment visit.

The analysis windows for safety urinalysis laboratory data are provided in Table 3-3.

Table 3-3. Analysis Visit Windows for Urinalysis Assessments

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	378
Week X* (Every 12 weeks post-Week 48, X > 48)	7*X	7*X - 41	7*X + 42

* After Week 48, visits will be conducted every 12 weeks until end of blinded treatment visit.

The analysis windows for safety metabolic assessment data are provided in Table 3-4.

Table 3-4. Analysis Visit Windows for Metabolic Assessments

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	420
Week X* (Every 24 weeks post-Week 48, X > 48)	7*X	7*X – 83	7*X + 84

* After Week 48, visits will be conducted every 24 weeks until end of blinded treatment visit.

The analysis windows for hemoglobin A1c data are provided in Table 3-5.

Table 3-5. Analysis Visit Windows for Hemoglobin A1c

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 48	336	2	≥ 336

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 per analysis window.

If multiple valid, nonmissing measurements (except for HIV-1 RNA) 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 dosing date of study drug will be selected. 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, 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:
  - For CD4 data, the record collected on the latest day in the analysis window will be selected.

- For other observations, the record closest to the nominal day for that visit will be selected. 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 values of HIV-1 RNA, if there are multiple valid nonmissing measurements existing in an analysis window, the latest (considering both collection date and time) record(s) in the analysis visit window will be selected. If both battery names "HIV-1 RNA COBAS 6800" and "HIV RNA REPEAT COBAS" (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 "HIV RNA REPEAT COBAS" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA COBAS 6800" 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) will be provided.

A summary of participant enrollment will be provided by treatment group for each country, investigator within a country, and overall. The summary will present the number and percentage of participants randomized using All Randomized Analysis set. 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 Interactive Response Technology (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.

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 for all screened participants. This summary will present the number of participants screened, the number of participants who had screen failures and were not randomized, the number of participants who met all eligibility criteria but were not randomized with reasons participants not randomized, the number of participants randomized, the number of participants randomized but never treated, and the number of participants in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- Per-Protocol Analysis Set
- PK Analysis Set
- Continuing study drug in blinded phase
- Did not complete study drug in blinded phase with reasons for premature discontinuation of study drug
- Completed Week 48 visit
- Continuing study

- Did not complete the study with reasons for premature discontinuation of study

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 addition, a flowchart will be provided to depict the disposition.

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 and day, last dose date and day, end of study date and day, study drug discontinuation, study discontinuation, and reasons for study drug or study discontinuation.
- Lot number and kit ID
- Participant profile, including treatment, date of randomization, first dose date and day, 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

Total duration of exposure to study drug will be defined as last dosing date – first dosing date + 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of participants exposed through the following time periods: $\geq$ 1 day, $\geq$ 4 weeks (28 days), $\geq$ 8 weeks (56 days), $\geq$ 12 weeks (84 days), $\geq$ 16 weeks (112 days), $\geq$ 24 weeks (168 days), $\geq$ 36 weeks (252 days), $\geq$ 48 weeks (336 days), etc. Summaries will be provided for the Safety Analysis Set.

Exposure to Oral loading LEN will be summarized using the number and percentage of participants exposed on Day 1, Day 2, and the reloading periods if any. Summaries will be provided for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The presumed total number of tablets administered to a participant for a study drug will be determined by the data collected on the drug accountability eCRF form using the following formulas:

$$\text{Total Number of Tablets Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a participant's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On} - \text{Treatment Adherence (\%)} = \left(\frac{\text{Total Number of Tablets Administered}}{\text{Tablets Expected to be Administered on Treatment}}\right) \text{x } 100$$

Total number of tablets administered is determined by summing number of tablets administered from all evaluable dispensing periods.

If the number of tablets dispensed is missing or any study drug bottle is not returned, that dispensing period is not evaluable and all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation of the adherence. If one drug bottle is returned but the number of tablets returned is missing, it is assumed the number of tablets returned was zero.

For each evaluable dispensing period, the number of tablets administered is calculated as the minimum of (a) the daily number of tablets prescribed for the study drug multiplied by the duration of treatment at the dispensing period, and (b) the number of tablets taken for the study drug (number of tablets dispensed minus the number of tablets returned).

Number of tablets expected to be administered is determined by summing the number of tablets prescribed as in protocol from all evaluable dispensing periods. Number of tablets prescribed at a distinct dispensing period is calculated as the daily number of tablets prescribed multiplied by the duration of treatment at the dispensing period.

The **duration of treatment** at a dispensing period is calculated as the minimum of {(a) the last bottle returned date at a dispensing period, (b) date of premature discontinuation of study drug + 1, and (c) next drug dispensing date} minus dispensing date in current dispensing period. The **next drug dispensing date** is the following dispensing date of the study drug regardless of the bottle return date. Total duration of treatment is the summation of duration of treatment at all evaluable dispensing periods.

Adherence in the blinded phase will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinue study drug or complete study drug in the blinded phase, or using all data available for participants who are ongoing on study drug.

Adherence up to the Week 48 visit will be calculated using data from all available dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinue study drug or up to the Week 48 study drug dispensing date, whichever occurs earliest.

Descriptive statistics for the level of on-treatment adherence to study drug with the number and percentage of participants belonging to adherence categories (eg, $< 80\%$, ≥ 80 to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-participant listing of study drug administrative and accountability (including the LEN oral loading doses and reloading doses if any) and adherence will be provided 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 deviations will be summarized by treatment group and by deviation category for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age at Day 1, sex at birth, gender identity, sexual orientation, race, ethnicity, and region) 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. For baseline body weight, height, and BMI, descriptive statistics will also be presented by sex in the same table. The summary of demographic and baseline characteristic data will be provided for the Safety Analysis Set.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- HIV-1 RNA level category: (a) < 50 copies/mL, (b) ≥ 50 copies/mL.
- CD4 cell count (/μL).
- CD4 cell count (/μL) category: (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500.
- CD4 percentage (%).
- Estimated glomerular filtration rate (Creatinine clearance by Cockcroft-Gault formula), $eGFR_{CG}$, mL/min
- HIV disease status: (a) AIDS, (b) asymptomatic, or (c) symptomatic HIV infection.
- Mode of infection (risk factors for HIV infection).
- Duration of HIV disease from diagnosis (in years): Calculated as (first dosing date of this study - date of initial diagnosis + 1 day) / 365.25. If the date of initial diagnosis is incomplete, then the following rules will be applied:
  - missing day: use the first day of the month.
  - missing month: use January.
- Duration since first HIV treatment (in years): Calculated as (first dosing date of this study - start date of the first HIV treatment + 1 day) / 365.25. If the date of first treatment start date is incomplete, rules same as above will be applied.

- Historical HIV-1 genotype resistance results: INSTI (Yes/No/Data Not Available), NNRTI (Yes/No/Data Not Available), NRTI (Yes/No/Data Not Available), PI (Yes/No/Data Not Available).

These baseline characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and using number and percentage of participants for categorical variables. The summary of these baseline characteristics will be provided for the Safety Analysis Set.

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

5.3. Medical History

Medical history data were collected at screening for general condition and will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). A summary of medical history will be provided by treatment group and overall by the number and percentage of participants with each prepopulated condition by coded terms based on the Safety Analysis Set.

Numbers and percentages of participants who had diabetes or prediabetes will be summarized.

No formal statistical testing is planned. A by-participant listing of medical history will also be provided.

6. EFFICACY ANALYSES

6.1. US FDA-Defined Snapshot Algorithm

The US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be used to determine the virologic outcomes at Week 48. The analysis window at Week 48 is defined as Study Day 295 to Study Day 378, inclusively. All HIV-1 RNA data collected on-treatment will be used in the US FDA-defined snapshot algorithm.

"On-treatment" is defined as all data collected up to 1 day after permanent discontinuation of study drug or all available data for participants who are still on study drug.

The virologic outcome will be defined as the following categories:

- **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.
- **HIV-1 RNA ≥ 50 copies/mL**: this includes participants
  a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or
  b) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and
     i) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or
     ii) 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 Window**: This includes participants who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:
  a) Discontinuation of study drug prior to or in the Week 48 analysis window due to AE or death, or
  b) 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
  c) Missing data during the window but on study treatment.

The flowchart of the US FDA-defined snapshot algorithm is provided in Figure 12-1.

All participants in FAS will be classified into 1 of the 3 categories indicated above (ie, HIV-1 RNA < 50 copies/mL, HIV RNA ≥ 50 copies/mL, or No Virologic Data) in the Week 48 Analysis Window. For the primary efficacy endpoint, the proportion of participants with HIV-1 RNA ≥ 50 copies/mL will be calculated as the number of participants classified as HIV-1 RNA ≥ 50 copies/mL divided by the number of participants in the FAS. For the key secondary efficacy endpoint, the proportion of participants with HIV-1 RNA < 50 copies/mL will be calculated as the number of participants classified as HIV-1 RNA < 50 copies/mL divided by the number of participants in FAS.

6.2. Estimand

The estimand for the virological outcomes is described in Table 6-1.

Table 6-1. Estimand and Handling for Intercurrent Events for Virologic Outcomes

Population	People with HIV-1 who are virologically suppressed
Treatment	BIC/LEN FDC and B/F/TAF FDC
Variable	HIV-1 RNA ≥ 50 copies/mL or HIV-1 RNA < 50 copies/mL at Week 48[a] (determined by the FDA-defined snapshot algorithm)
Intercurrent events & strategies	As defined by the snapshot algorithm, HIV-1 RNA ≥ 50 copies/mL is determined by the last available HIV-1 RNA measurement while the participant is on treatment in the Week 48 analysis visit window[a]. Participants who do not have on-treatment HIV-1 RNA data for Week 48[a] and discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or due to reasons other than AE, death, lack of efficacy while having the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, are treated as having HIV-1 RNA ≥ 50 copies/mL. HIV-1 RNA < 50 copies/mL is determined by the last available HIV-1 RNA measurement while the participant is on treatment in the Week 48 analysis visit window[a]. Participants who do not have on-treatment HIV-1 RNA data for Week 48[a] are treated as not having HIV-1 RNA < 50 copies/mL.
Population-level summary measure	Difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL or HIV-1 RNA < 50 copies/mL at Week 48 between BIC/LEN FDC and B/F/TAF FDC

BIC = bictegravir; FDA = Food and Drug Administration; FDC = fixed dose combination; HIV 1 = human immunodeficiency virus type 1; LEN = lenacapavir; RNA = ribonucleic acid; US = United States.
a Week 48 analysis window is defined as from Study Day 295 to Study Day 378, inclusively.

6.3. Primary Efficacy Endpoint

6.3.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The primary analysis of the efficacy will be based on the FAS.

6.3.2. Statistical Hypothesis for the Primary Efficacy Endpoint

In the primary analysis, proportion of participants with HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm at Week 48 in the Treatment Group 1 will be compared to the Treatment Group 2 for a non-inferiority test at the 2-sided 0.04998-level (after interim DMC analysis multiplicity adjustment as described in Section 3.5). If it is denoted that the proportion of participants with HIV-1 RNA ≥ 50 copies/mL in the Treatment Group 1 and Treatment Group 2 as P_1 and P_2, respectively, the null and alternative hypotheses for the non-inferiority test with a margin of θ on the primary efficacy endpoint are as follows:

H_0 (Null Hypothesis): $P_1 - P_2 \geq \theta$

vs.

H_1 (Alternatively Hypothesis): $P_1 - P_2 < \theta$

where the non-inferiority margin θ is 4%.

6.3.3. Primary Analysis of the Primary Efficacy Endpoint

The number and percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 based on the US FDA-defined snapshot algorithm will be summarized by treatment group for the analysis visit window of Week 48.

The treatment difference and the corresponding 2-sided 95.002% CI for the difference will be constructed based on Mantel-Haenszel (MH) stratum weights {Mantel 1959} and the variance estimator as described in {Koch 1989}, adjusted by geographic region as below:

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} \times SE(P_1 - P_2)$$

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$, is the MH estimate of the common difference in proportion, where $d_h = p_{1h} - p_{2h}$ is the proportion difference between Treatment Group 1 and Treatment Group 2 in stratum h.

- $w_h = \frac{n_{1h}n_{2h}}{n_{1h}+n_{2h}}$ is the MH weight for each stratum where n_{1h} and n_{2h} are the sample sizes of Treatment Group 1 and Treatment Group 2 in stratum h, respectively.

- And $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 [\frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1}]}{(\sum w_h)^2}}$, where $p_{1h}^* = \frac{m_{1h}+0.5}{n_{1h}+1}$ and $p_{2h}^* = \frac{m_{2h}+0.5}{n_{2h}+1}$. m_{1h} and m_{2h} are the number of participants with HIV-1 RNA ≥ 50 copies/mL in the Treatment Group 1 and Treatment Group 2 in stratum h, respectively.

- $\alpha = 0.04998$ for this study.

- $Z_{(1-\alpha/2)} = Z_{0.97501} = 1.9601$ is the 97.501th percentile of the normal distribution.

Note that if the computed lower confidence bound is less than -1, the lower bound is defined as -1. If the computed upper confidence bound is greater than 1, the upper bound is defined as 1.

If sparse region stratification is observed, combined region strata (US [including US and Puerto Rico] vs. Ex-US) will be used.

It will be concluded that BIC/LEN FDC is non-inferior to B/F/TAF if the upper bound of the 2-sided 95.002% CI of the treatment difference (Treatment Group 1 – Treatment Group 2) in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the two treatment groups is less than 4%.

A listing of the virologic outcome at Week 48 by the US FDA-defined snapshot algorithm along with the HIV-1 RNA data will be provided.

6.3.4. Sensitivity and Supportive Analysis of the Primary Efficacy Endpoint

Sensitivity analysis of the primary efficacy endpoint will be performed in the PP analysis set using the same method as specified in Sections 6.3.3.

Additional sensitivity analysis of the primary efficacy endpoint will be performed by using a "modified" US FDA-defined snapshot based on FAS. Under the modified algorithm, participants who don't have on-treatment HIV-1 RNA data in the Week 48 analysis window, discontinue study drug due to AE or death prior or in the Week 48 analysis window, and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL will be classified as "HIV-1 RNA ≥ 50 copies/mL". All other category definitions will remain the same as the FDA-defined snapshot algorithm in Section 6.1.

Sensitivity analysis of the primary efficacy endpoint will also be performed in the FAS using the MH stratum weights and the variance estimator as described in {Sato 1989}. Details are provided in Appendix 12.3.

6.3.5. Subgroup Analysis of the Primary Efficacy Endpoint

Subgroup analyses will be performed for the primary endpoint (HIV-1 RNA ≥ 50 copies/mL by US FDA-defined snapshot algorithm at Week 48) for the subgroups specified in Section 3.4 based on FAS. For each level of the subgroup factor, the 2-sided 95% CI for the difference in proportion of HIV-1 RNA ≥ 50 copies/mL between Treatment Group 1 and Treatment Group 2 will be constructed by an unconditional exact method using 2 invert 1-sided tests {Chan 1999}.

A forest plot of the treatment differences and their associated 95% CIs for each subgroup will be generated.

6.4. Secondary Efficacy Endpoints at Week 48

6.4.1. Definition of Secondary Efficacy Endpoints at Week 48

The secondary efficacy endpoints are defined as follows:

- Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm.
- Change from baseline in CD4 cell count at Week 48.

6.4.2. Primary Analysis of Secondary Efficacy Endpoints at Week 48

6.4.2.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL at Week 48 as Determined by the US FDA-Defined Snapshot Algorithm

The proportion of participants 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.

The treatment difference and the corresponding 2-sided 95.002% CIs for the difference in proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 between the Treatment Group 1 and Treatment Group 2 will be constructed based on the stratum-adjusted MH weight as described in Section 6.3.3 where m_{1h} and m_{2h} are the number of participants with HIV-1 RNA < 50 copies/mL in the Treatment Group 1 and the Treatment Group 2 in stratum h, respectively.

6.4.2.2. Change from Baseline in CD4 Cell Count at Week 48

The CD4 cell count will be summarized using observed, on-treatment data for participants in the FAS.

Least squares (LS) mean estimate of differences in changes from baseline in CD4 cell count between the Treatment Group 1 and Treatment Group 2 at Week 48 and associated 95% CI will be constructed using analysis of covariance (ANCOVA) model, including baseline CD4 cell count and geographic region (US [including US and Puerto Rico] vs. Ex-US) as covariates and treatment as a fixed effect in the model. The LS mean estimate and 95% CI of the changes from baseline in CD4 cell count will also be presented for each treatment group.

6.4.3. Sensitivity and Supportive Analysis of Secondary Efficacy Endpoints

Sensitivity analyses will be performed for the secondary efficacy endpoints using the PP analysis set.

The modified FDA snapshot algorithm will also be performed as a sensitivity analysis for the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48. The difference between treatment groups and the corresponding 95.002% CI will be calculated using the stratum- adjusted MH weight.

The following sensitivity analyses for CD4 cell count will also be conducted:

1) Change from baseline in CD4 cell count will be analyzed based on FAS using the mixed-effect model for repeated measures (MMRM) as a sensitivity analysis that includes all available data at postbaseline visits up to Week 48, under the missing at random assumption for missing CD4 cell count. The MMRM model will include baseline value of CD4 cell count, geographic region (US [including US and Puerto Rico] vs. Ex-US), treatment, visit, and treatment by visit interaction as fixed effects and participants being the random effect. An unstructured variance-covariance matrix will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Missing change from baseline values due to missing study visits or early withdrawal will not be otherwise imputed using the MMRM approach. The LS mean along with 95% CI and p-value for difference in mean change from baseline in CD4 cell count at Week 48 between treatment groups will be provided. Additionally, the LS mean and 95% CI for the change from baseline will be provided for each treatment group.

2) Multiple Imputation (MI) will be performed as a sensitivity analysis to handle missing values in CD4 cell count. All participants with nonmissing baseline measurement and at least one available postbaseline measurement up to Week 48 will be included. The MI method replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. Specifically, the missing CD4 cell count at each postbaseline visit will be imputed using a fully conditional specification (FCS) method, which uses a separate conditional distribution for each imputed variable. Three fully observed variables including treatment group, geographic region (US [including US and Puerto Rico] vs. Ex-US) and baseline CD4 cell count will also be included in the imputation model. Twenty imputed datasets will be generated. Each of the imputed datasets will be analyzed using the MMRM method as specified above. The results from the imputed datasets will then be combined using Rubin's rule {Rubin 1987} to generate a single set of estimates. The programming codes for PROC MI with the FCS statement are provided in Appendix 12.4.

6.4.4. Subgroup Analysis of the Secondary Efficacy Endpoints

Subgroup analyses will be performed for the key secondary endpoint (HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm at Week 48) for the subgroups specified in Section 3.4 based on FAS as applicable. For each level of the subgroup factor, the 2-sided 95% CI for the difference in proportion of HIV-1 RNA < 50 copies/mL between Treatment

Group 1 and Treatment Group 2 will be constructed by an unconditional exact method using 2 invert 1-sided tests {Chan 1999}.

A forest plot of the treatment differences and their associated 95% CIs for each subgroup will be generated.

6.5. Other Efficacy Evaluations

The FAS will be used for all summaries and analyses of other efficacy endpoints. Nominal p-values will be presented, if applicable.

6.5.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL by Visit

The proportion of participants with HIV-1 RNA < 50 copies/mL will be summarized by treatment groups and by visit using the following two imputation methods for missing HIV-1 RNA values:

- Missing = Failure (M = F): Participants with missing data in a specific analysis visit window will be treated as virologic failure (HIV-1 RNA ≥ 50 copies/mL) and will be summarized into the "Missing" category. Results will be summarized up to Week 48.
- Missing = Excluded (M = E): Participants with missing data will be excluded from analysis (ie, excluded from both the numerator and denominator in calculation of percentages). The denominator for percentages at a visit is the number of participants 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 2-sided 95% CIs for the difference in proportion of participants with HIV-1 RNA < 50 copies/mL at each postbaseline visit between Treatment Group 1 and Treatment Group 2 will be constructed based on the stratum-adjusted MH weight as described in Section 6.3.3 where m_{1h} and m_{2h} are the number of participants with HIV-1 RNA < 50 copies/mL in the Treatment Group 1 and the Treatment Group 2 in stratum h, respectively. The proportion of participants with HIV-1 RNA < 50 copies/mL at each visit will be plotted as well.

Analyses will be conducted using all available HIV-1 RNA data and on-treatment data only separately.

6.5.2. Change from Baseline in HIV-1 RNA Values by Visit

Change from baseline in HIV-1 RNA (log_{10} copies/mL) at each timepoint will be analyzed using the similar MMRM method as described above in Section 6.4.3, including all available data at post-baseline visits up to Week 48. The LS mean along with 95% CI and the p-value for the difference in mean change from baseline in HIV-1 RNA between treatment groups at each post-baseline visit up to Week 48 from MMRM will be provided. The LS mean along with 95% CI for the change from baseline will also be presented for each treatment group.

Absolute value and the change from baseline in HIV-1 RNA (log_{10} copies/mL) will be summarized by treatment groups and visits using descriptive statistics. Mean ± SD of the absolute value and change from baseline in HIV-1 RNA (log_{10} copies/mL) will be plotted by visit.

Analyses will be conducted using all available HIV-1 RNA data and on-treatment data only, separately.

6.5.3. Change from Baseline in CD4 Cell Count by Visit

The change from baseline in CD4 cell count at each postbaseline visit through Week 48 will be analyzed using similar MMRM method as specified in Section 6.4.3. The LS mean along with 95% CI and the p-value for the difference in mean change from baseline in CD4 cell count between treatment groups at each post-baseline visit up to Week 48 from the MMRM will be provided. The LS mean along with 95% CI for the change from baseline will also be presented for each treatment group.

Absolute value, changes from baseline, and percentage change from baseline in CD4 cell count will be summarized by treatment and by visit using descriptive statistics, respectively. In addition, plots of mean ± SD for absolute value and change from baseline by visit will be presented.

CD4 percentage values will be analyzed similarly as for CD4 cell count.

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the Safety Analysis Set.

The treatment-emergent (TE) period is defined as the time period from the first dose date up to and including 60 days after the last dose of study drugs for Treatment Group 1, or up to and including 30 days after the last dose of study drug for Treatment Group 2.

For participants who are ongoing on study drug, the TE period includes up to date of the database snapshot.

All safety data during the TE period will be summarized by treatment group, 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 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 lower-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 as specified in the protocol. The severity grade of events for which the investigator does 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 selects "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 does not record relationship to study drug will be considered related to study drug based on the drug received for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedure

Study procedure related AEs are those for which the investigator selects "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 does 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 meet 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 Patient Safety 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:

- Any AEs that start during the TE period (Section 7).
- Any AEs leading to premature discontinuation of study drug.

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 onset 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 alone) 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 alone) of the last day of the TE period.

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 TE. 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 TE.

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

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

In addition, a brief, high-level summary of TEAEs up to the Week 48 visit will also be provided. Any TEAE with start date on or before the Week 48 visit date will be included.

The number and percentage of participants who experience at least 1 TEAE during the blinded phase will be provided and summarized by SOC, HLT, PT, and treatment group.

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

- TEAE by maximum severity
- TEAEs with Grade 2 or higher
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs by maximum severity
- TE treatment-related AEs with Grade 2 or higher
- TE treatment-related AEs with Grade 3 or higher
- TEAEs related to study procedure
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of any study drug
- TEAEs leading to premature discontinuation of study
- TEAEs leading to death

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 HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the worst severity 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, TEAEs with Grade 3 or higher, TE SAEs, TE treatment-related AEs, TE treatment-related SAEs, TE treatment-related AEs with Grade 3 or higher, and TEAE leading to premature discontinuation of any study drug will be summarized by PT only and by treatment group, in descending order of total frequency. These summaries will also be provided for up to Week 48 visits, as appropriate.

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

- All AEs, indicating whether the event is treatment emergent
- All AEs with severity of Grade 3 or higher
- All AEs with severity of Grade 2 or higher
- All SAEs
- All treatment-related AEs
- All deaths
- All AEs leading to death
- All AEs leading to premature discontinuation of any study drug
- All AEs leading to premature discontinuation of study

7.2. Laboratory Evaluations

Laboratory data collected during the blinded phase 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 in the TE period defined at the beginning of Section 7.

A by-participant listing for all laboratory test results will be provided by participant ID number and visit in chronological order for hematology, chemistry, urinalysis, and metabolic assessments 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.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for laboratory tests specified in the study protocol (as appropriate) as follows:

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

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.

For metabolic assessments (glucose, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized.

Median (Q1, Q3) of the observed and change from baseline values for 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.

7.2.2. Graded Laboratory Values

The DAIDS Toxicity Grading Scale, Version 2.1 will be used to assign toxicity grades (0 to 5) 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.

For metabolic assessments, triglycerides, LDL, and cholesterol, the toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities (TELAs) are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point during the TE period defined at the beginning of Section 7.

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 TE.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point during the TE period. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered TE marked abnormalities.

7.2.2.3. 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 TELAs 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
- Marked laboratory abnormalities

In addition, summaries of graded TELAs through Week 48 will be provided. A laboratory test will be included in the summary if the test is taken on or before the Week 48 visit.

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values during the TE period.

A by-participant listing of all TELAs and Grade 3 or 4 TELAs 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.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial dosing of the study will be examined and summarized using the number and percentage of participants who are reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN

- Total bilirubin: (a) > 1 x ULN; (b) > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN
- AST or ALT > 3 x ULN and total bilirubin >= 2 x ULN and ALP < 2 x ULN

The summary will include data from all postbaseline visits during the TE period defined at the beginning of Section 7. For individual laboratory tests, participants will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin (and ALP), participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of participants who meet at least 1 of the above criteria will be provided.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs during blinded phase 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.

Median (Q1, Q3) of the changes from baseline for body weight and BMI will be plotted 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. No formal statistical testing is planned.

A by-participant listing of all 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. Antiretroviral Medications

7.4.1.1. Prior Antiretroviral Medications

Any ARV medications used prior to the study, during the study, or after the study (if collected) are recorded in the Non-Study ARV Medication eCRF form.

Prior ARV medications (with "Prior ARV" checked on the eCRF form) will be summarized based on the Safety Analysis Set.

All ARV medications will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.4.2. General Medications (Non-Antiretroviral)

7.4.2.1. Prior Medications

Prior non-ARV medications are defined as medications taken before a participant takes the first study drug.

Any medications with a start date prior to the first dosing date of study drugs will be taken as prior medications regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be taken as prior medications, unless otherwise specified.

Summary of prior medications will not be provided.

7.4.2.2. Concomitant Medications

Concomitant non-ARV medications are defined as medications taken while a participant takes study drug. Use of concomitant medications will be summarized by 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 Level 2 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 Level 2 medical class and then by preferred name in descending overall frequency within each ATC Level 2 medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of any study drug (and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of any study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of any study drug or with a start date after the last dosing date of all study drugs will be excluded from the concomitant medication summary. If a partial

stop date is entered, any medication with the stop month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the start month and year (if day is missing) or year (if day and month are missing) after all study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries of concomitant medication will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant general medications (non-ARV) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number.

7.6. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

Sparse PK blood samples are collected at on-treatment study visits for all participants at the time points specified in protocol.

8.2. PK Analysis Related to Sparse PK Sampling

BIC and LEN PK will be evaluated for participants in the PK Analysis Set. Concentrations of BIC and LEN in plasma are determined using validated bioanalytical assays.

The analytes presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

Treatment Group	Treatment	Analyte(s)
Group 1	BIC 75 mg/LEN 50 mg administered orally daily with oral loading doses of LEN 600 mg administered on Days 1 and 2	BIC and LEN

BIC = bictegravir; LEN = lenacapavir.

Individual participant concentration data will be listed and summarized using descriptive statistics. Descriptive statistics (number of participants, mean, SD, percentage coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual participant concentration data by nominal time point. Moreover, the geometric mean, 90% CI, and the mean and SD of the natural log-transformed values will also be presented.

Individual concentration data listings and summaries will include all participants in PK Analysis Set with concentration data. Any PK concentration samples not collected per protocol (eg, planned postdose samples collected at predose time) will be excluded from the summaries. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ, as well as an indicator if more than one-third of the participants are BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at all predose and postdose time points. If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point. Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

Pharmacokinetic sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age from the sparse PK samples will be provided in a listing.

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 data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

Additionally, the sparse PK data of BIC and LEN from this study may be combined with data from other studies and evaluated using population analysis approaches as applicable. Details of the population PK (popPK) analysis will be provided in a separate popPK analysis plan by the PK scientist.

8.3. 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.

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22 (4):719-48.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc; 1987.

Sato T, Greenland S, Robins JM. On the Variance Estimator for the Mantel Haenszel Risk Difference. Biometrics 1989;45 (4):1323-4.

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® Version 9.2. Statistical Solutions, Cork, Ireland.

Phoenix WinNonlin® Version 8.2. Pharsight Corporation, Princeton, NJ, USA.

11. SAP REVISION

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

12. APPENDICES

12.1. Schedule of Assessments

Table 12-1. Study Procedures Table

Study Procedures	Screening[a]	Day 1[b]	Day 2[c]	Week				Post-Endpoint Week 48	EBT Visit[d]	Open-label (OL)-Day 2[e]	OL-Week 4[f]	OL[g]	Early Study Drug DC (ESDD)[d]	30-Day Telephone Visit	60-Day In-clinic Follow-up Visit	Notes
				4 and 12	24	36	48	Every 12 weeks until EBT visit		Only for TG2 participant who enrolled in OL		Every 12 weeks from EBT				
Visit Window (Days)		± 30		± 6	± 6	± 6	± 6	± 6			± 6	± 6	≤ 3 (of last dose)	± 6	± 6	
Informed consent	X															
Medical history	X															
Concomitant medications	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete physical exam	X	X							X				X		X	
Symptom-directed physical exam				X	X	X	X	X			X	X				
12-Lead ECG	X															Performed supine
Height	X															
Vital signs	X	X		X	X	X	X	X	X		X	X	X		X	Blood pressure, pulse, respiration rate, and temperature

Study Procedures	Screening[a]	Day 1[b]	Day 2[c]	Week				Post-Endpoint Week 48	EBT Visit[d]	Open-label (OL)-Day 2[e]	OL-Week 4[f]	OL[g]	Early Study Drug DC (ESDD)[d]	30-Day Telephone Visit	60-Day In-clinic Follow-up Visit	Notes
				4 and 12	24	36	48	Every 12 weeks until EBT visit		Only for TG2 participant who enrolled in OL		Every 12 weeks from EBT				
Visit Window (Days)		+ 30		± 6	± 6	± 6	± 6	± 6			± 6	± 6	≤ 3 (of last dose)	± 6	± 6	
Weight	X	X		X	X	X	X	X	X		X	X	X		X	
Urinalysis	X	X			X		X	X	X			X	X		X	
Urine pregnancy test		X											X		X	Refer to protocol Appendix 11.5. Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Additional requirements for Argentina are provided in protocol Appendix 11.8.1.
Serum pregnancy test	X															Refer to protocol Appendix 11.5. Positive urine pregnancy tests will be confirmed with a serum test.
Chemistry profile	X	X		X	X	X	X	X	X		X	X	X		X	Refer to protocol Table 8
Metabolic assessment[i]		X			X		X	X	X			X	X		X	Only every 24 weeks during Post-Endpoint Week 48 and OL phase. Fasting is defined as 8 hours without food or drink (except water) prior to laboratory draw. Refer to protocol Section 6.3.7
Hemoglobin A1c		X					X								X	
Creatinine Clearance	X	X		X	X	X	X	X	X		X	X	X		X	

Study Procedures	Screening[a]	Day 1[b]	Day 2[c]	Week				Post-Endpoint Week 48	EBT Visit[d]	Open-label (OL)-Day 2[e]	OL-Week 4[f]	OL[g]	Early Study Drug DC (ESDD)[d]	30-Day Telephone Visit	60-Day In-clinic Follow-up Visit	Notes
				4 and 12	24	36	48	Every 12 weeks until EBT visit		Only for TG2 participant who enrolled in OL		Every 12 weeks from EBT				
Visit Window (Days)		+ 30		± 6	± 6	± 6	± 6	± 6			± 6	± 6	≤ 3 (of last dose)	± 6	± 6	
Hematology profile	X	X		X	X	X	X	X	X		X	X	X		X	Refer to protocol Table 8
Plasma HIV-1 RNA	X	X		X	X	X	X	X	X		X	X	X		X	
Whole blood storage sample for potential proviral DNA sequencing[j]		X														
CD4 cell count	X	X		X	X	X	X	X	X		X	X	X		X	
Plasma storage sample[k]	X	X		X	X	X	X	X	X		X	X	X		X	
HBV blood panel[l]	X								X						X	
Plasma samples stored for potential HIV-1 genotype/phenotype[m]		X		X[m]	X[m]	X[m]	X	X[m]	X			X	X		X	Plasma samples must be collected regardless of virologic status at Day 1, Week 48, EBT, OL every 12 weeks, ESDD (if applicable), and at 60-Day In-Clinic Follow up visit
Sparse PK trough and postdose sample [n, o, p]		X		X	X	X	X	X[o]	X[o]			X[o]				
Randomization		X														
Provide participant dosing diary to participants		X		X	X	X	X	X	X		X	X				

Study Procedures	Screening[a]	Day 1[b]	Day 2[c]	Week				Post-Endpoint Week 48	EBT Visit[d]	Open-label (OL)-Day 2[e]	OL-Week 4[f]	OL[g]	Early Study Drug DC (ESDD)[d]	30-Day Telephone Visit	60-Day In-clinic Follow-up Visit	
				4 and 12	24	36	48	Every 12 weeks until EBT visit		Only for TG2 participant who enrolled in OL		Every 12 weeks from EBT				
Visit Window (Days)		+ 30		± 6	± 6	± 6	± 6	± 6			± 6	± 6	≤ 3 (of last dose)	± 6	± 6	Notes
Study drug loading dose administration		X	X						X[q]	X[q]						Loading dose at EBT and OL Day 2 visits only for participants previously randomized to Treatment Group 2.
Study drug dispensation		X		X	X	X	X	X	X		X	X				
Study drug accountability				X	X	X	X	X	X		X	X	X			Investigators may perform a virtual visit or a phone call visit to review study drug and dosing diary adherence in between 2 in-clinic visits especially when the visits are 12 weeks apart.

AE = adverse event; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; CD4 = clusters of differentiation 4; DC = discontinuation; DNA = deoxyribonucleic acid; EBT = end of blinded treatment; ECG = electrocardiogram; ESDD = early study drug discontinuation; FDC = fixed-dose combination; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; LEN = lenacapavir; OL = open-label; PK = pharmacokinetic(s); PTM = placebo-to-match; RNA = ribonucleic acid; TG2 = Treatment Group 2

a Evaluations to be completed within 30 days prior to Day 1. Screening window can be extended to 45 days with sponsor approval.

b Day 1 visit up to 30 days after screening. Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit. Participants randomized to Treatment Group 1 will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN (75/50 mg) FDC tablet and PTM B/F/TAF tablet starting on Day 1. Participants randomized to Treatment Group 2 will receive PTM LEN loading dose tablets (2 tablets on Day 1 and on Day 2), in addition to the daily dose of B/F/TAF (50/200/25 mg) and the PTM BIC/LEN tablet starting on Day 1. The study drugs will be administered without regard to food.

c Day 2 visit is to be completed the day after Day 1 visit. Day 2 visit may be a virtual visit and the participants will self-administer the study drugs and be observed by site staff to confirm dosing. Please refer to protocol Section 6.3.8 for further details.

d Once the last participant completes the Week 48 visit and the analysis of safety and efficacy data of BIC/LEN FDC compared with B/F/TAF FDC is completed, all participants will attend an EBT visit at the next in-clinic visit (preferably within 12 weeks). At the EBT visit, participants in Treatment Group 1 will continue to receive BIC/LEN FDC until OL Week 48 and participants in Treatment Group 2 will be given the option to receive BIC/LEN FDC. All participants in the OL phase will continue to receive BIC/LEN FDC until study drug is available or until Gilead elects to discontinue the study, whichever occurs first. Participants in Treatment Group 2 who complete the study through the EBT visit, and do not wish to participate in the OL phase, must complete a 30-day telephone visit and a 60-day in-clinic follow-up visit after the EBT visit, and will be considered to have completed the study. Participants who discontinue study drug early will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the early study drugs DC visit.

e Participants from Treatment Group 2 enrolled in the OL phase will also require completing Day 2 visit. If virtual visit is not possible, an in-clinic visit will be performed.

f Week 4 visit at the OL phase is only for participants who are previously randomized to Treatment Group 2 and then enrolled in OL phase.

g Participants from Treatment Group 1 will receive BIC/LEN FDC through at least OL Week 48.

h At screening, details about medications taken within 30 days of the visit should be collected.

i Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

j Whole blood storage for possible proviral DNA sequencing needs to be done for all participants at Day 1. Proviral DNA sequencing will be performed on these samples in cases of virologic failure during the study. Separate consent for optional future research is not needed to collect this sample.

k Stored plasma samples may be used for evaluation of biomarker assays, PK analysis, and virology assays (as appropriate). Separate consent for optional future research is not needed to collect these samples unless required per local regulations and requirements.

l HBV blood panel (HBsAg, HBsAb, and HBcAb) will be performed at screening, EBT visit, and 60-day in-clinic follow-up visit. Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study. Participants who are HBsAg positive will have a plasma HBV DNA test performed.

m HIV 1 genotype and phenotype testing for participants with confirmed virologic failure only. In case of unconfirmed virologic rebound, refer to protocol Section 6.3.10.2. Plasma samples will be collected at all visits indicated in the notes column and at the virological failure confirmation visits.

n A single predose plasma PK sample (≤ 15 min before dose) **and** a single postdose plasma PK sample at[CCI] [CCI] (relative to study drugs administration) [CCI]. A single trough plasma PK sample approximately[CCI] after the previous dose and prior to dosing at[CCI], **and** a single postdose plasma PK sample at[CCI] (relative to study drugs administration) at Weeks[CCI]. For participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at Weeks 4, 12, 24, 36, and 48.

o For participants who become pregnant and provide reconsent to remain on study, sparse PK samples will be collected as follows: at all specified time points described above in footnote 'n' during blinded treatment visits until Week 48. A single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12-week visit (as possible) until the EBT visit and during the OL phase. For pregnant participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at every 12 week visit (as possible) until the EBT visit and during the OL phase. These additional trough samples will continue to be collected until the next 2 scheduled visits postdelivery or until the end of the study participation or OL phase, whichever occurs first.

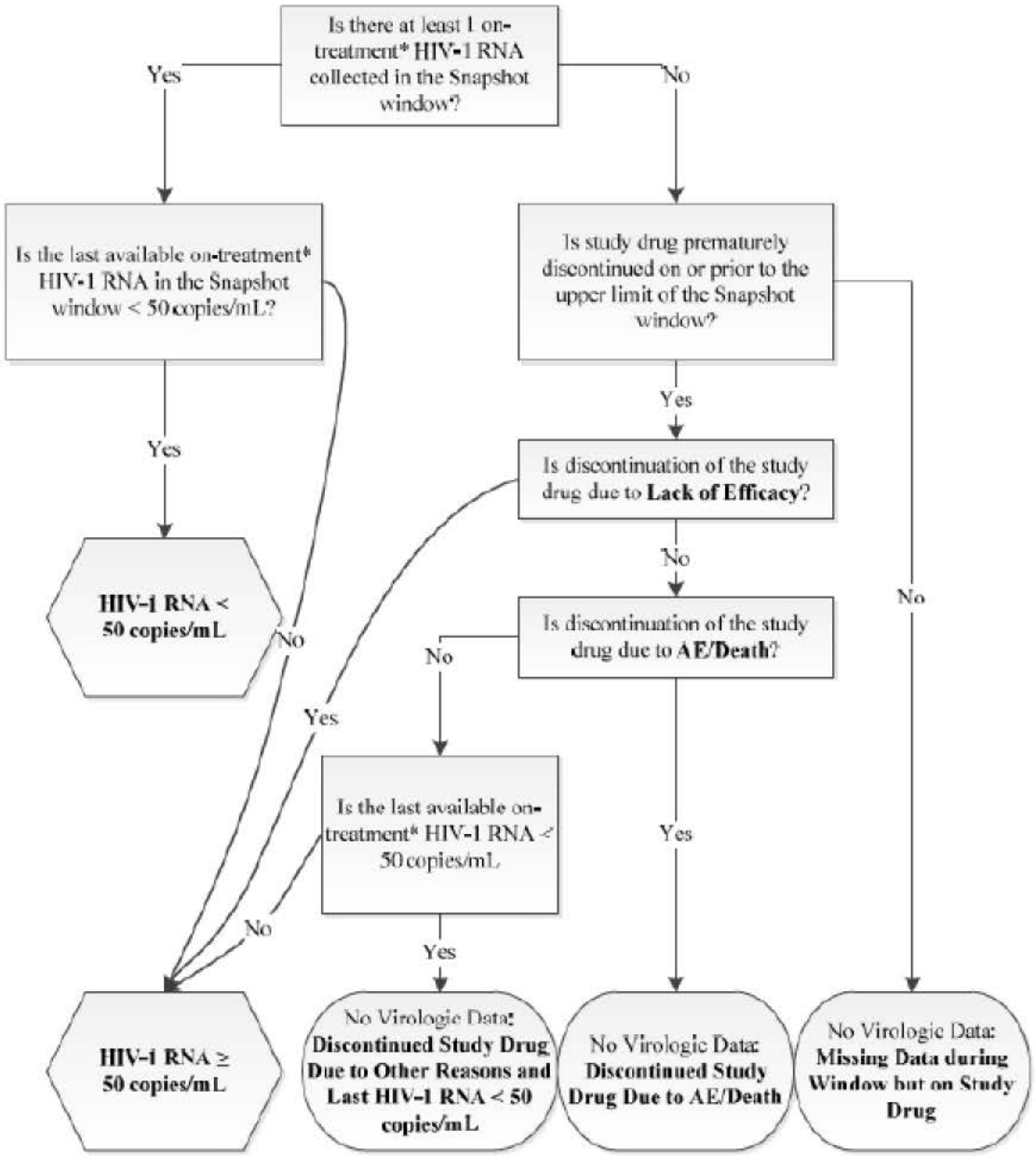
p At each on-treatment study visit, participants are to take study drug in the clinic **after** collection of predose or trough sparse PK sample.

q Participants from Treatment Group 2 who enter the OL phase will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2, without regard to food), in addition to the daily doses of BIC/LEN FDC starting on Day 1 of the OL phase. Please refer to protocol Section 6.3.8 for further details.

12.2. US FDA-Defined Snapshot Algorithm

The flowchart of the US FDA-defined snapshot algorithm 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} is provided in Figure 12-1.

Figure 12-1. Flowchart of US FDA-Defined Snapshot Algorithm



*On-treatment data include all data collected up to 1 day after permanent discontinuation of study drug or all available data for participants who were still on study drug.

12.3. Stratified Mantel-Haenszel Method with the Sato Variance Estimator

The treatment difference in proportions and the corresponding 2-sided CI will be constructed based on stratified Mantel-Haenszel (MH) stratum weights and the variance estimator as described in {Sato 1989} as below:

$$d_{MH} \pm Z_{(1-\alpha/2)} \times SE(d_{MH})$$

where

- $d_{MH} = \frac{\sum w_h d_h}{\sum w_h}$ is the MH estimate of the common difference in proportion, where $d_h = p_{1h} - p_{2h}$ is the proportion difference between Treatment Group 1 and Treatment Group 2 in stratum h.
- $w_h = \frac{n_{1h} n_{2h}}{n_{1h}+n_{2h}}$ is the MH weight for each stratum where n_{1h} and n_{2h} are the sample sizes of Treatment Group 1 and Treatment Group 2 in stratum h, respectively.
- And $SE(d_{MH}) = \sqrt{(d_{MH} \sum P_h + \sum Q_h)/(\sum \frac{n_{1h} n_{2h}}{n_{1h}+n_{2h}})^2}$, where

$$P_h = (n_{1h}^2 m_{2h} - n_{2h}^2 m_{1h} + n_{1h} n_{2h}(n_{2h} - n_{1h})/2)/(n_{1h} + n_{2h})^2$$

$$Q_h = \big(m_{1h}(n_{2h} - m_{2h}) + m_{2h}(n_{1h} - m_{1h})\big)/2(n_{1h} + n_{2h})$$

  m_{1h} and m_{2h} are the number of participants with event of interest in Treatment Group 1 and Treatment Group 2 in stratum h, respectively.

- $\alpha = 0.04998$ for this study.
- $Z_{(1-\alpha/2)} = Z_{0.97501} = 1.9601$ is the 97.501^{th} percentile of the normal distribution.

12.4. Programming Codes for Multiple Imputation

SAS programming codes for the multiple imputation described in Section 6.4.3 are provided below.

```
/*Below is the MI step;*/
proc mi data=data_ready_for_mi out=DATA_MI nimpute=20 seed=12345 minimum=. .
. 0 0 0 0 0;
*There is no restriction for the first three variables (TRT01PN REGION2N
v 1); when an intended imputed value is less than 0 for v_2 to v_6, PROC MI
redraws another value for imputation;
    class TRT01PN REGION2N;
    fcs nbiter=20;
*Default, v_2 to v_6 is imputed via the regression method;
    var TRT01PN REGION2N v_1 v_2 v_3 v_4 v_5 v_6;
*v_1 is baseline; v_2 to v_6 are Week 4,Week 12,Week 24,Week 36,and Week 48;
run;

/*Run MMRM on each of the imputed datasets;*/
proc mixed data=mifinal NOCLPRINT;
    by  Imputation ;
    class usubjid REGION2N TRT01PN visit;
    model chg = base REGION2N TRT01PN visit TRT01PN*visit/ ddfm=kr s covb;
    repeated visit / type=un subject=usubjid;
    lsmeans trt01pn*visit /diff cl alpha=0.05;
    ods output lsmeans=sum_lsmean diffs=sum_diff;
run;

/*Combine estimates from all imputed datasets and get a single value;*/
/*Estimate for each treatment group;*/
proc mianalyze parms = sum_lsmeans2;
    by trt01pn;
    modeleffects TRT01PN*Visit;
    ods output ParameterEstimates = ESTIMATE_MI;
run;

/*Estimate for difference between treatment groups;*/
proc mianalyze parms = sum_diff2;
    modeleffects TRT01PN*Visit;
    ods output ParameterEstimates = DIFF_MI;
run;
```

12.5. Handling of Laboratory Values

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 – albumin (g/dL))

Toxicity grading for calcium will be applied based on the corrected values.

Estimated Glomerular Filtration Rate

The following formulae will be used to calculate the estimated glomerular filtration rate using Cockcroft-Gault formula ($eGFR_{CG}$):

$eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

where weight is total body mass in kilograms and SCr is serum creatinine.

Direct/Indirect Bilirubin: Conversions between 1st and 2nd generation assays

Direct bilirubin is analyzed by 2 different assays in the study: 1st generation (LBTSTCD = 'RCT29') and 2nd generation (LBTSTCD = 'RCT6557'). Samples collected at earlier visits are analyzed using direct bilirubin 1st generation assay. Samples collected at later visits are analyzed using direct bilirubin 2nd generation assay. The conversion formulas are as follows:

1st Gen (µmol/L) = (2nd Gen - 2.832) / 1.032

For this analysis, we requested conversion from 2nd generation to 1st generation. Any converted results below the limit of quantitation (<2 umol/L) for the 1st Gen assay will be assigned a value of <2 umol/L. This includes records where the 2nd Gen result is "<1.4 umol/L".

For indirect bilirubin,

1st Gen indirect bilirubin (umol/L) = total bilirubin – 1st Gen direct bilirubin

- If the result for total bilirubin or 1st Gen direct bilirubin is blank or missing, then the result for 1st Gen indirect bilirubin will be blank.
- For any instances where 1st Gen direct bilirubin = "<2 umol/L", the 1st Gen indirect bilirubin calculation should equal the total bilirubin result (in umol/L) preceded by "<". If the total bilirubin result already has a "<", the indirect bilirubin result should match.

For the analysis of change from baseline in direct bilirubin: the sample analyzed by 2nd generation assay will be converted to 1st generation. Indirect bilirubin will be handled similarly.

For the analysis of toxicity grade for direct bilirubin: toxicity grade will be based on the Gilead grading results (ie, toxgrg) from original values. Indirect bilirubin will be handled similarly.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D



Gilead Sciences, Inc.
333 Lakeside Ave
Foster City, CA 94404

DATA MONITORING COMMITTEE (DMC) CHARTER

Study Title:	Phase 3 Double-Blind Multicenter Randomized Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide) in Virologically Suppressed People with HIV-1
Name of Test Drug:	Bictegravir/Lenacapavir
Study Number:	GS-US-621-6290
Protocol Version (Date):	Original (16-Jan-2024)
DMC Charter Version:	Final
DMC Charter Date:	26-Aug-2024
DMC Charter Author:	PPD

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

DMC CHARTER APPROVALS

DMC Chair	PPD Professor of Medicine, Johns Hopkins University School of Medicine

PPD

DMC Chai

Gilead Representative	PPD SVP, Clinical Development Virology Gilead Sciences, Inc.

PPD

Gilead Represent

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

VERSION HISTORY

Version	Date (DDMMMYYYY)	Author	Description of Changes
	Click or tap to enter a date.		
	Click or tap to enter a date.		

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

TABLE OF CONTENTS

TABLE OF CONTENTS 4
LIST OF FIGURES 5
GLOSSARY OF ABBREVIATIONS 6
GLOSSARY OF TERMS 7
1. INTRODUCTION 8
2. ROLE OF THE COMMITTEE 11
2.1. Safety 11
2.1.1. Signal Management 11
2.2. Efficacy 11
2.3. Study Conduct 11
3. COMMITTEE MEMBERSHIP 12
3.1. DMC Members 12
3.2. Selection and Replacement of DMC Members 12
3.3. Conflict of Interest 13
3.4. Confidentiality 13
3.5. Duration of DMC Membership 14
3.6. Compensation for DMC Service 14
3.7. Establishing or Changing the DMC Charter 14
4. COMMITTEE MEETINGS 15
4.1. Kick-off Meeting 15
4.2. Data Review Meetings 15
4.2.1. Meeting Schedule 15
4.2.2. Open Session 15
4.2.3. Closed Session 16
4.2.4. Wrap-up Session 16
4.3. Ad hoc Data Review and Unscheduled Meetings 16
4.4. DMC Meeting Minutes 16
5. COMMUNICATION 18
5.1. Data Flow 18
5.2. Reporting Statistician 18
5.3. Unblinding 19
5.4. Ad hoc Analysis Requests 19
6. DMC RECOMMENDATIONS AND GILEAD DECISION 20
6.1. Development of DMC Recommendations 20
6.2. Communication of DMC Recommendations 20
6.3. Gilead Decision on DMC Recommendation 21
7. DMC ROLE AS AN UNBLINDED REVIEW TEAM IN GLPS MSS SIGNAL MANAGEMENT 22
8. APPENDICES 23
PROTOCOL SYNOPSIS 24

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

LIST OF FIGURES

Figure 1. Information & Communications Flow 18

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

GLOSSARY OF ABBREVIATIONS

AEs	adverse events
CDA	confidentiality disclosure agreement
DMC	data monitoring committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	good clinical practice
Gilead	Gilead Sciences, Inc.
GLPS	Global Patient Safety
GSL	Global Safety Lead
GSLC	Global Safety & Labeling Committee
IACP	Interim Analysis Communication Plan
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MSS	Medical Safety Science
PSC	Product Safety Committee
SAEs	serious adverse events
SMT	study management team
TA	therapeutic area
TOC	table of contents

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

GLOSSARY OF TERMS

Blinded data	data for which certain information (e.g., treatment group) is kept hidden in order to avoid bias and maintain study integrity
Gilead Representative	the Clinical Development therapeutic area (TA) head (or designee) (not involved in the day-to-day conduct of the study) who approves the DMC charter and receives DMC recommendations as needed
PS Global Safety Lead (GSL)	for purposes of this charter, a scientist or physician within a specific TA in Patient Safety (PS) who is the expert, go-to person regarding the safety profile of a product/compound or group of products/compounds
Medical Monitor	the appropriately trained and qualified person at Gilead who monitors the progress of a clinical investigation
Reporting Statistician	a statistician, usually not a Gilead employee, who provides statistical support to the DMC. This person is not a DMC member and does not vote with the DMC
Unblinded data	data for which treatment groups are separated and identified by actual treatment assignment

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

1. INTRODUCTION

This charter describes the roles and responsibilities of the Data Monitoring Committee (DMC) for study GS-US-621-6290. This charter outlines the plan for the management and dissemination of study data, the conduct of committee meetings, and the documentation of committee activities.

Primary Study Objectives	• To evaluate the efficacy of switching to bictegravir/lenacapavir (BIC/LEN) (75/50 mg) fixed-dose combination (FDC) tablets versus continuing on bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) (50/200/25 mg) FDC tablets in virologically suppressed people with HIV-1
Secondary Study Objectives	• To evaluate the efficacy of study drug(s) for the 2 treatment groups in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count • To evaluate the long-term efficacy of BIC/LEN in participants from Treatment Group 1 as determined by viral load suppression rate and CD4 cell count • To evaluate the safety and tolerability of the study drug(s) for the 2 treatment groups • To evaluate the long-term safety and tolerability of BIC/LEN in participants from Treatment Group 1
Study Design	This study is a Phase 3 double-blind, multicenter, randomized, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus B/F/TAF in virologically suppressed people with HIV-1 on B/F/TAF for at least 6 months prior to screening.
Target Population	People with HIV-1 (≥ 18 years of age) who are on B/F/TAF FDC tablets and have been virologically suppressed for at least 6 months prior to screening.
Treatment Groups and Planned Sample Size	Approximately 546 participants in total (364 in Treatment Group 1 and 182 in Treatment Group 2).

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Duration of Treatment	Participants will be treated for at least 48 weeks during the blinded phase; participants from Treatment Group 1 will be treated with BIC/LEN FDC tablets for at least 96 weeks, including the blinded and (OL) phases, up to OL Week 48. After blinded Week 48, all participants will continue to take their blinded study drug and attend visits every 12 weeks. Once the last participant completes the Week 48 visit and the analysis of safety and efficacy data of BIC/LEN FDC compared with B/F/TAF FDC is completed, all participants will attend an end of blinded treatment (EBT) visit at the next in-clinic visit (preferably within 12 weeks). At the EBT visit, participants in Treatment Group 1 will enter the OL phase, and will continue to receive BIC/LEN FDC tablets through at least OL Week 48. At the OL Week 48 visit, participants in Treatment Group 1 will be given option to continue to receive BIC/LEN FDC tablets. At the EBT visit, participants from Treatment Group 2 will be given the option to enter the OL phase to receive BIC/LEN FDC tablets and continue in the study. All participants who enter the OL phase may continue to receive BIC/LEN FDC tablets until study drug is available, or until Gilead Sciences (Gilead) elects to discontinue the study, whichever occurs first.
Key Eligibility Criteria	• Currently receiving B/F/TAF for at least 6 months prior to screening. • If plasma HIV-1 RNA measurements in the 6 months prior to screening are available, all levels must be < 50 copies/mL. • At least one documented HIV-1 RNA level measured between 6 and 12 months (± 2 months) prior to screening. This and any other HIV-1 RNA measurements documented in this period must be < 50 copies/mL. • Plasma HIV-1 RNA levels < 50 copies/mL at screening. • No documented or suspected resistance to BIC (including INSTI-R mutations T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene).

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

	• No documented or suspected resistance to tenofovir alafenamide (TAF; mutations K65R, K65N, K70E, Q151M or T69 insertion, or ≥ 3 of the following thymidine analog mutations [M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R] in the reverse transcriptase gene). • Estimated glomerular filtration rate ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance. • No prior use of, or exposure to, LEN. • No chronic hepatitis B virus (HBV) infection, as determined by either: — Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit. — Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit.

The full study synopsis can be found in Appendix A.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

2. ROLE OF THE COMMITTEE

The primary responsibility of the DMC is to monitor available safety data. The DMC may also alert Gilead regarding study conduct issues.

2.1. Safety

The DMC shares responsibility with Gilead for regularly monitoring the overall safety of the subjects in the study. After careful review of overall safety data (e.g., adverse events and laboratory abnormalities), the DMC will alert Gilead to any areas of concern related to safety in order to minimize subject exposure to unnecessary risk.

2.1.1. Signal Management

Gilead Patient Safety (PS) may request for the DMC to review an unblinded version of a Safety Review on a specific topic as part of signal management processes. A high-level description of this activity is provided in Section 7.

2.2. Efficacy

Efficacy data will also be provided for DMC review.

Descriptive statistics for the efficacy endpoints such as the proportion of participants with HIV-1 RNA < 50 copies/mL (by Missing = Excluded and Missing = Failure approaches), and change from baseline in CD4+ cell count will be included.

The DMC members will review the interim efficacy results in order to evaluate the risks and benefits for participants treated with BIC/LEN FDC.

The study will not be stopped early for positive efficacy findings. Conservatively an alpha penalty of 0.00001 will be applied for each DMC efficacy evaluation performed prior to the analysis of the primary efficacy endpoint.

2.3. Study Conduct

The Gilead clinical study management team (SMT) is primarily responsible for monitoring study conduct. The DMC may also alert the Gilead Representative of possible concerns related to the conduct of the study.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

3. COMMITTEE MEMBERSHIP

A DMC member should be an expert in one or more fields relevant to the disease under study, the evaluation of safety to be monitored during the trials, and/or the biostatistical evaluation of the study results. The DMC members should have experience in the conduct of clinical trials and knowledge of good clinical practice (GCP) guidelines, and a general understanding of regulatory requirements for drug development. Ideally, DMC members (particularly the Chair and Biostatistician) will have prior DMC experience. The Chair should be capable of facilitating discussion, integrating differing points of view, and moving toward consensus on recommendations to be provided to Gilead.

The committee, including the Chair, will be selected by Gilead.

3.1. DMC Members

Name	Specialty	Affiliation
DMC Chair: PPD	Infectious Diseases	School of Medicine Johns Hopkins University
PPD	Infectious Diseases	Department of Medicine Harvard Medical School
PPD	Biostatistics	Department of Biostatistics Harvard University

See Appendix C for contact details.

Each member's curriculum vitae will be available in Gilead's files and will be provided to any Regulatory Authority upon request.

3.2. Selection and Replacement of DMC Members

Gilead will choose and appoint the initial DMC members. Gilead or the DMC may request a change (e.g., an addition) to DMC membership.

A DMC member can be replaced for any of the following reasons if that member:

- elects not to continue with participation
- becomes incapable of fulfilling DMC responsibilities
- cannot adhere to the DMC charter
- develops an unacceptable conflict of interest

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

In consultation with the DMC, Gilead will make the final decisions regarding replacement or addition of DMC members.

3.3. Conflict of Interest

Before a confidentiality disclosure agreement (CDA) and/or a contract is set up for each DMC member, members must confirm that serving on the DMC does not present a conflict of interest. If a new conflict of interest arises during the course of the study, the DMC member must promptly inform the DMC Chair and the Study Medical Monitor (or designee).

Members of the DMC who develop significant potential or perceived conflicts of interest that could materially impact objectivity will be asked to resign from the DMC.

3.4. Confidentiality

Members of the DMC (and additional experts) must sign a CDA and/or a contract with Gilead prior to Gilead's distribution of any proprietary information. Members of or advisors to the DMC must hold in confidence all study data or analyses, documents, emails, printed or electronic files, communications, deliberations, recommendations, or other actions relating to their role on the DMC. As a component of maintaining confidentiality, unblinded interim data and the results of comparative interim analyses must not be shared with anyone other than fellow DMC members and those support personnel attending closed sessions of the DMC. Printed or electronic files (particularly unblinded data or minutes of closed session discussions) must be secured or destroyed in accordance with instructions provided by DMC support personnel. To protect the integrity of the clinical trial and the regulatory review process, the period of confidentiality extends beyond the specific period of service on the DMC.

Intentional or inadvertent disclosures of DMC related confidential information must be revealed to the DMC. In the closed sessions of DMC meetings, the DMC Chair will call for a review of any potential breaches of confidentiality by all DMC members. Any perceived breaches of confidentiality will be discussed and recorded in the minutes of DMC deliberations such that the breach of confidentiality is not further extended. In the case of a suspected breach of confidentiality, the DMC will make a recommendation to Gilead regarding actions to be taken.

During open discussions of data or written, electronic, or oral communications regarding DMC deliberations or recommendations, DMC members (and any additional experts) must carefully consider their communications and actions to avoid inadvertent disclosure of unblinded or confidential information.

No DMC member shall contact or communicate with any Regulatory Authority without Gilead's permission and inclusion.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

3.5. Duration of DMC Membership

DMC members will be requested to serve throughout the duration of the blinded portion of the study. It is expected that this period will begin when the DMC is constituted at the start of the clinical trial until approximately 12 months from the date the last participant is randomized. With the continuing agreement of each member, Gilead may request that DMC members extend their duration of service if it is needed to monitor study drug safety beyond the specific duration of the study or to assist Gilead in discussions regarding study conduct during regulatory proceedings.

The duration of service of any additional experts will be based on the availability of the experts and needs of the DMC.

3.6. Compensation for DMC Service

Gilead will compensate DMC members (and any additional experts) for any time and expense that they incurred while performing their duties on the DMC. The specific details of compensation will be incorporated separately from this charter in a contract between each individual and Gilead.

3.7. Establishing or Changing the DMC Charter

Gilead will draft the initial DMC charter and send this document to the DMC members for review prior to the initial meeting of the DMC. The DMC may make recommendations to Gilead regarding the charter. Prior to the initial data review meeting of the DMC, Gilead will finalize the charter. Gilead will provide a copy of the final charter to each DMC member.

DMC members or Gilead may suggest amendments to the charter (e.g., for change of DMC Chair, conduct and/or expectations of the DMC) during the time that the DMC is constituted. Gilead will incorporate any changes and provide a copy of the final amended charter to each DMC member.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

4. COMMITTEE MEETINGS

The DMC will meet by teleconference or face-to-face according to the schedule outlined in Section 4.2.1.

A quorum (defined as 2 DMC members, including the DMC Chair and the DMC Statistician) must be in attendance for a DMC data review meeting to be convened, and for voting to proceed. Any absent member(s) should provide their input to the DMC Chair prior to the meeting, if possible. The DMC Chair will share the input of the absent member(s) with the other DMC members.

4.1. Kick-off Meeting

A DMC kick-off meeting may be held, if needed, shortly after the protocol is finalized and a draft charter is ready for DMC review. The purpose of the meeting is to introduce the SMT to the DMC members and Reporting Statistician, and to review the final protocol and the draft DMC charter.

4.2. Data Review Meetings

4.2.1. Meeting Schedule

The initial DMC data review meeting will be based on data collected after approximately the first 50% of participants enrolled have completed their Week 12 visit or prematurely discontinued the study drug. The second DMC data review meeting will be after all participants enrolled have completed their Week 24 visit or prematurely discontinued the study drug. The DMC charter must be approved prior to the initial DMC data review meeting.

4.2.2. Open Session

The open session will immediately precede the closed session. The DMC members, Reporting Statistician, Gilead Representative, Study Medical Monitor, Study Biostatistician, PS Global Safety Lead (GSL), and other appropriate Gilead personnel may attend the open session. The Study Medical Monitor will facilitate the open session.

Approximately 5 business days prior to the scheduled DMC meeting date, the Reporting Statistician will prepare the final open session report and provide it to the DMC as well as the Study Biostatistician for distribution to the Gilead meeting attendees. The open session report, reviewed at the open session, will present data (pooled treatment groups), including enrollment, baseline characteristics, subject disposition, and overall safety. A list of planned tables, figures, and listings to be included in the open session report is provided in Appendix B.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

4.2.3. Closed Session

The closed session will be attended only by the DMC members and the Reporting Statistician. If this takes place as a teleconference, the Reporting Statistician will provide a dial-in number for DMC members, which will be different from the open session number. The DMC Chair will facilitate the closed session.

Approximately 5 business days prior to the scheduled DMC meeting date, the Reporting Statistician will prepare the final unblinded closed session report and provide it to the DMC. The closed session report, reviewed at the closed session, will present data by treatment group. A list of planned tables, figures, and listings to be included in the closed session report is provided in Appendix B. At the completion of the meeting, the DMC members will ensure that any hard copies of shared study materials must be secured or destroyed.

DMC may meet with Reporting Statistician and/or Gilead Representative after the closed session as needed for further question discussions, data requests and/or recommendation communication.

4.2.4. Wrap-up Session

All of the open session meeting attendees may attend the wrap-up session. During this session, the DMC will address any outstanding questions from the Gilead attendees in a manner that maintains the study blind. This wrap-up session will also serve as an opportunity for the Gilead attendees to clarify or answer any questions the DMC members may have regarding the study procedures and the study data. DMC Chair will facilitate the wrap-up session.

During the wrap-up session, the DMC may communicate their recommendation for the study based on their review of the open and closed session reports only if the recommendation is to continue the study without modification (refer to Section 6).

4.3. Ad hoc Data Review and Unscheduled Meetings

Both Gilead and the DMC members may request an ad hoc review of the study data for the reasons including but not limited to a perceived concern for subject safety, an additional safety monitoring requested by the agency, or to support the conduct of the study. The Study Medical Monitor (or designee) will inform the PS GSL if the ad hoc data review is related to safety. Additionally, the Study Medical Monitor (or designee) will work in collaboration with relevant functions to prepare the study data. An unscheduled meeting may be held if needed.

4.4. DMC Meeting Minutes

Meeting minutes (including DMC recommendations, action items resulting from the meeting, and status updates of previous action items, if applicable) for open [including wrap-up session if applicable] and closed sessions will be prepared by the Reporting Statistician. The Reporting Statistician will distribute (for review) draft open session minutes to all attendees and draft closed session minutes to DMC members only.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

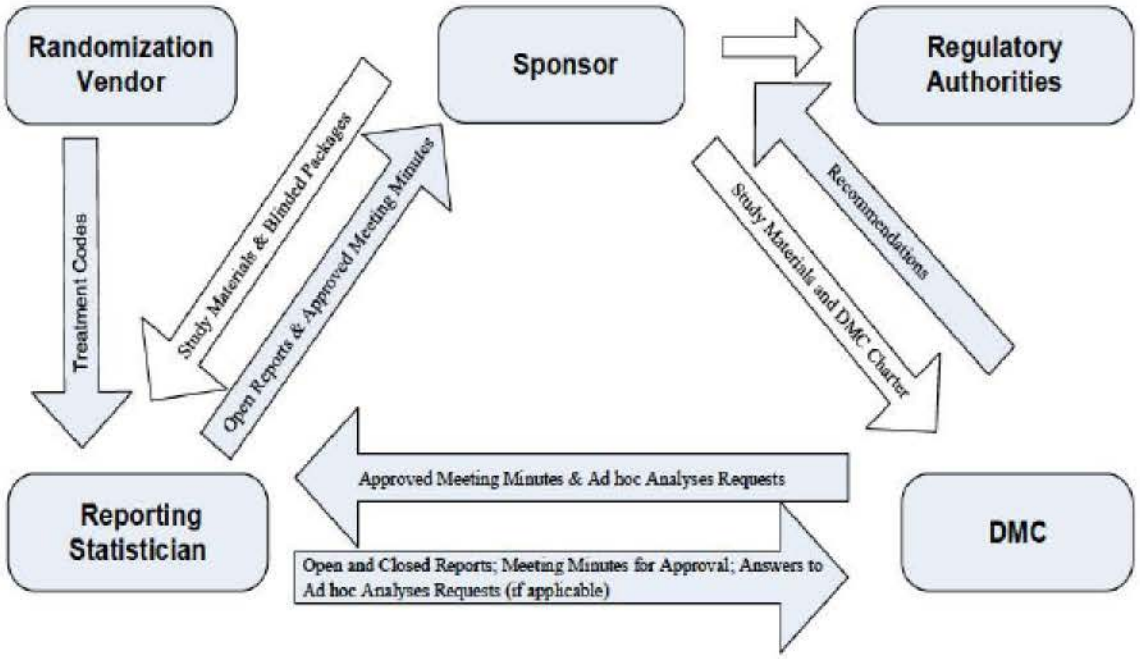
The DMC Chair will approve both open and closed session minutes. Once approved, the Reporting Statistician will distribute the final open session minutes to all meeting attendees. If warranted, the open session minutes may be distributed to relevant Regulatory Authorities, investigators, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and/or consultants, and partners.

Minutes from the closed session will not be accessible to Gilead personnel (refer to Section 6 for exception) and will be maintained by the Reporting Statistician until the study has been unblinded per Gilead's Unblinding process.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

5. COMMUNICATION

Figure 1. Information & Communications Flow



5.1. Data Flow

Gilead's clinical and Biostatistics personnel will oversee all activities and final decision-making regarding data flow and other DMC activities.

If additional DMC data reviews are requested by Gilead for safety reasons, the reports from safety database may be generated internally by the designated personnel within PS and sent to the Reporting Statistician for distribution to the DMC. The Biostatistician will provide support to PS to establish the communication channel.

5.2. Reporting Statistician

An unblinded Reporting Statistician will be designated to provide statistical support to the DMC. This statistician will be independent of Gilead (i.e., will be neither a Gilead employee nor an on-site contractor).

Gilead will provide the Reporting Statistician with the datasets and programs necessary to generate the interim analysis reports. The Reporting Statistician will apply the unblinded treatment codes to the datasets and generate the open session report (pooled treatment) and closed session report (unblinded). The Reporting Statistician will provide the open and closed session reports to the DMC approximately 5 business days prior to each data review meeting. If

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

it is necessary to provide unblinded treatment codes to DMC members prior to data review meetings or at other times, these codes will be provided in a separate transmittal from those containing the interim reports.

During all DMC meetings, the Reporting Statistician will have access to the randomization codes and will be able to provide treatment assignments for individual subjects or groups of subjects, as needed.

Until the database is finalized and the study is unblinded, the Reporting Statistician will not disclose any study information presented or discussed in closed sessions to the Gilead SMT or to any other party (refer to Section 6 for exception).

5.3. Unblinding

Gilead personnel will remain blinded to the treatment assignments throughout the study and will not have access to unblinded closed session reports and any other unblinded information until the study has been unblinded (per Gilead's unblinding process). Unblinding of specific Gilead personnel will be documented per the appropriate procedural documents.

The Gilead Representative may be provided with the unblinded closed session reports, as needed for the communication of DMC recommendation (refer to Section 6).

If any SMT member becomes unblinded, they will terminate their participation in the SMT no later than the day they are approved for unblinding.

5.4. Ad hoc Analysis Requests

If the DMC requests additional information concerning the study data, the DMC Chair will contact the Reporting Statistician, who will work together with the Study Biostatistician on the data analysis requests. The Reporting Statistician will ensure that no unblinding information is disclosed during the communication. The Study Biostatistician will coordinate obtaining additional information with the appropriate personnel (e.g., Study Medical Monitor or PS GSL).

The PS GSL should always be informed if the request is related to subject safety.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

6. DMC RECOMMENDATIONS AND GILEAD DECISION

6.1. Development of DMC Recommendations

During the closed session, based on the review of the open and closed session reports, the DMC will agree on a recommendation as to whether the study should continue as planned, continue with modification, be temporarily suspended, or be terminated prematurely. If there is no consensus on the recommendation within the DMC, then the majority decision will be taken forward. If there is no majority decision after extensive discussions, the DMC Chair will present all viewpoints from the DMC members to the Gilead Representative in order to give a complete overview of the DMC discussions.

Barring unforeseen circumstances, a recommendation to stop the study early will be based primarily on risk-benefit assessments at the planned interim analyses. Specific decision rules to be considered by the DMC will be derived from the version of the protocol and statistical analysis plan that are in operation at the time of the interim analysis. Gilead will review those rules in detail with the DMC members at the time of the open session for the planned interim efficacy and safety analysis meeting.

In the absence of predefined stopping rules, it is anticipated that the DMC will permit the study to continue to completion unless there are serious emerging safety concerns.

6.2. Communication of DMC Recommendations

The DMC Chair will contact the Gilead Representative via phone call or email within one business day after DMC meeting to communicate the DMC recommendation. (The recommendation for study continuation without any modification may be provided in wrap-up session if applicable).

Recommendations for modifications should be accompanied by the minimum amount of data required for Gilead to make a reasoned decision about the recommendation, and the rationale for such recommendations should be as clear and precise as possible. The recommendations should be provided in a manner that avoids compromising confidential information or the integrity and scientific validity of the study (as defined in Section 3.4). For a double blinded study, FRM-04853 Request for Unblinding Clinical Study Data must be approved prior to communication of any unblinded data to the Gilead Representative.

The DMC recommendations for each meeting will be documented in the meeting minutes. The recommendations and corresponding rationale should be crafted in a manner that, if warranted, Gilead can circulate to investigators, IRB/IECs, Regulatory Authorities, and/or other interested parties separately from the meeting minutes.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

6.3. Gilead Decision on DMC Recommendation

If the DMC recommends any modifications to the study, temporary suspension, or early study termination, due to safety concerns, the Gilead Representative will confer with the Study Medical Monitor and PS GSL to follow the PS signal management process.

The Gilead Representative will then communicate to the DMC whether Gilead has decided to accept or reject the DMC's recommendations. The Gilead Representative will also inform SMT to implement the Gilead final decision, if applicable.

If Gilead agrees to act upon a DMC recommendation to amend the protocol or to stop the study early, the appropriate SMT functions will inform all applicable Regulatory Authorities in writing of the decision prior to notifying the investigational centers. The DMC members will not make any public announcements, including direct communication with Regulatory Authorities, without prior approval from Gilead and attendance by Gilead personnel in the communication meeting.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

7. DMC ROLE AS AN UNBLINDED REVIEW TEAM IN GLPS MSS SIGNAL MANAGEMENT

Gilead PS may request a DMC to review an unblinded Safety Review for a specific topic as part of Gilead's signal management processes. Such a request may occur for a signal from blinded data if a Gilead safety governance meeting requests for a DMC to serve as the unblinded review team. After DMC review of the safety data or Safety Review, the DMC recommendation is taken back to the same safety governance meeting (where the blind is maintained) and the signal is managed per Gilead's signal management processes.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

8. APPENDICES

Appendix A. Protocol Synopsis

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title: Phase 3 Double-blind Multicenter Randomized Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide) in Virologically Suppressed People With HIV-1

Study Acronym: ARTISTRY-2

Plain Language Short Title: Study to Compare Bictegravir/Lenacapavir Versus Current Therapy in People With HIV-1 Who Are Successfully Treated With Biktarvy

Regulatory Agency Identifier Number(s):

IND Number: 158963
EU CT Number: 2023-510022-33
ClinicalTrials.gov Identifier: Not Available

Study Sites Planned: Approximately 120 sites globally

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the efficacy of switching to bictegravir/lenacapavir (BIC/LEN) (75/50 mg) fixed-dose combination (FDC) tablets versus continuing on bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) (50/200/25 mg) FDC tablets in virologically suppressed people with HIV-1	• 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
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of study drug(s) for the 2 treatment groups in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count	• Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm • Change from baseline in CD4 cell count at Week 48

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Secondary Objectives	Secondary Endpoints
• To evaluate the long-term efficacy of BIC/LEN in participants from Treatment Group 1 as determined by viral load suppression rate and CD4 cell count	• Proportion of participants from Treatment Group 1 with HIV-1 RNA ≥ 50 copies/mL at Week 96 (96 weeks on BIC/LEN including blinded and open-label [OL] phases) as determined by US FDA–defined snapshot algorithm • Proportion of participants from Treatment Group 1 with HIV-1 RNA < 50 copies/mL at Week 96 (96 weeks on BIC/LEN including blinded and OL phases) as determined by US FDA–defined snapshot algorithm • Change from baseline in CD4 cell count at Week 96 for participants from Treatment Group 1 (96 weeks on BIC/LEN including blinded and OL phases)
• To evaluate the safety and tolerability of the study drug(s) for the 2 treatment groups	• Proportion of participants experiencing treatment-emergent adverse events (AEs) through Week 48
• To evaluate the long-term safety and tolerability of BIC/LEN in participants from Treatment Group 1	• Proportion of participants from Treatment Group 1 experiencing treatment-emergent AEs through Week 96 (96 weeks on BIC/LEN including blinded and OL phases)

Study Design: This study is a Phase 3 double-blind, multicenter, randomized, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus B/F/TAF in virologically suppressed people with HIV-1 on B/F/TAF for at least 6 months prior to screening.

Participants will be randomized in a 2:1 ratio to one of the following treatment groups during the blinded phase:

- **Treatment Group 1 (n = 364):** Participants will switch from B/F/TAF (50/200/25 mg) FDC tablets to BIC/LEN (75/50 mg) FDC tablets + placebo-to-match (PTM) B/F/TAF tablets administered orally, once daily, without regard to food. Participants will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN tablets on Day 1 and on Day 2, without regard to food), in addition to the daily doses of BIC/LEN FDC tablet starting on Day 1.
- **Treatment Group 2 (n = 182):** Participants will continue with B/F/TAF (50/200/25 mg) FDC tablets and start PTM BIC/LEN tablets on Day 1 administered orally, once daily, without regard to food. Participants will receive PTM LEN tablets for 2 days (2 PTM LEN tablets on Day 1 and on Day 2, without regard to food).

Randomization will be stratified by geographic region.

Number of Participants Planned: Approximately 546 participants in total (364 in Treatment Group 1 and 182 in Treatment Group 2).

Study Population: People with HIV-1 (≥ 18 years of age) who are on B/F/TAF FDC tablets and have been virologically suppressed for at least 6 months prior to screening.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Diagnosis and Main Eligibility Criteria: (Inclusion and Exclusion Criteria)

Medically stable people with HIV-1 who meet the following criteria:

- Currently receiving B/F/TAF for at least 6 months prior to screening.
- If plasma HIV-1 RNA measurements in the 6 months prior to screening are available, all levels must be < 50 copies/mL.
- At least one documented HIV-1 RNA level measured between 6 and 12 months (± 2 months) prior to screening. This and any other HIV-1 RNA measurements documented in this period must be < 50 copies/mL.
- Plasma HIV-1 RNA levels < 50 copies/mL at screening.
- No documented or suspected resistance to BIC (including INSTI-R mutations T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene).
- No documented or suspected resistance to tenofovir alafenamide (TAF; mutations K65R, K65N, K70E, Q151M or T69 insertion, or ≥ 3 of the following thymidine analog mutations [M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R] in the reverse transcriptase gene).
- Estimated glomerular filtration rate ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance.
- No prior use of, or exposure to, LEN.
- No chronic hepatitis B virus (HBV) infection, as determined by either:
  - Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit.
  - Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit.

Test Product, Dose, and Mode of Administration: BIC/LEN (75/50 mg) FDC, administered orally, once daily, without regard to food. Participants randomized to Treatment Group 1 will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2, without regard to food), in addition to the daily dose of BIC/LEN FDC starting on Day 1.

Reference Therapy, Dose, and Mode of Administration: Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide [B/F/TAF; 50/200/25 mg]) administered orally, once daily, without regard to food.

Duration of Intervention: Participants will be treated for at least 48 weeks during the blinded phase; participants from Treatment Group 1 will be treated with BIC/LEN FDC tablets for at least 96 weeks, including the blinded and (OL) phases, up to OL Week 48. After blinded Week 48, all participants will continue to take their blinded study drug and attend visits every 12 weeks. Once the last participant completes the Week 48 visit and the analysis of safety and efficacy data of BIC/LEN FDC compared with B/F/TAF FDC is completed, all participants will attend an end of blinded treatment (EBT) visit at the next in-clinic visit (preferably within 12 weeks).

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

At the EBT visit, participants in Treatment Group 1 will enter the OL phase, and will continue to receive BIC/LEN FDC tablets through at least OL Week 48. At the OL Week 48 visit, participants in Treatment Group 1 will be given option to continue to receive BIC/LEN FDC tablets.

At the EBT visit, participants from Treatment Group 2 will be given the option to enter the OL phase to receive BIC/LEN FDC tablets and continue in the study.

All participants who enter the OL phase may continue to receive BIC/LEN FDC tablets until study drug is available, or until Gilead Sciences (Gilead) elects to discontinue the study, whichever occurs first.

Study Procedures/Frequency:

Blinded Phase:

After screening procedures, eligible participants will be randomized 2:1 to Treatment Group 1 or Treatment Group 2 and treated for at least 48 weeks. Following the Day 1 visit, participants will be required to return for study visits at Day 2 (option to conduct this as a virtual visit will be available, as appropriate), Weeks 4, 12, 24, 36, and 48. After the Week 48 visit and until the EBT visit, all participants will be required to return for visits every 12 weeks.

The timings of efficacy, safety, and all other assessments for the blinded phase are detailed in Table 1.

Open-label Phase:

Participants from Treatment Group 1 will receive BIC/LEN FDC tablets through at least OL Week 48. At the OL Week 48 visit, participants from Treatment Group 1 will be given the option to continue to receive BIC/LEN FDC tablets. Participants from Treatment Group 1 who complete the OL Week 48 visit and do not wish to continue the OL phase will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the OL Week 48 visit, and will be considered to have completed the study.

Participants in Treatment Group 2 who complete the EBT visit will be given the option to enter the OL phase to receive BIC/LEN FDC tablets. Participants from Treatment Group 2, who complete the study through the EBT visit and do not wish to participate in the OL phase, will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the EBT visit and will be considered to have completed the study.

All participants enrolled in the OL phase will return for clinic visits every 12 weeks and will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the end of the OL phase.

Participants from Treatment Group 1 will continue the BIC/LEN FDC tablets in the OL phase without any oral loading doses of LEN.

Participants from Treatment Group 2 who enter the OL phase will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily BIC/LEN FDC tablet starting on Day 1 of the OL phase. Following the Day 1 visit, participants will be required to return for the study visit on Day 2 (option to conduct this as a virtual visit will be available, as appropriate) and will attend a Week 4 visit during the OL phase.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Statistical Methods: The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized participants who receive at least one dose of study drug.

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA–defined snapshot algorithm. The primary analysis will consist of a noninferiority test of switching to BIC/LEN versus B/F/TAF, with respect to the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48. It will be concluded that BIC/LEN is noninferior to B/F/TAF if the upper bound of the 2-sided 95% CI of the treatment difference (BIC/LEN − B/F/TAF) in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL between 2 treatment groups is < 4% (ie, a margin of 4% is applied to noninferiority assessment). The 2-sided 95% CIs will be constructed based on stratum-adjusted Mantel-Haenszel (MH) proportion, adjusted by geographic regions.

The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA–defined snapshot algorithm will also be analyzed using the same methods as for the primary efficacy endpoint based on the FAS. Noninferiority will be assessed using a margin of 10%. It will be concluded that BIC/LEN is noninferior to B/F/TAF if the lower bound of the 2-sided 95% CI of the difference between treatment groups (BIC/LEN − B/F/TAF) in proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 is greater than −10%.

The change from baseline in CD4 cell count at Week 48 will be compared between treatment groups using analysis of covariance (ANCOVA) models, including baseline CD4 cell count and geographic region as covariates, and treatment (BIC/LEN vs B/F/TAF) as a fixed effect in the model. The least-squares mean and associated 95% CI of treatment difference from the ANCOVA model will be provided.

Longer term antiviral effect including proportion of participants with HIV-1 RNA ≥ 50 copies/mL, HIV-1 RNA < 50 copies/mL and change from baseline in CD4 cell count will also be assessed for participants randomized in Treatment Group 1 through Week 96 (96 weeks on BIC/LEN including the blinded phase and the OL phase).

Safety endpoints will be analyzed by the number and percent of participants with AEs or laboratory abnormalities for categorical values or 8-number summary (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, maximum) for continuous data by treatment groups.

For the general pharmacokinetic (PK) analyses, PK of BIC and LEN may be evaluated using descriptive statistics and/or population analysis approaches.

Sample size calculations are based on the historical Gilead Genvoya® and B/F/TAF studies. Assuming that the virologic failure rate is 2% for both treatment groups, and a noninferiority margin of 4%, a total of approximately 546 participants, with 2:1 randomization ratio of BIC/LEN versus B/F/TAF, will provide approximately 90% power to show noninferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/mL) at Week 48 at a 1-sided significance level of 0.025.

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Appendix B. Open and Closed Session Reports

The following summary tables and listings are planned for the open and closed session reports of interim safety reviews. The Safety Analysis Set, which includes all subjects who took at least 1 dose of study drug, will be used for all safety endpoints. The Full Analysis Set (FAS), which will include all randomized participants who have received any dose of study drug.

Additional summaries and listings (e.g., efficacy tables, figures, and listings) may be used for the DMC meetings. Any updates to the initial list of DMC outputs will be presented in a separate table of contents (TOC) prior to each meeting and will not require reapproval of the DMC charter.

Table Number	Title	Analysis Set
1	Enrollment by Country and Investigator	Safety Analysis Set
2	Participant Disposition	All Randomized Analysis Set
3.1	Demographics and Baseline Characteristics	Safety Analysis Set
3.2	Other Baseline Characteristics: Disease Characteristics	Safety Analysis Set
3.3	Other Baseline Characteristics: HIV and Antiretroviral Medication History	Safety Analysis Set
4	Extent of Exposure to Study Drug	Safety Analysis Set
5	Treatment-Emergent Adverse Events: Overall Summary	Safety Analysis Set
6.1	Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term	Safety Analysis Set
6.2	Treatment-Emergent Adverse Event by Preferred Term	Safety Analysis Set
7	Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
8	Treatment-Emergent Study Drug-Related Adverse Event	Safety Analysis Set
9	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
10	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term	Safety Analysis Set
11.1	Treatment-Emergent Laboratory Abnormalities	Safety Analysis Set
11.2	Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities	Safety Analysis Set
12	Number and Percentage of Participants with HIV-1 RNA < 50 copies/mL by Visit (Missing=Failure)	Full Analysis Set
13	Number and Percentage of Participants with HIV-1 RNA < 50 copies/mL by Visit (Missing=Excluded)	Full Analysis Set
14	Absolute Value and Change from Baseline in CD4 Cell Count (cell/uL) by Visit While On Treatment	Full Analysis Set

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Figure Number	Title	Analysis Set
1	Swimmer Plots for Participants with Treatment-Emergent Serious Adverse Events by Treatment Group	Safety Analysis Set
2	Swimmer Plots for Participants with Grade 3 or 4 Treatment-Emergent Adverse Events by Treatment Group	Safety Analysis Set

Listing Number	Title	Analysis Set
1	Demographics and Baseline Characteristics	All Randomized Analysis Set
2	Other Baseline Characteristics: Disease Characteristics	All Randomized Analysis Set
3	Adverse Events	All Randomized Analysis Set
4	Adverse Events with Severity of Grade 3 or Higher	All Randomized Analysis Set
5	Study Drug-Related Adverse Events	All Randomized Analysis Set
6	Serious Adverse Events	All Randomized Analysis Set
7	Adverse Events Leading to Premature Discontinuation of Study Drug	All Randomized Analysis Set
8	Deaths	All Randomized Analysis Set
9	Treatment-Emergent Laboratory Abnormalities	All Randomized Analysis Set
10	Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities	All Randomized Analysis Set
11	HIV-1 RNA, CD4 Cell Counts and Percentages	All Randomized Analysis Set

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Appendix C. DMC Membership and Contact Information

DMC Chair

PPD
Professor of Medicine, Johns Hopkins University School of Medicine
Director, Division of Infectious Diseases, Johns Hopkins Bayview Medical Center
Senior Associate Dean for Clinical Trials, Johns Hopkins University School of Medicine
Address: 4940 Eastern Ave, Mason F. Lord Building, Suite 379 Baltimore, MD 21224
Phone: PPD
Email: PPD

PPD
Francis and Dorothea Reed Endowed Chair in Infectious Diseases, Department of Medicine, Harvard Medical School
Address: 55 Fruit Street, Bulfinch 130, PPD Boston, MA 02114
Phone: PPD
Email: PPD

PPD
Professor of Biostatistics
Department of Biostatistics, Harvard University
677 Huntington Avenue
Boston, MA 02115
Phone: PPD
E-mail: PPD

Docusign Envelope ID: A8820B74-84D2-4345-922E-22876E86FF5D

Appendix D. Gilead and Reporting Statistician Contacts

Gilead Representative

PPD
SVP, Clinical Development
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: PPD
Email: PPD

Study Medical Monitor

PPD
Director, Clinical Development
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Phone: PPD
Email: PPD

Study Biostatistician

PPD
Senior Manager, Biostatistics
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Email: PPD

PS GSL

PPD
Sr Director, Patient Safety
Gilead Sciences International, Ltd
Granta Park
Abington, Cambridge CB21 6GT, UK
Phone: PPD
Email: PPD

Reporting Statistician

PPD
Director
Biostatistics
Catalyst Clinical Research, LLC
2528 Independence Blvd, Suite 100
Wilmington, NC 28412
Phone : PPD
E-mail: PPD