



STATISTICAL ANALYSIS PLAN

Study Title:	An Operationally Seamless Phase 2/3 Randomized, Open-label, Multicenter, Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Stable Baseline Regimen in Virologically Suppressed People With HIV-1 on Stable Complex Treatment Regimens
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

%CV	percentage coefficient of variation
AE	adverse event
AI	attachment inhibitor
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
CCR5	chemokine receptor type 5
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
EQ-5D-3L	EuroQoL (5 dimensions, 3 levels)
ERT	end of randomized treatment
ESDD	early study drug discontinuation
ET	early termination
EU	Europe
FAS	Full Analysis Set
FDC	fixed-dose combination
HDL	high-density lipoprotein
HIVTSQc-12	HIV Treatment Satisfaction Questionnaire Change-12 Questions
HIVTSQs-12	HIV Treatment Satisfaction Questionnaire Status-12 Questions
HLGT	high-level group term
HLT	high-level term
HRQOL	health-related quality of life
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
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	protease inhibitor
PK	pharmacokinetic(s)
PKE	pharmacokinetic enhancer
PP	per protocol
PRO	patient-reported outcome
PT	preferred term
PWH	people with HIV-1
Q1	first quartile
Q3	third quartile
QD	once daily
rBA	relative bioavailability
SAP	statistical analysis plan
SAE	serious adverse event
SBR	stable baseline regimen
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
WPAI-HIV	Work Productivity and Activity Impairment Questionnaire: HIV

PHARMACOKINETIC ABBREVIATIONS

AUC_{0-t}	area under the concentration versus time curve from time zero to any given time 't'
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{τ}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_t	concentration of drug at any given time 't'
C_{trough}	concentration at the end of the dosing interval
CL/F	apparent oral clearance after administration of the drug: at steady state: $CL/F = Dose/AUC_{\tau}$, where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve
V_z/F	apparent volume of distribution

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 the Phase 3 portion of Study GS-US-621-6289 for the primary and secondary endpoints. The analysis will be performed after all participants enrolled in the Phase 3 portion of the study complete their Week 48 visit or prematurely discontinue from the study drug.

This SAP is based on the study protocol amendment 4 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

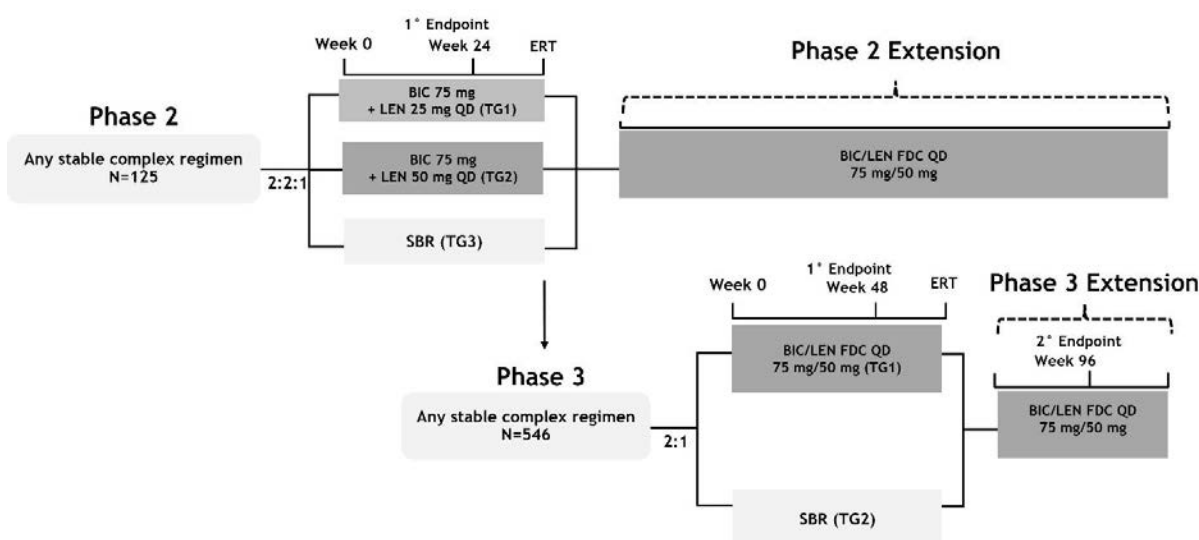
Primary Objective	Primary Endpoint
To evaluate the efficacy of switching to bictegravir/lenacapavir (BIC/LEN) fixed-dose combination (FDC) tablet regimen (BIC 75 mg/LEN 50 mg) versus continuing on a stable baseline regimen (SBR) in virologically suppressed people with HIV-1 as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48	Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm
Secondary Objectives	Secondary Endpoints
To evaluate the efficacy of the 2 treatment groups in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count at Week 48	- 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 efficacy of BIC/LEN in participants from Treatment Group 1 as determined by viral load suppression rate and CD4 cell count at Week 96	- Proportion of participants from Treatment Group 1 with HIV-1 RNA ≥ 50 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm - Change from baseline in CD4 cell count at Week 96 for participants from Treatment Group 1
To evaluate the safety and tolerability of the 2 treatment groups through Week 48	Proportion of participants experiencing treatment-emergent adverse events (AEs) through Week 48
To evaluate the safety and tolerability of BIC/LEN in participants from Treatment Group 1 through Week 96	Proportion of participants from Treatment Group 1 experiencing treatment-emergent AEs through Week 96

Exploratory Objectives	Exploratory Endpoints
To evaluate quality of life as measured by the PozQoL of the 2 treatment groups through Week 48	PozQoL: changes from baseline for each score at Weeks 4, 12, 24, and 48
To evaluate the quality of life of participants receiving BIC/LEN in Treatment Group 1 through Week 96	PozQoL: change from baseline for each score at Weeks 60, 72, 84, and 96 for participants in Treatment Group 1
To evaluate treatment satisfaction of the 2 treatment groups through Week 48	- HIVTSQs-12: absolute scores at Weeks 4, 12, 24, and 48 - HIVTSQc-12: absolute score at Week 48
To evaluate participant satisfaction with BIC/LEN treatment in participants in Treatment Group 1 through Week 96	HIVTSQs-12: absolute scores at Weeks 60, 72, 84, and 96 for participants in Treatment Group 1
To evaluate work productivity of the 2 treatment groups through Week 48	WPAI-HIV: change from baseline for each score at Weeks 24 and 48
To evaluate work productivity of participants receiving BIC/LEN in Treatment Group 1 through Week 96	WPAI-HIV: change from baseline for each score at Weeks 60, 72, 84, and 96 for participants in Treatment Group 1
To evaluate treatment preference of the 2 treatment groups through Week 48	Treatment Preference Questionnaire absolute scores at Weeks 4, 12, 24, and 48
To evaluate treatment preference of participants receiving BIC/LEN in Treatment Group 1 through Week 96	Treatment Preference Questionnaire: absolute scores at Weeks 60, 72, 84, and 96 for participants in Treatment Group 1
To evaluate meaningful change of the PozQoL by administering the PGIC and PGIS patient-reported outcome (PRO) instruments	- PGIC Impact Questionnaire: absolute scores at Weeks 4, 12, 24, and 48 - PGIC Impact Questionnaire: absolute scores at Weeks 60, 72, 84, and 96 for participants in Treatment Group 1 - PGIS Impact Questionnaire: change from baseline at Week 4, 12, 24, and 48 - PGIS Impact Questionnaire: change from baseline at Weeks 60, 72, 84, and 96 for participants in Treatment Group 1
To evaluate health states of the 2 treatment groups at Week 48	EQ-5D-3L: change from baseline at Week 48 for index scores and visual analogue scale
To evaluate health states of participants receiving BIC/LEN in Treatment Group 1 at Week 96	EQ-5D-3L: change from baseline at Week 96 for index scores and visual analogue scale for participants in Treatment Group 1

1.2. Study Design

This study is an operationally seamless Phase 2/3 randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus SBR in virologically suppressed people with HIV-1 on a stable complex treatment regimen for at least 6 months prior to screening. The study entry eligibility criteria are listed in Sections 4.2 and 4.3 of the protocol. In the Phase 2 portion, single agent BIC and LEN tablets (BIC + LEN) were coadministered to determine the optimal doses to be used in subsequent portions of the study. In the Phase 3 portion of the study, a single BIC/LEN FDC tablet is administered.

Figure 1-1. Study Schema



1° = primary; 2° = secondary; BIC = bictegravir; ERT = end of randomized treatment; FDC = fixed-dose combination; LEN = lenacapavir; QD = once daily; SBR = stable baseline regimen; TG = treatment group.
 For Phase 3, Week 96 will be considered as a secondary endpoint for Treatment Group 1.

In the Phase 3 portion, participants were randomized in a 2:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1 (n = 364):** Participants switched from their SBR to a regimen of BIC 75 mg/LEN 50 mg administered orally, without regard to food. Participants received a 2-day oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily doses of BIC/LEN FDC starting on Day 1.
- **Treatment Group 2 (n = 182):** Participants continue with their SBR.

Randomization was stratified by geographic region.

The Phase 3 portion consists of two periods: the Randomized Period and the Extension Period.

Participants will be treated for at least 48 weeks during the Randomized Period. After Week 48, participants will continue to take their study drug (BIC 75 mg/LEN 50 mg FDC tablets or SBR) and attend visits every 12 weeks. Once the last participant completes the Week 48 visit and the safety and efficacy of BIC/LEN FDC compared with the baseline regimen are demonstrated and the Week 48 analysis is completed, all participants will attend the end of randomized treatment (ERT) visit (preferably within 30 days).

Participants from Treatment Group 1 will continue to receive BIC/LEN FDC tablets until at least Week 96. At the Week 96 or ERT visit, whichever occurs later, participants from Treatment Group 1 will be given the option to enter the Extension Period to continue to receive BIC/LEN FDC tablets. Participants from Treatment Group 2 at ERT will be given the option to receive BIC/LEN FDC tablets during the Extension Period. All participants who enter the Extension Period may continue to receive the BIC 75 mg/LEN 50 mg FDC tablets until the product becomes available, or until Gilead elects to discontinue the study, whichever occurs first.

Following the Day 1 visit, participants will be required to return for study visits at Day 2 (oral LEN loading dose for Treatment Group 1), Weeks 4, 12, 24, 36, and 48. Participants will be followed every 12 weeks after the Week 48 visit until the ERT visit (Treatment Group 2) and ERT/Week 96 visit (Treatment Group 1).

All participants enrolled in the Extension Period will return for study visits every 12 weeks and will have a telephone visit at 30 days and a clinic visit at 60 days after the end of the Extension Period. Participants who received the BIC/LEN FDC tablet (ie, Treatment Group 1) during the Randomized Period will continue their treatment in the Extension Period without any oral loading doses of LEN. Participants from Treatment Group 2 who enroll in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC tablets starting on Day 1 of the Extension Period. Following the Day 1 visit, participants will be required to return for the study visit at Day 2 (option to conduct this as a virtual visit will be available, as appropriate).

Additional details regarding study assessment can be found in [Table 13-1](#) and [Table 13-2](#).

1.3. Sample Size and Power

In the Phase 3 portion of the study, a total of approximately 546 participants, randomized in a 2:1 fashion to the BIC/LEN FDC versus SBR, achieves at least 90% power to detect a noninferiority (NI) margin of 4% in difference in percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups. For the sample size and power computation, it is assumed that both treatment groups have 2% of participants with virologic failure (HIV-1 RNA ≥ 50 copies/mL) at Week 48 (based on the historical Gilead Genvoya® and BVY studies), that a NI margin is 4%, and that the significance level of the test is at a 1-sided 0.025 level.

1.3.1. Rationale for Noninferiority 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 $\geq$ 50 copies/mL) is considered clinically tolerable, with typical observed rates of virological failure seen in switch studies ranging 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 the Phase 3 portion of this study.

2.1. Interim Analyses

Prior to the final analysis of Phase 3 portion of the study, 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 the 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 in the Phase 3 portion 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.

For the Phase 3 portion, 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

For the Phase 3 portion, the Week 96 interim analysis will be conducted after all participants enrolled in Treatment Group 1 either complete their Week 96 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.

2.2. Week 48 Primary Analysis

The primary analysis for the primary endpoint of proportion of participants with HIV-1 RNA ≥ 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 in the Phase 3 portion will serve as the final analysis for this endpoint and will be used to evaluate the efficacy of BIC/LEN FDC in the Phase 3 portion.

2.3. Final Analysis

The final analysis for the Phase 3 portion of the study 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 randomized period of the Phase 3 portion of the study. No participant will be enrolled into the extension period 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 randomized drug (BIC/LFN FDC for Treatment Group 1, or continuing with their SBR for Treatment Group 2). 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 active study drug BIC/LEN FDC up to Week 48.
- Did not have at least one documented plasma HIV-1 RNA level measured between 6 and 12 months ($\pm$ 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 ($\pm$ 2 months) prior to screening were < 50 copies/mL (inclusion criterion 4b 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 randomized drug (BIC/LEN FDC for Treatment Group 1, or continuing with their SBR for Treatment Group 2). This is the primary analysis set for safety analyses.

3.1.5. Pharmacokinetic Analysis Set

The **Pharmacokinetic (PK) Analysis Set** includes participants who (1) were randomized to Treatment Group 1, (2) took at least 1 dose of study drug BIC/LEN FDC, and (3) have at least 1 nonmissing concentration value reported by the PK laboratory. This is the analysis set for general/sparse PK analyses.

3.1.6. Pharmacokinetic Substudy Analysis Set

The **PK Substudy Analysis Set** will include participants who (1) were randomized to Treatment Group 1, (2) took at least 1 dose of study drug BIC/LEN FDC, (3) participated in the intensive PK substudy, and (4) have at least 1 nonmissing intensive postdose concentration value reported by the PK laboratory. This is the primary analysis set for analysis of intensive PK sampling.

3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set or the FAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on the PP Analysis Set, Safety Analysis Set, and PK/PK Substudy Analysis Sets, 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

In the Phase 3 portion, 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.

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

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 the FAS:

- Age (< 55 years and $\geq$ 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 Phase 3 portion, noninferiority evaluation of the proportion of participants with HIV-1 RNA $\geq$ 50 copies/mL at Week 48 as determined by US FDA-defined snapshot algorithm is the prespecified primary comparison.

A superiority hypothesis testing of difference in proportion of HIV-1 RNA $\geq$ 50 copies/mL at Week 48 between Treatment Groups 1 and 2 will commence after the primary analysis reaches statistical significance and will be tested according to the hierarchical testing principle at the 1-sided 0.025 level Type I error rate adjusted for the number of DMC analyses prior to the primary analysis. This sequential testing procedure controls the Type I error rate at the nominal level.

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 $\geq$ 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) for both noninferiority and superiority tests 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 start date 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 and PK parameters. 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”.

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

For participants randomized to Treatment Group 1, 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 (ie, BIC/LEN FDC or LEN oral loading dose) is considered as the first dose date of the study drug.

For participants randomized to Treatment Group 2, the first dosing date of antiretroviral (ARV) regimen is defined as Day 1 visit date recorded on the Visit Date eCRF form. Study Day will be calculated from Day 1 visit date as follows:

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

Study Day 1 is the day of the first dose of study drug administration for Treatment Group 1, or the day of Day 1 visit in the randomized period for Treatment Group 2.

Last Dose Date in randomized period is defined as follows:

- For participants randomized to Treatment Group 1, the last dose date is the latest of study drug stop dates recorded on the Study Drug Administration eCRF form for participants who prematurely discontinue or complete study drug in the randomized period.
- For participants randomized to Treatment Group 2, the last dose date is the latest of the stop dates among all ARVs recorded on the Non-Study ARV Medication eCRF form with ‘Current ARV’ checked for participants who prematurely discontinue or complete the drugs in the randomized period.

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/SBR 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/SBR in the randomized period, or the data 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 (for Treatment Group 1), study drug/SBR 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 randomized period is the latest date among the study drug/SBR 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 randomized period 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 randomized period visits will be assigned to analysis windows.

Analysis windows for the randomized period analysis are derived relative to Study Day 1 in the randomized period.

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 randomized 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 randomized 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 12	84	2	168
Week 36	252	169	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 randomized treatment visit.

The analysis windows for safety electrocardiogram data are provided in [Table 3-5](#).

Table 3-5. Analysis Visit Windows for Safety Electrocardiogram Results

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	126
Week 24	168	127	≥ 168

The analysis windows for HBV blood panel and hemoglobin A1c data are provided in [Table 3-6](#).

Table 3-6. Analysis Visit Windows for HBV Blood Panel and 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-1 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
- PK Substudy Analysis Set
- Continuing study drug/SBR in randomized period
- Did not complete study drug/SBR in randomized period with reasons for premature discontinuation of study drug/SBR

- 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 Medication Exposure and Adherence

Extent of exposure to study drug in Treatment Group 1 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. The extent of exposure to SBR for participants in Treatment Group 2 will also be examined.

4.2.1. Duration of Exposure to Study Drug

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

Exposure to the 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. Duration of Exposure to SBR

The exposure to SBR will be examined based on the records collected from “Non-Study ARV Medication” eCRF form with a “Current ARV” checked. The total duration of exposure of SBR will be defined as Current ARV stop date – Day 1 visit date + 1 for the randomized period, regardless of any temporary interruptions, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Current ARV stop date is the latest stop date among all current ARVs taken during the randomized period.

A by-participant listing of all current ARV administrations will be provided by participant ID number (in ascending order) and visit (in chronological order) along with the durations of exposure during randomized period.

4.2.3. Adherence to Study Drug

During the study, drug accountability (ie, numbers of tablets dispensed and returned) is only captured for BIC/LEN FDC and LEN loading dose. Therefore, adherence will only be computed for Treatment Group 1. Adherence to oral loading LEN doses will not be derived. Adherence for daily dose of BIC/LEN FDC until data snapshot for the analysis and up to Week 48 will be calculated separately.

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:

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

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:

$$\begin{aligned} &\text{On – Treatment Adherence (\%)} \\ &= \left(\frac{\text{Total Number of Tablets Administered}}{\text{Tablets Expected to be Administered on Treatment}} \right) \times 100 \end{aligned}$$

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 randomized period 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 randomized period, 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 BIC/LEN FDC with the number and percentage of participants belonging to adherence categories (eg, < 80%, ≥ 80 to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided for Treatment Group 1 for the Safety Analysis Set. No formal statistical testing is planned.

A by-participant listing of study drug administration 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 one 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 one 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/m²]) 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 (eGFR, mL/min).
- HIV disease status: (a) AIDS, (b) asymptomatic, or (c) symptomatic HIV infection.
- Mode of infection (risk factors for HIV infection).
- Reasons to be on a complex regimen.
- 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.
- Number of prior ARV medication used (recorded on the Non-Study ARV Medication eCRF form with “Prior ARV” checked).
- Prior ARV medication (same as above) drug class: AI, CCR5, CAI, Fusion, INI, INI/NNRTI, NRTI/INI, NRTI/NNRTI, NRTI/PI, NNRTI, NRTI, PI, PI/PKE, PKE, Post-Attachment Inhibitor, or Other.
- Antiretroviral (ARV) medication use at baseline: Defined as the ARV medications taken on or up to 14 days prior to first dosing date of study drugs for Treatment Group 1, or taken on Day 1 for Treatment Group 2. This will be grouped by composite drug class category as defined in Appendix 13.3 and summarized by PI-containing or not.
- Number of ARV medication used at baseline.
- Dosing frequency of ARVs used at baseline: once daily, twice per day, three times per day, every two weeks, once, and other.
- Number of ARV pills taken per day at baseline.
- Number of ARV pills taken per day at baseline by category: 2, 3, 4, 5, >=6
- 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 SBR for Treatment Group 2), or all available data for participants who are still on study drug or SBR.

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 13-1](#).

All participants in FAS will be classified into 1 of the 3 categories indicated above (ie, HIV-1 RNA < 50 copies/mL, HIV RNA $\geq$ 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 $\geq$ 50 copies/mL will be calculated as the number of participants classified as HIV-1 RNA $\geq$ 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 SBR
Variable	HIV-1 RNA $\geq$ 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 $\geq$ 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 $\geq$ 50 copies/mL, are treated as having HIV-1 RNA $\geq$ 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 $\geq$ 50 copies/mL or HIV-1 RNA < 50 copies/mL at Week 48 between BIC/LEN FDC and SBR

BIC = bictegravir; FDA = Food and Drug Administration; FDC = fixed dose combination; HIV 1 = human immunodeficiency virus type 1; LEN = lenacapavir; RNA = ribonucleic acid; SBR = stable baseline regimen; 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 $\geq$ 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, the 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 noninferiority 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 Treatment Groups 1 and 2 as P_1 and P_2 , respectively, the null and alternative hypotheses for the noninferiority test with a margin of θ on the primary efficacy endpoint are as follows:

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

vs.

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

where the noninferiority 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 $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 \left[\frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1} \right]}{(\sum w_h)^2}}$, 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 noninferior to SBR if the upper bound of the 2-sided 95.002% CI for 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%.

If noninferiority is shown, the same 95.002% CI used in evaluating noninferiority at Week 48 will be used to evaluate superiority. If the upper bound of the 95.002% CI is below zero, superiority of BIC/LEN FDC over SBR is established.

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 Section 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 13.4.

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 Groups 1 and 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 Treatment Groups 1 and 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 Treatment Group 1 and 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 Treatment Groups 1 and 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 as described in Section 6.3.3.

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 13.5.

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 groups 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 group 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 $\geq$ 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 groups 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 Treatment Group 1 and 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 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 group and visit using descriptive statistics. Mean $\pm$ 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 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 $\pm$ 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 SBR for Treatment Group 2.

For participants who are ongoing on study drug/SBR at the time of analysis, 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 the toxicity criteria 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 or SBR

Related AEs are those for which the investigator selects “Related” on the AE CRF to the question of “Related to Study Treatment” for participants receiving BIC/LEN FDC in Treatment Group 1, or ‘Related to SBR’ for participants receiving SBR in Treatment Group 2. 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 or SBR will be considered related to study drug or SBR 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 drugs or SBR.

7.1.6.2. Incomplete Dates

If the start date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of start date 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 randomized period 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 randomized period 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:

- TEAEs 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 or SBR
- 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 AEs with Grade 3 or higher, TE treatment-related SAEs, and TEAEs leading to premature discontinuation of study drug or SBR during the randomized period 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 visit, 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 or SBR
- All AEs leading to premature discontinuation of study

7.2. Laboratory Evaluations

Laboratory data collected during the randomized period 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 BIC/LEN FDC for Treatment Group 1, or Day 1 visit date for Treatment Group 2. 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, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized.

Median (Q1, Q3) of the 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) $> 5 \times \text{ULN}$; (c) $> 10 \times \text{ULN}$; (d) $> 20 \times \text{ULN}$
- Alanine aminotransferase (ALT): (a) $> 3 \times \text{ULN}$; (b) $> 5 \times \text{ULN}$; (c) $> 10 \times \text{ULN}$; (d) $> 20 \times \text{ULN}$
- AST or ALT: (a) $> 3 \times \text{ULN}$; (b) $> 5 \times \text{ULN}$; (c) $> 10 \times \text{ULN}$; (d) $> 20 \times \text{ULN}$
- Total bilirubin: (a) $> 1 \times \text{ULN}$; (b) $> 2 \times \text{ULN}$
- Alkaline phosphatase (ALP) $> 1.5 \times \text{ULN}$
- AST or ALT $> 3 \times \text{ULN}$ and total bilirubin: (a) $> 1.5 \times \text{ULN}$; (b) $> 2 \times \text{ULN}$
- AST or ALT $> 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ and ALP $< 2 \times \text{ULN}$

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 randomized period 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 BIC/LEN for Treatment Group 1, or the date of Day 1 visit for Treatment Group 2. 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 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

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 for Treatment Group 1 or before Day 1 for Treatment Group 2. Any medications with a start date prior to the first dosing date of study drugs or prior to Day 1 for Treatment Group 2 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 BIC/LEN for Treatment Group 1 or medications taken on or after Day 1 for Treatment Group 2. 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 (or Day 1 for Treatment Group 2) 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 (or SBR) 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 (or SBR) will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of any study drug (or SBR) or with a start date after the last dosing date of all study drugs (or SBR) 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 (or Day 1 for Treatment Group 2) 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 (or SBR) 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 medications 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. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at Week 12 and Week 24 compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-participant listing for ECG assessment results will be provided by participant ID number and visit in chronological order.

7.6. Other Safety Measures

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

7.7. 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 from Treatment Group 1 at the time points specified in protocol.

An intensive PK substudy is performed in a subset of participants in Treatment Group 1 at selected study sites. Participants may choose to participate at either one of the visits. Intensive PK blood samples are collected for this subset of participants instead of the sparse plasma PK samples on those specific visits (Week 24 or 36 or 48 visit) as specified in protocol.

8.2. PK Analyses Related to Intensive PK Sampling

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

8.2.1. Estimation of PK Parameters

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

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

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

Pharmacokinetic parameters such as AUC_{inf} , λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist and accordingly these parameters may be excluded from the overall summary statistics, as appropriate.

8.2.2. PK Parameters

PK parameters will be generated for all participants for whom parameters can be derived in the PK Substudy Analysis Set. 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.

The PK parameters presented in [Table 8-2](#) will be used to evaluate the PK objectives of the study as appropriate. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
BIC	AUC _{last} , AUC _{tau} , AUC _{0-t} , C _{max} , T _{max} , C _{last} , T _{last} , C _{trough} , C _t , λ _z , V _z /F, CL/F, and t _{1/2} (as applicable)
LEN	AUC _{last} , AUC _{tau} , AUC _{0-t} , C _{max} , T _{max} , C _{last} , T _{last} , C _{trough} , C _t , λ _z , V _z /F, CL/F, and t _{1/2} (as applicable)

BIC = bictegravir; LEN = lenacapavir.

Individual participant concentration data and individual participant PK parameters 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 both individual participant concentration data by nominal time point and individual participant PK parameters for Treatment Group 1. 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.

Individual PK parameter data listings and summaries will include all participants in PK Substudy Analysis Set for whom relevant PK parameters can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter. Data and summary statistics will be presented to three significant digits.

The following tables will be provided for each analyte in Treatment Group 1:

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

The following figures may be provided for each analyte:

- Mean ($\pm$ SD) concentration data versus time (on linear and semilogarithmic scales). 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 and remaining points connected. If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales). If more than one-half of the values at a timepoint are BLQ then the median and quartile values will not be presented at that timepoint, and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as lower LOQ at that timepoint.
- Individual participant concentration data versus time (on linear and semilogarithmic scales). Values of BLQ will be displayed as 0 on the linear scale and missing on the semi-logarithmic scale.

8.2.3. Sensitivity Analyses

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.

8.3. PK Analyses Related to Sparse PK Sampling

The sparse PK sample concentrations will be summarized using descriptive statistics as for intensive PK concentrations.

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

Additionally, both the sparse and intensive 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.

8.4. Changes from Protocol-Specified PK Analyses

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

9. EVALUATION OF PATIENT-REPORTED OUTCOMES

Exploratory analyses for PRO will be described in a separate PRO analysis document.

10. 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.

11. 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.

12. SAP REVISION

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

13. APPENDICES

13.1. Schedule of Assessments

Table 13-1. Schedule of Assessments in Phase 3 – Treatment Groups 1 and 2: Screening through Post-Endpoint Week 48

Study Procedures	Screening ^a	Day 1 ^b		Week					Post-Endpoint Week 48 ^d
				4	12	24	36	48	Every 12 weeks
Visit Window		30 days after screening visit	Day 2 ^c	± 6 days	± 6 days	± 6 days	± 6 days	± 6 days	± 6 days
Informed consent	X								
Medical history	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events ^e	X	X	X	X	X	X	X	X	X
Complete physical exam	X	X			X			X	
Symptom-directed physical exam ^f				X		X	X		X
12-Lead ECG (performed supine)	X				X	X			
Treatment Expectations Questionnaire		X							
PozQoL		X		X	X	X		X	X
HIVTSQs-12		X		X	X	X		X	X
HIVTSQc-12								X	
Treatment Preference Questionnaire				X	X	X		X	X
WPAI-HIV Questionnaire		X				X		X	X
EQ-5D-3L Questionnaire		X						X	X ^v

Study Procedures	Screening ^a	Day 1 ^b		Week					Post-Endpoint Week 48 ^d
				4	12	24	36	48	Every 12 weeks
Visit Window		30 days after screening visit	Day 2 ^c	± 6 days	± 6 days	± 6 days	± 6 days	± 6 days	± 6 days
PGIC: Impact Questionnaire				X	X	X		X	X
PGIS: Impact Questionnaire		X		X	X	X		X	X
Height	X								
Weight	X	X		X	X	X	X	X	X
Vital signs ^g	X	X		X	X	X	X	X	X
Urinalysis	X	X				X		X	X
Urine pregnancy test ^h		X							
Serum pregnancy test ^h	X								
FSH ⁱ	X								
Chemistry profile ^j	X	X		X	X	X	X	X	X
Metabolic assessment ^k		X			X		X	X	X
Creatinine clearance	X	X		X	X	X	X	X	X
Hemoglobin A1c		X						X	
Hematology profile ^l	X	X		X	X	X	X	X	X
Plasma HIV-1 RNA	X	X		X	X	X	X	X	X
CD4 cell count	X	X		X	X	X	X	X	X
Plasma and urine storage sample ^m	X	X		X	X	X	X	X	X
HBV blood panel ⁿ	X							X	
Plasma samples stored for potential HIV-1 genotype/phenotype ^o		X		X	X	X	X	X	X

Study Procedures	Screening ^a	Day 1 ^b		Week					Post-Endpoint Week 48 ^d
				4	12	24	36	48	Every 12 weeks
Visit Window		30 days after screening visit	Day 2 ^c	± 6 days	± 6 days	± 6 days	± 6 days	± 6 days	± 6 days
Whole blood for proviral DNA sequencing ^p		X							
Sparse PK: trough and postdose PK sample(Treatment Group 1) ^{q,r,s}		X		X	X	X	X	X	X ^r
Optional intensive PK substudy (Treatment Group 1) ^{s,t}						X ^t	X ^t	X ^t	
Randomization		X							
Provide participant dosing diary to participants		X		X	X	X	X	X	X
Study drug dispensation		X		X	X	X	X	X	X
Study drug accountability ^u			X	X	X	X	X	X	X

AE = adverse event; BIC = bictegravir; CD4 = clusters of differentiation 4; ECG = electrocardiogram; ERT = end of randomized treatment; EQ-5D-3L = EuroQol (5 dimensions, 3 levels); FDC = fixed-dose combination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B virus core antibody; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; HIVTSQc-12 = HIV Treatment Satisfaction Questionnaire-Change 12-item version; HIVTSQs-12 = HIV Treatment Satisfaction Questionnaire-Status 12-item version; LDL = low-density lipoprotein; LEN = lenacapavir; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); PRO = patient-reported outcome; WPAI - HIV = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

- a Evaluations to be completed within 30 days prior to Day 1. Screening window can be extended to 45 days with sponsor approval.
- b 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 PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1. The study drugs will be administered without regard to food.
- c Day 2 visit is not applicable to participants in Treatment Group 2. 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 After Week 48, all participants will return for visits every 12 weeks until the ERT visit.
- e Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
- f Symptom-directed physical examination as needed.
- g Blood pressure, pulse, respiration rate, and temperature.
- h Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.

- i At screening, a FSH is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
- j Chemistry profile per Protocol Table 12.
- k Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) 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.
- l Hematology profile per Protocol Table 12.
- m Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate) in accordance with local regulations. Separate consent for optional future research is not needed to collect or use these samples unless required per local regulations and requirements.
- n HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb), at Week 48 of randomized treatment, at Week 48 of the Extension Period visits, and at the 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.
- o HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Protocol Section 6.3.10.2).
- p Proviral DNA sequencing is for research use only. Sample is to be collected for all participants on study. Separate consent is not required for this test.
- q For participants in Treatment Group 1, a single predose plasma PK sample (≤ 5 min before dose) and a postdose plasma PK sample at 4 hours (± 1 hours) (relative to BIC/LEN FDC dosing and oral loading dose of LEN) will be collected on Day 1. A single trough plasma PK sample approximately 23 to 24 hours after the previous dose and prior to dosing at Weeks 4, 12, 24, 36, and 48, and a single postdose plasma PK sample at 2 hours (± 1 hours) (relative to BIC/LEN dosing) at Weeks 4, 12, 24, 36, and 48 will be collected. 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 (except for participants enrolled in the intensive PK substudy), a PK sample prior to dosing in clinic should be collected at Weeks 4, 12, 24, 36, and 48.
- r 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 'q' during randomized 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) after Week 48 until ERT visit and during Extension Period. See Protocol Section 6.3.9.2 for additional information. 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) after Week 48 until the ERT visit and during Extension Period.
- s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse intensive PK sample (as applicable).
- t An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites. Participants may select to participate in either one of the visits. Intensive PK blood samples will be collected for the subset of participants as described below **instead of** the sparse plasma PK samples on those specific visits.
Week 24 or 36 or 48 visit: Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose that was administered the day before and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC/LEN FDC dosing).
- u 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.
- v EQ-5D-3L Questionnaire will only be collected at Week 96 visit.

Table 13-2. Schedule of Assessments in Phase 3 – Treatment Groups 1 and 2: ERT Visit through 60-Day In-Clinic Follow-up Visit

Study Procedures	ERT Visit ^a	Phase 3 Extension ^b			Early Study Drugs DC Visit	30-day Telephone Visit ^e	60-day In-clinic Follow-up Visit ^e
		Only for TG2 participants who enroll in the Extension Period		Every 12 weeks ^d			
		Day 2	Week 4 ^c				
Visit Window			± 6 days	± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Concomitant medications	X	X	X	X	X	X	X
Adverse events ^f	X	X	X	X	X	X	X
Complete physical exam	X				X		X
Symptom-directed physical exam ^g			X	X			
12-Lead ECG (performed supine)					X		
PozQoL ^h				X			
HIVTSQs-12 ^h				X			
Treatment Preference Questionnaire ^h				X			
WPAI - HIV Questionnaire ^h				X			
EQ-5D-3L Questionnaire ^h				X ⁱ			
PGIC: Impact Questionnaire ^h				X			
PGIS: Impact Questionnaire ^h				X			
Weight	X			X	X		X
Vital signs ^j	X		X	X	X		X
Urinalysis	X			X	X		X
Urine pregnancy test ^k					X		X
Chemistry profile ^l	X		X	X	X		X
Metabolic assessment ^m	X			X			
Creatinine clearance	X		X	X	X		X
Hematology profile ⁿ	X		X	X	X		X
Plasma HIV-1 RNA	X		X	X	X		X

Study Procedures	ERT Visit ^a	Phase 3 Extension ^b			Early Study Drugs DC Visit	30-day Telephone Visit ^e	60-day In-clinic Follow-up Visit ^e
		Only for TG2 participants who enroll in the Extension Period		Every 12 weeks ^d			
		Day 2	Week 4 ^c				
CD4 cell count	X		X	X	X		X
Plasma and urine storage sample ^o	X		X	X	X		X
HBV blood panel ^p				X			X ^o
Plasma samples stored for potential HIV-1 genotype/phenotype ^q	X		X	X	X		X
Sparse PK: trough PK sample (Treatment Group 1) ^{r,s}				X			
Provide participant dosing diary to participants	X		X	X			
Study drug dispensation	X		X	X			
Study drug accountability ^t	X		X	X	X		

AE = adverse event; BIC = bictegravir; CD4 = clusters of differentiation 4; DC = discontinuation; ECG = electrocardiogram; ERT = end of randomized treatment; EQ-5D-3L = EuroQol (5 dimensions, 3 levels); FDC = fixed-dose combination; HBV = hepatitis B virus; HBcAb = hepatitis B virus core antibody; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; HIVTSQs-12 = HIV Treatment Satisfaction Questionnaire–Status 12-item version; LDL = low-density lipoprotein; LEN = lenacapavir; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); TG2 = Treatment Group 2; WPAI - HIV = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

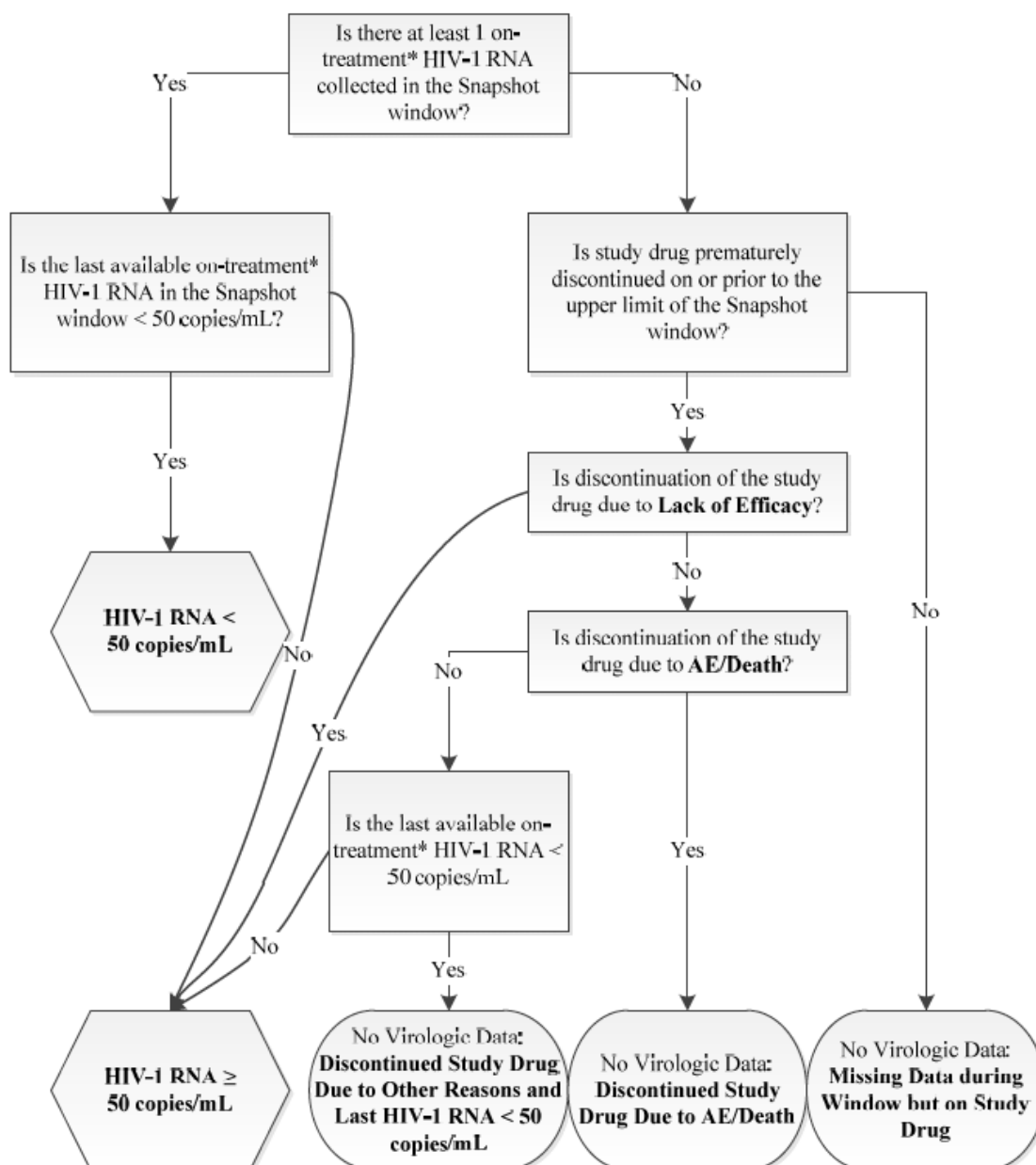
- a Once the last participant completes the Week 48 visit and Gilead completes the Week 48 analysis, all participants will return to the clinic (preferably within 30 days) on their next follow-up visit for an ERT visit. At the ERT visit, participants will be given BIC/LEN FDC in an Extension Period until drug is available or until Gilead elects to discontinue the study, whichever occurs first. Participants in Treatment Group 1 will continue to the Extension Period until Week 96, if they do not wish to continue in the Extension Period after Week 96, they will be required to return to the clinic 60 days after the Week 96 visit for a 60-day follow-up visit and will be considered to have completed the Phase 3 portion of the study. Participants in Treatment group 2 who complete the study through the ERT visit, and do not wish to participate in the Extension Period, will be required to return to the clinic 60 days after the ERT visit for a 60-day follow-up visit, and will be considered to have completed the Phase 3 portion of the study.
- b Participants from Treatment Group 2 who enroll in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1 of the Extension Period. Day 2 may be a virtual visit and the participants will self-administer study drugs and be observed by the site to confirm dosing. Please refer to Protocol Section 6.3.8 for further details.
- c Week 4 visit at the extension phase is only for participants who are previously randomized to Treatment Group 2 and then enrolled in extension phase.
- d Every 12 week visits will follow the schedule of previously scheduled visits in the randomized phase and not from the ERT Visit for Treatment Group 1.
- e Required for participants who enroll in the Extension Period or discontinue study drugs early. Participants who enroll in the Extension Period or discontinue study early should have a 30-day telephone visit conducted. They will be required to return to clinic for a 60 day follow-up visit. For the purpose of scheduling a 60-day follow-up visit, a ± 6 days window may be used.

- f Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
- g Symptom-directed physical examination as needed.
- h After the ERT visit, these questionnaires will only be administered to participants in Treatment Group 1 every 12 weeks until the Week 96 visit.
- i During the Phase 3 Extension Period, EQ-5D-3L should only be collected at Week 96.
- j Blood pressure, pulse, respiration rate, and temperature.
- k Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.
- l Chemistry profile per Protocol Table 12.
- m Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) 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.
- n Hematology profile per Protocol Table 12.
- o Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate). Separate consent for optional future research is not needed to collect or use these samples unless required per local regulations and requirements.
- p HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb), at Week 48 of randomized treatment, at Week 48 of the Extension Period visits, and at the 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.
- q HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Protocol Section 6.3.10.2).
- r For participants who become pregnant and provide reconsent to remain on study, 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) during the Extension Period. See Protocol Section 6.3.9.2 for additional information. 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 every 12 week visit (as possible) during the Extension Period.
- s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse intensive PK sample (as applicable).
- t 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.

13.2. 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 13-1.

Figure 13-1. Flowchart of US FDA-Defined Snapshot Algorithm



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

13.3. Stable Baseline Regimen Categories

Each participant's SBR will be classified into categories according to the below table based on the unique drug classes from eCRF options (all composite classes will be viewed as separated single ones, eg, NRTI/NNRTI will be viewed as separate NRTI and NNRTI).

Table 13-3. Stable Baseline Regimen Categories

Unique Drug Class Combination from eCRF Options	Category
INI, PI	PI + INSTI
INI, PI, PKE	
INI, NRTI, PI	PI + INSTI + NRTIs
INI, NRTI, PI, PKE	
INI, NNRTI, PI	PI + INSTI + NNRTI (+/- NRTIs)
INI, NNRTI, PI, PKE	
INI, NNRTI, NRTI, PI	
INI, NNRTI, NRTI, PI, PKE	
AI, INI, NRTI, PI	PI + INSTI + Entry Inhibitor (+/- NRTIs)
AI, INI, NRTI, PI, PKE	
AI, INI, PI	
AI, INI, PI, PKE	
CCR5, INI, NRTI, PI	
CCR5, INI, NRTI, PI, PKE	
CCR5, INI, PI	
CCR5, INI, PI, PKE	
NNRTI, NRTI, PI	PI + NNRTI (+/- NRTIs)
NNRTI, NRTI, PI, PKE	
NNRTI, PI	
NNRTI, PI, PKE	
INI, NNRTI	INSTI + NNRTI (+/- NRTIs)
INI, NNRTI, NRTI	
AI, INI	INSTI + Entry Inhibitor (+/- NRTIs)
AI, INI, NRTI	
CCR5, INI	
CCR5, INI, NRTI	

Unique Drug Class Combination from eCRF Options	Category
AI, INI, NNRTI	INSTI + Entry Inhibitor + NNRTI (+/- NRTIs)
AI, INI, NNRTI, NRTI	
CCR5, INI, NNRTI	
CCR5, INI, NNRTI, NRTI	
All other combinations	Other

13.4. 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 {Koch 1989} 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

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

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

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 97.501th percentile of the normal distribution.

13.5. 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;
```

13.6. 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) + $0.8 \times (4.0 - \text{albumin (g/dL)})$

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}):

$\text{eGFR}_{\text{CG}} (\text{mL/min}) = [(140 - \text{age (yrs)}) \times \text{weight (kg)} \times (0.85 \text{ if female})] / (\text{SCr (mg/dL)} \times 72),$

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:

$1\text{st Gen } (\mu\text{mol/L}) = (2\text{nd Gen} - 2.832) / 1.032$

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

For indirect bilirubin,

$1\text{st Gen indirect bilirubin } (\mu\text{mol/L}) = \text{total bilirubin} - 1\text{st Gen direct bilirubin}$

- 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 $\mu\text{mol/L}$ ", the 1st Gen indirect bilirubin calculation should equal the total bilirubin result (in $\mu\text{mol/L}$) 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.

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