



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		
Name of Test Drug:	Bictegravir/Lenacapavir		
Study Number:	GS-US-621-6289		
Protocol Version (Date):	Original:	26 April 2022	
	Amendment 1:	19 July 2022	
	Amendment 1.1:	15 December 2022	
Analysis Type:	Phase 2 Week 24 Primary Analysis		
Analysis Plan Version:	Version 1.0		
Analysis Plan Date:	16 August 2023		
Analysis Plan Author(s):	PPD		

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

%CV	coefficient of variation
AE	adverse event
AI	Attachment Inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
BIC	bictegravir
BLQ	below the limit of quantification
BMI	body mass index
CCR5	C-C Chemokine Receptor Type 5
CI	confidence interval
CRF	case report form
CSR	clinical study report
DAIDS	the Division of AIDS
DMC	data monitoring committee
ECG	electrocardiogram
eGFR _{CG}	estimated glomerular filtration rate by Cockcroft-Gault formula
ERT	end of randomized treatment
ET	early termination
FAS	Full Analysis Set
FDC	fixed-dose combination
HDL	high-density lipoprotein
HLGT	high-level group term
HLT	high-level term
HRQOL	health-related quality of life
ID	identification
INI	Integrase Inhibitor
ITT	intent to treat
LEN	lenacapavir
LDL	low-density lipoprotein
LLT	lower-level term
LOQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
NLP	Natural Language Processing

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
PK	pharmacokinetics
PKE	Pharmacokinetic Enhancer
PI	Protease Inhibitor
PP	per protocol
PT	preferred term
PWH	people with HIV
Q1, Q3	first quartile, 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
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
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_{tau}	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_{tau}	observed drug 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 24 of the Phase 2 portion of Study GS-US-621-6289. The analysis will be performed after all participants enrolled in the Phase 2 portion have completed the Week 24 visit or have prematurely discontinued the study drugs. Results from Week 24 primary analysis of the Phase 2 portion will be used in conjunction with the relevant data from the Phase 1 relative bioavailability (rBA) Study GS-US-621-6292 to select the dose of the BIC/LEN FDC tablet to be used in Treatment Group 1 of the Phase 3 portion of Study GS-US-621-6289, and the Extension periods in both Phase 2 and Phase 3 portions of Study GS-US-621-6289.

This SAP is based on the study protocol Amendment 1.1 dated 15 December 2022 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 clinical study report (CSR).

1.1. Study Objectives

The primary objective of the Phase 2 portion of this study is as follows:

- To evaluate the efficacy of switching to a bictegravir (BIC) plus lenacapavir (LEN) regimen (BIC 75 mg plus LEN 25 mg or BIC 75 mg plus LEN 50 mg) versus continuing on a stable baseline regimen (SBR) in virologically suppressed people with HIV (PWH) as determined by the proportion of participants with HIV-1 RNA $\geq$ 50 copies/mL at Week 24.

The secondary objectives of the Phase 2 portion of this study are as follows:

- To evaluate the efficacy of the 3 treatment regimens in virologically suppressed PWH as determined by viral load suppression rate and CD4 cell count at Week 24.
- To evaluate the safety and tolerability of the 3 treatment groups through Week 24.
- To evaluate the pharmacokinetics (PK) of BIC and LEN for participants receiving BIC 75 mg plus LEN 25 mg and BIC 75 mg plus LEN 50 mg.

The primary objective of the Phase 3 portion of this study is as follows:

- To evaluate the efficacy of switching to BIC/LEN fixed-dose combination (FDC) tablet regimen (BIC 50 to 75 mg/LEN 25 or 50 mg) versus continuing on a SBR in virologically suppressed PWH as determined by the proportion of participants with HIV-1 RNA $\geq$ 50 copies/mL at Week 48.

The secondary objectives of the Phase 3 portion of this study are as follows:

- To evaluate the efficacy of the 2 treatment groups in virologically suppressed PWH as determined by viral load suppression rate and CD4 cell count at Week 48.
- To evaluate the safety and tolerability of the 2 treatment groups through Week 48.

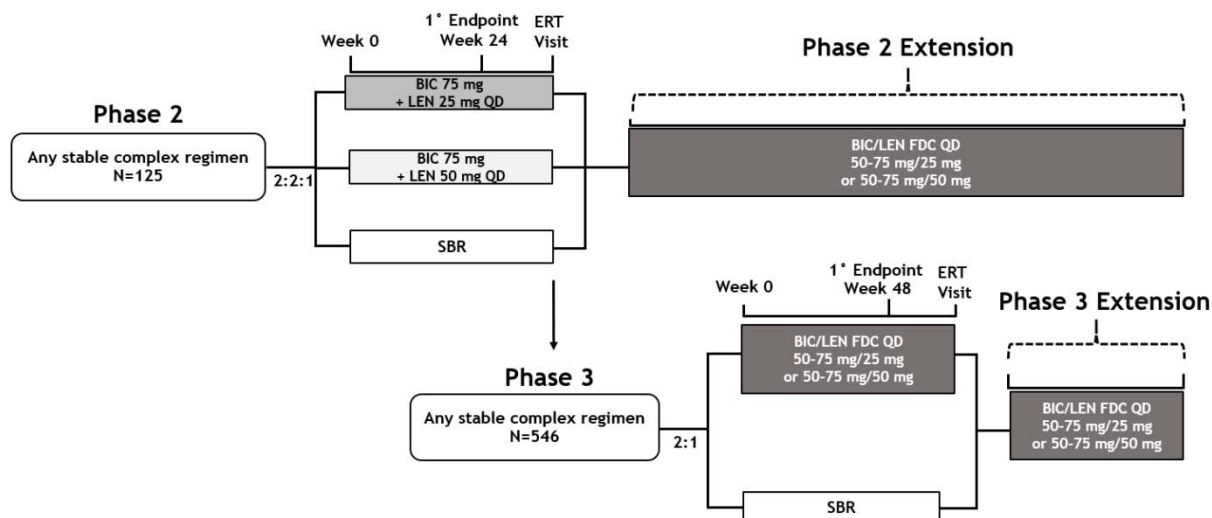
The exploratory objectives of the Phase 3 portion of this study are as follows:

- To evaluate the PK of BIC and LEN for participants receiving a BIC/LEN FDC tablet regimen (BIC 50 to 75 mg/LEN 25 or 50 mg).
- To evaluate the effect of the 2 treatment groups on treatment satisfaction and health-related quality of life (HRQOL).

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 PWH 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 plus LEN) will be 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 will be administered.

Figure 1-1. Study Schema



1° = primary; BIC = bictegravir; ERT = end of randomized treatment; FDC = fixed-dose combination; LEN = lenacapavir; QD = once daily; SBR = stable baseline regimen

Phase 2:

A randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of BIC plus LEN versus SBR in PWH who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable complex treatment regimen for at least 6 months prior to screening.

Participants are randomized in a 2:2:1 ratio to one of the following 3 treatment groups:

- Treatment Group 1 (n = 50): Participants switch from their SBR to a regimen of BIC 75 mg plus LEN 25 mg administered orally, without regard to food. Participants receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and 2 × 300 mg LEN on Day 2), in addition to the daily doses of BIC 75 mg plus LEN 25 mg starting on Day 1.
- Treatment Group 2 (n = 50): Participants switch from their SBR to a regimen of BIC 75 mg plus LEN 50 mg administered orally, without regard to food. Participants receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and 2 × 300 mg LEN on Day 2), in addition to the daily doses of BIC 75 mg plus LEN 50 mg starting on Day 1.
- Treatment Group 3 (n = 25): Participants continue with their SBR as defined above.

Participants will be treated for at least 24 weeks during the Randomized Period. After Week 24, participants will continue to take their study drug (BIC plus LEN or SBR) and attend visits every 12 weeks. Once the last participant completes Week 24 and the dose is selected for the BIC/LEN FDC, all participants will attend the end of randomized treatment (ERT) visit and will be given the option to participate in an Extension Period to receive BIC/LEN FDC at the selected dose, until this product becomes commercially available or accessible to participants through an access program, or until Gilead Sciences (Gilead) elects to discontinue the study, whichever occurs first.

Phase 3:

A randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of FDC tablets containing either BIC 50 to 75 mg/LEN 25 mg or BIC 50 to 75 mg/LEN 50 mg (dose selection per the Week 24 data from Phase 2 portion of the current study and relevant data from Phase 1 rBA Study GS-US-621-6292) versus SBR in PWH who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a SBR for at least 6 months prior to screening.

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

- Treatment Group 1 (n = 364): Participants will switch from their SBR to a regimen of BIC 50 to 75 mg/LEN 25 mg or 50 mg (final dose to be decided) administered orally, without regard to food. Participants will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and 2 × 300 mg LEN on Day 2), in addition to the daily doses of BIC/LEN FDC starting on Day 1.
- Treatment Group 2 (n = 182): Participants will continue with their SBR as defined above.

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/LEN FDC at the selected dose 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 compared to the baseline regimen are demonstrated by the Week 48 analysis, all participants will attend the ERT visit and will be given the option to receive the BIC/LEN FDC tablet at the selected dose in an Extension Period until the product becomes commercially available or accessible to participants through an open access program, or until Gilead elects to discontinue the study, whichever occurs first.

Study Procedures/Frequency:

Phase 2:

Randomization Period: Following the Day 1 visit, participants will be required to return for study visits at Day 2 (oral loading dose for Treatment Groups 1 and 2), Weeks 4, 12, and 24. According to the participant preference, an optional visit at Week 16 may be scheduled for blood collection for the optional intensive PK substudy to facilitate study procedures scheduled for visit Week 24. Participants will be followed every 12 weeks after the Week 24 visit until the ERT visit. The timings of efficacy and safety assessments for the Phase 2 Randomized Period are detailed in [Table 12-1](#).

Sparse PK blood samples will be collected at on-treatment study visits for all participants in Treatment Groups 1 and 2 at the time points specified in [Table 12-1](#). An intensive PK substudy will be performed in a subset of participants in Treatment Groups 1 and 2 at selected study sites ([Table 12-1](#)).

Extension Period: Participants from Treatment Groups 1, 2, and 3 who complete the ERT visit will be given the option to enter an Extension Period. Participants who received BIC plus LEN tablets (ie, Treatment Groups 1 and 2) during the Randomized Period will continue treatment at the selected dose of BIC/LEN FDC tablet without any oral loading doses of LEN. Participants who received their SBR (ie, Treatment Group 3) during the Randomized Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2×300 mg LEN on Day 1 and 2×300 mg LEN on Day 2), in addition to the daily selected dose of BIC/LEN FDC tablet starting on Day 1 of the Extension Period.

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 complete the study through the ERT visit of the Randomized Period and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit, and will be considered to have completed the Phase 2 portion of the study. The timings of efficacy and safety assessments for the Phase 2 Extension Period are detailed in [Table 12-1](#).

Phase 3:

Randomization Period: Following the Day 1 visit, participants will be required to return for study visits at Weeks 4, 12, 24, 36, and 48. Participants will be followed every 12 weeks after the Week 48 visit until the ERT visit. The timings of efficacy and safety assessments for the Phase 3 Randomized Period are detailed in [Table 12-2](#).

Sparse PK blood samples will be collected at on-treatment study visits for all participants in Treatment Group 1 at the time points specified in [Table 12-2](#). An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites ([Table 12-2](#)).

Extension Period: Participants from Treatment Groups 1 and 2 who complete the ERT visit will be given the option of receiving continued treatment with the BIC/LEN FDC tablet every 12 weeks. Participants who received the BIC/LEN FDC tablet (ie, Treatment Group 1) during the Randomized Period will continue treatment at the selected dose of BIC/LEN FDC tablet 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 2 × 300 mg LEN on Day 2), in addition to the daily doses of BIC/LEN FDC starting on Day 1 of the Extension Period.

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 complete the study through the ERT visit of the Randomized Period and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit, and will be considered to have completed the Phase 3 portion of the study. The timings for efficacy and safety assessments for the Phase 3 Extension Period are detailed in [Table 12-2](#).

1.3. Sample Size and Power

Phase 2:

The target sample size is 125 participants, with 50 participants in each of the BIC plus LEN groups and 25 participants on SBR. The sample size in Phase 2 portion of this study is determined based on practical considerations and past experience with similar types of studies. Phase 2 portion is not formally powered. The sample size will provide an assessment of safety, efficacy, and PK to inform dose selection of BIC and LEN as individual components for the FDC tablet to be used in Phase 3 portion of the study.

Phase 3:

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 margin of 4% in difference in percentage of participants with HIV-1 RNA $\geq$ 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 $\geq$ 50 copies/mL) at Week 48 (based on the historical Gilead Genvoya[®] and BVY studies), that a noninferiority margin is 4%, and that the significance level of the test is at a 1-sided 0.025 level.

2. TYPE OF PLANNED ANALYSIS

This SAP will only describe the analyses planned for the Phase 2 portion of this study. A separate SAP will be developed for the Phase 3 portion of this study.

2.1. Interim Analyses

Prior to the Phase 2 final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program. Also, interim analyses may be used for publication and presentation at scientific meetings.

2.1.1. DMC Analysis

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform 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 will make 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.

The initial review will be conducted after all participants enrolled in Phase 2 portion of the study have completed their Week 12 visit or prematurely discontinued the study drug. Additional meetings may be conducted as requested.

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

No formal stopping rules will be used by the DMC for safety outcomes. For the Phase 2 portion, no alpha penalty will be applied for the primary analysis of the primary efficacy endpoint, given that the Phase 2 portion of the study is not adequately powered for a formal efficacy evaluation.

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

2.2. Primary Analysis

The primary analysis for the Phase 2 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 24. The primary analysis will be conducted after all participants enrolled in the Phase 2 portion have completed the Week 24 visit or have prematurely discontinued the study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis of the primary endpoint will serve as the final analysis for this endpoint and will be used to evaluate the efficacy of BIC plus LEN in the Phase 2 portion.

This SAP describes the analysis plan for the Phase 2 Week 24 primary analysis.

2.3. Final Analysis

The final analysis for the Phase 2 portion of the study will be performed after all participants have completed the study or prematurely discontinued the study for the Phase 2 portion (randomized period and extension period), outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The Phase 2 Week 24 primary analysis will include all data collected from the randomized period of the Phase 2 portion of the study. No participant will be enrolled into the Phase 2 extension phase before the completion of the Phase 2 Week 24 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 for descriptive purpose unless otherwise specified.

By-participant listings will be presented for all participants in the All Randomized Analysis Set unless otherwise specified and sorted by participant ID number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (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 were excluded and the reasons for their exclusion will be summarized by treatment group. A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were randomized in the study. This is the primary analysis set for by-participant listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who took at least 1 dose of any study drug for Treatment Groups 1 and 2, or continued with their SBR for Treatment Group 3. Participants will be grouped according to the randomized treatment group. This is the primary analysis set for efficacy analyses.

3.1.3. Per-Protocol Analysis Set

The Week 24 Per-Protocol (PP) Analysis Set includes all participants in the FAS excluding participants meeting any of the following criteria:

- Did not have on-treatment HIV-1 RNA data in the Week 24 analysis window, except when missing was 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 Phase 2 Week 24 Per-Protocol Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 24 Analysis Window

Discontinuation from Study Drug prior to or on the Upper Bound of Week 24 Analysis Window		On-Treatment HIV-1 RNA Data Available in Week 24 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Reasons Other Than Lack of Efficacy	+	-
No		+	-

“+” = Inclusion of participants in Week 24 Per-Protocol analysis set; “-” = Exclusion of participants in Week 24 Per-Protocol analysis set.

- Non-adherence to study drug: adherence rate for active study drugs up to Week 24 below the 2.5th percentile.

The Week 24 PP Analysis Set is the secondary analysis set for efficacy analyses.

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all randomized participants who took at least 1 dose of any study drug for Treatment Groups 1 and 2, or continue with their SBR for Treatment Group 3. Participants will be grouped according to the actual received treatment. This is the primary analysis set for safety analyses.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include participants who were randomized to Treatment Groups 1 and 2, took at least 1 dose of any study drug, and have at least 1 nonmissing concentration value reported by the PK laboratory. This is the analysis set for general PK analyses.

3.1.6. Pharmacokinetic Substudy Analysis Set

The PK Substudy Analysis Set will include participants who were randomized to Treatment Groups 1 and 2, took at least 1 dose of any study drug, participated in the intensive PK substudy, and 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 FAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on the PP Analysis Set and Safety Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

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

3.3. Strata and Covariates

The Phase 2 portion does not use a stratified randomization schedule when enrolling participants. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Participant Subgroups

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

- Age (< 50 years and $\geq$ 50 years)
- Sex (male and female)
- Race (white and non-white)
- Region (US [including 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 2 portion, no alpha penalty will be applied for the primary analysis of the primary efficacy endpoint, given that the Phase 2 portion of the study is not adequately powered for a formal efficacy evaluation. All endpoint tests will be done at the significance level of 0.05 with no multiplicity adjustment.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications is in Section 7.4.

3.6.2. Outliers

Outliers 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. Outliers of PK data may be identified during review of data by the PK scientist, and if necessary, appropriate sensitivity analyses may be conducted.

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 at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the randomization 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 (e.g., 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 (other than HIV-1 RNA data) that are continuous in nature but are less than the lower limit of quantification (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).

Logarithm (base 10) transformation will be applied to HIV-1 RNA levels 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. HCV RNA reported results of “No HCV RNA detected” and “<15 IU/mL HCV RNA Detected” will be imputed as 14 IU/mL for analysis purposes.

Natural logarithm transformation will be used for analyzing concentrations and PK parameters. Concentration values that are below the limit of quantification (BLQ) will be presented as “BLQ” in the concentration data listing. Values that are BLQ will be treated as 0 at all predose and postdose time points for summary purposes.

The following conventions will be used for the presentation of summary and order statistics for intensive 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”.
- If more than 1/3 of the participants have a concentration data value of BLQ for a given time point, only order statistics will be presented.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

For participants randomized to Treatment Groups 1 and 2, Study Day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days : $\text{Assessment Date} - \text{First Dosing Date} + 1$.
- For days prior to the first dose: $\text{Assessment Date} - \text{First Dosing Date}$.

The earliest of the first dosing date of any component (i.e., BIC or LEN) is considered as the first dose date of the study drug.

For participants randomized to Treatment Group 3 (SBR group), the first dosing date of antiretroviral (ARV) 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 : $\text{Assessment Date} - \text{Day 1 Visit Date} + 1$.
- For days prior to the first dose: $\text{Assessment Date} - \text{Day 1 Visit Date}$.

Study Day 1 is the day of the first dose of study drug (BIC+LEN) for Treatment Groups 1 and 2, or the day of Day 1 visit at the randomized period for Treatment Group 3.

Last Dose Date in randomized period is defined as follows:

- For participants randomized to Treatment Groups 1 and 2, the last dose date is defined as the latest study drug stop date recorded on the Study Drug Administration eCRF form in randomized period for participants who prematurely discontinued from study drug, or who completed study drug in the randomization period.
- For participants randomized to Treatment Group 3 (SBR group), 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 discontinued, or who completed the drugs in randomization period.

If last dose date is incomplete or missing (i.e., only year of last dose date is known or completely missing due to lost to follow-up) for participants who prematurely discontinued study drug/SBR in the randomized period, the latest of the study drug/SBR nonmissing start dates and stop dates, the clinic visit dates and the laboratory visit will be used to impute the last dose date.

If the last dose date is with known year and month but with missing day, the latest of the dispensing dates of study drug tablets (for Treatment Groups 1 and 2), study drug/SBR start dates and stop dates, and the imputed last dose date (day imputed as 15) will be used as the last dose date.

Last Study Date in randomized period is the latest of the study drug/SBR start dates and stop dates, the clinic visit dates, and the laboratory visit dates, including the 30-day and 60-day follow-up visit dates, for participants who prematurely discontinued study, or who completed the study for randomized period.

Baseline value is defined as the last value obtained on or prior to Study Day 1 at 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.

The analysis windows are provided in [Table 3-2](#), [Table 3-3](#), and [Table 3-4](#).

Table 3-2. Analysis Visit Windows for HIV-1 RNA, CD4 Cell Count, Chemistry, Hematology, Urinalysis Assessments, eGFR_{CG} and Vital Signs

Analysis Visit	Nominal 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 X* (Post-Week 24, X > 24)	7*X	7*X - 41	7*X + 42

eGFR_{CG} = estimated glomerular filtration rate by Cockcroft-Gault formula.
 After Week 24, visits will be conducted every 12 weeks.

Table 3-3. Analysis Visit Windows for Metabolic Assessments and Safety Electrocardiogram Results

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	126
Week 24	168	127	210
Week X* (Post-Week 24, X > 24)	7*X	7*X - 41	7*X + 42

For metabolic assessments, visits will be conducted every 12 weeks after Week 24.

Table 3-4. Analysis Visit Windows for HCV Serology and HBV Blood Panel

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	(none)

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

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

If multiple valid, nonmissing measurements (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 (e.g., 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 “HIV-1 RNA COBAS 6800” and “HIV RNA REPEAT COBAS” (i.e., the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the “HIV RNA REPEAT COBAS” will be selected for analysis purposes; otherwise, if there are multiple “HIV RNA COBAS 6800” records with the same collection time, the geometric mean will be taken for analysis purposes.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (i.e., 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.

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
- Still on study drug/SBR in randomized period
- Did not complete study drug/SBR in randomized period with reasons for premature discontinuation of study drug/SBR
- Still on study
- Completed Week 24 visit
- Did not complete the study in randomized period 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 participant profile listing will be provided by participant identification (ID) number in ascending order to support the above summary tables and a listing of participants who prematurely discontinued study drug or study will also be provided.

4.2. Extent of Study Medication Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol. The extent of exposure to SBR for participants in Treatment Group 3 will also be examined.

4.2.1. Duration of Exposure to Study Drug

Exposure to study drug will be calculated as follows:

- Daily doses (non-PK-oral-loading dose) in Treatment Groups 1 and 2: Total duration of exposure to study drug will be defined as last dose date (as defined in Section 3.8.1) in randomized period - first dose date in randomized period + 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (e.g., 4.5 weeks).

For the daily doses in Treatment Groups 1 and 2, the total duration of exposure to BIC and to LEN in randomized period will be summarized using descriptive statistics and using the number (i.e., 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), and ≥ 24 weeks (168 days), etc. Summaries will be provided by treatment group for the Safety Analysis Set.

A by-participant listing of all study drug administrations will be provided by participant ID number (in ascending order) and visit (in chronological order) along with the durations of exposure for daily doses of BIC and LEN.

4.2.2. Duration of Exposure to SBR

For participants in Treatment Group 3, their extent of 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 (e.g., 4.5 weeks).

Current ARV stop date is the last stop date among all ARVs taken during the randomization period.

A by-participant listing of all 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 Phase 2 portion of the study, drug accountability (i.e., numbers of tablets dispensed and returned) is only captured for BIC and LEN. Therefore, adherence will only be computed for Treatment Groups 1 and 2 in the randomized period. Adherence to PK oral loading LEN doses will not be derived. Adherence for daily doses of BIC and LEN in the randomized period and up to Week 24 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:

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

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

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

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

For a record where the drug bottle was returned but the number of tablets returned was missing, it is assumed the number of tablets returned was zero. If the number of tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, all

records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation of the adherence.

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 discontinued study drug or completed study drug in the randomized period, or using all data available for participants who are ongoing on study drug.

Adherence up to the Week 24 visit 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 discontinued study drug or completed study drug up to the Week 24 study drug dispensing date, whichever occurs earliest.

Descriptive statistics for the level of adherence to BIC and LEN with the number and percentage of participants belonging to adherence categories (e.g., < 80%, ≥ 80 to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by treatment group (Treatment Groups 1 and 2) for the Safety Analysis Set. No formal statistical testing is planned.

A by-participant listing of study drug accountability (including the LEN PK loading doses) and adherence will be provided by participant ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

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

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation category (e.g., eligibility criteria, informed consent) will be summarized by treatment group for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus disease 2019 (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Adverse Events Due to COVID-19

Adverse events of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ narrow search. A by-participant listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (i.e., age at Day 1, sex at birth, gender identity, sexual orientation, race, ethnicity, and region [US, Ex-US]) 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.

For categorical demographics and baseline characteristics, the Fisher exact test will be used to compare between treatment groups. For continuous demographic and baseline characteristics, the Wilcoxon rank sum test will be used to compare between treatment groups.

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:

- Baseline HIV-1 RNA level category: < 50 copies/mL, ≥ 50 copies/mL.
- Baseline CD4 cell count per µL.
- Baseline CD4 cell count per µL category: (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500.
- Baseline CD4 percentage (%).
- Baseline eGFR (mL/min).
- HIV disease status: AIDS, asymptomatic, or 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 dose 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 dose 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 medications.
- Prior ARV medication drug class: AI, CCR5, 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 dose date of study drugs for Treatment Groups 1 and 2, or taken on Day 1 for Treatment Group 3. This will be grouped by drug class (AI, CCR5, Fusion, INI, INI/NNRTI, NRTI/INI, NRTI/NNRTI, NRTI/PI, NNRTI, NRTI, PI, PI/PKE, PKE, Post-Attachment Inhibitor, Other).
- Number of ARVs used at baseline.
- ARVs used at baseline by dosing frequency: once daily, twice per day, three times per day, every two weeks, once, and other.
- ARVs used at baseline in numbers of pills per day.
- 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).
- Other non-resistant substitutions: integrase substitution (Yes/No/Unknown), protease substitution (Yes/No/Unknown), reverse transcriptase substitution (Yes/No/Unknown).

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 the above baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

General medical history data will be collected at screening and listed only, and be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

5.4. Changes from Protocol-Specified Analysis

Update the analysis for demographics and baseline characteristics to use the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables, to provide pairwise treatment comparisons.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 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.

6.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 24 is defined as Study Day 127 to Study Day 210, inclusively. All HIV-1 RNA data collected on-treatment will be used in the US FDA-defined snapshot algorithm. On-treatment is defined for Treatment Groups 1 and 2 as all data collected up to 1 day after permanent discontinuation of study drug, or all available data for participants who were still on study drug. On-treatment is defined for Treatment Group 3 as all data collected up to 1 day after permanent discontinuation of SBR, or all available data for participants who were still on 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 24 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 24 analysis window, or
 - B) Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and
 - i) Who discontinue study drug prior to or in the Week 24 analysis window due to lack of efficacy, or
 - ii) Who discontinue study drug prior to or in the Week 24 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or
 - iii) Who discontinue study drug prior to or in the Week 24 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 24 window: This includes participants who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:
 - A) Discontinuation of study drug prior to or in the Week 24 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

- B) Discontinuation of study drug prior to or in the Week 24 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 drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in [Figure 12-1](#).

For switch trials, the US FDA-defined snapshot algorithm classifies participants who discontinue study drug due to AE or death and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL in the “HIV-1 RNA ≥ 50 copies/mL” category. For treatment naïve study population, these participants will be classified in the “No Virologic Data in the Week 24 Window” category.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The number and percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 based on the US FDA-defined snapshot algorithm will be summarized by treatment group for the analysis visit window of Week 24.

The 2-sided 95% CIs for the difference in proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 between each of the BIC plus LEN groups (Treatment Groups 1 and 2) and SBR group (Treatment Group 3) based on the FAS will be constructed based on an unconditional exact method using 2 invert 1-sided tests {[Chan 1999](#)}.

A listing of the virologic outcome at Week 24 by the US FDA-defined snapshot algorithm along with the HIV-1 RNA data will be provided.

6.1.4. Sensitivity Analysis of the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint will be performed in the PP analysis set.

6.1.5. 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 24) for the subgroups specified in [Section 3.4](#) based on FAS.

If the percentage of participants is small within a particular subgroup, then descriptive analysis rather than statistical comparison may be performed.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined as follows:

- Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm.
- Change from baseline in CD4 cell count at Week 24.

6.2.2. Primary Analysis of Secondary Efficacy Endpoints

6.2.2.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL at Week 24 as Determined by the US FDA-Defined Snapshot Algorithm

The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm will be analyzed based on the FAS.

The 2-sided 95% CIs for the difference in proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 between each of the BIC plus LEN groups (Treatment Groups 1 and 2) and SBR group (Treatment Group 3) based on the FAS will be constructed based on an unconditional exact method using 2 invert 1-sided tests {[Chan 1999](#)}.

6.2.2.2. Change from Baseline in CD4 Cell Count at Week 24

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

Least square mean estimate of differences in changes from baseline in CD4 cell count between each of the BIC plus LEN groups and SBR group at Week 24 and associated 95% CIs will be constructed using analysis of covariance (ANCOVA) model, including baseline CD4 cell count as a covariate and treatment (each of the BIC plus LEN groups and SBR) as a fixed effect in the model. Least squares mean estimate and 95% CI will also be presented for each treatment group.

6.2.3. Sensitivity Analysis of Secondary Efficacy Endpoints

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

Additionally, change from baseline in CD4 cell count at Week 24 will also be analyzed based on FAS using the mixed-effects model for repeated measures (MMRM) that include all available data at post-baseline visits up to Week 24. The MMRM model will include baseline value of CD4 cell count, 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 least squares means along with 95% CIs and the p-value for the difference in mean change from baseline in CD4 cell count at Week 24 between each BIC plus LEN group and SBR group from MMRM will be provided.

6.2.4. Subgroup Analysis of the Secondary Efficacy Endpoints

Subgroup analyses will be performed for the secondary endpoint (HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm at Week 24) for the subgroups specified in Section 3.4 based on FAS as applicable.

6.3. Other Efficacy Evaluation

6.3.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL

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

- Missing = Failure (M = F): Participants with missing data in a specific analysis visit window will be treated as virologic failure (HIV-1 RNA $\geq$ 50 copies/mL) and will be summarized into the “Missing” category. Results will be summarized up to Week 24.
- Missing = Excluded (M = E): Participants with missing data will be excluded from analysis (i.e., 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
- $\geq$ 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 Week 24 between each of the BIC plus LEN groups (Treatment Groups 1 and 2) and SBR group (Treatment Group 3) will be constructed based on an unconditional exact method using 2 invert 1-sided tests.

6.3.2. Change from Baseline in HIV-1 RNA Values

Absolute value and the change from baseline in HIV-1 RNA ($\log_{10}$ copies/mL) will be summarized based on FAS by treatment groups and visits 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.

6.3.3. Change from Baseline in CD4 Cell Count

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

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the Safety Analysis Set. All safety data collected up to 60 days after permanent discontinuation of study drugs BIC and LEN for Treatment Groups 1 and 2, or up to 30 days for Treatment Group 3, or all available data at the time of the database snapshot for participants who were still ongoing at the time of this primary analysis will be included in the table summary, unless specified otherwise. All collected data will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory 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 Division of AIDS (DAIDS) Toxicity Grading Scale, Version 2.1 as specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug or SBR

Related AEs are those for which the investigator selected “Related” on the AE CRF to the question of “Related to Study Treatment” for participants receiving BIC plus LEN in Treatment Groups 1 and 2, or ‘Related to SBR’ for participants receiving SBR in Treatment Group 3. Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug 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. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

- Any AEs with an onset date on or after the study drug start date and up to 60 days after permanent discontinuation of the study drug (BIC or LEN) for participants receiving BIC plus LEN in Treatment Groups 1 and 2, or an onset date on or after Day 1 visit date and up to 30 days after permanent discontinuation of SBR for participants receiving SBR in Treatment Group 3.
- Any AEs leading to premature discontinuation of study drugs (BIC or LEN) or SBR.

7.1.5.2. Incomplete Dates

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

- The AE onset is the same as or after the month and year (or year alone) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year alone) of the date corresponding to the date of last study assessment.

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

7.1.6. Summaries of Adverse Events and Deaths

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

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE 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 nominal Week 24 visit will also be provided. Any TEAE with onset date on or before the nominal Week 24 visit date will be included.

The number and percentage of participants who experienced at least 1 TEAE during the randomized period will be provided and summarized by SOC, HLT (if applicable), PT, and treatment group.

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

- TEAEs with Grade 2 or higher
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs by Severity Grade
- 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

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

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs during the randomized period will be summarized by PT only, in descending order of total frequency. All TEAEs up to nominal Week 24 visit will also be summarized by PT only.

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

- All AEs, indicating whether the event is treatment emergent
- All AEs up to nominal Week 24 visit, indicating whether the event is treatment emergent
- All AEs with severity of Grade 3 or higher

- All SAEs
- All treatment-related AEs
- All Deaths
- 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. Summaries of laboratory data will be provided for the Safety Analysis Set and will include all available data at the time of the database snapshot for this primary analysis. 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.

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 on the DAIDS Toxicity Grading Scale 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 each laboratory test specified in the study protocol for hematology, chemistry, and metabolic as follows:

- Baseline values
- Values at each postbaseline analysis visit
- Change from baseline at each postbaseline analysis visit
- Percentage change from baseline at each postbaseline analysis visit (if specified)

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drugs BIC plus LEN for Treatment Groups 1 and 2, or Day 1 visit date for Treatment Group 3. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

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

For metabolic assessments, including fasting glucose and the lipid panel (i.e., total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized.

7.2.2. Graded Laboratory Values

The DAIDS Toxicity Grading Scale, Version 2.1 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., 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 are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the last available study drug dose date plus 60 days for participants from Treatment Groups 1 and 2 (or plus 30 days for participants from Treatment Group 3) who permanently discontinued study drug (or SBR), or the last available date for participants who were still on treatment at the time of this primary analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

7.2.2.2. 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, up to and including the last available study drug dose date plus 60 days for participants from Treatment Groups 1 and 2 (or plus 30 days for participants from Treatment Group 3) who permanently discontinued study drug (or SBR), or the last available date for participants who were still on treatment at the time of this primary analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data collected 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 subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Graded laboratory abnormalities through Week 24
- Grade 3 or 4 laboratory abnormalities
- Marked laboratory abnormalities

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

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

7.2.3. Liver-related Laboratory Evaluations

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

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 x ULN; (b) > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN

The summary will include data from all postbaseline visits up to 60 days after the last dose of study drug BIC or LEN for participants in Treatment Groups 1 and 2, or up to 30 days after the last dose of SBR for participants in Treatment Group 3, or the last available date in the database snapshot for participants who were still on treatment at the time of this primary analysis.

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, 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 met 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 and LEN for Treatment Groups 1 and 2, or the date of Day 1 visit for Treatment Group 3. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be only included for the baseline value selection.

Median (Q1, Q3) of the absolute values for body weight will be plotted by treatment group and visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

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

7.4. Prior and Concomitant Medications

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 and will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

Prior ARV medications are defined as any ARV medications taken before a participant took the first study drug or first SBR on Day 1 for SBR group. Prior ARV medications will be summarized by WHO drug class 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 term in order of 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 ARV medications with a start date prior to the first dosing date of study drugs or first SBR on Day 1 will be included in the prior ARV medication summary 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 included in the prior medication summary, unless otherwise specified.

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

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

7.4.2. Prior and Concomitant Non-Antiretroviral Medications

Medications collected at screening and during the study will be coded using the current version of the WHO Drug dictionary.

Concomitant non-ARV medications are defined as medications taken while a participant took study drugs BIC plus LEN for Treatment Groups 1 and 2 or took on-study SBR for Treatment Group 3. Use of concomitant medications will be summarized by WHO drug class 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 term 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 SBR) 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 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 month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug (or SBR) administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after all study drugs (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.

Prior non-ARV medications are defined as medications taken before a participant took the first study drugs (Treatment Groups 1 and 2) or first SBR on Day 1 (SBR group). Any medications with a start date prior to the first dosing date of study drugs or first SBR on Day 1 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.

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

All data collected in the Prior and Concomitant Medication eCRF form 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 data listing will be provided for participants that get pregnant during the study and participants using/misusing any substances (i.e., illicit drug, etc.) during the study, respectively. Physical examination was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Sparse PK blood samples will be collected at on-treatment study visits for all participants in Treatment Groups 1 and 2 at the time points as specified in protocol:

- A single predose plasma PK sample (≤ 5 min before dose) **and** a single postdose plasma PK sample at 4 hours (± 1 hours) (relative to BIC plus LEN dosing and oral loading dose of LEN) 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, and 24, **and** a single postdose plasma PK sample at 2 hours (± 1 hours) (relative to BIC plus LEN dosing) at Weeks 4, 12, and 24.
 - Should a participant become pregnant and provide reconsent to remain on the study, sparse PK samples will continue to be collected as specified in protocol.
- During the Randomized Treatment Period (until the Week 24 visit): At all the protocol-specified visits/time points (as described above).
- After Week 24 visit (until the ERT) and during the Extension Period: A single trough plasma PK sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at once every 12 Week visit (as possible). These additional trough samples will continue to be collected until the next 2 scheduled visits postdelivery or until the end of the study participation or Extension Period, whichever occurs first.

An optional intensive PK Substudy will be performed in a subset of participants in Treatment Groups 1 and 2 at selected study sites as specified in protocol. Participants may choose to participate at 1 or more visit(s). Intensive PK blood samples will be collected as described below **instead of** the sparse plasma PK samples on those specific visits:

- **Day 1:** Single PK sample predose (≤ 5 min before dose), and at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC plus LEN dosing and oral loading dose of LEN).
- **Day 2:** Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose on Day 1 and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, and 6 hours postdose (relative to BIC plus LEN dosing and oral loading dose of LEN).
- **Week 16 or Week 24 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 plus LEN dosing).

8.2. PK Analyses Related to Intensive PK Sampling

8.2.1. Intensive PK Analyses

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

8.2.2. Estimation of PK Parameters

Relevant PK parameters will be estimated using Phoenix WinNonlin[®] software using standard noncompartmental methods. The linear up log down trapezoidal 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.

8.2.3. PK Parameters

Relevant PK parameters will be generated for all participants for whom those 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 plus LEN 25 mg daily administered orally with oral loading doses of LEN 600 mg on Days 1 and 2	BIC, LEN
Group 2	BIC 75 mg plus LEN 50 mg daily administered orally with oral loading doses of LEN 600 mg on Days 1 and 2	BIC, LEN

BIC = bictegravir; LEN = lenacapavir.

The analytes and 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. The primary PK parameters are C_{max} , AUC_{tau} , and C_{tau} (as applicable) of BIC and LEN.

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
BIC	AUC_{last} , AUC_{tau} , AUC_{0-t} , AUC_{inf} , $\%AUC_{exp}$, C_{max} , T_{max} , C_{last} , T_{last} , C_{tau} , C_t , λ_z , V_z/F , CL/F , and $t_{1/2}$ (as applicable)
LEN	AUC_{last} , AUC_{tau} , AUC_{0-t} , AUC_{inf} , $\%AUC_{exp}$, C_{max} , T_{max} , C_{last} , T_{last} , C_{tau} , C_t , λ_z , V_z/F , CL/F , and $t_{1/2}$ (as applicable)

BIC = bictegravir; LEN = lenacapavir.

Individual participant concentration data will be listed and summarized by treatment group and nominal time points. Individual participant PK parameters for BIC and LEN will be listed and summarized by treatment group.

Descriptive statistics (n, mean, SD, 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 by treatment. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for PK parameter data.

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 (e.g., planned postdose timepoints actually collected predose, or trough samples collected outside of the 20 - 28 hours [inclusively] postdose collection window) 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 will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at all predose and postdose time points.

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.

The following tables will be provided for each analyte by treatment:

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

The following figures may be provided for each analyte by treatment:

- Mean ($\pm$ SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)
- Individual concentration data versus time (on linear and semilogarithmic scales)

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

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

8.2.4. Statistical Analysis Methods

The comparison between different LEN dose levels in Treatment Groups 1 and 2 may be assessed (as appropriate) using a parametric (normal theory) analysis of variance (ANOVA) model which will be fitted to the natural log-transformed PK parameters ($C_{\max}$, C_{tau} , AUC_{tau} , and/or AUC_{0-t} as applicable) for LEN at the last available intensive PK sampling (Week 16 or Week 24 visit). The statistical modeling will be based on the PK Substudy Analysis Set for LEN. All participants with available data for the LEN PK parameter under evaluation will be included in the modeling.

The statistical model will include dose level (or treatment group) as a fixed effect. The following SAS PROC MIXED code will provide the treatment comparison analysis and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed data=myPKparm;  
  where analyte='LEN' and param='AUCtau';  
  class treatment;  
  model lnest = treatment / ddfm=kr;  
  lsmeans treatment / diff cl alpha = 0.1;  
  estimate 'Group 2 versus Group 1' treatment -1 1 / cl alpha = 0.10;  
  ods output Estimates = LS_Diffs LSMeans = LS_Means CovParams = MSE;  
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {[U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research \(CDER\) 2001](#), [U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research \(CDER\) 2003](#)}.

8.2.5. 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 samples may be evaluated as applicable.

Additionally, for the general PK analyses, the sparse and intensive PK sampling data of BIC and LEN from this study may be evaluated using population analysis approaches as applicable. Details of the population PK (popPK) analysis may be provided in a separate popPK analysis plan.

9. REFERENCES

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10. SOFTWARE

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

nQuery Advisor® Version 9.2. Statistical Solutions, Cork, Ireland.

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

11. SAP REVISION

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

12. APPENDICES

12.1. Schedule of Assessments

Table 12-1. Schedule of Assessments in Phase 2 – Treatment Groups 1, 2, and 3

Study Procedures	Screening ^a	Day 1 ^b	Day 2 ^c	Week				Post-Endpoint Week 24 ^d	ERT Visit ^e	Phase 2 Extension Period	Early Study Drugs DC Visit	30-day Telephone Visit ^g	60-day In-Clinic Follow-up Visit ^h
				4	12	16 (optional)	24	Every 12 weeks		Every 12 weeks ^f			
Visit Window		30 days after screening visit		± 6 days	± 6 days	± 6 days	± 6 days	± 6 days		± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Informed consent	X												
Medical history	X												
Concomitant medications	X	X	X	X	X		X	X	X	X	X	X	X
Adverse events ^h	X	X	X	X	X		X	X	X	X	X	X	X
Complete physical exam	X	X			X		X		X		X		X
Symptom-directed physical exam ⁱ				X				X		X			
12-Lead ECG (performed supine)	X				X		X				X		
Height	X												
Vital signs ^j	X	X		X	X		X	X	X	X	X		X
Urinalysis	X	X		X	X		X	X	X	X	X		X
Urine pregnancy test ^k		X									X		
Serum pregnancy test ^k	X												
FSH ^l	X												

Study Procedures	Screening ^a	Day 1 ^b	Day 2 ^c	Week				Post-Endpoint Week 24 ^d	ERT Visit ^e	Phase 2 Extension Period	Early Study Drugs DC Visit	30-day Telephone Visit ^g	60-day In-Clinic Follow-up Visit ^h
				4	12	16 (optional)	24	Every 12 weeks		Every 12 weeks ^f			
Visit Window		30 days after screening visit		± 6 days	± 6 days	± 6 days	± 6 days	± 6 days		± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Chemistry profile ^m	X	X		X	X		X	X	X	X	X		X
Metabolic assessments ⁿ		X			X		X	X	X	X			
Estimated glomerular filtration rate	X	X		X	X		X	X	X	X	X		X
Hematology profile ^o	X	X		X	X		X	X	X	X	X		X
Plasma HIV-1 RNA	X	X		X	X		X	X	X	X	X		X
CD4 cell count	X	X		X	X		X	X	X	X	X		X
Plasma and urine storage sample	X	X		X	X		X	X	X	X	X		X
HCV serology ^p	X						X						X ^p
HBV blood panel ^q	X						X						X ^q
Plasma samples stored for potential HIV-1 genotype/phenotype ^r		X		X	X		X	X	X	X	X		X
Whole blood sample stored for Genosure archive testing		X											

Study Procedures	Screening ^a	Day 1 ^b	Day 2 ^c	Week				Post-Endpoint Week 24 ^d	ERT Visit ^e	Phase 2 Extension Period	Early Study Drugs DC Visit	30-day Telephone Visit ^g	60-day In-Clinic Follow-up Visit ^h
				4	12	16 (optional)	24	Every 12 weeks		Every 12 weeks ^f			
Visit Window		30 days after screening visit		± 6 days	± 6 days	± 6 days	± 6 days	± 6 days		± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Sparse PK: trough and postdose PK sample (Treatment Groups 1 and 2) ^{s, t, v}		X		X	X		X						
Optional intensive PK substudy (Treatment Groups 1 and 2) ^{u, v}		X	X			X	X						
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				X	X		X	X	X	X	X		

AE = adverse event; BIC = bictegravir; CBC = complete blood count; CD4 = clusters of differentiation 4; DC = discontinuation; ECG = electrocardiogram; ERT = end of randomized treatment; 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; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; LEN = lenacapavir; PK = pharmacokinetic(s)

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 Groups 1 and 2 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and 2 × 300 mg LEN on Day 2), in addition to the daily dose of BIC plus LEN starting on Day 1. The study drugs will be administered without regard to food, except for participants enrolled in the intensive PK substudy who will receive study drugs under fasted conditions on Days 1 and 2, and at Weeks 16 or 24 visits.

- c Day 2 visit is not applicable to participants in Treatment Group 3. 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. Participants in the optional intensive PK substudy, and/or when a virtual visit cannot be performed, will dose in clinic and optional PK samples will be obtained (as applicable) as described in protocol Section 6.3.9.
- d After Week 24, all participants will return for visits every 12 weeks until the FDC is determined.
- e Once the last participant completes the Week 24 visit and Gilead completes the Week 24 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 commercially available or until Gilead elects to discontinue the development of BIC/LEN FDC, whichever occurs first. Participants 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 2 portion of the study.
- f Participants from Treatment Group 3 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 2 × 300 mg LEN on Day 2), in addition to the daily doses 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.
- g Participants must complete a 30-day follow-up telephone visit after completion of the Extension Period. Participants who choose to not continue the study after the ERT visit, must return for a 30-day follow-up visit. Participants must also complete a 60-day in-clinic follow-up visit after the completion of the Extension Period.
- h 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.
- i Symptom-directed physical examination as needed.
- j Blood pressure, pulse, respiration rate, temperature, and weight.
- 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 At screening, a FSH test 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.
- m Chemistry profile per protocol Table 6.
- n 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.
- o Hematology profile per protocol Table 6.
- p HCVAb serology to be performed at screening and Week 24 of randomized treatment and at the 60-day follow-up visit. Participants who are HCVAb positive will have an HCV RNA test performed.
- q HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb). To be performed at screening and Week 24 of Randomized Treatment Period and 60-day 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.
- r 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 genotypic and phenotypic testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (protocol Section 6.3.10.2).
- s For participants in Treatment Groups 1 and 2 not enrolled in the intensive PK substudy, a single predose plasma PK sample (≤ 5 min before dose) **and** a single postdose plasma PK sample at 4 hours (± 1 hours) (relative to BIC plus LEN dosing and oral loading dose of LEN) 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, and 24, **and** a single postdose plasma PK sample at 2 hours (± 1 hours) (relative to BIC plus LEN dosing) at Weeks 4, 12, and 24.

- t 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 's' during randomized treatment visits until Week 24. 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 24 until ERT visit and during Extension Period. See protocol Section 6.3.9.1 for additional information.
- u An intensive PK substudy will be performed in a subset of participants in Treatment Groups 1 and 2 at selected study sites. Participants may select to participate in 1 or more visit(s). 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.
Day 1: Single PK sample predose (≤ 5 min before dose), and at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC plus LEN dosing and oral loading dose of LEN).
Day 2: Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose on Day 1 and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, and 6 hours postdose (relative to BIC plus LEN dosing and oral loading dose of LEN).
Week 16 or Week 24 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 plus LEN dosing).
All participants enrolled in the intensive PK substudy on Days 1 and 2, and at Weeks 16 or 24 will receive BIC plus LEN under fasted conditions.
- v 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).

Table 12-2. Schedule of Assessments in Phase 3 – Treatment Groups 1 and 2

Study Procedures	Screening ^a	Day 1 ^b	Day 2 ^c	Week					Post-Endpoint Week 48 ^d	ERT Visit ^e	Phase 3 Extension	Early Study Drugs DC	30-day Telephone Visit ^g	60-day In-clinic Follow-up Visit ^g
				4	12	24	36	48	Every 12 weeks		Every 12 weeks ^f			
Visit Window		30 days after screening visit		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 6 days		± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Informed consent	X													
Medical history	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete physical exam	X	X			X			X		X		X		X
Symptom- directed physical exam ⁱ				X		X	X		X		X			
12-Lead ECG (performed supine)	X				X	X						X		
Questionnaires		X			X	X		X		X	X	X		
Height	X													
Vital signs ^j	X	X		X	X	X	X	X	X	X	X	X		X
Urinalysis	X	X		X	X	X	X	X	X	X	X	X		X
Urine pregnancy test ^k		X										X		
Serum pregnancy test ^k	X													
FSH ^l	X													
Chemistry profile ^m	X	X		X	X	X	X	X	X	X	X	X		X
Metabolic assessment ⁿ		X			X		X	X	X	X	X			
Estimated glomerular filtration rate	X	X		X	X	X	X	X	X	X	X	X		X
Hematology profile ^o	X	X		X	X	X	X	X	X	X	X	X		X

Study Procedures	Screening ^a	Day 1 ^b	Day 2 ^c	Week					Post-Endpoint Week 48 ^d	ERT Visit ^e	Phase 3 Extension	Early Study Drugs DC	30-day Telephone Visit ^g	60-day In-clinic Follow-up Visit ^g
				4	12	24	36	48	Every 12 weeks		Every 12 weeks ^f			
Visit Window		30 days after screening visit		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 6 days		± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Plasma HIV-1 RNA	X	X		X	X	X	X	X	X	X	X	X		X
CD4 cell count	X	X		X	X	X	X	X	X	X	X	X		X
Plasma and urine storage sample ^p	X	X		X	X	X	X	X	X	X	X	X		X
HCV serology ^q	X							X			X ^q			X ^q
HBV blood panel ^r	X							X						X ^r
Plasma samples stored for potential HIV-1 genotype/ phenotype ^s		X		X	X	X	X	X	X	X	X	X		X
Whole blood sample stored for Genosure archive testing		X												
Sparse PK: trough and postdose PK sample (Treatment Group 1) ^{u, w}		X		X	X	X	X	X						
Optional intensive PK substudy (Treatment Group 1) ^{v, w}						X ^v	X ^v	X ^v						
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	X	X			
Study drug accountability			X	X	X	X	X	X	X	X	X	X		

AE = adverse event; BIC = bictegravir; CBC = complete blood count; CD4 = clusters of differentiation 4; DC = discontinuation; ECG = electrocardiogram; ERT = end of randomized treatment; 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; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; LEN = lenacapavir; PK = pharmacokinetic(s)

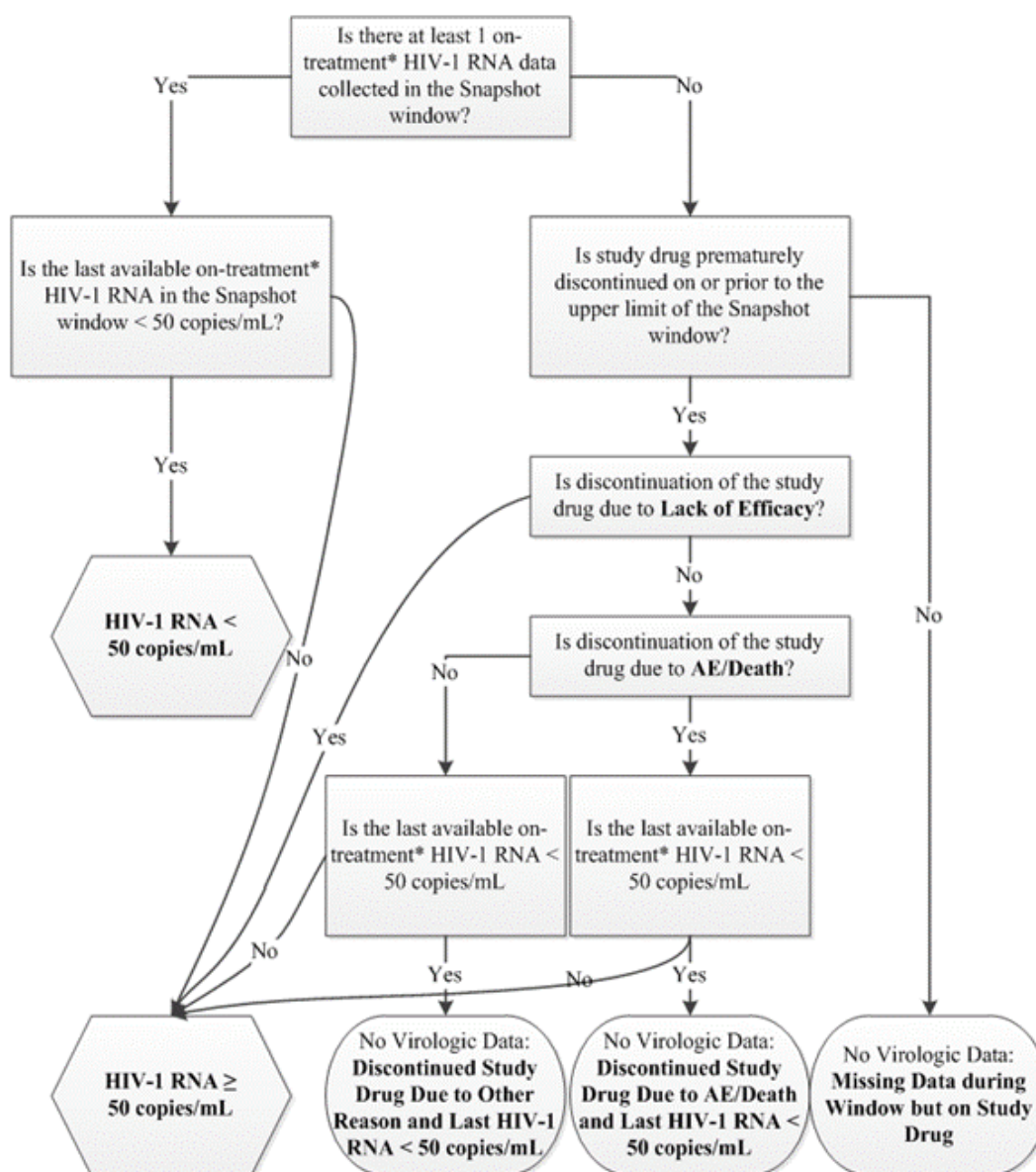
- a Evaluations to be completed within 30 days prior to Day 1. Screening window can be extended to 45 days with sponsor approval.
- b Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit. Participants randomized to Treatment Group 1 will receive a 2-day PK oral loading dose regimen of LEN (2×300 mg LEN on Day 1 and 2×300 mg LEN 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, except for participants enrolled in intensive PK substudy who will receive study drugs under fasted conditions on Day 1 and Day 2, and at Weeks 16 or 24 visits.
- 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. Participants in the optional intensive PK substudy, and/or when a virtual visit cannot be performed, will dose in clinic and optional PK samples will be obtained (as applicable) as described in protocol Section 6.3.9.
- d After Week 48, all participants will return for visits every 12 weeks until the FDC is determined.
- e 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 commercially available or until Gilead elects to discontinue the development of BIC/LEN FDC, whichever occurs first. Participants 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.
- f 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 2×300 mg LEN on Day 2), in addition to the daily doses 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.
- g Only required for participants who enroll in the Extension Period. Participants who enroll in the Extension Period 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.
- h 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.
- i Symptom-directed physical examination as needed.
- j Blood pressure, pulse, respiration rate, temperature, and weight
- 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 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.
- m Chemistry profile per protocol Table 6.
- n 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.
- o Hematology profile per protocol Table 6.
- p Stored plasma samples collected may be used to test for inflammatory markers: Cystatin, d-Dimer, IL-6, C-Reactive Protein, sCD14, and sCD163.
- q HCVAb serology to be performed at screening and Week 48 of Randomized Treatment Period and at Week 48 of the Extension Period visits. Participants who are HCVAb positive will have an HCV RNA test performed.
- r 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.

- s 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 genotypic and phenotypic testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (protocol Section 6.3.10.2).
- t For participants in Treatment Group 1 not enrolled in the intensive PK substudy, 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 dosing and oral loading dose of LEN) 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.
- u 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 't' 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.
- v 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).
- w 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).

12.2. US FDA-Defined Snapshot Algorithm (for Switch Trial)

The flowchart of the US FDA-defined snapshot algorithm based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment {U. S. Department of Health and Human Services 2015} is provided in Figure 12-1.

Figure 12-1. Flowchart of US FDA-Defined Snapshot Algorithm (Switch Trial)



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.

GS-US-621-6289-ph2-wk24-SAP-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM- yyyy hh:mm:ss)
PPD	Clinical Development eSigned	16-Aug-2023 22:42:13
PPD	Clinical Pharmacology eSigned	19-Aug-2023 04:38:08
PPD	Biostatistics eSigned	19-Aug-2023 23:48:14