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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Meissner EG, Ramgopal M, Ruane PJ, et al. Safety and efficacy of switching to bictegravir–lenacapavir versus continuing bictegravir–emtricitabine–tenofovir alafenamide in virologically suppressed people with HIV-1 (ARTISTRY-2): a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet HIV* 2026; published online May 6. https://doi.org/10.1016/S2352-3018(26)00078-0.

SUPPLEMENTARY APPENDIX

Safety and efficacy of switching to bictegravir–lenacapavir versus continuing bictegravir–emtricitabine–tenofovir alafenamide in virologically suppressed people with HIV-1 (ARTISTRY-2): a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial

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Supplementary Methods

Study Protocol Amendments

Key Changes in Amendment 1 (Jun 18, 2024)
• Inclusion criterion 9 was revised to replace "estimated glomerular filtration rate > 30 mL/min" with "estimated glomerular filtration rate ≥ 30 mL/min" as this was missing. • In Korea, "adult" is considered >19 years of age and not >18 years of age, which can cause confusion regarding the eligibility criteria for the age at which participants can enrol in this study; therefore, the word "Adults" in the phrase "Virologically Suppressed Adults with HIV-1" was replaced with "Participants". • Footnotes "n" and "o" in the Study Procedures Table were updated for additional information pertaining to participants or pregnant participants taking evening doses. • Pandemic risks to study conduct were broadened to include unanticipated events (disasters and public health emergencies). • Subsection 3.3.1.1.1 for partial withdrawal information was added per updated protocol template. • "Participant request to discontinue for any reason" was added as criterion for discontinuation from study per protocol template. • Exclusion criterion 16 was added to exclude participants under guardianship, curatorship, or legal protection from the study. • Section 5.1.2 was updated for information on blinding for the purpose of population PK modelling. • Acid reducing agents/antacids/buffered medications row in Table 6 was updated to provide more information on antacids, vitamins or mineral supplements, and to provide information regarding precautions for use of antacids in pregnant participants on the study drug and to align with the latest investigator's brochure updates. In addition, this row was updated to reflect how the drug should be taken together with supplements or antacids containing calcium, iron, and/or zinc. • Oral hypoglycaemic agents row in Table 6 was updated for metformin to "refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of the study drug and metformin." • Language was updated for stored plasma samples that may be used for PK analysis. • Information was updated to include participants with documented nonadherence who will be tested for resistance. • Language was added regarding additional unscheduled visits between every-12-week visits during pregnancy. • Updates were made to clarify interim analysis time points, ie, interim analysis may be conducted after Week 96 but not before Week-48 primary analysis. • The safety analysis set was updated to include "all participants" instead of "all randomised participants". • Statistical test to be used for analysis of categorical and continuous demographic and baseline characteristics was deleted. • Summary analysis for demographic and baseline characteristics by geographical region was deleted. • Updates were made on primary analysis of the study to use the estimand framework for the primary endpoint, including the addition of Table 10. • Updates were made on secondary analysis of the study to use the estimand framework for the key secondary endpoint, including the addition of Table 11. • Wording relating to the hypothesis testing for superiority of bictegravir-lenacapavir over bictegravir-emtricitabine-tenofovir alafenamide was removed. • Text pertaining to publication of clinical trial as per local regulatory requirements was updated. • New Section 9.3.6 for data protection language was added. • Text was updated to clarify no interim futility analysis is planned for data monitoring committee. • Heading and text of the "Disaster or public health emergency" section was updated as per protocol template. • Appendix was updated to include language for the definition of fertility in a participant assigned male at birth, and to clarify that no contraception is required for participants in the study and the current available data do not suggest pregnancy should be avoided by participants on the study. Heading of appendix was updated to align with protocol template.
Key Changes in Amendment 1.1 (Jul 29, 2024)
• Per request of the health authority ANMAT, language for the additional Argentina-specific requirement to perform pregnancy testing during the study was added to a new Appendix 11.8.1. Cross-references to this content in Appendix 11.8.1 have also been added to the body of the protocol where indicated.

- Per request of ANMAT, Argentina-specific inclusion criterion #ARG1 was added to Appendix 11.8.1 that requires participants assigned female at birth and of childbearing potential to agree to use protocol-specified methods of contraception also described in Appendix 11.8.1. Cross-references to this content in Appendix 11.8.1 have also been added to the body of the protocol where indicated.
- Per request of the health authority European Medicines Agency (EMA), additional EU-specific exploratory objectives and endpoints evaluating bictegravir–lenacapavir in participants from Treatment Group 2 who enter the open-label phase were added in Appendix 11.8.2. In addition, an analysis for participants in Treatment Group 2 switching to bictegravir–lenacapavir fixed-dose combination in the open-label phase has been added in Appendix 11.8.2. Cross-references to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.
- Per request of EMA, EU-specific inclusion criterion #EU1 was added to Appendix 11.8.2 that requires participants assigned female at birth and of childbearing potential to agree to use protocol-specified methods of contraception also described in Appendix 11.8.2. A cross-reference to this content in Appendix 11.8.2 has also been added to the body of the protocol where indicated.
- Per request of EMA, an EU-specific sensitivity analysis including the missing data handling strategies was added to Appendix 11.8.2. Cross-references to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.
- Per request of EMA, an EU-specific definition of the Per Protocol (PP) Analysis Set was added to Appendix 11.8.2. Detail of the analysis using the PP Analysis Set for the primary and key secondary efficacy endpoints has also been added to Appendix 11.8.2. Cross-references to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.
- Per request of EMA an EU-specific table showing power to establish non-inferiority with various assumptions of treatment failure rate was added to Appendix 11.8.2. A cross-reference to this content in Appendix 11.8.2 has also been added to the body of the protocol where indicated.

Key Changes in Amendment 2 (Apr 3, 2025)

- It was clarified that non-inferiority test with a 10% non-inferiority margin will not be performed for the secondary efficacy endpoint (HIV-1 RNA <50 copies per mL) at Week 48 in accordance with a request from United States (US) Food and Drug Administration (FDA).
- Clarification was added that future research is optional and collection subject to local regulations.
- Text was added regarding follow-up visits for participants who discontinue study drugs early to align with protocol body.
- Clarifying statement was added for metformin exposure when co-administered with bictegravir.
- Time frame for virological rebound reflex testing and re-testing was updated to align with current testing policy
- Estimand framework for virological outcomes and the Snapshot algorithm were updated in accordance with request from the US FDA.
- Country-specific requirements for Argentina were updated to align with Gilead practice.

ARTISTRY-2 Eligibility Criteria

Inclusion criteria

Participants must have met all of the following inclusion criteria to be eligible for participation in the study:

- Willing and able to provide informed written consent
- Aged ≥18 years at screening
- Currently receiving bictegravir–emtricitabine–tenofovir alafenamide for ≥6 months prior to screening
- If plasma HIV-1 RNA measurements in the last 6 months prior to screening are available, all levels must be <50 copies per mL
- At least one documented HIV-1 RNA level measured between 6 and 12 months (±2 months) prior to screening. This and any other HIV-1 RNA measurements documented in this period must be <50 copies per mL
- Plasma HIV-1 RNA levels <50 copies per mL at screening
- No documented or suspected resistance to bictegravir (including integrase strand-transfer inhibitor resistance mutations T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene)
- No documented or suspected resistance to tenofovir alafenamide (mutations K65R, K65N, K70E, Q151M or T69 insertion, or ≥3 of the following thymidine analogue mutations in the reverse transcriptase gene: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R)
- Estimated glomerular filtration rate ≥30 mL/min according to the Cockcroft–Gault formula for creatinine clearance
- Female participants of childbearing potential who engage in heterosexual intercourse must agree to use contraception

Exclusion criteria

Participants who met any of the following exclusion criteria were not eligible to be enrolled in the study:

- Positive serum pregnancy test result at screening or a positive pregnancy test result before day 1 randomisation
- Breastfeeding
- Prior use of, or exposure to, lenacapavir
- Active, serious infections (other than HIV-1) requiring parenteral therapy <30 days prior to randomisation
- Active tuberculosis infection
- Acute hepatitis <30 days before randomisation
- Chronic hepatitis B virus (HBV) infection, as determined by either:
    - Positive HBV surface antigen and negative HBV surface antibody status, regardless of HBV core antibody status, at the screening visit
    - Positive HBV core antibody and negative HBV surface antibody status, regardless of HBV surface antigen status, at the screening visit

- Known hypersensitivity to the study drug, its metabolites, or any formulation excipient
- History of or current clinical decompensated liver cirrhosis (e.g., ascites, encephalopathy, or variceal bleeding)
- Abnormal electrocardiogram at the screening visit that is clinically significant as determined by the investigator
- Active malignancy requiring acute systemic therapy
- Any of the following laboratory values at screening:
    - Alanine aminotransferase >5 × upper limit of normal (ULN)
    - Direct bilirubin >1·5 × ULN
    - Platelets <50,000/mm^3
    - Haemoglobin <8·0 g/dL
- Requirement for ongoing therapy with or prior use of any prohibited medications
- Participation or planned participation in any other clinical study (including observational studies) without prior approval from the sponsor
- Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements
- Participants under guardianship, curatorship, or legal protection may not participate in the study

Geographical Stratification Used for Randomisation

Region	Countries and territories
Asia	Japan, Republic of Korea, and Taiwan
Central and South America	Argentina and Dominican Republic
Europe	Germany, Italy, Spain, and United Kingdom
North America	Canada, Mexico and United States (including Puerto Rico)
Oceania	Australia

Details of Statistical Analysis

The proportion of participants with HIV-1 RNA ≥50 copies per mL at week 48 was summarised by treatment group and by visit using the following two imputation methods:

- Missing=failure: Participants with missing data in a specific analysis visit window were treated as virologic failure (HIV-1 RNA ≥50 copies per mL) and summarised into the “Missing” category.
- Missing=excluded: Participants with missing data were excluded from analysis (i.e., excluded from both the numerator and denominator in calculation of percentages). The denominator for percentages at a visit was the number of participants with non-missing HIV-1 RNA value at that visit.

Handling of Missing Data

Missing data were not imputed, except for in the following instances:

Missing last dosing date of study drug

If the last dosing date was incomplete (only the year of the last dosing date was known) or completely missing: for participants who prematurely discontinued study drug in the blinded phase, the latest date among the following was used: study drug non-missing start and stop dates, clinic visit dates (excluding the follow-up dates after early study drug discontinuation), or the laboratory sample collection dates (excluding follow-up dates after early study drug discontinuation); for participants who were still on treatment at the time of an interim analysis, the last available date in the database snapshot was used.

If only the month and year of the last dosing date were known, the latest date among the following was used as the last dosing date: study drug dispensing date, study drug start and stop dates, or the imputed last dosing date (day imputed as 15). If a participant died, and the death date was complete and fell before the imputed last dosing date by the above rules, the complete death date was used as the imputed last dosing date.

Missing/incomplete dates for adverse event start date

If the adverse event start date was incomplete and the adverse event stop date was on or after the first dosing date of study drug, the month and year (or year alone if month was not recorded) of the start date determined whether an adverse event was deemed treatment emergent. The event was considered treatment emergent if both of the following two criteria were met:

(1) the adverse event start date was the same as or fell after the month and year (or year alone) of the first dosing date of study drug

(2) the adverse event start date was the same as or fell before the month and year (or year alone) of the date corresponding to 60 days (for bictegravir–lenacapavir) or 30 days (for bictegravir–emtricitabine–tenofovir alafenamide) after the last dosing date of bictegravir–lenacapavir or bictegravir–emtricitabine–tenofovir alafenamide.

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

Supplementary Results

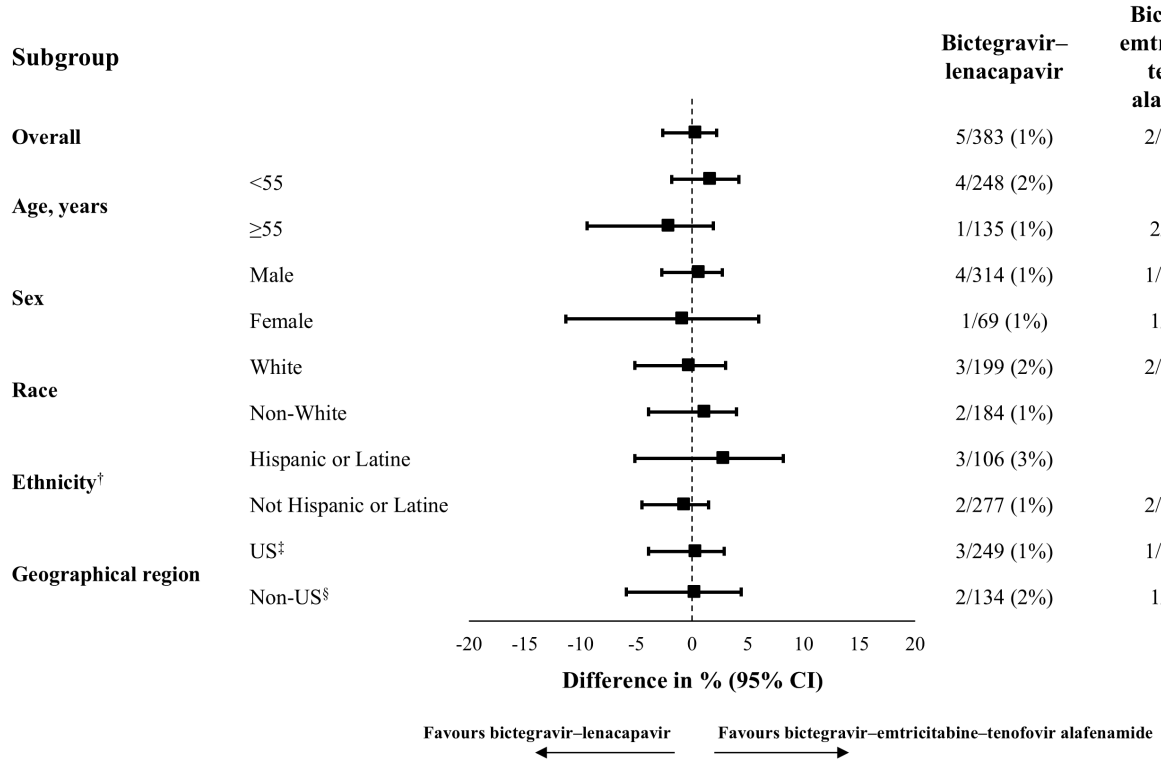
Rhabdomyolysis Case

The participant with rhabdomyolysis was asymptomatic. A DAIDS grade of 3 was assigned initially due to the magnitude of increase in creatine kinase concentration. As the participant was asymptomatic, without evidence of end-organ damage (such as impact on renal function), and with agreement from the participant, study drug was continued. Per DAIDS, grading is based on symptomatology and not the magnitude of the laboratory abnormality and thus, the Principal Investigator revised the grade from 3 to 1. Per the investigator's assessment, the temporal nature of the adverse event, with onset following initiation of study drug, and the lack of an alternate aetiology led to the adverse event being judged as related to study procedures. The participant continued study drug and the elevated creatine kinase concentration returned to normal limits. The participant continued to be asymptomatic, without evidence of end-organ damage throughout.

Table S1: Reasons for screen failure

Reasons for screen failure	Total (n=71)
Inclusion Criteria Not Met	51 (71.8%)
Plasma HIV-1 RNA levels <50 copies/mL at screening	29 (40.8%)
At least one documented HIV-1 RNA level measured between 6 and 12 months (+/− 2 months) prior to screening. This and any other HIV-1 RNA measurements documented in this period must be <50 copies/mL	11 (15.5%)
If plasma HIV-1 RNA measurements in the last 6 months prior to screening are available, all levels must be <50 copies/mL	10 (14.1%)
No documented or suspected resistance to bictegravir (including INSTI-R mutations T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene)	2 (2.8%)
Currently receiving bictegravir–emtricitabine–tenofovir alafenamide for ≥6 months prior to screening	1 (1.4%)
For EU: Participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified methods of contraception	1 (1.4%)
No documented/suspected resistance to tenofovir alafenamide (mutations K65R, K65N, K70E, Q151M, or T69 insertion or ≥3 thymidine analogue mutations: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R in the reverse transcriptase gene)	1 (1.4%)
Willing and able to provide written informed consent prior to performing study procedures	1 (1.4%)
Exclusion Criteria Met	25 (35.2%)
Chronic HBV infection as determined by positive HBV surface antigen and negative HBV surface antibody, or positive HBV core antibody and negative HBV surface antibody at screening	14 (19.7%)
Abnormal electrocardiogram at the screening visit that is clinically significant as determined by the investigator	3 (4.2%)
Any of the laboratory values at screening: a. ALT >5 × ULN; b. Direct bilirubin >1.5 × ULN; c. Platelets <50,000/mm^3; d. Haemoglobin <8.0 g/dL	3 (4.2%)
Acute hepatitis <30 days before randomisation	2 (2.8%)
Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements	2 (2.8%)
Participation or planned participation in any other clinical study (including observational studies) without prior approval from the sponsor	2 (2.8%)
Active tuberculosis infection	1 (1.4%)
Active, serious infections (other than HIV-1) requiring parenteral therapy <30 days prior to randomisation	1 (1.4%)
Prior use of, or exposure to, lenacapavir	1 (1.4%)
Requirement for ongoing therapy with or prior use of any prohibited medications listed in the protocol	1 (1.4%)

Figure S1: Treatment difference in the percentage of participants with HIV-1 RNA ≥50 copies per mL by subgroup US FDA Snapshot algorithm at week 48 (full analysis set, while on treatment)



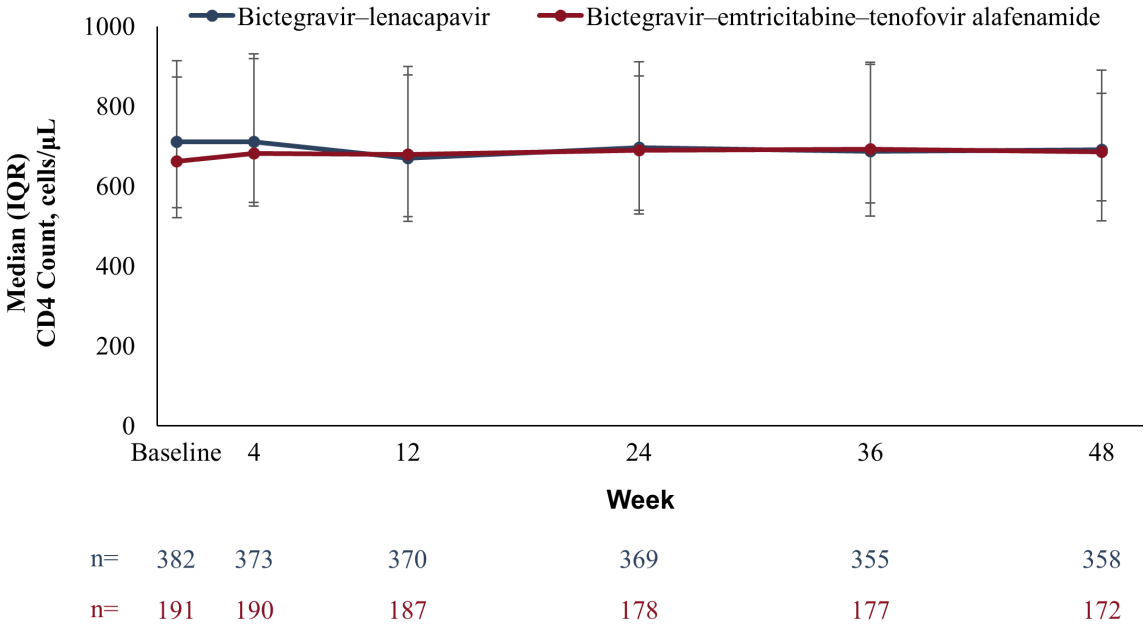
Data are n/N (%) unless otherwise specified.
*Differences in percentages of participants between treatment groups (bictegravir–lenacapavir minus bictegravir–emtricitabine–tenofovir alafenamide) and 95% CIs were calculated based on an unconditional exact method using two inverted one-sided tests.
On-treatment values included all available data for ongoing participants or up to the last dose date + 1 day for participants who prematurely discontinued study drug.
†One participant in the bictegravir–emtricitabine–tenofovir alafenamide group was from a country where reporting of ethnicity was not permitted, difference in percentage could not be calculated for the group "not permitted".
‡Participants from US and Puerto Rico.
§Participants from all countries excluding US and Puerto Rico.

Table S2: HIV treatment history at baseline (safety analysis set)

	Bictegravir–lenacapavir (n=383)	Bictegravir–emtricitabine–tenofovir alafenamide (n=191)	Total (n=574)
Number of prior antiretroviral therapies*	2 (1–5)	3 (1–6)	2 (1–5)
Participants with B/F/TAF as first antiretroviral therapy	167 (44%)	71 (37%)	238 (41%)
Prior antiretroviral therapy			
NRTI/INSTI	372 (97%)	185 (97%)	557 (97%)
NRTI	139 (36%)	74 (39%)	213 (37%)
PI	78 (20%)	45 (24%)	123 (21%)
INSTI	64 (17%)	34 (18%)	98 (17%)
NNRTI	60 (16%)	30 (16%)	90 (16%)
NRTI/NNRTI	59 (15%)	43 (23%)	102 (18%)
Other	14 (4%)	16 (8%)	30 (5%)
INSTI/NNRTI	9 (2%)	3 (2%)	12 (2%)
PI/PKE	8 (2%)	7 (4%)	15 (3%)
NRTI/PI	7 (2%)	6 (3%)	13 (2%)
CCR5	5 (1%)	3 (2%)	8 (1%)
PKE	0	2 (1%)	2 (<1%)

Data are n (%) or median (IQR).
*Data available for 374 participants in the bictegravir–lenacapavir group, and 186 participants in the bictegravir–emtricitabine–tenofovir alafenamide group.
CCR5=chemokine receptor type 5. INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. PKE=pharmacokinetic enhancer.

Figure S2: Median CD4 cell count over time (full analysis set, while on treatment*)



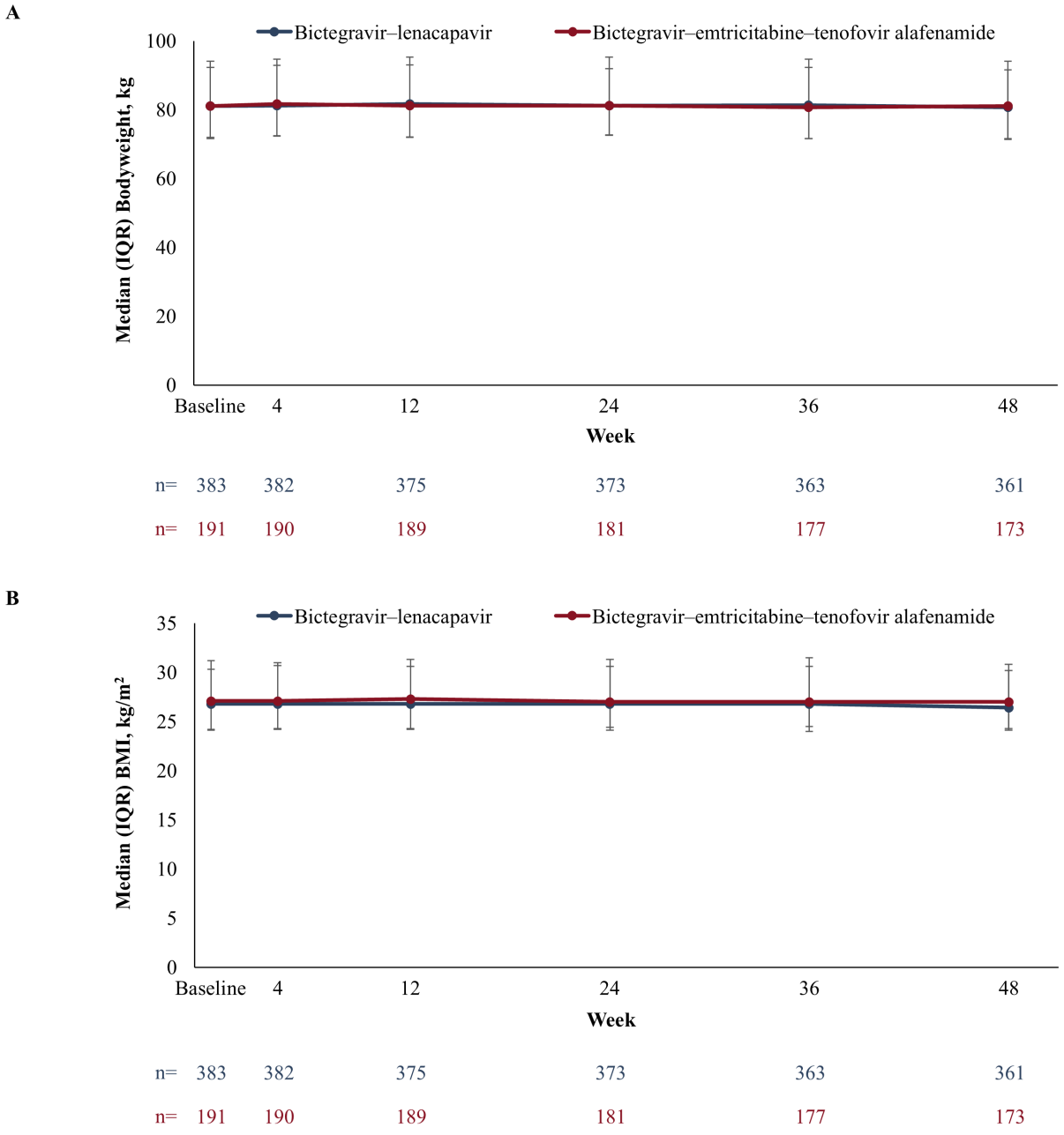
*On-treatment values included all available data for ongoing participants or up to the last dose date + 1 day for participants who prematurely discontinued study drug.

Table S3: Laboratory abnormalities (safety analysis set)

	Bictegravir–lenacapavir (n=383)	Bictegravir–emtricitabine–tenofovir alafenamide (n=191)
Laboratory abnormalities – any grade	346/382 (91%)	174/190 (92%)
Grade 3 or higher	93/382 (24%)	44/190 (23%)
Grade 3 or higher laboratory abnormalities reported in ≥2% of participants in any group		
Decreased creatinine clearance	23/382 (6%)	21/190 (11%)
Increased direct bilirubin level	36/382 (9%)	7/190 (4%)
Increased creatinine level	4/382 (1%)	6/190 (3%)
Increased fasting serum glucose level	10/381 (3%)	2/189 (1%)
Increased creatine kinase level	10/382 (3%)	5/190 (3%)
Increased non-fasting serum glucose level	3/235 (1%)	3/126 (2%)
Glycosuria	7/379 (2%)	4/181 (2%)
Increased fasting triglyceride level	5/377 (1%)	4/180 (2%)
Increased lipase level	8/382 (2%)	2/190 (1%)

Data are n/N (%). Severity grades were defined by the DAIDS Toxicity Grading Scale, version 2·1.
For maximum post-baseline toxicity grade, the most severe graded abnormality from all tests was counted for each participant. For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant. Laboratory abnormalities were defined as an increase of at least one toxicity grade from baseline at any time post-baseline up to and including last dose date plus 60 days in bictegravir–lenacapavir group or plus 30 days in bictegravir–emtricitabine–tenofovir alafenamide group.

Figure S3: Bodyweight (A) and BMI (B) over time (safety analysis set)



Baseline value was the last available value collected on or prior to first dose of study drug.
BMI=body mass index.

CLINICAL STUDY PROTOCOL

Study Title:	Phase 3 Double-blind Multicenter Randomized Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide) in Virologically Suppressed People With HIV-1
Study Acronym:	ARTISTRY-2
Plain Language Short Title:	Study to Compare Bictegravir/Lenacapavir Versus Current Therapy in People With HIV-1 Who Are Successfully Treated With Biktarvy
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	158963 2023-510022-33 NCT06333808
Population Diagnosis or Condition:	HIV-1 Infection
Protocol ID:	GS-US-621-6290
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 2: 03 April 2025
Amendment History:	Original: 16 January 2024 Amendment 1: 18 June 2024 Amendment 1.1: 29 July 2024 A high-level summary of the changes in each amendment is provided in Appendix 11.9.

Country-Specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 11.8.

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are not considered to be investigational new drug application sites.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANCOVA	analysis of covariance
ART	ARV therapy
ARV	antiretroviral
AUC	area under the concentration versus time curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
$AUC_{0\text{-}8\ days}$	partial area under the concentration versus time curve from time “0” to time “8 days”
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BIC	bictegravir
BIC/LEN	bictegravir/lenacapavir
BLQ	below the limit of quantitation
CD4	clusters of differentiation 4
CI	confidence interval
CIPHER	International AIDS Society and the Pregnancy and the International AIDS Society’s Collaborative Initiative for Paediatric HIV Education and Research
CL_{cr}	creatinine clearance
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTD	Common Technical Document
CTR	Clinical Trail Regulation
C_{trough}	concentration at the end of the dosing interval
DDI	drug-drug interaction
DMC	data monitoring committee
EACS	European AIDS Clinical Society
EBT	end of blinded treatment
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESDD	early study drug discontinuation
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HBV	hepatitis B virus

HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HLT	high-level term
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	investigational new drug
INSTI	integrase strand-transfer inhibitor
INSTI-R	integrase strand-transfer inhibitor resistant
IQ	inhibitory quotient
IRB	institutional review board
IRT	Interactive Response Technology
LEN	lenacapavir
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NA	not applicable
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OL	open label
PDE-5	phosphodiesterase 5
PK	pharmacokinetic(s)
PP	per protocol
PS	Patient Safety
PT	preferred term
PTM	placebo-to-match
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SBR	stable baseline regimen
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SSR	special situation report
STR	single-tablet regimen
SUSAR	suspected unexpected serious adverse reaction

TAF	tenofovir alafenamide (Vemlidy®)
ULN	upper limit of normal
US	United States
VR	virologic rebound
WHO	World Health Organization

PROTOCOL SYNOPSIS

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

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

Study Acronym: ARTISTRY-2

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

Regulatory Agency Identifier Number(s):

IND Number: 158963
EU CT Number: 2023-510022-33
ClinicalTrials.gov Identifier: NCT06333808

Study Sites Planned: Approximately 120 sites globally

Objectives and Endpoints:

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

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

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

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

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

Randomization will be stratified by geographic region.

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

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

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

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

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

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

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

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

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

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

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

Study Procedures/Frequency:

Blinded Phase:

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

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

Open-label Phase:

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

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

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

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

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

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

The primary analysis will consist of a noninferiority test of switching to BIC/LEN versus B/F/TAF, in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48. It will be concluded that BIC/LEN FDC is noninferior to B/F/TAF if the upper bound of the 2-sided 95% CI for the treatment difference (BIC/LEN − B/F/TAF) in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups is less than 4%. The 2-sided 95% CIs will be constructed based on stratum-adjusted Mantel-Haenszel (MH) proportion, adjusted by geographic regions.

The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 will also be analyzed using the same methods as for the primary efficacy endpoint based on the FAS.

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

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

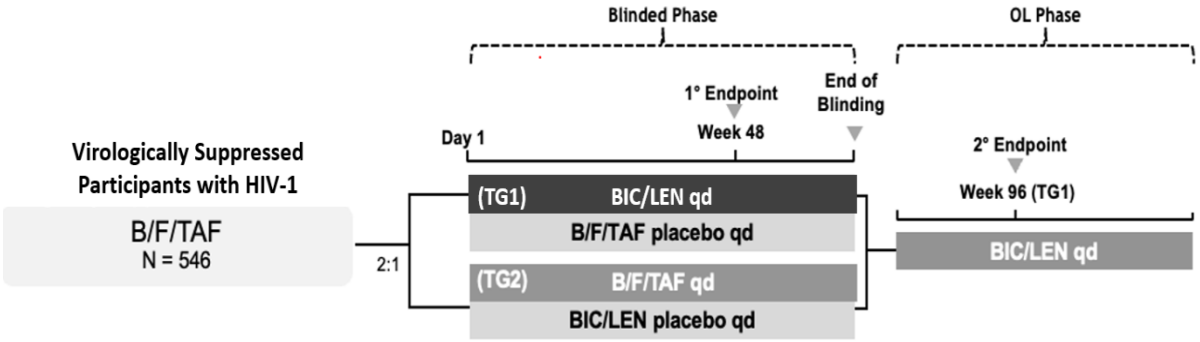
Safety endpoints will be analyzed by the number and percent of participants with AEs or laboratory abnormalities for categorical values or 8-number summary (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, maximum) for continuous data by treatment groups.

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

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

STUDY SCHEMA

Figure 1. Study Schema



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

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table

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

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

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

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

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

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

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

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

d Once the last participant completes the Week 48 visit and the analysis of safety and efficacy data of BIC/LEN FDC compared with B/F/TAF FDC is completed, all participants will attend an EBT visit at the next in-clinic visit (preferably within 12 weeks). At the EBT visit, participants in Treatment Group 1 will continue to receive BIC/LEN FDC until OL Week 48 and participants in

Treatment Group 2 will be given the option to receive BIC/LEN FDC. All participants in the OL phase will continue to receive BIC/LEN FDC until study drug is available or until Gilead elects to discontinue the study, whichever occurs first. Participants in Treatment Group 2 who complete the study through the EBT visit, and do not wish to participate in the OL phase, must complete a 30-day telephone visit and a 60-day in-clinic follow-up visit after the EBT visit, and will be considered to have completed the study. Participants who discontinue study drug early will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the early study drugs DC visit.

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

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

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

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

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

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

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

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

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

n A single predose plasma PK sample (≤ 15 min before dose) **and** a single postdose plasma PK sample at 4 hours (± 1 hour) (relative to study drugs administration) 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 hour) (relative to study drugs administration) at Weeks 24 and 36. For participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at Weeks 4, 12, 24, 36, and 48.

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

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

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

1. INTRODUCTION

1.1. Background

HIV-1 infection is a life-threatening and serious disease of major public health significance with approximately 38 million people with HIV-1 worldwide and approximately 28.7 million taking antiretroviral (ARV) treatment {UNAIDS 2022}. Standard of care for the treatment of HIV-1 infection uses combination ARV therapy (ART) to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive people with HIV-1, current treatment guidelines suggest that initial preferred therapy consists of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and an integrase strand-transfer inhibitor (INSTI), 1 NRTI and 1 INSTI, or alternatively 2 N(t)RTIs and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor, depending on the clinical situation{Department of Health and Human Services (DHHS) 2023, EACS European AIDS Clinical Society 2023, Panel on Antiretroviral Guidelines for Adults and Adolescents 2023, Saag 2020}. Virologically suppressed people with HIV-1 may switch from their current regimen due to safety or tolerability concerns, regimen simplification, or to prevent or mitigate drug-drug interactions (DDIs). All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}.

1.1.1. Rationale for Development of Bictegravir/Lenacapavir Fixed-Dose Combination Tablet

Currently available single-tablet regimen (STR) options for people with HIV-1 commonly include a combination of an INSTI, a boosted protease inhibitor, or an NNRTI with a backbone of 1 or 2 NRTIs. Emergence of resistance mutations to 1 or more classes of ART in people with HIV-1, particularly those associated with the NRTI class, preclude in many cases their ability to take an STR for HIV treatment.

The efficacy and safety of bictegravir (BIC) and lenacapavir (LEN) are well established. In addition, BIC has a high barrier to resistance and LEN, a potent HIV-1 first-in-class capsid inhibitor, is expected to have an absence of resistance in unexposed patients. The BIC/LEN FDC has the potential to offer a once-daily regimen, which does not require a boosting agent or include an NRTI.

In addition, based on Gilead Sciences' (Gilead's) claims analyses, 6% to 8% of total treated people with HIV-1 in the United States (US) are taking multiple-tablet or multiple-dosing complex ARV regimens, and it is expected that this percentage of people with HIV-1 on complex regimens is generally similar between the US and European Union (EU). The BIC/LEN FDC tablet also has the potential to address an important unmet medical need for virologically suppressed people with HIV-1 who are taking a complex regimen by offering a treatment simplification option of 1 tablet once a day, as well as for virologically suppressed people with HIV-1 who need to switch their ART due to resistance, intolerance, or contraindications to their current STR treatment.

This study will evaluate the safety, efficacy, and tolerability of BIC/LEN FDC versus Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [B/F/TAF]) FDC in virologically suppressed people with HIV-1 who have been on B/F/TAF for at least 6 months prior to screening. B/F/TAF was selected as the active comparator for this study to allow comparison of BIC/LEN with a once-daily STR with well-established safety and tolerability that is a recommended regimen for the treatment of HIV in current US and EU guidelines.

1.2. Background on Study Interventions

A list of study interventions and their marketing authorization status is provided in Appendix 11.2.

1.2.1. Bictegravir/Lenacapavir

BIC/LEN FDC is a once-daily tablet of BIC, a potent INSTI, in combination with LEN, a novel, first-in-class, multistage selective inhibitor of HIV-1 capsid function. No clinically relevant pharmacokinetic (PK) or toxicological interactions are expected between BIC and LEN as components of the BIC/LEN FDC.

For further information on BIC/LEN FDC, refer to the current investigator's brochure (IB), including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.2. Lenacapavir

1.2.2.1. General Information

LEN is a novel, first-in-class, multistage selective inhibitor of HIV-1 capsid function, which has potent antiviral activity, low human clearance, and physiochemical properties well suited for extended-release parenteral or oral formulations.

For further information on LEN, refer to the current IB, including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.3. Information About Reference Product

B/F/TAF (50/200/25 mg) FDC tablet was selected as the active comparator for this study. The B/F/TAF FDC tablet is a safe and highly effective INSTI-based treatment regimen, offering minimal pill burden, once-daily dosing, and excellent tolerability. The B/F/TAF FDC tablet is a recommended initial treatment for people with HIV-1 {Panel on Antiretroviral Guidelines for Adults and Adolescents 2023}.

For more detailed information, including information on pregnancy and lactation, refer to the current local Prescribing Information or IB for B/F/TAF.

1.2.4. Information About Auxiliary Medicinal Products/Noninvestigational Medicinal Products

Auxiliary medicinal products/noninvestigational medicinal products are not used in this study.

1.3. Rationale for This Study

There is an unmet medical need for new safe and effective treatment options for all people with HIV-1, including those who are virologically suppressed. This patient population may also include those with resistance, intolerance, or contraindication to current STRs that include NRTIs. To that end, Gilead is developing a once-daily FDC tablet of BIC, a potent INSTI, in combination with LEN, a novel, first-in-class, multistage selective inhibitor of HIV-1 capsid function, both of which have been evaluated for the treatment of HIV-1 infection in combination with other agents and have established efficacy and safety profiles. The BIC/LEN FDC tablet would represent another STR option for people with HIV-1 who are virologically suppressed.

This study is a Phase 3 double-blind, multicenter, randomized, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus B/F/TAF in virologically suppressed people with HIV-1 who have been on B/F/TAF for at least 6 months prior to screening. Overall, data from this study are intended to support the ongoing clinical development of BIC/LEN FDC for people with HIV-1.

1.4. Rationale for Dose Selection of Study Drugs

1.4.1. Phase 2 Experience

Week 24 data from the Phase 2 portion of Study GS-US-621-6289 supports the safety and efficacy of BIC and LEN exposures following administration of single agent oral LEN 25 mg or 50 mg administered with oral loading doses of LEN 600 mg on Days 1 and 2. Based on the US Food and Drug Administration (FDA)–defined snapshot algorithm, the percentages of participants with HIV-1 RNA < 50 copies/mL at Week 24 were shown to be similar for both BIC+LEN treatment groups and the stable baseline regimen (SBR) treatment group (BIC 75 mg + LEN 25 mg 96.1%; BIC 75 mg + LEN 50 mg 96.2%; SBR 100.0%), with a treatment difference of −3.9% (95% CI:−13.9%, 10.7%) for the BIC 75 mg + LEN 25 mg treatment group and −3.8% (95% CI: −13.4%, 10.7%) for the BIC 75 mg + LEN 50 mg treatment group,

compared with the SBR treatment group. BIC and LEN coadministered through Week 24 were safe and well tolerated as demonstrated by the low percentages of participants who had Grade 3 or higher adverse events (AEs) (4/51 participants [7.8%] for BIC 75 mg + LEN 25 mg; 2/52 participants [3.8%] for BIC 75 mg + LEN 50 mg), low percentage of participants who discontinued study drug due to an AE (1/51 participants [2.0%] for BIC 75 mg + LEN 25 mg; 1/52 participants [1.9%] for BIC 75 mg + LEN 50 mg) with no participants reporting serious adverse events (SAEs) related to study drug. Common AEs were generally consistent with those expected in the participant population and the known safety profiles of BIC and LEN. Overall, steady-state exposures of BIC + LEN were consistent with historical data associated with efficacy and safety.

1.4.2. Bictegravir Dose Selection

In Phase 2 portion of Study GS-US-621-6289, the BIC 75 mg + LEN 50 mg group showed similar efficacy and safety as the BIC 75 mg + LEN 25 mg group. Preliminary PK analysis based on intensive PK sampling substudy showed that BIC exposures in both arms were comparable (Table 2), which is as expected based on the same dose of BIC (75 mg) dosed in both treatment groups and no clinically significant impact of DDI with LEN expected. These steady-state BIC exposures were also comparable with those attained in the Phase 2 Studies GS-US-141-1475 and GS-US-200-4334 wherein the same dose of single agent BIC (ie, 75 mg once daily) was administered once daily. The mean C_{trough} achieved in both treatment groups of Phase 2 portion of current Study GS-US-621-6289 (4330 and 4540 mg/mL) are approximately 27- to 28-fold of protein-adjusted 95% effective concentration (paEC95/inhibitory quotient [IQ] of 1; 162 ng/mL), which is the threshold indicative of efficacious exposures for BIC.

The single dose rBA Study GS-US-621-6292 showed that BIC exposures in BIC 75 mg/LEN 50 mg FDC arm were similar to those observed with BIC 75 mg + LEN 25 mg coadministration arm (Table 3) based on preliminary PK data, suggesting that the BIC 75 mg/LEN 50 mg FDC in Phase 3 will achieve similar concentrations of BIC as that studied in Phase 2 portion of GS-US-621-6289, where adequate efficacy/safety has been observed. Additionally, no clinically significant impact of food was observed with the BIC 75 mg/LEN 50 mg FDC as shown by marginally impacted (~12%-16% higher) BIC exposures relative to the fasted arm.

Table 2. Comparison of Steady State PK Parameters for BIC 75 mg Once Daily Dosing Across Studies

BIC PK Parameter Mean (%CV)	BIC 75 mg + LEN 25 mg (Phase 2 of GS-US-621-6289; N = 26)	BIC 75 mg + LEN 50 mg (Phase 2 of GS-US-621-6289; N = 21)	SS BIC 75 mg Exposures (GS-US-200-4334; TG3; N = 12)[a]	SS BIC 75 mg Exposures (GS-US-141-1475; N = 23)[b]
C_{max} (ng/mL)	9740 (31.3)	9460 (37.3)	10180.0 (42.8)	9344.3 (26.8)
C_{8h}[c] (ng/mL)	7140 (28.4)	6520 (39.0)	—	—
C_{trough} (ng/mL)	4330 (46.9)	4540 (63.5)	4167.8 (48.9)[c]	3508.6 (36.7)[d]
$AUC_{0\text{-}8h}$[c] (h•ng/mL)	64200 (30.6)	59600 (36.9)	72865.9 (31.0)[e]	—
AUC_{tau} (h•ng/mL)	150000 (30.9)	137000 (43.6)	167620.6 (37.6)[c]	139778.8 (27.0)[f]

%CV = percentage coefficient of variation; BIC = bictegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic; SC = subcutaneous; SS = steady state; TAF = tenofovir alafenamide; TG3 = Treatment Group 3

a In this Phase 2 study, treatment naive people with HIV-1 received oral LEN 600 mg on Days 1 and 2, and oral LEN 300 mg on Day 8 in conjunction with oral daily FTC/TAF (200 mg/25 mg) doses from Day 1 onwards for a total of 28 weeks with SC LEN 927 mg dosed on Day 15. At Week 28, maintenance dose of SC LEN 927 mg was given with oral once daily dose of single agent BIC 75 mg from Week 28 onwards, SS BIC PK was sampled at Week 38 from 0-8 hours postdose.

b In this Phase 2 study, single agent BIC 75 mg was dosed orally once daily with FTC/TAF (200 mg/25 mg) and SS BIC PK was sampled at Week 4 or 8 visits from 0-24 hours postdose.

c N = 9.

d N = 21.

e N = 11.

f N = 22.

Table 3. Study GS-US-621-6292: Preliminary PK Parameters of BIC Following Single Dose Coadministration of BIC 75 mg + LEN 25 mg (Reference Arm) Versus BIC 75 mg/LEN 50 mg FDC Under Fasted or Fed Conditions

BIC PK Parameter	BIC+LEN (75 + 25 mg) Coadministration; Fasted (N = 60)	BIC 75 mg/LEN 50 mg FDC; Fasted (N = 60)	FDC vs Coadministration %GLSM (90% CI)	BIC 75 mg/LEN 50 mg FDC; High-Fat Meal (N = 30)	FDC Fed vs Fasted %GLSM (90% CI)
C_{max} (ng/mL)	5790 (29.0)	6580 (22.0)	117 (108, 127)	7580 (20.3)	116 (107, 126)
$AUC_{0\text{-Day 8}}$ (h•ng/mL)	129000 (34.5)	159000 (27.4)	127 (115, 141)	177000 (26.2)	112 (101, 125)
AUC_{inf} (h•ng/mL)	129000 (34.3)	160000 (27.6)	127 (115, 141)	178000 (26.4)	112 (101, 125)
$\%AUC_{exp}$	1.04 (173)	0.787 (42.6)	—	0.585 (59.4)	—
T_{max} (h)	2.00 (2.00, 4.00)	2.00 (1.25, 4.00)	—	2.00 (2.00, 4.00)	—

%CV = percentage coefficient of variation; BIC = bictegravir; CI = confidence interval; FDC = fixed-dose combination; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile
PK parameters are presented as mean (%CV) except T_{max}, which is presented as median (Q1, Q3).

1.4.3. Lenacapavir Dose Selection

Preliminary PK analysis based on intensive PK sampling substudy in Phase 2 of Study GS-US-621-6289 showed that the 50 mg LEN group had nearly dose-proportional higher LEN exposure compared with 25 mg at steady state (mean AUC_{tau} of 2690 and 1460 h•ng/mL, respectively, and mean C_{trough} of 108 and 58.4 ng/mL, respectively, ie, approximately1.84-fold higher AUC_{tau} and approximately 1.85-fold higher C_{trough}) (Table 4). Mean steady state LEN exposures in BIC 75 mg + LEN 50 mg treatment group were comparable to those associated with the same dosing regimen in Cohort 3 of Study GS-US-200-4334 in the HIV-1 treatment naive population (AUC_{tau} of 2759 h•ng/mL and C_{tau} of 113 ng/mL). Overall, the mean steady state LEN C_{trough} values were approximately 3.8- and approximately 7.0-fold of the therapeutic IQ4 threshold of 15.5 ng/mL established for LEN, in the LEN 25 mg and 50 mg groups, respectively, in the Phase 2 portion of Study GS-US-621-6289. LEN exposures exhibit high interindividual variability that could result in lower exposures for some participants in the population for the same dose. This is further illustrated based on data of the Phase 2 portion of Study GS-US-621-6289 in Figure 2, which shows that there are more individuals closer to IQ4 threshold at C_{trough} in the LEN 25 mg group compared with the LEN 50 mg group with an approximately 2.1-fold higher median C_{trough} observed for the higher dose of LEN. In such a scenario, given that the safety profile across the 2 LEN dose levels (25 and 50 mg once daily) are similar up to 24 weeks of dosing, the maintenance dose of LEN 50 mg may afford better coverage of trough concentrations under routine daily dosing as well as any potential missed dose scenarios, to minimize the likelihood of resistance development.

Table 4. Comparison of Steady State PK Parameters for LEN 25 or 50 mg Once Daily Dosing Versus SC LEN Dosing Across Studies

LEN PK Parameter Mean (%CV)	BIC 75 mg + LEN 25 mg QD at SS (Phase 2 of GS-US-621-6289; N = 26)[a]	BIC 75 mg + LEN 50 mg QD at SS (Phase 2 of GS-US-621-6289; N = 21)[a]	SS SC LEN Exposures (GS-US-200-4334; Cohorts 1 and 2; N = 98)[b, c]	SS SC LEN Exposures (GS-US-200-4625; N = 62)[c, d]	LEN 50 mg QD at SS (GS-US-200-4334; Cohort 3; N = 51)[a, c]
C_{max} (ng/mL)	81.7 (99.8)	134 (73.6)	93.1 (61.9)	136.2 (75.2)	116 (60)
C_{8h} (ng/mL)	65.4 (82.9)	117 (80.7)	—	—	—
C_{trough} (ng/mL)	58.4 (76.8)	108 (80.2)	22.5 (63.4)[e]	35.1 (59.2)[e]	113 (61)
$AUC_{0\text{-}8h}$ (h•ng/mL)	501 (79.4)	906 (75.1)	—	—	—
AUC_{tau} (h•ng/mL)	1460 (76.7)	2690 (79.3)	1116 (47.8)[f]	1418 (46.7)[f]	2759 (61)

%CV = percentage coefficient of variation; BIC = bictegravir; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic; PopPK = population pharmacokinetic; QD = once daily; SC = subcutaneous; SS = steady state; TAF = tenofovir alafenamide

a These treatments were administered in conjunction with loading doses of oral LEN 600 mg on Days 1 and 2.

b In this Phase 2 study, treatment naive people with HIV-1 received oral LEN 600 mg on Days 1 and 2, and oral LEN 300 mg on Day 8 in conjunction with oral daily FTC/TAF (200 mg/25 mg) doses from Day 1 onwards for a total of 28 weeks with SC LEN 927 mg dosed on Day 15 to be administered every 26 weeks thereafter.

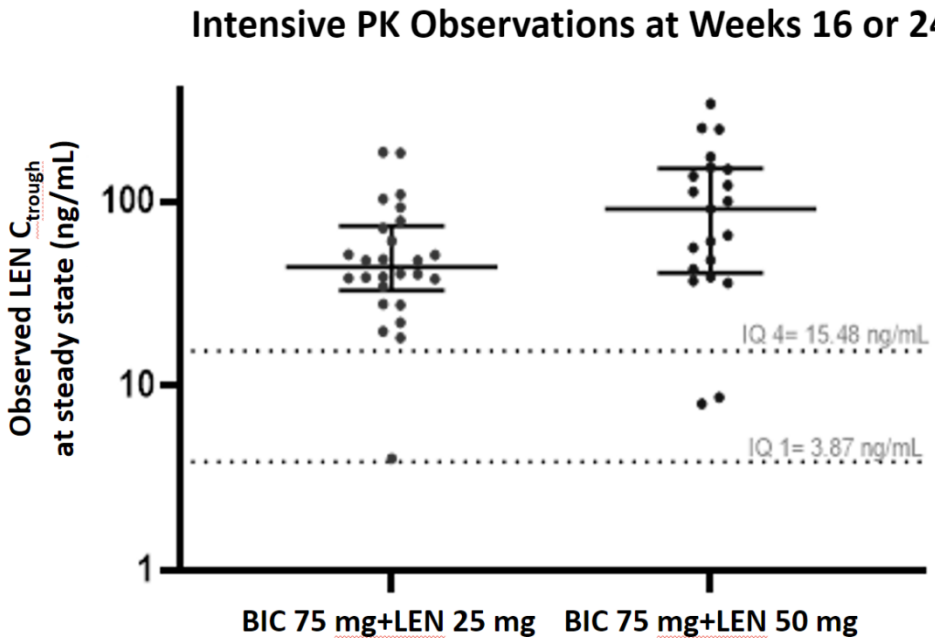
c Bayesian post hoc model parameter estimates derived using the PopPK model developed for the LEN treatment program are presented here

d In this Phase 2/3 study, heavily treatment experienced people with HIV-1 received oral LEN 600 mg on Days 1 and 2, and oral LEN 300 mg on Day 8 with SC LEN 927 mg dosed on Day 15 to be administered every 26 weeks thereafter.

e C_{min} values at Week 28 (Day 196) are presented.

f Average daily AUC values were estimated by dividing $AUC_{0\text{-Week 28}}$ by 196.

Figure 2. **Study GS-US-621-6289: Preliminary Distribution of LEN Trough Concentrations at Steady State (Weeks 16 or 24) Following Once Daily Coadministration of BIC 75 mg + LEN 25 mg (Treatment Group 1; N = 26) or 50 mg (Treatment Group 2; N = 21) Starting From Day 1 With Loading Doses of Oral LEN 600 mg Given on Days 1 and 2 (Intensive PK Substudy Analysis Set)**



BIC = bictegravir; IQ = inhibitory quotient; LEN = lenacapavir; PK = pharmacokinetic; QD = once daily; SC = subcutaneous
The horizontal line represents the median with the whiskers representing the interquartile range, and the dots represent the observed data points for individual participants.

The single dose rBA Study GS-US-621-6292 showed that LEN exposures in the cohort with BIC 75 mg/LEN 50 mg FDC administered in fasted state were nearly dose-proportionally higher than the cohort with BIC 75 mg + LEN 25 mg coadministration in fasted state (Table 5, $AUC_{0\text{-}8\ days}$ 800 vs 329 h•ng/mL), based on preliminary data through Day 8 postdose. This suggests that the 75/50 mg BIC/LEN FDC in Phase 3 would likely achieve similar dose-proportionally higher concentrations of LEN compared to the BIC 75 mg + LEN 25 mg treatment group in Phase 2 portion of Study GS-US-621-6289, ie, similar LEN concentrations as that experienced with the BIC 75 mg + LEN 50 mg treatment group in the Phase 2 portion of Study GS-US-621-6289. Additionally, food effect evaluation conducted with the 75/50 mg BIC/LEN FDC showed that mean LEN exposures were marginally impacted (~20% lower) relative to the fasted arm (mean $AUC_{0\text{-}8\ days}$ 800 vs 937, with %GLSM of 79.6%). Thus, usage of 75/50 mg BIC/LEN FDC in the Phase 3 portion of Study GS-US-621-6289 with dosing irrespective of food status will have high likelihood of replicating the PK/efficacy/safety experience as that observed in the Phase 2 portion of Study GS-US-621-6289 following BIC+LEN coadministration. Furthermore, there is reasonable safety experience with 50 mg once-daily maintenance dosing of LEN (n = 51 in Cohort 3 of Study GS-US-200-4334, n = 52 in the Phase 2 part of Study GS-US-621-6289) in conjunction with a significant safety margin for

higher exposures of LEN established in the LEN development program (thorough QT Study GS-US-200-4332).

Note: Data up to Day 8 postdose are adequate to reasonably indicate the formulation effect as well as food effect quantification for the LEN PK profile, as these effects are expected to impact the bioavailability and absorption lag time, if at all, and not the clearance of LEN and thus changes in the early part of PK profile will be indicative of these effects in the single dose rBA Study GS-US-621-6292.

Table 5. Study GS-US-621-6292: Preliminary Pharmacokinetic Parameters of LEN Following Single Dose Coadministration of BIC 75 mg + LEN 25 mg (Reference Arm) Versus BIC 75 mg/LEN 50 mg FDC Under Fasted or Fed Conditions

LEN PK Parameter	BIC+LEN (75 + 25 mg) Coadministration; Fasted (N = 60)	BIC 75 mg/ LEN 50 mg FDC; Fasted (N = 60)	FDC vs Coadministration %GLSM (90% CI)	BIC 75 mg/ LEN 50 mg FDC; High-Fat Meal (N = 30)	FDC Fasted vs Fed %GLSM (90% CI)
C_{max} (ng/mL)	3.66 (57.7)	7.39 (61.4)	200 (164, 243)	9.35 (212)	85.9 (67.4, 109)
$AUC_{0\text{-Day }8}$ (h•ng/mL)	329 (62.0)	800 (60.4)	241 (199, 292)	937 (205)	79.6 (62.3, 102)
T_{max} (h)	4.00 (4.00, 6.00)	4.00 (4.00, 4.00)	—	4.00 (4.00, 8.00)	—

%CV = percentage coefficient of variation; BIC = bictegravir; CI = confidence interval; FDC = fixed-dose combination; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, which is presented as median (Q1, Q3).

Overall, based on the totality of data from the Phase 2 portion of Study GS-US-621-6289 and multiple cohorts/formulations evaluated in rBA Study GS-US-621-6292, the BIC 75 mg/LEN 50 mg FDC would be expected to provide reasonable operating characteristics with respect to considerations of PK, efficacy, safety, including better coverage for efficacious exposures in the setting of high LEN interindividual variability, and any potential for missed doses with a chronic once-daily regimen.

1.5. Rationale for Allowing Pregnant People to Remain on Study Drug

Traditionally, pregnant and lactating people have been systematically excluded from clinical research of new HIV treatment options. This exclusion leads to significant delays in access to next-generation treatment options, potentially leading to worse health outcomes for pregnant and lactating people and their offspring. Substantial need exists for more information from studies to guide the use of ARVs in pregnant people.

These challenges have led clinicians, ethicists and community advocates from the World Health Organization (WHO), the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), and the International AIDS Society and the Pregnancy and the International AIDS Society's Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) to develop and adopt a framework for accelerating inclusion of pregnant and breastfeeding people in prelicensure clinical studies, with a goal to have PK and preliminary safety data on all new HIV agents in pregnancy available at the time of drug approval. This framework calls for stakeholders involved in studying ARV agents for treatment and prevention of HIV to support greater inclusion of pregnant people and breastfeeding and contribute to a more equitable investigation of new HIV agents {World Health Organization (WHO) 2022}.

Clinical data on LEN in pregnancy are limited. Data available on BIC in pregnant people indicate no adverse effect on embryo-fetal development. Data from nonclinical toxicity studies of BIC and LEN have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicates that BIC and LEN are not expected to reduce the clinical efficacy of hormonal contraception.

In animal studies, BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, without effects on nursing pups. After administration to rats during pregnancy, LEN was detected at low levels in the plasma of nursing rat pups, without effects on these nursing pups. It is not known if BIC or LEN are secreted in human breast milk.

For these reasons, it is appropriate to allow people who become pregnant during the study to remain on study drug after discussion of potential risks and benefits and provision of additional informed consent.

Refer to the BIC/LEN IB for additional information on pregnancy and lactation.

1.6. Benefit-Risk Assessment for the Study

Potential risks associated with the study include the occurrence of AEs associated with each of the study drugs BIC and LEN. Adverse drug reactions (ADRs) are those deemed by the sponsor to be causally related to study drug. No events have been identified as ADRs in clinical studies that evaluated BIC as a single agent. BIC is a component of the marketed product Biktarvy (B/F/TAF); ADRs identified for B/F/TAF include abdominal pain, diarrhea, dyspepsia, flatulence, nausea, vomiting, fatigue, headache, angioedema, rash, Stevens-Johnson syndrome, and urticaria. Nausea has been identified as an ADR for LEN. Other potential risks include the unknown occurrence of AEs associated with the novel combination of BIC/LEN, and general risks associated with frequent clinic visits and laboratory blood draws. Strategies to mitigate these risks include close monitoring of laboratory values and AEs. Parameters for monitoring of AEs will be well defined and closely followed.

In addition, potential risks to people with HIV-1 include virologic breakthrough with exposure to subtherapeutic concentrations of BIC or LEN, or unrecognized preexisting resistance to BIC and/or LEN. These risks could lead to development of resistance to either BIC, LEN, or both. Strategies to mitigate these risks include frequent assessments of plasma HIV-1 RNA levels to ensure that virologic breakthrough is rapidly identified, thus limiting the time during which drug resistance mutations could emerge.

Risks for participants who choose to continue study drug during pregnancy may include the potential for lower drug levels which could lead to loss of virologic control and the potential for vertical transmission to the child. Additionally, there are limited data on the efficacy of 2-drug regimens in pregnancy; alternative ARVs should be carefully considered during pregnancy. The risk of lack of efficacy during pregnancy may be mitigated by frequent HIV-1 RNA monitoring. Data from nonclinical toxicity studies of BIC and LEN have demonstrated no adverse effect on fertility or embryo-fetal development. However, clinical data on LEN during pregnancy are limited therefore, the risk of AEs in infants resulting from in utero exposure to LEN is unknown.

Although the benefits of breastfeeding are well described, there is still the risk of HIV transmission to the infant when people with HIV-1 breastfeed. The risk is low (< 1%) with consistent sustained virologic suppression. An infant who acquires HIV while breastfeeding may also be at risk for developing ARV drug resistance due to subtherapeutic drug levels in breast milk. Additionally, there is the risk of infants who are breastfed being exposed to study drugs via breastmilk and experiencing unknown AEs. Participant-centered and evidence-based counseling on infant feeding options should be discussed with the participant to allow for shared decision-making. In participants who chose to breastfeed, HIV transmission to the infant can be mitigated by frequent HIV-1 RNA monitoring.

Benefits to pregnant participants include continued access during pregnancy to a regimen the participant is currently tolerating, and contributing to understanding of pregnancy data for BIC/LEN or B/F/TAF. Potential benefits of BIC/LEN may include provision of a new STR that may have fewer side effects than alternative therapies. BIC/LEN may also be the only STR option for patients who are virologically suppressed and have had history of resistance, intolerance or contraindication to existing STRs, and who may be taking complex ART regimens with higher risk of inadequate adherence and subsequent emergence of resistance. Participants will also be contributing to an understanding of the safety, tolerability, and PK of a novel ARV treatment regimen, thus contributing to the development of an ART with novel mechanisms of action with potential applications for HIV-1 treatment.

An unanticipated event such as a disaster or public health emergency may pose additional risks to study drug availability, the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.4 for further details on the risks and risk mitigation strategy.

Considering the above, the benefit-risk balance for this study is considered positive.

2. OBJECTIVES AND ENDPOINTS

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

See Appendix 11.8.2 for EU-specific exploratory objectives and endpoints.

3. STUDY DESIGN

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

3.1. Study Design Overview

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

Blinded Phase

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

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

Randomization will be stratified by geographic region.

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

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

Open-label Phase

After completion of the Week 48 safety and efficacy data analysis, all participants will attend an EBT visit at the next in-clinic visit (preferably within 12 weeks).

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

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

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

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

Participants from Treatment Group 2 who enter the OL phase will receive a 2-day oral loading dose of LEN 600 mg for 2 days (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily BIC/LEN FDC tablet starting on Day 1 of the OL phase. Following the Day 1 visit, participants will be required to return for the study visit on Day 2 (option to conduct this as a virtual visit will be available, as appropriate) and will attend a Week 4 visit during the OL phase. If a virtual visit is not available, Day 2 of the oral loading dose will be administered at the clinic.

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

3.2. Duration of Intervention

Participants will be treated for at least 48 weeks during the blinded phase; participants from Treatment Group 1 will be treated with BIC/LEN FDC tablets for at least 96 weeks, including the blinded and OL phases, up to OL Week 48.

After blinded Week 48, all participants will continue to take their blinded study drug and attend visits every 12 weeks. Once the last participant completes the Week 48 visit and the analysis of safety and efficacy data of BIC/LEN FDC compared with B/F/TAF FDC is completed, all participants will attend an EBT visit at the next in-clinic visit (preferably within 12 weeks).

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

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

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

3.2.1. Poststudy Care

After each participant in Treatment Group 1 completes the OL Week 48 visit, and after the EBT visit for participants in Treatment Group 2, participants will be given the option to continue or begin (as applicable) BIC/LEN FDC dosing during the OL phase until the drug is available, or until Gilead elects to discontinue the study, whichever occurs first. After the participant has completed/terminated the participation in the study, long-term care of the participant will remain the responsibility of the primary treating physician.

If Gilead discontinues development of the study drug, further provision of study drug to the participants may be discontinued, independent of treatment effect.

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participant

3.3.1.1. Criteria for Early Discontinuation for the Individual Participant From Study Intervention

Study interventions will be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the participant may resume study dosing at the discretion of the investigator.
- An AE that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of the AE, the participant may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity, as defined in Section 7.7, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest.
- Lack of efficacy.
- Participant request to discontinue for any reason (see Section 3.3.1.1.1).
- Participant noncompliance.
- Loss to follow-up (see Section 3.3.3).
- Investigator decision.
- Discontinuation of the study at the request of Gilead, regulatory agency, an institutional review board (IRB), or independent ethics committee (IEC).
- Disaster or public health emergency (Appendix 11.4 provides information on risk assessment and mitigation that may allow continued participation).

3.3.1.1.1. Partial Withdrawal

Participants may decide to partially withdraw from the study (eg, discontinue from study intervention and/or procedures but agree to continue to be followed for study endpoints [eg, overall survival]). Such partial withdrawals should be fully documented.

3.3.1.2. Criteria for Early Discontinuation for the Individual Participant From the Study

The participant will be discontinued from the study early in the following instances:

- Participant request to discontinue for any reason (see Section 3.3.1.1.1).
- Withdrawal of consent.
- Death.
- Investigator decision to remove participant from the study.
- Loss to follow-up (see Section 3.3.3).
- Discontinuation of the study at the request of Gilead, regulatory agency, an IRB or IEC.
- Disaster or public health emergency (Appendix 11.4 provides information on risk assessment and mitigation that may allow continued participation).

3.3.2. Criteria for Early Discontinuation of the Study

The study will be discontinued in the following instance:

- Discontinuation of the study at the request of Gilead, regulatory agency, an IRB, or IEC.

3.3.3. Loss to Follow-up

Should the participant fail to attend a scheduled protocol-specified visit (eg, in-person, telephone, or virtual), sites will need to make at least 3 attempts separated by at least 2-week intervals by a combination of telephone and certified (where possible) mail to contact the participant. Sites must document all attempts to contact the participant. If no response is received after 3 attempts are made to contact a participant after the first missed outpatient visit, the participant will be considered lost to follow-up and no additional contact will be required.

3.4. Definitions for Primary Analysis Completion and End-of-Study Dates

3.4.1. Primary Analysis Completion Date

The primary analysis completion date is the date when the last participant receives a protocol-specified procedure or assessment for the purposes of final collection of data for the primary endpoint analysis.

3.4.2. End-of-Study Date

The end of this study will be the date of the last participant's last observation (or visit) for all the protocol-specified procedures or assessments, including any follow-up procedures or assessments.

3.5. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, participant charts, central and local laboratory, Interactive Response Technology [IRT], and specialty laboratory [eg, for PK data]). Electronic data capture (EDC) is not considered source data.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 546 participants in total: 364 participants in Treatment Group 1, and 182 in Treatment Group 2. The collection of race and ethnicity information allows for the analysis and reporting of study data by demographic subgroups as required by certain health authorities.

4.1.1. Participant Replacement

Participants who discontinue before the end of the study will not be replaced.

4.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Willing and able to provide written informed consent prior to performing study procedures.

2) Aged ≥ 18 years at screening.

3) Currently receiving B/F/TAF for at least 6 months prior to screening.

4) If plasma HIV-1 RNA measurements in the last 6 months prior to screening are available, all levels must be < 50 copies/mL.

5) At least one documented HIV-1 RNA level measured between 6 and 12 months (± 2 months) prior to screening. This and any other HIV-1 RNA measurements documented in this period must be < 50 copies/mL.

6) Plasma HIV-1 RNA levels < 50 copies/mL at screening.

7) No documented or suspected resistance to BIC (including INSTI-R mutations T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene).

8) No documented or suspected resistance to tenofovir alafenamide (TAF; mutations K65R, K65N, K70E, Q151M or T69 insertion, or ≥ 3 of the following thymidine analog mutations [M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R] in the reverse transcriptase gene).

9) Estimated glomerular filtration rate ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance (CL_{cr}) {Cockcroft 1976}.

See Appendix 11.8.1 and 11.8.2 for additional inclusion criteria for Argentina and the EU, respectively.

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Positive serum pregnancy test or pregnant at screening or a positive pregnancy test prior to Day 1 randomization (Appendix 11.5).

2) Breastfeeding (nursing).

3) Prior use of, or exposure to, LEN.

4) Active, serious infections (other than HIV-1) requiring parenteral therapy < 30 days prior to randomization.

5) Active tuberculosis infection.

6) Acute hepatitis < 30 days before randomization.

7) Chronic hepatitis B virus (HBV) infection, as determined by either:

   a) Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit.

   b) Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit.

8) Known hypersensitivity to the study drug, its metabolites, or any formulation excipient.

9) History of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, or variceal bleeding).

10) Abnormal electrocardiogram (ECG) at the screening visit that is clinically significant as determined by the investigator.

11) Active malignancy requiring acute systemic therapy.

12) Any of the following laboratory values at screening:

   a) Alanine aminotransferase > 5 × upper limit of normal (ULN).

   b) Direct bilirubin > 1.5 × ULN.

   c) Platelets < 50,000/mm^3.

   d) Hemoglobin < 8.0 g/dL.

13) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.3.

14) Participation or planned participation in any other clinical study (including observational studies) without prior approval from the sponsor.

15) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements.

16) Participants under guardianship, curatorship, or legal protection may not participate in the study.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Randomization, Blinding, and Treatment Code Access

5.1.1. Randomization

Participants will be assigned a screening number in the IRT system at the time of consent.

Randomization and Day 1 visit must not occur until participant eligibility has been confirmed.

Once eligibility has been confirmed, the investigator or designee will randomize the participant using the IRT system. Once a participant number has been assigned to a participant, it will not be reassigned to any other participants. The participant number assignment and randomization may be performed up to 3 days prior to Day 1 visit provided all screening procedures have been completed and participant eligibility criteria has been confirmed.

Participants who meet eligibility criteria will be randomized in a 2:1 ratio to Treatment Groups 1 and 2.

Randomization will be stratified by geographic region.

5.1.2. Blinding

During the blinded phase, participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Study personnel who may be unblinded because of the nature of their function or study role without additional documentation, as specified in Gilead procedural documents, include the following:

- Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in an IRT for purposes of study drug inventory management.
- Individuals in Patient Safety (PS) who review individual case data and/or group-level summaries contained within the safety database when they are involved in activities such as aggregate report generation, signal management, or expedited reporting of suspected unexpected serious adverse reactions (SUSARs).
- Individuals who are involved in bioanalytical/biomarker data transfer and sample/assay review.
    - The Bioanalytical File Administrator in either Bioanalytical Lab Clinical Data Management or Biomarker and Bioanalytical Operations who facilitates the transfer of bioanalytical (eg, PK) files between Gilead and bioanalytical laboratories.

  - Bioanalytical Chemistry scientists who monitor the development, validation, and performance of bioanalytical assays.
  - The personnel in bioanalytical laboratories involved in sample receipt, analysis, data review, and data transfer.
  - Personnel (eg, Biomarker Sciences) not serving on the study management team who review assay results for samples collected per the study procedures.

- Regulatory Quality and Medical Governance personnel in Research and Development (R&D Q&MG) not serving on the study management team to support Quality Assurance activities and/or regulatory agency inspections.
- Biostatisticians and programmers employed by contract research organizations who develop datasets and outputs for purposes such as development of randomization schedule and data monitoring committee (DMC).
- Designated Gilead personnel from Clinical Development, Clinical Virology, and Clinical Operations, not serving on the study management team, will manage communication with investigators for resistance analyses results in participants who meet criteria for resistance evaluation.

Clinical site personnel and participants will remain blinded until the EBT visit. For the purpose of population PK modeling to support the regulatory submissions, an independent Clinical Pharmacology team (or vendor) may have access to individual participants' PK and relevant data for modeling while remaining blinded to participant identification until the primary analysis of efficacy and safety. Sponsor personnel involved in performing and reviewing results of the Week 48 analysis will be unblinded after the Week 48 database finalization. All sponsor personnel who have access to unblinded information will maintain the confidentiality of unblinded information stored in the restricted area as specified in the sponsor procedural documents.

5.1.3. Procedures for Breaking the Blind on Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain the participant's treatment assignment directly from the IRT for that participant. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in any case of treatment unblinding.

Blinding of study drug is critical to the integrity of this clinical study. Therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study drug discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

5.2. Description and Handling of Bictegravir/Emtricitabine/Tenofovir Alafenamide, Lenacapavir, and Bictegravir/Lenacapavir Study Drugs and Placebo-to-Match Tablets

5.2.1. Bictegravir/Emtricitabine/Tenofovir Alafenamide and Placebo-to-Match Tablets

5.2.1.1. Formulation

B/F/TAF tablets are available as 50/200/25 mg strength FDC tablets. B/F/TAF FDC tablets are capsule shaped, film-coated, purplish-brown tablets, debossed with "GSI" on one side of the tablet and "9883" on the other side of the tablet. In addition to the active ingredients, B/F/TAF FDC tablets contain microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, and iron oxide black.

Placebo-to-match B/F/TAF tablets are identical in size, shape, color, and appearance to the corresponding active B/F/TAF FDC tablets. Placebo-to-match B/F/TAF tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, and iron oxide black.

5.2.1.2. Packaging and Labeling

B/F/TAF FDC tablets and PTM B/F/TAF tablets are packaged in white, high-density polyethylene (HDPE) bottles with silica gel desiccant and polyester coil in each bottle. Each bottle is capped with a white, continuous-thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to study sites in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice—Annex 13 (Investigational Medicinal Products) for Common Technical Document (CTD), or Annex 6 for Clinical Trail Regulation (CTR), as applicable, and/or other local regulations.

5.2.1.3. Storage and Handling

B/F/TAF FDC tablets and PTM B/F/TAF tablets should be stored at 25 °C (excursions permitted 15 °C to 30 °C). Storage conditions are indicated on the label.

B/F/TAF FDC tablets should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of B/F/TAF FDC tablets and proper identification, the drug product should not be stored in a container other than the container in which it is supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study drug should be disposed of in accordance with local requirements.

5.2.2. Lenacapavir Tablets and Placebo-to-Match Tablets

5.2.2.1. Formulation

LEN tablets are available as 300 mg strength tablets. LEN tablets are capsule-shaped, film-coated, beige tablets, debossed with "GSI" on one side of the tablet and "62L" on the other side of the tablet. In addition to the active ingredient, LEN tablets contain copovidone, poloxamer 407, mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide black, and iron oxide red.

Placebo-to-match LEN tablets are identical in size, shape, color, and appearance to the corresponding active LEN tablets. Placebo-to-match LEN tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide black, and iron oxide red.

5.2.2.2. Packaging and Labeling

LEN tablets and PTM LEN tablets are packaged in white, HDPE bottles with silica gel desiccant and polyester coil in each bottle. Each bottle is capped with a white, continuous-thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to study sites in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice—Annex 13 (Investigational Medicinal Products) for CTD, or Annex 6 for CTR, as applicable, and/or other local regulations.

5.2.2.3. Storage and Handling

LEN tablets and PTM LEN tablets should be stored below 30 °C. Storage conditions are indicated on the label.

LEN tablets should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of LEN tablets and proper identification, the drug product should not be stored in a container other than the container in which it is supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study drug should be disposed of in accordance with local requirements.

5.2.3. Bictegravir/Lenacapavir FDC Tablets and Placebo-to-Match Tablets

5.2.3.1. Formulation

BIC/LEN FDC tablets are available as BIC/LEN 75/50 mg strength FDC tablets. BIC/LEN FDC tablets are capsule shaped, film-coated, yellow tablets, debossed with "GSI" on one side of the tablet and "B/L" on the other side of the tablet. In addition to the active ingredients, BIC/LEN FDC tablets contain copovidone, poloxamer 407, mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxide yellow.

Placebo-to-match BIC/LEN tablets are identical in size, shape, color, and appearance to the corresponding active BIC/LEN FDC tablets. Placebo-to-match BIC/LEN tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxide yellow.

5.2.3.2. Packaging and Labeling

BIC/LEN FDC tablets and PTM BIC/LEN tablets are packaged in white, HDPE bottles with silica gel desiccant in each bottle. Each bottle will be capped with a white, continuous-thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to study sites in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice—Annex 13 (Investigational Medicinal Products) for CTD, or Annex 6 for CTR, as applicable, and/or other local regulations.

5.2.3.3. Storage and Handling

BIC/LEN FDC tablets and PTM BIC/LEN tablets should be stored below 30 C. Storage conditions will be indicated on the label.

BIC/LEN FDC tablets should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of BIC/LEN FDC tablets and proper identification, the drug product should not be stored in a container other than the container in which it is supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study drug should be disposed of in accordance with local requirements.

5.3. Prior and Concomitant Medications

5.3.1. Prior and Concomitant Medications That Are Prohibited or To Be Used With Caution

Medications in Table 6 are prohibited or should be used with caution by all participants in the blinded phase (until the EBT visit), and participants taking BIC/LEN FDC in the OL phase. Additionally, the investigator should follow the local prescribing information for B/F/TAF until the EBT visit. Should participants have a need to initiate treatment with any prohibited concomitant medication, the Gilead medical monitor must be consulted, and approval granted before initiation of the new medication. In instances where a prohibited medication is initiated before discussion with the Gilead medical monitor, the investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

Table 6. Examples of Prior and Concomitant Medications That Are Prohibited or to be Used With Caution With BIC/LEN FDC Because of the Potential for Pharmacokinetic Drug-Drug Interaction or Impact on Efficacy Assessments or Participant Safety[a]

Medication Class[a]	Use Discouraged and To Be Used With Caution[b]	Prohibited Medications[c]
Acid reducing agents Antacids Buffered medications	Concentration of study drug may decrease with antacids. Administer study drug with or without food at least 2 hours before or 2 hours after taking antacids containing aluminum, magnesium, calcium, and/or iron (eg, Tums® or Rolaids®); the ulcer medication sucralfate (Carafate®); or vitamins or mineral supplements that contain calcium, iron, and/or zinc. Study drug and medications or oral supplements containing calcium, iron, and/or zinc can be taken together with food at any time In pregnant participants: for antacids containing aluminum and/or magnesium: study drug can be taken at least 2 hours before or 6 hours after antacids containing aluminum and/or magnesium regardless of food intake. For supplements or antacids containing calcium, iron, and/or zinc: study drug and supplements or antacids containing calcium, iron, and/or zinc can be taken together with food at any time; but when taken on an empty stomach, study drug should be taken at least 2 hours before or 6 hours after supplements or antacids containing calcium, iron, and/or zinc.	—
Antiarrhythmic agents	—	Dofetilide
Anticoagulants	Dabigatran etexilate: monitoring and/or dose reduction may be needed for certain populations[d]	—
Anticonvulsants	—	Phenobarbital, phenytoin, carbamazepine, oxcarbazepine
Antimycobacterials	—	Rifampin, rifabutin, rifapentine
Antiretrovirals	—	Any antiretroviral drug that is not part of the study treatment regimen
Digoxin	Digoxin: Concomitant use may result in increased levels of digoxin; use with caution and with appropriate monitoring of serum digoxin levels	—

Medication Class[a]	Use Discouraged and To Be Used With Caution[b]	Prohibited Medications[c]
Ergot derivatives	—	Ergotamine, ergonovine, dihydroergotamine, methylergonovine, ergometrine
GI motility agents	Cisapride (consider staggering cisapride dosing by ~12 hours relative to study drug dosing)	—
Herbal/natural supplements	—	St John's wort, echinacea, milk thistle (ie, silymarin), chinese herb sho-saiko-to (or xiao-shai-hu-tang)
HMG-CoA reductase inhibitors	Concentrations of statins may increase with LEN. Start with the lowest dose and titrate to clinical response. For each of the following statins, the maximum allowed dose is: Simvastatin: 10 mg Lovastatin: 20 mg Atorvastatin: 40 mg Careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis	—
Oral hypoglycemic agents	Metformin: refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of the study drug and metformin[e]	—
PDE-5 inhibitors	Concentrations of PDE-5 inhibitors may increase with study drug. Sildenafil, vardenafil, tadalafil: It is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered	—
Sedatives/hypnotics	Midazolam, triazolam, alprazolam	—
Systemic corticosteroids	Concomitant use may increase corticosteroid exposure. Limit use to 7 days or less	Use of all systemic corticosteroids for greater than 7 days

BIC = bictegravir; DDI = drug-drug interaction; eGFR = estimated glomerular filtration rate; FDC = fixed-dose combination; GI = gastrointestinal; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LEN = lenacapavir; PDE-5 = phosphodiesterase-5

a This table represents examples of the most common concomitant medications and is not meant to be exhaustive. If the investigator is unsure if a medication is allowed per protocol, he/she should consult with the sponsor.

b Administration of these medications are discouraged and should be done with caution (with consideration of dose reduction, as applicable) for the duration of the study.

c Administration of any of the above medications must be discontinued at least 30 days prior to Day 1 visit and for the duration of the study.

d Dose adjustment for dabigatran etexilate may be warranted based on the eGFR status (refer to the prescribing information for additional details).

e Metformin exposure (AUC) was increased by 39% when coadministered with BIC in DDI studies.

5.3.2. Concomitant Administration of COVID-19 Vaccines and Study Drugs

There are no substantial safety data regarding the concomitant administration of the COVID-19 vaccines and BIC/LEN FDC. Participants are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the participant is on the study. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drug(s).

5.4. Dosage and Administration

Blinded Phase

Treatment Group 1: Participants will switch from B/F/TAF FDC tablets to BIC/LEN (75/50 mg) FDC tablets, once daily, orally; and PTM B/F/TAF tablets, once daily, orally.

Participants randomized to Treatment Group 1 will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN tablets on Day 1 and on Day 2), in addition to the daily doses of BIC/LEN FDC starting on Day 1. All study drugs will be administered without regard to food.

Treatment Group 2: Participants will continue on B/F/TAF FDC tablets, once daily, orally; and start PTM BIC/LEN tablets, once daily, orally on Day 1.

Participants randomized to Treatment Group 2 will receive PTM LEN tablets for 2 days (2 PTM LEN tablets on Day 1 and on Day 2), in addition to the daily dose of B/F/TAF FDC starting on Day 1. All study drugs will be administered without regard to food.

Open-label Phase

Participants from Treatment Groups 1 and 2 enrolled in the OL phase will receive BIC/LEN (75/50 mg) FDC tablets, once daily, orally, without regard to food.

Participants from Treatment Group 2 enrolled in the OL phase will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN tablets on Day 1 and on Day 2, without regard to food), in addition to the daily BIC/LEN FDC tablet starting on Day 1 of the OL phase.

5.4.1. Missed Dose Recommendations for Study Drugs

If a participant misses the scheduled daily dose(s) of the study drugs, recommendations for restarting the treatment are summarized below in Table 7.

Table 7. Missed Daily Dose Recommendation for Study Drugs

Number of Days Since Missed Scheduled Daily Dose	Recommendation
1 to 7 days (1 to 7 missed daily doses)	Take study drug orally as soon as possible. Then resume normal schedule by taking study drug the next day and daily thereafter.
More than 7 days (more than 7 consecutive missed daily doses)[a]	Reload by dosing the 2-day oral loading dose (2 × 300 mg LEN on Day 1 and on Day 2, or 2 PTM LEN tablets on Day 1, and 2 PTM LEN tablets on Day 2, as applicable, of treatment reinitiation from reloading bottles specified by the IRT system)[b] in addition to restarting the normal schedule of dosing by taking study drug on Day 1 of treatment reinitiation and daily thereafter.

IRT = Interactive Response Technology; LEN = lenacapavir; PTM = placebo-to-match
a Participants will be asked to come to the clinic for a scheduled or unscheduled blood draw before treatment reinitiation.
b Administration of the first dose on Day 1 of treatment reinitiation will occur on-site; on Day 2 of treatment reinitiation, participants will be given the option to self-administer via a virtual visit to observe/confirm dosing (the Day 2 visit may occur on-site if a participant is unable to conduct a virtual visit).

5.5. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to participants must be returned to the site.

Each investigational site must keep accountability records that capture:

- The date received, quantity, and condition of study drug bottles.
- The date, participant number, and the quantity of study drug bottles dispensed.
- The date, quantity of used and unused study drug bottles returned, along with the initials of the person recording the information.

5.5.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drugs, which includes bottles, be destroyed at the site. If the site has an appropriate standard operating procedure for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug bottles in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If the study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drugs. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be provided to Gilead.

If the site does not have an appropriate standard operating procedure for study drug destruction, used and unused study drugs are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant screened or enrolled in the study are presented in tabular form in Table 1 and described in the sections below.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any study-related procedures. Refer to Section 9.1.3 for further information regarding informed consent.

6.2. Screening, Participant Enrollment, and Treatment Assignment

Participants will be screened within 30 days before enrollment in the study. Screening window can be extended to 45 days with sponsor approval. Each participant will be assigned a unique screening number using an IRT. Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for randomization into the study on Day 1. HIV-1 RNA test cannot be repeated at screening. It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study. The medical monitor may be contacted regarding any questions related to eligibility.

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.3. Instructions for Study Procedures

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-required procedures, on the AE electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After study drug administration, report all AEs and SAEs. See Section 7 for additional details.

6.3.2. Medical History and Demography

Medical history and demographic information are to be collected for each participant at screening as follows:

- Review medical history including disease-specific history, disease-related events, available historical genotype/phenotype reports, available disease treatment history, substance (ie, illicit drug, tobacco) use, and medications taken within 30 days of the screening visit.
- Review past medical history of comorbid conditions (ie, hypertension, diabetes, chronic kidney disease).
- Obtain demographic information, including sex at birth, sexual orientation, and gender identity.
- Investigators are asked to document prior resistance data from available HIV-1 genotype and/or phenotype reports.

6.3.3. Concomitant Medications

Review of concomitant medications will occur at the time points presented in Table 1. Further information about concomitant medications is provided in Sections 4.3 and 5.3.

6.3.4. Physical Examination

Physical examinations conducted, will be complete or symptom directed. Refer to Table 1.

6.3.5. Electrocardiograms

Resting 12-lead ECGs will be obtained for all participants according to Table 1. The ECG should be obtained after the participant has been resting in the supine position for at least 5 minutes and will include heart rate, respiratory rate interval, QRS, uncorrected QT, QT, QT interval corrected for heart rate (QTc), morphology, and rhythm analysis. Electrocardiograms will be interpreted by the investigator for clinical significance, and results will be entered into the eCRF.

6.3.6. Vital Signs

Vital signs will be recorded as outlined in Table 1. Vital signs include blood pressure, heart rate, respiratory rate, body temperature, and weight. Vital signs will be obtained and recorded after the participant has been resting for at least 5 minutes.

6.3.7. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined in Table 1. See Table 8 for a summary of the laboratory analytes.

The laboratory analyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes. The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Blood samples will be collected by venipuncture in the arm according to Table 1. In addition, urine samples for the clinical laboratory assessment will be collected according to Table 1. Participants only need to be fasted on days where lipid or fasting glucose profiling is scheduled. Fasting is defined as 8 hours without food or drink (except water) prior to laboratory draw.

More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator. Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days, with the exception of creatinine, which should be retested 7 to 14 days apart) after the investigator has consulted with the Gilead medical monitor (or designee). A decision regarding participant discontinuation should be made after the results from the retest are available (see Section 3.3 for additional information).

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

Table 8. Laboratory Analytes

Safety Laboratory Measurements				Other Laboratory Measurements
Chemistry (Serum or Plasma)	**Metabolic Assessments**	**Hematology**	**Urinalysis**	
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or urea Creatinine[a] Creatine kinase Creatinine clearance Uric acid Total bilirubin Direct bilirubin Indirect bilirubin AST ALT Alkaline phosphatase TSH Hemoglobin A1c Lactic acid dehydrogenase Amylase Lipase	Fasting Glucose Direct LDL HDL Total cholesterol Triglycerides	Hemoglobin Hematocrit Platelets RBC WBC total WBC differential Neutrophils (Absolute and %) Eosinophils (Absolute and %) Basophils (Absolute and %) Lymphocytes (Absolute and %) Monocytes (Absolute and %) Reticulocytes (%) MCV	Color and clarity Specific gravity pH Glucose Protein Blood and microscopic Pregnancy test[b]	Serum pregnancy test[b] Plasma HIV-1 RNA CD4 cell count HBV blood panel: HBcAb, HBsAg, and HBsAb Plasma HBV DNA[c] Plasma storage samples Plasma storage sample for potential HIV-1 genotype/phenotype Whole blood for potential proviral DNA sequencing[d] Sparse PK

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIC = bictegravir; BUN = blood urea nitrogen; CD4 = clusters of differentiation 4;DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; LEN = lenacapavir; MCV = mean corpuscular volume; PK = pharmacokinetic; RBC = red blood cell; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WBC = white blood cell

a Creatinine clearance to be calculated according to the Cockcroft-Gault formula for creatinine clearance: male: [(140 − age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] = CL_{cr} (mL/min); female: [(140 − age in years) × (weight in kg) × 0.85]/[72 × (serum creatinine in mg/dL)] = CL_{cr} (mL/min).
b For participants assigned female at birth of childbearing potential only.
c Participants who are HBsAg positive will have a plasma HBV DNA test performed.
d Whole blood storage sample will be collected for all participants at Day 1. Proviral DNA sequencing will be performed in cases of virologic failure to evaluate the presence of mutations prior to BIC/LEN treatment (research use only). This test does not require optional future research consent.

6.3.8. Virtual Visits

Blinded Phase

All participants may have a virtual visit on Day 2 and will be required to self-administer the loading dose of LEN 600 mg (2 × 300 mg) or PTM LEN tablets (2 tablets) orally during the visit. The site will confirm dosing by observing the participants during the visit and document this in the source documentation. The virtual visit may be conducted as a video conference or a video call to ensure the required dose has been appropriately administered.

The Day 2 visit will be performed in the clinic when site or participant is not able to conduct a virtual visit.

A review of AEs and changes in concomitant medications is to be performed and documented by the site in the source documentation.

Open-label Phase

Participants in Treatment Group 2 may have a virtual visit on Day 2 of the OL phase and will be required to self-administer the loading dose of LEN 600 mg (2 × 300 mg) orally during the visit. The site will confirm dosing by observing participants during the visit and document this in the source documentation. The virtual visit may be conducted as a video conference or a video call to ensure the required dose has been appropriately administered.

The Day 2 visit will be performed in the clinic when site or participant is not able to conduct a virtual visit.

A review of AEs and changes in concomitant medications is to be performed and documented by the site in the source documentation.

Investigators may perform a virtual or a phone call visit between 2 in-clinic visits and/or when the visits are 12 weeks apart to remind participants of dosing diary completion and of upcoming study visits. Any such visit will be documented in the source documentation.

6.3.9. Pharmacokinetics

Sparse PK blood samples will be collected at on-treatment study visits from all participants in the blinded phase until the Week 48 visit. Following the Week 48 visit, additional sparse PK samples will be collected from participants who become pregnant and provide reconsent to

remain on study until the EBT visit, and during the OL phase at the time points specified in Table 1. Additionally, stored plasma samples at all available time points may be used for PK analysis (as appropriate).

6.3.10. Clinical Virology

6.3.10.1. Virology Testing

6.3.10.1.1. Virology Samples to Address the Study Objectives

Whole blood and plasma samples will be collected from all participants who have provided consent for this study to assess HIV-1 RNA viral load at the time points specified in Table 1, including potential HIV-1 viral load retesting. Whole blood and plasma samples may be used to assess HIV-1 genotype at baseline and HIV-1 genotype and phenotype in confirmed cases of virologic failure as defined in Section 6.3.10.2.

6.3.10.1.2. Virology Samples for Optional Future Research

The remainder of already-collected virology samples may be used for possible future optional research including virology-related testing, PK assessments, and evaluation of biomarker assays. The specimens collected for optional future research may be used to advance development of the study drug and/or increase our knowledge and understanding of the biology of the disease under investigation and related diseases. These stored samples may be used by the sponsor or its research partners for viral genotyping/phenotyping assays or their development, or for testing to learn more about the study drug or clinical laboratory testing to provide additional clinical safety data.

6.3.10.2. Virologic Failure

Virologic failure will be managed according to the management of virologic rebound (VR; Section 6.3.10.2.1) and participant may be subject to resistance analysis.

6.3.10.2.1. Management of Virologic Rebound

Participants who meet VR criteria will be considered to be in a situation of virologic failure. VR criteria are as follows:

- At any visit after Day 1, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit, or
- Any participant with HIV-1 RNA ≥ 50 copies/mL at the last on-treatment study visit (including early study drug discontinuation [ESDD], lost to follow-up or key study endpoints).

At any visit after screening, if the HIV-1 RNA is ≥ 50 and < 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma samples by the study central laboratory, if available. If the repeat result is < 50 copies/mL, participants will resume scheduled study visits.

If the repeat result is ≥ 50 copies/mL (ie, unconfirmed VR), participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 4 weeks after the date of the original test that resulted in HIV-1 RNA VR) for confirmation of VR. Confirmation of VR is not required for Day 1 HIV-1 RNA ≥ 50 copies/mL.

If VR is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the plasma sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing. All participants with documented nonadherence will be tested for resistance, regardless of their adherence status. After a participant's first postbaseline resistance test, additional testing will be conducted on a case-by-case basis. Any participant may be discontinued at investigator's discretion or per local treatment guidelines.

If no resistance to study drugs is detected from the genotype/phenotype testing, the participant may remain on study drugs and HIV-1 RNA viral load should be retested (2 to 4 weeks after date of confirmatory test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual participant and document this assessment in the on-site medical record.

Participants with HIV-1 RNA ≥ 200 copies/mL at the last visit while on study drugs will be evaluated for resistance.

Participants with inadequate levels of adherence to study drugs on an ongoing basis will be considered for discontinuation per the investigator's discretion or local treatment guidelines. Investigators who opt to discontinue study drugs for an individual participant must discuss with the medical monitor prior to study drug discontinuation.

For participants who are off study drug but remain on study, it will be the investigator's discretion to manage VR.

6.3.11. Pregnancy

Participants randomized into the study must have a negative pregnancy test at the screening and Day 1 visit. Any participant who becomes pregnant after randomization may remain in the study and continue to receive study drug(s) after providing written consent in which they will be informed of the benefits and risks of continuing to receive study drug and the collection of birth outcomes for the child and lactation information, if applicable per local practice (Sections 1.6, 7.4.2.3, and 9.1.3, Appendix 11.5, and Argentina-specific requirements in Appendix 11.8.1). Participants who continue on study drug during pregnancy may also provide sparse PK samples. The investigators will be requested to perform at least one additional unscheduled visit per local guidance between two scheduled study visits when the next study visit is 12-weeks apart. The unscheduled visit will be utilized to collect additional HIV-1 RNA viral load, CD4 cell count, and chemistry and hematology safety laboratories. Additionally, these visits will allow for more frequent monitoring of AEs that may occur during the study. Prenatal care will be at the investigator's discretion per local standard of care and will not be provided as part of the study.

Participants who provide reconsent and elect to remain on study drug and have a live birth during the study will be asked to report on the child's overall health at subsequent visits, including serious medical problems and HIV-1 status (negative and positive), and previously unrecognized congenital abnormalities in the Pregnancy Outcome Report Form.

6.4. Assessments for Early Discontinuation From Study Intervention or From the Study

If a participant discontinues study dosing (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (Section 3.3). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.4.1. Assessments for Early Discontinuation From Study Intervention

A participant who discontinues study drug early will be asked to return to the investigational site within 3 days of stopping study drug to attend an ESDD visit for assessments and procedures specified in Table 1. Participants who discontinue study drug early will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the ESDD visit.

At the ESDD visit, any assessment showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drugs 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. For participants who discontinued study drugs and are confirmed to have HIV-1 RNA ≥ 50 copies/mL at the ESDD visit, the participant will be followed until resuppression of HIV-1 RNA to < 50 copies/mL or for 3 months, whichever occurs first.

6.4.2. Assessments for End-of-Study

Participants from Treatment Group 1 who complete the OL Week 48 visit and participants from Treatment Group 2 who complete the study through the EBT visit and do not wish to participate in the OL phase will have a telephone visit at 30 days and an in-clinic follow-up visit at 60 days after the EBT visit, and will be considered to have completed the study.

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

Assessments for follow-up visits are specified in Table 1.

At the 60-day in-clinic follow-up visit, as applicable, any assessment showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drugs 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. Gilead may request that certain AEs and changes to ART regimens be followed beyond the protocol-defined follow-up period.

6.5. Sample Storage

The stored biological samples may be used by Gilead or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements if shorter.

6.6. Poststudy Care

After each participant in Treatment Group 1 completes the OL Week 48 visit, and after the EBT visit for participants in Treatment Group 2, participants will be given the option to receive BIC/LEN FDC during the OL phase until study drug is available, or until Gilead elects to discontinue the study, whichever comes first. Should development be stopped and the study terminated early, consideration for continued access to the study drug for a defined period of time may be given to those participants continuing to receive benefit if there are not increased safety concerns and if local regulations allow.

After the participant has completed/terminated the participation in the study, long-term care of the participant will remain the responsibility of the primary treating physician.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.4).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, or transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 7.1.4).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form (ICF) is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death.
- A life-threatening situation (Note: the term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization.

- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.3. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

7.1.4. Study Drugs and Gilead Concomitant Medications Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, DDIs, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, participant, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any report of drug/drug, drug/food, drug/alcohol, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship for each study drug using clinical judgment and the following considerations:

- **No**: evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: there is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** the AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Toxicity Grading Scale, Version 2.1 (Appendix 11.7). For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

After informed consent, but before initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs that are related to protocol-required procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, throughout the duration of the study, including the protocol-defined posttreatment follow-up period (including OL phase) and report the AEs on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to PS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.3.1. Protocol-Specific Serious Adverse Event Definitions

In this study, vertical transmission to the child, in participants who get pregnant during the study is to be considered medically important and therefore “serious.”

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situations Report

Special situations reports involving a Gilead concomitant medication (not considered study drug), that occur after the participant first consents to participate in the study (ie, signing of the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Medications Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs because of a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE eCRF. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all initial or follow-up SAE data (including updates to the reported event term[s]) on the applicable eCRFs within 24 hours of the investigator's knowledge of the initial event/update in order for the SAE information to be transmitted timely to PS. Serious adverse event information must be reported from the time of the ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, site personnel must record the SAE on the paper Initial or Follow-up SAE Report Form and transmit by emailing or faxing the report within 24 hours of the investigator's knowledge of the initial event/update using the contact information below:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information within 24 hours of the investigator's knowledge to PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason it is not possible to record and transmit the SSR information electronically, record the SSR on the paper SSR form and submit within 24 hours to:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

See Section 7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to PS utilizing the paper SSR form and transmitted to:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs because of a non-Gilead concomitant medication, must be reported on the AE eCRF.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period in participants. Pregnancies should be reported to PS within 24 hours of becoming aware of the pregnancy using the pregnancy report form. Contact details for transmitting the pregnancy report form are as follows:

Gilead Patient Safety:
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to PS using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to PS (email: Safety_FC@gilead.com and fax: 1-650-522-5477).

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy of the participant (eg, a spontaneous abortion, an induced therapeutic abortion because of complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after the study must be reported to the PS.

In addition, vertical transmission to the child, in participants who get pregnant during the study is to be considered medically important and therefore reported as an SAE for the infant, as described in Section 7.3.3.1.

Refer to Appendix 11.5 for pregnancy precautions, definition of childbearing potential, and contraceptive requirements.

7.4.2.3.1. Reporting Breastfeeding Exposure When A Participant Breastfeeds During the Study

If a breastfeeding exposure occurs and the participant will continue to breastfeed while enrolled in the study, then a special situations report should be submitted within 24 hours of awareness of the event. A follow-up "breastfeeding exposure" special situations report will need to be submitted to capture the end of exposure to study drug via breast milk.

Refer to Section 7.4.2.1 and the eCRF completion guidelines for instructions on submitting special situations reports involving study drug.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Regulation 536/2014 and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, SADRs, or SUSARs. In accordance with the EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter or a quarterly SAE line listing notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity of laboratory abnormalities should be recorded and graded according to the DAIDS Toxicity Grading Scale, Version 2.1 (Appendix 11.7). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 11.6 and as outlined below.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before study drug discontinuation, unless such a delay is not consistent with good medical practice. Repeat testing may occur within 4 to 14 calendar days per the investigator's discretion.

The Gilead medical monitor should be consulted prior to study drug discontinuation, when medically feasible.

8. STATISTICAL CONSIDERATIONS

This section provides a high-level description of the planned analyses, assessed statistical power with assumptions, and any applicable multiplicity adjustments. Additional details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

There are 2 analyses planned to be conducted to evaluate primary and secondary objectives of the study, one after all participants have completed their visits at Week 48, and the other after all participants in Treatment Group 1 have completed 96 weeks of study intervention starting from Day 1.

The Week 48 analysis will be the primary analysis.

8.2.1. Interim Analysis

Before the final analysis, additional interim analyses may be conducted as necessary after Week 96 and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program or to support regulatory filings. Also, interim analyses may be used for publication and/or presentation at scientific meetings. No interim analysis will be conducted before Week 48 primary analysis.

8.2.1.1. Week 96 Interim Analysis

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

8.2.1.2. Data Monitoring Committee Analysis

There will be 2 planned DMC analyses conducted after approximately the first 50% of participants enrolled have completed their Week 12 visit or prematurely discontinued the study drug, as well as after all participants enrolled have completed their Week 24 visit or prematurely discontinued the study drug.

A DMC meeting may be convened, and the supporting analyses conducted at other times during the study as deemed necessary. No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and

severity of AEs associated with a study drug regimen warrant the early termination of the study in the best interest of the participants.

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

Further details are provided in the DMC charter and further details on the DMC are provided in Appendix 11.3.

8.2.2. Primary Analysis

The primary analysis of the primary endpoint will be conducted after all participants enrolled have completed the Week 48 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/LEN FDC.

8.2.3. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

The datasets for analyses are defined in Table 9.

Table 9. Analysis Set Definitions

Analysis Set	Description
Full Analysis Set	The primary analysis set for efficacy analyses is defined as the Full Analysis Set (FAS), which will include all randomized participants who have received any dose of study drug. Participants will be grouped according to the treatment to which they were randomized.
Safety Analysis Set	The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who have received any dose of study drug. Participants will be grouped according to the treatment they actually received.
Pharmacokinetic Analysis Set	The primary analysis set for general PK analyses is defined as the PK Analysis Set, which includes all randomized participants who have received any dose of study drug, and have at least 1 nonmissing PK concentration value for the analyte(s) under evaluation reported by the PK laboratory. The PK Analysis Set will be used for analyses of general PK.

FAS = Full Analysis Set; PK = pharmacokinetic(s)

See Appendix 11.8.2 for EU-specific Per-Protocol (PP) Analysis Set definition.

8.3.2. Data Handling Conventions

HIV-1 RNA reported results of "No HIV-1 RNA detected" and "< 20 copies/mL HIV-1 RNA detected" will be imputed as 19 copies/mL for analysis purposes. Logarithm (base 10) transformation will be applied to HIV-1 RNA levels for analysis of change from baseline in HIV-1 RNA. The HIV-1 RNA reported results will be used for listing purposes.

Laboratory data (other than HIV-1 RNA) that are continuous in nature but are above the upper limit of quantitation or less than the lower limit of quantitation (LLOQ) will be imputed to the value of the upper or lower limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 5.4, a value of 5.3 will be assigned).

Pharmacokinetic plasma concentration values below the limit of quantitation (BLQ) will be treated as zero at predose and postdose time points. If the PK plasma samples are diluted during sample analysis, a corrected LLOQ × dilution factor would be used. The PK plasma concentrations will be transformed using natural logarithm for PK analysis. The reported values that are BLQ will be presented as "BLQ" in the concentration data listing.

Missing data can have an impact upon the interpretation of the study data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group including sample size, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables, and frequency and percentages for categorical variables.

Demographic summaries will include sex at birth, sexual orientation, gender identity, race, ethnicity, and age.

Baseline data will include a summary of body weight, height, body mass index, and HIV-1 infection (eg, CD4 cell count).

8.5. Efficacy Analysis

The efficacy analysis will be based on the FAS. The US FDA–defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be used to determine virologic outcomes at Week 48. The estimand for the virological outcomes is described in Table 10.

The virologic outcomes are defined with detailed categories based on the US FDA–defined snapshot algorithm as follows:

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

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

Table 10. Estimand and Handling for Intercurrent Events for Virologic Outcomes

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

AE = adverse event; BIC = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); FDA = Food and Drug Administration; FDC = fixed-dose combination; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; RNA = ribonucleic acid; US = United States

8.5.1. Primary Analysis

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

The primary analysis will consist of a noninferiority test of switching to BIC/LEN versus B/F/TAF, in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48. It will be concluded that BIC/LEN FDC is noninferior to B/F/TAF if the upper bound of the 2-sided 95% CI for the treatment difference (BIC/LEN − B/F/TAF) in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 between the 2 treatment groups is less than 4%. The 2-sided 95% CIs will be constructed based on stratum-adjusted Mantel-Haenszel (MH) proportion, adjusted by geographic regions. If the adjusted treatment difference is not estimable due to overly sparse stratification and/or low number of participants with virologic failure, then the primary comparison will be based on the unadjusted analysis.

See Appendix 11.8.2 for EU-specific analysis of the primary efficacy endpoint.

8.5.2. Secondary Analyses

The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 will be analyzed using the same methods as for the primary efficacy endpoint based on the FAS.

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

See Appendix 11.8.2 for EU-specific sensitivity analysis of key secondary efficacy endpoints.

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

See Appendix 11.8.2 for EU-specific analysis for participants switching to BIC/LEN FDC in the Extension Phase.

8.6. Safety Analysis

Safety data from participants in the Safety Analysis Set collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 60 days for participants receiving BIC/LEN or 30 days for participants receiving B/F/TAF will be summarized by treatment group (according to the study drug received) using the Safety Analysis Set.

All collected data will be included in data listings for all enrolled participants.

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

8.6.1. Extent of Exposure

Data for a participant's extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

Dosing information for individual participants will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using MedDRA. System organ class (SOC), high-level group term, high-level term (HLT), preferred term (PT), and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 60 days (for BIC/LEN) or 30 days (for B/F/TAF) or any AE leading to study drug discontinuation.

The number and proportion of participants experiencing treatment-emergent AEs (by SOC, HLT [if applicable], and PT) and AEs leading to discontinuation of study drugs, and treatment-emergent laboratory abnormalities will be summarized by treatment using descriptive statistics.

Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drugs, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

Selected laboratory test data (using conventional units) will be summarized using only observed data. Absolute values and change from baseline at all scheduled visits will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, available as follows: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

The percentage of participants experiencing treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last dose of study drugs plus 60 days (for BIC/LEN) or 30 days (for B/F/TAF) will be summarized by treatment group. If baseline data are missing, then any postbaseline graded abnormality (ie, at least Grade 1) will be considered treatment-emergent. The maximum postbaseline toxicity grade will be summarized by laboratory parameter.

All laboratory abnormalities will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and safety ECG data will be summarized as appropriate.

8.7. Adjustments for Multiplicity

The noninferiority evaluation of the proportion of participants with HIV-1 RNA $\geq$ 50 copies/mL at Week 48 as determined by US FDA–defined snapshot algorithm is the prespecified primary comparison.

There will be 2 interim DMC analyses performed prior to the primary analysis for the primary endpoint. Efficacy analysis will be performed for DMC review. The study will not be stopped for positive efficacy findings. Conservatively, an alpha of 0.00001 will be applied for each interim DMC analysis on efficacy. The primary analysis will be performed at an alpha of 0.04998, to control the overall Type I error rate.

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

8.8. Pharmacokinetic Analysis

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

8.9. Sample Size

Sample size calculations are based on the historical Gilead Genvoya® and B/F/TAF studies. Assuming that the virologic failure rate is 2% for both treatment groups, and a noninferiority margin of 4%, a total of approximately 546 participants, with 2:1 randomization ratio of BIC/LEN versus B/F/TAF, will provide approximately 90% power to show noninferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/mL) at Week 48 at a 1-sided significance level of 0.025. PASS (Power Analysis and Sample Size) software Version 14 are used for sample size and power calculations.

See Appendix 11.8.2 for EU-specific power table under various assumptions for treatment failure rates.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. The end of study is defined in Section 3.4.2.

9.1.2. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC for any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the purpose (aims), methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved ICF for documenting written informed consent/assent. Each ICF will be appropriately signed and dated by the participant, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements). A copy of the signed ICF will be provided to the participant.

The ICF will inform participants about optional future research, and/or planned sample retention. Including the following use of collected samples: to allow the use of the remainder of their already-collected specimens for optional future research and allow the use of already-collected data for optional future research, in accordance with applicable regulations.

The results of the tests performed on the samples will not be given to the participant or the investigator. The stored biological samples will be destroyed no later than 15 years after the end of study or per country requirements, whichever is shorter; but participants may at any time request that their stored samples be destroyed.

In addition to the study-specific ICF to be signed by each participant taking part in the study, participants who become pregnant after randomization may remain on the study after the reconsent process, as applicable according to local rules and regulation, where they will be informed of the benefits and risks of continuing to receive study drug while pregnant and, if applicable, of breastfeeding and of the collection of birth outcomes for the child.

9.1.4. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions or in accordance with local regulations. Note: the investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRFs, study drug information, and any other study information, remains the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IRB/IEC, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification.
- Documentation that participant meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria]).
- Documentation of the reason(s) a consented participant is not enrolled.
- Participation in study (including study number).
- Study discussed and date of informed consent/assent.
- Dates of all visits.
- Documentation that protocol-specific procedures were performed.
- Results of efficacy parameters, as required by the protocol.
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return.
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE.
- Concomitant medication (start and end date; dose if relevant; dose changes).
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an International Council for Harmonisation (ICH) region (ie, the US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.6. Electronic Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a non-EDC vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the eCRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.4.2).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical study agreement. Study results will be made publicly available (including posted to the Clinical Trials Information System and ClinicalTrials.gov) in accordance with local regulatory requirement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- The ethical principles of the Declaration of Helsinki.
- ICH Good Clinical Practice (GCP).
- Applicable laws and regulatory requirements.

9.3.2. Payment Reporting

Investigators and their study personnel may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.3. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the eCRF form at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

9.3.4. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.5. Study Discontinuation

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies), and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

9.3.6. Data Protection

Enterprise level technical and organizational controls have been developed at Gilead for the purpose of data protection. This includes user authentication and identification, fine grained access controls, end-to-end data encryption, security monitoring, network segregation, and physical security controls. Users of Gilead systems are provided training for security awareness and privacy.

To prepare for the possibility of a data security breach, Gilead maintains a business continuity and disaster recovery plan and conducts regular disaster recovery testing to ensure that Gilead systems are recoverable if a cyber or data security incident is experienced. Gilead's detailed incident response plan for any cyber or data security incident is based on the following 5 steps: detection, analysis, containment, eradication, and recovery. Gilead's standard clinical trial agreement with study sites also includes data privacy language and arrangements in case of data security breaches as follows:

Gilead and institutions will both act in accordance with the applicable data protection law. Furthermore, the study site and Gilead will cooperate with each other to take the necessary measures in order to comply with the applicable data protection law. Both Gilead and the study site shall implement appropriate technical and organizational measures to meet the requirements of the EU General Data Protection Regulation. If either party becomes aware of a personal data breach related to data processed under this agreement, that party shall promptly notify the other party. In such a case, parties will fully cooperate with each other to remedy the personal data breach and promptly fulfill the (statutory) notification obligations. A personal data breach refers to a personal data breach as described in Article 4, Article 33, and Article 34 of the European Union General Data Protection Regulation and applicable national data protection laws.

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404
USA

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

Protocol Amendment 2, 03 April 2025

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

11.2. Marketing Authorization Status of Study Interventions

Study Intervention Name	Category	Authorized in at least 1 Country Following EU Regulation No. 536/2014	Authorized in at least 1 ICH Country	To Be Used per Label (Marketed Products Only)
Lenacapavir (LEN) 300 mg tablets	Study drug	Yes	Yes	No
Bictegravir/lenacapavir (BIC/LEN) 75/50 mg FDC tablets	Study drug	No	No	NA
Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®; B/F/TAF) 50/200/25 mg FDC tablets	Comparator	Yes	Yes	Yes

EU = European Union; FDC = fixed-dose combination; ICH = International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use); NA = not applicable

11.3. Committees

11.3.1. Data Monitoring Committee

A multidisciplinary data monitoring committee (DMC) consisting of non-Gilead personnel will review the progress of the study, perform interim reviews of safety and efficacy data, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse events associated with study treatment warrant the early termination of the study in the best interests of the participant, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

11.4. Disaster and Public Health Emergency Risk Assessment and Mitigation Plan

During an ongoing disaster or public health emergency (hereafter referred to as an event), potential risks associated with participant being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

    a) Participants may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any participant visits. Without study drugs, the participant would not be able to continue receiving the study drug as planned per protocol.

    Mitigation plan: study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drug as determined by the principal investigator. A remote study visit, via phone or video conferencing, must be performed before remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by the local ethics committee/institutional review board (IRB)/regulatory authority as applicable and with sponsor's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug, the participant would not be able to continue receiving the study drug as planned per protocol.

    Mitigation plan: the site's study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered, as necessary.

2) Participant safety monitoring and follow-up:

    a) Participant may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

    Mitigation plan: for participants who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the participant within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

i) Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

ii) Review the current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm dosing diary have been completed.

iv) If applicable, confirm the participant's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in (1).

v) If applicable, remind the participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participant may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: local laboratories or other vendors may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the event will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Participant may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: the site staff will follow their approved consent process and remain in compliance with the local ethics committee/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur in case scheduled visits cannot be conducted as planned per protocol.

Mitigation plan: if it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol because of the event must be reported in the electronic case report form (eCRF) and described in the clinical study report (CSR). Any remote study visits that are conducted in lieu of clinic visits because of the event will be documented as a protocol deviation.

b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice (GCP)

compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

Mitigation plan: the study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

There may be an increased amount of missing data because of participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

Mitigation plan: implications of an event on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the CSR will describe the impact of the event on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of bictegravir (BIC)/lenacapavir (LEN) fixed-dose combination (FDC) in study participants remains unchanged.

11.5. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

See Appendix 11.8.1 and 11.8.2 for additional county-specific requirements for Argentina and the EU, respectively.

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

b. Definition of Fertility in a Participant Assigned Male at Birth

For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Participants

No contraception required.

3) Study Drug Effects on Pregnancy and Hormonal Contraception

Clinical data on LEN in pregnancy are limited. Clinical data available on BIC in pregnant women indicate no adverse effect on embryo-fetal development. Data from nonclinical toxicity studies of BIC and LEN have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicates that BIC and LEN are not expected to reduce the clinical efficacy of hormonal contraception.

Available data suggests pregnancy should not be avoided by participants on the study. Refer to the latest version of the BIC/LEN and Biktarvy (B/F/TAF) IBs.

Participants assigned female at birth and of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the admission (Day 1) visit before randomization.

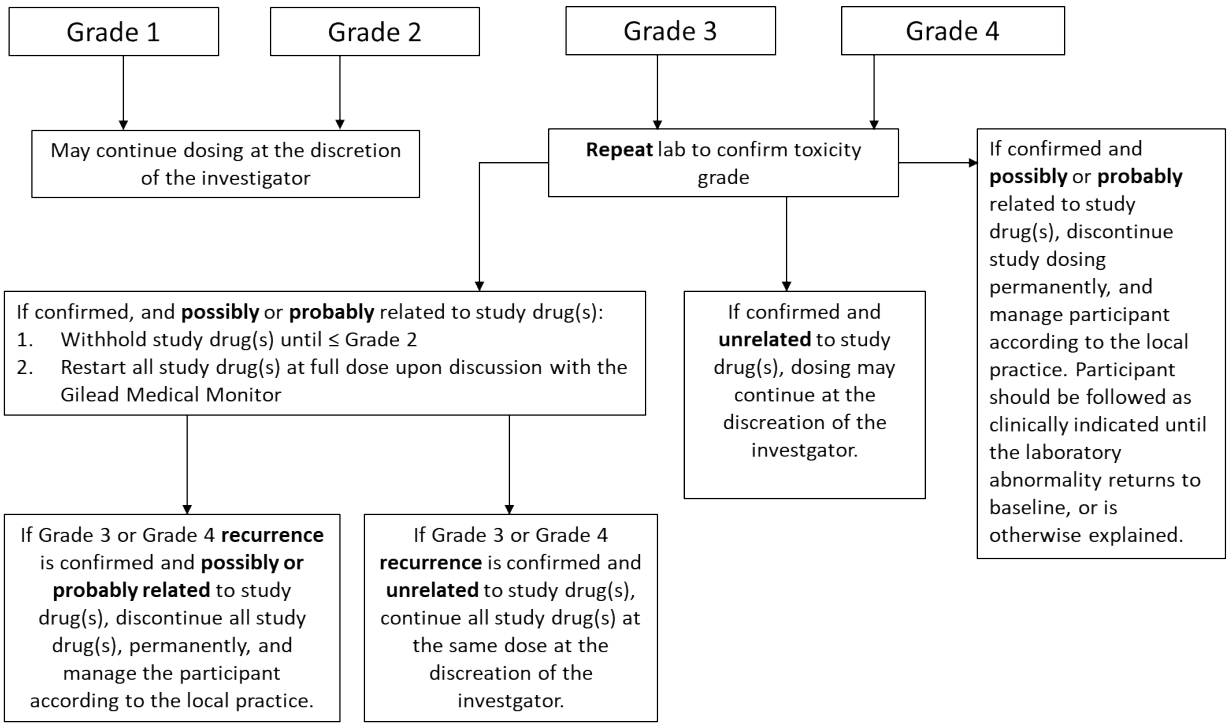
4) Procedures to Be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study until 60 days after the last study drug dose.

For every participant who becomes pregnant after study drug initiation:

- Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.
- Investigators will ensure that pregnant participants have been referred for antenatal care. Antenatal care is not provided as part of the study.
- Investigators will discuss the risks and benefits of remaining on study drug with the participant. Participants who choose to remain on study drug may do so after providing informed consent (see Section 6.3.11 and 9.1.3).
- Upon completion of the pregnancy, the investigators will document pregnancy outcomes including relevant dates, maternal history and complications, viability, delivery method and complications, congenital abnormalities, and overall infant health.
- Participants who provide reconsent and elect to remain on study drug and have a live birth during the study will be asked to report on the child's overall health at subsequent visits, including serious medical problems, the infant’s HIV-1 status (negative and positive), and previously unrecognized congenital abnormalities in the Pregnancy Outcome Report Form.

11.6. Management of Clinical and Laboratory Adverse Events



Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before study drug discontinuation, unless such a delay is not consistent with good medical practice. Repeat testing may occur within 4 to 14 calendar days per the investigator's discretion.

11.7. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

The Division of AIDS Toxicity Grading Scale (Version 2.1) is available at the following location:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

11.8. Country-Specific Requirements

11.8.1. Additional Country-Specific Requirements for Argentina

The following requirements apply for Argentina.

Country-Specific Requirements	Protocol Section
The National Administration of Drugs, Food, and Medical Devices (ANMAT) requires pregnancy tests be performed periodically (approximately every 4 weeks) for participants of childbearing potential. Since the test is performed more frequently than study visits, participants will be required to complete a pregnancy test at home and the study site will document the outcome of the at-home test via phone visit.	Study Procedures Table, 6.3.11
In addition to the inclusion criteria indicated in Section 4.2, participants from Argentina must meet the following additional inclusion criterion to be eligible for participation in this study: ARG1) Participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified methods of contraception as described below.	4.2
Argentina-specific contraception requirements are listed below: **1) Definitions** **a. Definition of Childbearing Potential** For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure. Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age. **b. Definition of Fertility in a Participant Assigned Male at Birth** For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation. **2) Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential** Clinical data on LEN in pregnancy are limited. Data available on BIC in pregnant women indicate no adverse effect on embryo-fetal development. Data from nonclinical toxicity studies of BIC and LEN have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that BIC and LEN have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Please refer to the latest version of the IB for additional information. Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®) data on pregnant women are limited. Data from nonclinical toxicity studies of B/F/TAF have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that B/F/TAF has demonstrated there is no reduction in the clinical efficacy of hormonal contraception. Refer to the latest version of the B/F/TAF IB for additional information. The inclusion of participants assigned female at birth and of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the admission (Day 1) visit before randomization.	11.5

Country-Specific Requirements	Protocol Section
The duration of required contraception for participants assigned female at birth and of childbearing potential enrolled in this clinical study should start from the screening visit until 60 days after the last study drug dose. Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods: Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle. Or Consistent and correct use of 1 of the following methods of birth control listed below: • Hormonal and nonhormonal intrauterine device • Bilateral tubal occlusion (upon medical assessment of surgical success) • Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success) Or Participants assigned female at birth and of childbearing potential who initiate use of a hormonal contraceptive greater than 5 days after onset of menses as their method of birth control should use additional backup contraception (eg, condoms) for 7 days or avoid sexual intercourse for 7 days. Hormonally based contraceptives or barrier methods permitted for use in this protocol are as follows: • Hormonal methods — Oral contraceptives (either combined or progesterone only) — Injectable progesterone — Subdermal contraceptive implant — Transdermal contraceptive patch — Contraceptive vaginal ring • Barrier methods — Male condom (with or without spermicide) — Female condom (with or without spermicide) — Diaphragm with spermicide — Cervical cap with spermicide — Sponge with spermicide Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved. Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement. **3) Contraception Requirements for Participants Assigned Male at Birth** Condom use is recommended to avoid transmission of sexually transmitted diseases. **4) Unacceptable Birth Control Methods** Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together. **5) Procedures to Be Followed in the Event of Pregnancy** Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study until 60 days after the last study drug dose.	

11.8.2. Additional Country-Specific Requirements for the European Union

The following requirements apply for the European Union (EU).

Country-Specific Requirements	Protocol Section
Exploratory Objectives: • To evaluate the safety and tolerability of BIC/LEN in participants from Treatment Group 2 who enter the open-label (OL) phase • To evaluate the efficacy of BIC/LEN in participants from Treatment Group 2 who enter the OL phase as determined by viral load suppression rate and CD4 cell count **Exploratory Endpoints:** • Proportion of participants from Treatment Group 2 in the OL phase experiencing treatment-emergent AEs • Proportion of participants from Treatment Group 2 with HIV-1 RNA ≥ 50 copies/mL in the OL phase • Proportion of participants from Treatment Group 2 with HIV-1 RNA < 50 copies/mL in the OL phase • Change from baseline in CD4 cell count for participants from Treatment Group 2 in the OL phase	2
In addition to the inclusion criteria indicated in Section 4.2, participants from the EU must meet the following additional inclusion criterion to be eligible for participation in this study: EU1) Participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified methods of contraception as described below.	4.2
The primary efficacy endpoint will also be evaluated using the Per-Protocol (PP) Analysis Set	8.5.1
The key secondary efficacy endpoints will also be evaluated using the PP Analysis Set	8.5.2
Sensitivity analysis will also be conducted for change from baseline in CD4 cell count at Week 48 using the mixed-effect model for repeated measures (MMRM) that includes all available data at postbaseline visits up to Week 48, under the Missing at Random assumption for missing CD4 cell count. The MMRM model will include baseline value of CD4 cell count, geographic region, treatment, visit, and treatment by visit interaction as fixed effects and participants being the random effect. 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 for treatment difference from the MMRM model will be provided.	8.5.2
Antiviral effect, safety, and tolerability of BIC/LEN FDC will also be evaluated for participants switching to BIC/LEN FDC in the Extension Phase	8.5.2
Table 9: Analysis Set Definitions The PP Analysis Set will include all participants in the Full Analysis Set excluding participants meeting any of the following criteria: • Did not have on-treatment HIV-1 RNA data in the Week 48 analysis window, except when missing was due to discontinuation of study drug for lack of efficacy. • Nonadherence to study drug: adherence rate for study drug up to Week 48 below the 2.5th percentile.	8.3.1

Country-Specific Requirements	Protocol Section
Appendix Table 1 summarizes the power for the primary comparison under various assumptions for the failure rate of the control group and underlying difference in the failure rate (the percentage of participants with HIV-1 RNA ≥ 50 copies/mL). For example, if the true failure rates are 1.5% in both groups, this study has approximately 95.5% power to demonstrate noninferiority. If the true failure rates are 2.0% in both groups, this study has approximately 90% power to demonstrate noninferiority.	8.9

Appendix Table 1. Power (%) to Establish Noninferiority at Week 48 Under Various Failure Rate Assumption (2:1 Ratio, 546 Participants)

True Failure Rate in B/F/TAF	True Difference in Failure Rates (BIC/LEN Minus B/F/TAF)				
	−1%	−0.5%	0%	0.5%	1%
1%	100	99.9	99	92.5	77.1
1.5%	99.9	99.5	95.5	84.8	67.9
2.0%	99.7	97.4	90.2	77.3	60.3
2.5%	98.5	93.9	84.2	69.9	53.4
3%	96.2	89.3	77.8	63	47.5

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; LEN = lenacapavir

EU-specific contraception requirements for participants assigned female at birth and of childbearing potential are listed below:

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. 11.5

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

b. Definition of Fertility in a Participant Assigned Male at Birth

For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

Clinical data on LEN in pregnancy are limited. Data available on BIC in pregnant women indicate no adverse effect on embryo-fetal development. Data from nonclinical toxicity studies of BIC and LEN have demonstrated no adverse effect on fertility or embryo-fetal

Country-Specific Requirements	Protocol Section
development. Available data indicate that BIC and LEN have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Please refer to the latest version of the IB for additional information. B/F/TAF data on pregnant women are limited. Data from nonclinical toxicity studies of B/F/TAF have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that B/F/TAF has demonstrated there is no reduction in the clinical efficacy of hormonal contraception. Refer to the latest version of the B/F/TAF IB for additional information. The inclusion of participants assigned female at birth and of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the admission (Day 1) visit before randomization. The duration of required contraception for participants assigned female at birth and of childbearing potential enrolled in this clinical study should start from the screening visit until 60 days after the last study drug dose. Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods: Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle. Or Consistent and correct use of 1 of the following methods of birth control listed below: • Hormonal and nonhormonal intrauterine device • Bilateral tubal occlusion (upon medical assessment of surgical success) • Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success) Or Participants assigned female at birth and of childbearing potential who initiate use of a hormonal contraceptive greater than 5 days after onset of menses as their method of birth control should use additional backup contraception (eg, condoms) for 7 days or avoid sexual intercourse for 7 days. Hormonally based contraceptives or barrier methods permitted for use in this protocol are as follows: • Hormonal methods — Oral contraceptives (either combined or progesterone only) — Injectable progesterone — Subdermal contraceptive implant — Transdermal contraceptive patch — Contraceptive vaginal ring • Barrier methods — Male condom (with or without spermicide) — Female condom (with or without spermicide)	

Country-Specific Requirements	Protocol Section
— Diaphragm with spermicide — Cervical cap with spermicide — Sponge with spermicide Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved. Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement. **3) Contraception Requirements for Participants Assigned Male at Birth** No contraception required. **4) Unacceptable Birth Control Methods** Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together. **5) Procedures to Be Followed in the Event of Pregnancy** Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study until 60 days after the last study drug dose.	

11.9. Amendment History

A high-level summary of amendment history is provided in tabular form below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the previous version of the protocol to this amendment will be made available upon the publication of this protocol.

11.9.1. Amendment 2 (03 April 2025)

Rationale for Key Changes Included in Amendment 2	Affected Sections
Noninferiority test with a 10% noninferiority margin will not be performed for the secondary efficacy endpoint (HIV-1 RNA < 50 copies/mL) at Week 48 in accordance with request from United States (US) Food and Drug Administration (FDA).	Synopsis, Sections 8.5.2 and 8.7
Clarified that future research is optional and collection subject to local regulations.	Study Procedures Table (Table 1), Table 8
Added text regarding follow-up visits for participants that discontinue study drugs early to align with protocol body.	Study Procedures Table (Table 1)
Updated text to align with current Gilead protocol template and practices.	Study Procedures Table (Table 1), Sections 4.1, 6.2, 6.4, and 7.4.1.1
Clarified how communication with investigators for resistance analyses results will be managed.	Section 5.1.2
Clarifying statement added for metformin exposure when coadministered with bictegravir.	Table 6
Updated time frame for virologic rebound reflex testing and retesting to align with current testing policy.	Section 6.3.10.2.1
Updated the estimand framework for virologic outcomes and the snapshot algorithm in accordance with request from the US FDA.	Section 8.5
Country-specific requirements for Argentina updated to align with Gilead practice.	Section 11.8.1
Minor changes to correct typographic errors.	Throughout, as needed

11.9.2. Amendment 1.1 (29 July 2024)

Rationale for Key Changes Included in Amendment 1.1	Affected Sections
Per request of the health authority ANMAT, language for the additional Argentina-specific requirement to perform pregnancy testing during the study was added to a new Appendix 11.8.1. Cross-references to this content in Appendix 11.8.1 have also been added to the body of the protocol where indicated.	Study Procedures Table; Section 6.3.11; Section 11.5; Section 11.8.1
Per request of ANMAT, Argentina-specific inclusion criteria #ARG1 was added to Appendix 11.8.1 that requires participants assigned female at birth and of childbearing potential to agree to use protocol-specified methods of contraception also described in Appendix 11.8.1. Cross-references to this content in Appendix 11.8.1 have also been added to the body of the protocol where indicated.	Section 4.2; Section 11.8.1
Per request of the health authority European Medicines Agency (EMA), additional EU-specific exploratory objectives and endpoints evaluating BIC/LEN in participants from Treatment Group 2 who enter the OL phase were added in Appendix 11.8.2. In addition, an analysis for participants in Treatment Group 2 switching to BIC/LEN FDC in the OL Phase has been added in Appendix 11.8.2. Cross-references to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.	Section 2; Section 8.5.2; Section 11.8.2
Per request of EMA, EU-specific inclusion criteria #EU1 was added to Appendix 11.8.2 that requires participants assigned female at birth and of childbearing potential to agree to use protocol-specified methods of contraception also described in Appendix 11.8.2. A cross-reference to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.	Section 4.2; Section 11.8.2
Per request of EMA, an EU-specific sensitivity analysis including the missing data handling strategies was added to Appendix 11.8.2. Cross-references to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.	Section 8.5.2; Section 11.8.2
Per request of EMA, an EU-specific definition of the PP Analysis Set was added to Appendix 11.8.2. Detail of the analysis using the PP analysis set for the primary and key secondary efficacy endpoints has also been added to Appendix 11.8.2. Cross-references to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.	Section 8.3.1, Section 8.5.1, Section 8.5.2; Section 11.8.2
Per request of EMA an EU-specific table showing power to establish noninferiority with various assumptions of treatment failure rate was added to Appendix 11.8.2. A cross-reference to this content in Appendix 11.8.2 have also been added to the body of the protocol where indicated.	Section 8.9; Section 11.8.2
Minor changes to correct typographic errors.	Throughout, as needed

11.9.3. Amendment 1 (18 June 2024)

Rationale for Key Changes Included in Amendment 1	Affected Sections
NCT number added.	Cover page and Synopsis
Inclusion criteria 9 was revised to replace "estimated glomerular filtration rate > 30 mL/min" with "estimated glomerular filtration rate ≥ 30 mL/min" as this was missing.	Synopsis and Section 4.2
In Korea, "adult" is considered > 19 years of age and not > 18 years of age, which can cause confusion regarding the eligibility criteria for the age at which participants can enroll in this study; therefore, the word "Adults" in the phrase "Virologically Suppressed Adults with HIV-1" was replaced with "Participants."	Study Schema
Footnotes "n" and "o" were updated for additional information pertaining to participants or pregnant participants taking evening doses.	Study Procedures Table
Pandemic risks to study conduct broadened to include unanticipated events (disasters and public health emergencies).	Section 1.6, Section 3.3.1.1, and Section 3.3.1.2
Subsection 3.3.1.1.1 for partial withdrawal information was added per updated protocol template.	Section 3.3.1.1
Added "Participant request to discontinue for any reason" as criteria for discontinuation from study per protocol template.	Section 3.3.1.2
Exclusion criteria 16 was added to exclude participants under guardianship, curatorship, or legal protection from the study.	Section 4.3
This section was updated for information of blinding for the purpose of population PK modeling.	Section 5.1.2
Acid reducing agents/antacids/buffered medications row in Table 6 was updated to provide more information on antacids, vitamins or mineral supplements, and to provide information regarding precautions for use of antacids in pregnant participants on the study drug and to align with the latest investigator's brochure updates. In addition, this row was updated to reflect how the drug should be taken together with supplements or antacids containing calcium, iron, and/or zinc.	Section 5.3.1, Table 6
Oral hypoglycemic agents row in Table 6 was updated for metformin to "refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of the study drug and metformin."	Section 5.3.1, Table 6
Updated language for stored plasma samples that may be used for PK analysis.	Section 6.3.9
Information was updated to include participants with documented nonadherence who will be tested for resistance.	Section 6.3.10.2.1
Language was added for unscheduled visits between every 12 weeks visits during pregnancy.	Section 6.3.11
Link to Appendix 15 was updated to reflect per new appendix heading.	Section 7.4.2.3
Updates made for clarity on interim analysis time points, ie, interim analysis may be conducted after Week 96 but not before Week 48 primary analysis.	Section 8.2.1

Rationale for Key Changes Included in Amendment 1	Affected Sections
The Safety Analysis Set was updated to included "all participants" instead of "all randomized participants."	Section 8.3.1, Table 9
Deletion of statistical test to be used for analysis of categorical and continuous demographic and baseline characteristics. Deletion of summary analysis for demographic and baseline characteristics by geographic region.	Section 8.4
Updates made on primary analysis of the study to use the estimand framework for the primary endpoint, including the addition of Table 10.	Synopsis, Section 8.5.1, and Table 10
Updates made on secondary analysis of the study to use the estimand framework for the key secondary endpoint, including the addition of Table 11.	Synopsis, Section 8.5.2, and Table 11
Language about the hypothesis testing for superiority of bictegravir/lenacapavir (BIC/LEN) over bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) was removed.	Section 8.7
Text pertaining to publication of clinical trial as per local regulatory requirements was updated.	Section 9.2.2
New Section 9.3.6 for data protection language was added.	Section 9.3.6
Text updated for clarification of no interim futility analysis is planned for data monitoring committee.	Appendix 11.3.1
Heading and disaster or public health emergency text updated as per protocol template.	Appendix 11.4
Appendix was updated to include language for the definition of fertility in a participant assigned male at birth, and to clarify that no contraception is required for participants in the study and the current available data does not suggest pregnancy should be avoided by participants on the study. Heading of appendix was updated to align with protocol template.	Appendix 11.5
Sponsor Signatory Page was updated to replace PPD	Appendix 11.10
Minor changes to correct typographic errors.	Throughout, as needed

11.10. Sponsor Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404
USA

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

Protocol Amendment 2, 03 April 2025

APPROVAL OF CLINICAL STUDY PROTOCOL

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD	*[See appended electronic signature]*
Director, Clinical Development	Signature
[See appended electronic signature]	
Date	

Prot GS-US-621-6290 amd-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	07-Apr-2025 20:17:13

STATISTICAL ANALYSIS PLAN

Study Title:	Phase 3 Double-Blind Multicenter Randomized Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide) in Virologically Suppressed People with HIV-1
Name of Test Drug:	Bictegravir/Lenacapavir
Study Number:	GS-US-621-6290
Protocol Version (Date):	Original: 16 January 2024
Analysis Type:	Primary Analysis at Week 48
Analysis Plan Version:	Final Draft
Analysis Plan Date:	25 April 2024
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF IN-TEXT FIGURES

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
ATC	Anatomical Therapeutic Chemical
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
$eGRF_{CG}$	estimated glomerular filtration rate by Cockcroft-Gault formula
EQ-5D-3L	EuroQoL 5 Dimensions, 3 Levels
ERT	end of randomized treatment
ESDD	early study drug discontinuation
ET	early termination
FAS	Full Analysis Set
FDC	fixed-dose combination
HDL	high-density lipoprotein
HIVTSQc-12	HIV Treatment Satisfaction Questionnaire Change-12 item
HIVTSQs-12	HIV Treatment Satisfaction Questionnaire Status-12 item
HLGT	high-level group term
HLT	high-level term
HRQOL	health-related quality of life
ID	identification
INSTI	Integrase Strand-Transfer 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
NI	non-inferiority
NLP	Natural Language Processing
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Protease Inhibitor
PK	pharmacokinetics
PKE	Pharmacokinetic Enhancer
PP	per protocol
PRO	Patient-reported outcome
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
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
WPAI-HIV	Work Productivity and Activity Impairment Questionnaire: HIV

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the primary analysis at Week 48 of Study GS-US-621-6290 for primary and key secondary endpoints. The analysis will be performed after all participants enrolled have completed the Week 48 visit or have prematurely discontinued the study drugs.

This SAP is based on the original study protocol dated 16 January 2024 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).

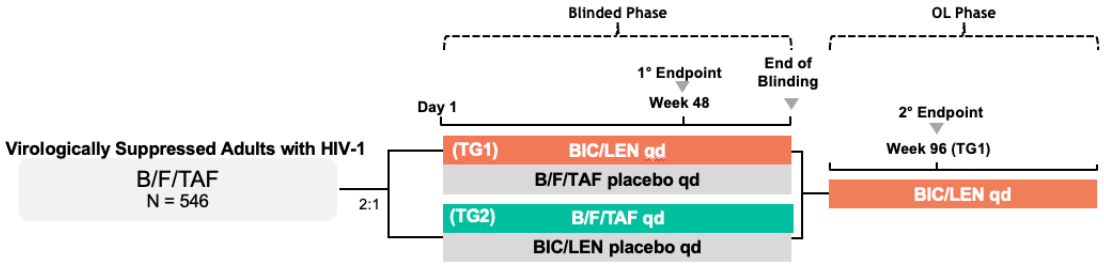
1.1. Study Objectives and Endpoints

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

1.2. Study Design

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

Figure 1-1. Study Schema



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

Blinded Phase

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

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

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

Randomization will be stratified by geographic region.

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

The timings of efficacy, safety, and all other assessments for the blinded phase are detailed in Table 12-1.

Open-label Phase

After completion of the Week 48 safety and efficacy data analysis, all participants will attend an EBT visit at the next in-clinic visit (preferably within 12 weeks).

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

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

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

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

Participants from Treatment Group 2 who enter the OL phase will receive a 2-day oral loading dose of LEN 600 mg for 2 days (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily BIC/LEN FDC tablet starting on Day 1 of the OL phase. Following the Day 1 visit, participants will be required to return for the study visit on Day 2 (option to conduct this as a virtual visit will be available, as appropriate) and will attend a Week 4 visit during the OL phase. If a virtual visit is not available, Day 2 of the oral loading dose will be administered at the clinic.

Study Procedures/Frequency:

Blinded Phase:

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

The timings of efficacy, safety, and all other assessments for the blinded phase are detailed in Table 12-1.

Open-label Phase:

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

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

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

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

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

1.3. Sample Size and Power

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

1.3.1. Rationale for Non-Inferiority Margin

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

Additionally, for the secondary endpoint of the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA–defined snapshot algorithm, noninferiority will be assessed using a margin of 10% for this comparison. Gilead considers the choice of a NI margin of 10% for the secondary endpoint analysis of virologic suppression (HIV-1 RNA < 50 copies/mL) reasonable and clinically acceptable for the patient population enrolled and the treatment regimens that participants switch to in this study.

The NI margin of 10% used for the secondary endpoint is consistent with industry common practice for switch studies. The NI margin generally ranged between 8% to 12% in recently completed switch studies with designs similar to Study GS-US-62-6290 used to support approval of new drugs. For example, a NI margin of 10% was used in the Phase 3 FLAIR and ATLAS switch studies, which supported the recent approval of Cabenuva (cabotegravir; rilpivirine). Furthermore, a NI margin of 8% was used in the Phase 3 TANGO switch study (ie, switching from ≥ 3-drug TAF based regimen to a 2-drug regimen) which supported the approval of Dovato, and a NI margin of 12% was used in the Phase 3 SALSA switch study (ie, switching from various 3- or 4-drug regimens to a 2-drug regimen). Considering both BIC and LEN have been evaluated for the treatment of HIV-1 infection in combination with other agents and have established efficacy and safety profiles, Gilead believes that the 10% NI margin selected for the secondary endpoint analysis of virologic suppression (HIV-1 RNA < 50 copies/mL) is clinically acceptable.

If assuming 2% virologic failure rate at Week 48 in both treatment arms, then the proposed study sample size to assess the primary endpoint of virologic failure (proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48) using an NI margin of 4% provides comparable power to assess the secondary endpoint of virologic suppression (proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48) using a NI margin of 10%, assuming 91% virologic success rate in both treatment groups.

2. TYPE OF PLANNED ANALYSES

This SAP will only describe the analyses for primary and key secondary endpoints planned for Week 48 primary analysis of this study. No participant will be enrolled into the open-label phase before the completion of the Week 48 primary analysis.

2.1. Interim Analyses

Before the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program or to support regulatory filings. Also, interim analyses may be used for publication and/or presentation at scientific meetings.

2.1.1. Data Monitoring Committee Analyses

There will be 2 planned DMC analyses conducted after approximately the first 50% of participants enrolled have completed their Week 12 visit or prematurely discontinued the study drug, as well as after all participants enrolled have completed their Week 24 visit or prematurely discontinued the study drug.

A DMC meeting may be convened, and the supporting analyses conducted at other times during the study as deemed necessary. No formal stopping rules will be used by the DMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of AEs associated with a study drug regimen warrant the early termination of the study in the best interest of the participants.

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

Further details are provided in the DMC charter and further details on the DMC are provided in Appendix 11.3.

2.1.2. Week 96 Interim Analysis

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

2.2. Primary Analysis

The primary analysis of the primary endpoint will be conducted after all participants enrolled have completed the Week 48 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/LEN FDC.

2.3. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

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

3.1. Analysis Sets

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

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

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

3.1.3. Per-Protocol Analysis Set

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

- Did not have on-treatment HIV-1 RNA data in the Week 48 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 Week 48 Per-Protocol Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 48 Analysis Window

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

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

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

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

3.1.4. Safety Analysis Set

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

3.2. 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.

3.3. Strata and Covariates

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

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

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

Efficacy endpoints will be evaluated using stratification factors as covariates or stratification variables for analyses, as specified in Section 6.

3.4. Examination of Participant Subgroups

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

- Age (< 50 years and ≥ 50 years)
- Sex (male and female)
- Race (white and non-white)
- Region (as specified in Section 3.3)

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

3.5. Multiple Comparisons

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

The following hypothesis testing will commence after the primary analysis reaches statistical significance and will be tested according to the hierarchical testing principle at the 1-sided 0.025 level Type 1 error rate adjusted for the number of DMC analyses prior to the primary analysis. If a null hypothesis is not rejected, formal sequential testing will be stopped. This sequential testing procedure controls the Type I error rate at the nominal level.

- Non-inferiority of HIV-1 RNA < 50 copies/mL between Treatment Group 1 and Treatment Group 2 at Week 48.

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

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

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for prior and concomitant medications is in Section 7.4.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

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

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age 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 (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data (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.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

- For postdose study days : Assessment Date – First Dosing Date + 1.

- For days prior to the first dose: Assessment Date – First Dosing Date.

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

Last Dose Date is the latest of the blinded study drug end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for subjects who prematurely discontinued or completed study drug in the blinded phase.

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

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

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

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

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

3.8.2. Analysis Visit Windows

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

The analysis windows are provided in Table 3-2, Table 3-3, Table 3-4.

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

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

$eGRF_{CG}$ = estimated glomerular filtration rate by Cockcroft-Gault formula.
* After Week 48, visits will be conducted every 12 weeks until EBT visit.

Table 3-3. Analysis Visit Windows for Urinalysis Assessments

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	378
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

* After Week 48, visits will be conducted every 12 weeks until EBT visit.

Table 3-4. Analysis Visit Windows for Metabolic Assessments

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	378
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

* After Week 48, visits will be conducted every 12 weeks until EBT visit.

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 (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- For postbaseline values:

  — For CD4 data, the record collected on the latest day in the analysis window will be selected.

  — For other observations, the record closest to the nominal day for that visit will be selected. If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  — If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

For baseline and postbaline 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" (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the "HIV RNA REPEAT COBAS" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA COBAS 6800" records with the same collection time, the geometric mean will be taken for analysis purposes.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (ie, first participant screened, first participant randomized, last participant randomized, last participant last visit for the primary endpoint, and last participant last visit) will be provided.

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

A similar enrollment table will be provided by randomization stratum (geographic region). The denominator for the percentage of participants in the stratum will be the total number of randomized participants. If there are discrepancies in the value used for stratification assignment between the IRT and the clinical database, the value collected in the clinical database will be used for the summary. A listing of participants with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided.

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 in blinded phase
- Did not complete study drug in blinded phase with reasons for premature discontinuation of study drug
- Still on study
- Completed Week 48 visit
- Did not complete the study in blinded phase 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.

4.2.1. Duration of Exposure to Study Drug

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

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

No formal statistical testing is planned.

A by-participant listing of all study drug administrations including the oral loading dose will be provided by participant ID number (in ascending order) and visit (in chronological order) along with the durations of exposure for study drug.

4.2.2. Adherence to Study Drug

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

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

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

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

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

Total number of tablets administered is determind 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 blinded phase will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinued study drug or completed study drug in the blinded phase, or using all data available for participants who are ongoing on study drug.

Adherence up to the Week 48 visit will be calculated using 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 48 study drug dispensing date, whichever occurs earliest.

Descriptive statistics for the level of on-treatment adherence to study drug with the number and percentage of participants belonging to adherence categories (eg, < 80%, ≥ 80 to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided for Treatment Group 1 for the Safety Analysis Set. No formal statistical testing is planned.

The adherence to oral loading LEN doses will not be summarized given participants only take at Day 1 and Day 2

A by-participant listing of study drug accountability (including the LEN 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 (eg, 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 (ie, age at Day 1, sex at birth, gender identity, sexual orientation, race, ethnicity, and region) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. For baseline body weight, height, and BMI, descriptive statistics will also be presented by sex in the same table. The summary of demographic and baseline characteristic data will be provided for the Safety Analysis Set.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- Baseline HIV-1 RNA level category: < 50 copies/mL, ≥ 50 copies/mL.
- Baseline CD4 cell count (/μL).
- Baseline CD4 cell count (/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).
- Duration of HIV disease from diagnosis (in years): Calculated as (first dosing date of this study - date of initial diagnosis + 1 day) / 365.25. If the date of initial diagnosis is incomplete, then the following rules will be applied:
  - missing day: use the first day of the month.
  - missing month: use January.
- Duration since first HIV treatment (in years): Calculated as (first dosing date of this study - start date of the first HIV treatment + 1 day) / 365.25. If the date of first treatment start date is incomplete, rules same as above will be applied.

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

- Other non-resistant substitutions: integrase substitution (Yes/No/Unknown), protease substitution (Yes/No/Unknown), reverse transcriptase substitution (Yes/No/Unknown).

- Diabetes history:

  — Diabetes (Yes/No).

  — Prediabetes (Yes/No).

- Substance use/misuse: Yes/No.

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 be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). A summary of medical history will be provided by treatment group and overall by the number and percentage of participants with each prepopulated condition by coded terms based on the Safety Analysis Set. No formal statistical testing is planned. A by-participant listing of medical history will also be provided.

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 48 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The primary analysis of the efficacy will be based on the FAS.

6.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 48 is defined as Study Day 295 to Study Day 378, inclusively. All HIV-1 RNA data collected on-treatment will be used in the US FDA-defined snapshot algorithm. On-treatment is defined as all data collected up to 1 day after permanent discontinuation of study drug, or all available data for participants who were still on study drug.

The virologic outcome will be defined as the following categories:

- HIV-1 RNA < 50 copies/mL: This includes participants who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 48 analysis window.

- HIV-1 RNA ≥ 50 copies/mL: This includes participants

A) Who have the last available on-treatment HIV-1 RNA ≥50 copies/mL in the Week 48 analysis window, or

B) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and

    i) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or

    ii) Who discontinue study drug prior to or in the Week 48 analysis window due to 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 48 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL.

- No virologic data in the Week 48 window: This includes participants who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:

A) Discontinuation of study drug prior to or in the Week 48 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

B) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

C) Missing data during the window but on study treatment.

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

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 48 Window" category.

6.1.3. Statistical Hypothesis for the Primary Efficacy Endpoint

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

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

vs

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

Where the non-inferiority margin θ is 4%.

6.1.4. Primary Analysis of the Primary Efficacy Endpoint

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

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

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

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h = p_{1h}$-p_{2h} is the proportion difference between BIC/LEN FDC group (Treatment Group 1) and the B/F/TAF group (Treatment Group 2) in stratum *h* (*h*=1 to 6 for 6 regions).
- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$ is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample sizes of the BIC/LEN FDC group (Treatment Group 1) and the B/F/TAF group (Treatment Group 2) in stratum *h*, respectively.
- And $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 [\frac{p_{1h}^*(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_{2h}^*)}{n_{2h}-1}]}{(\sum w_h)^2}}$, where $p_{1h}^* = \frac{m_{1h} + 0.5}{n_{1h} + 1}$ and $p_{2h}^* = \frac{m_{2h} + 0.5}{n_{2h} + 1}$. m_{1h} and m_{2h} are the number of participants with HIV-1 RNA ≥ 50 copies/mL in the BIC/LEN FDC group (Treatment Group 1) and the B/F/TAF group (Treatment Group 2) in stratum *h*, respectively.
- α = 0.04998 for this study.
- $Z_{(1-\alpha/2)} = Z_{0.97501} = 1.9601$ is the 97.501th percentile of the normal distribution.

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

If the adjusted treatment difference is not estimable due to overly sparse stratification and/or low number of participants with virologic failure, then the primary comparison will be based on the unadjusted analysis.

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

The associated p-value will also be provided based on the Cochran-Mantel-Haenszel (CMH) test stratified by geographic region.

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

The primary efficacy endpoint will also be evaluated using 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 48) 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. Key Secondary Efficacy Endpoints at Week 48

6.2.1. Definition of Key Secondary Efficacy Endpoints at Week 48

The secondary efficacy endpoints are defined as follows:

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

6.2.2. Primary Analysis of Key Secondary Efficacy Endpoints

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

The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm will be analyzed based on the FAS.

The treatment difference and the corresponding 2-sided 95.002% CIs for the difference in proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 between the BIC/LEN FDC group (Treatment Group 1) and B/F/TAF group (Treatment Group 2) based on the FAS will be constructed based on the stratum-adjusted MH proportion as described in Section 6.1.3 where m_{1h} and m_{2h} are the number of participants with HIV-1 RNA < 50 copies/mL in the BIC/LEN FDC group (Treatment Group 1) and the B/F/TAF group (Treatment Group 2) in stratum h, respectively.

It will be concluded that BIC/LEN FDC is non-inferior to B/F/TAF if the lower bound of the 2-sided 95.002% CI of the difference between treatment groups (BIC/LEN FDC − B/F/TAF) is greater than −10%.

The associated p-value will also be provided based on the Cochran-Mantel-Haenszel (CMH) test stratified by geographic region.

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

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

Least squares mean estimate of differences in changes from baseline in CD4 cell count between the BIC/LEN FDC group and B/F/TAF group at Week 48 and associated 95% CI will be constructed using analysis of covariance (ANCOVA) model, including baseline CD4 cell count and geographic region as covariates and treatment (BIC/LEN FDC vs. B/F/TAF) as a fixed effect in the model. Least squares mean estimate and 95% CI of the changes from baseline in CD4 cell count will also be presented for each treatment group.

The key secondary efficacy endpoints will also be evaluated using the PP analysis set.

6.2.3. Sensitivity Analysis of Key Secondary Efficacy Endpoints

Change from baseline in CD4 cell count at Week 48 will also be analyzed based on FAS using the mixed-effect model for repeated measures (MMRM) that includes all available data at post-baseline visits up to Week 48, under the Missing at Random assumption for missing CD4 cell count. The MMRM model will include baseline value of CD4 cell count, geographic region, 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 48 between BIC/LEN FDC group and B/F/TAF 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 48) for the subgroups specified in Section 3.4 based on FAS as applicable.

6.3. Other Efficacy Evaluations

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 ≥ 50 copies/mL) and will be summarized into the "Missing" category. Results will be summarized up to Week 48.
- Missing = Excluded (M = E): Participants with missing data will be excluded from analysis (ie, excluded from both the numerator and denominator in calculation of percentages). The denominator for percentages at a visit is the number of participants with nonmissing HIV-1 RNA value at that visit.

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

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

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

The 2-sided 95% CIs for the difference in proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 between BIC/LEN FDC group (Treatment Group 1) and B/F/TAF group (Treatment Group 2) will be constructed based on the stratum-adjusted MH proportion as described in Section 6.1.3 where m_{1h} and m_{2h} are the number of participants with HIV-1 RNA < 50 copies/mL in the BIC/LEN FDC group (Treatment Group 1) and the B/F/TAF group (Treatment Group 2) in stratum h, respectively.

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 ± 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 ± 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 for Treatment Group 1, or up to 30 days for Treatment Group 2, 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

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

7.1.4. Relationship of Adverse Events to Study Procedure

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

7.1.5. Serious Adverse Events

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

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

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

- Any AEs with an onset date on or after study drug start date and up to 60 days after permanent discontinuation of study drug for participants receiving BIC/LEN FDC in Treatment Group 1, or on or after the B/F/TAF start date and up to 30 days after permanent discontinuation of B/F/TAF for participants receiving B/F/TAF in Treatment Group 2.

- Any AEs leading to premature discontinuation of study drug.

7.1.6.2. 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 60 days for BIC/LEN Group (or 30 days for B/F/TAF Group) after the date of last dose of study drug.

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.

7.1.7. Summaries of Adverse Events and Deaths

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

7.1.7.1. Summaries of AE incidence in Combined Severity Grade Subsets

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

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

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

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

- 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
- 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 HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the worst severity will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TEAEs with Grade 2 or higher, TEAEs with Grade 3 or higher, TE SAEs, TE treatment-related AEs, TE treatment-related AEs with Grade 2 or higher, TE treatment-related AEs with Grade 3 or higher, and TE treatment-related SAEs during the blinded phase will be summarized by PT and treatment group only, in descending order of total frequency. All TEAEs, TEAEs with Grade 2 or higher, TEAEs with Grade 3 or higher, TE SAEs, TE treatment-related AEs, TE treatment-related AEs with Grade 2 or higher, TE treatment-related AEs with Grade 3 or higher, and TEAEs leading to premature discontinuation of any study drug up to Week 48 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 Week 48 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
- All AEs leading to premature discontinuation of study

7.2. Laboratory Evaluations

Laboratory data collected during the blinded phase will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 60 days for treatment group 1, or last dose of B/F/TAF plus 30 days for treatment group 2 for participants who have permanently discontinued study drug, or all available data at the time of the database snapshot for participants who were ongoing at the time of 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

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

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

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

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

7.2.2. Graded Laboratory Values

The DAIDS Toxicity Grading Scale, Version 2.1 will be used to assign toxicity grades (0 to 5) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities 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 Group 1 (or plus 30 days for participants from Treatment Group 2) who permanently discontinued study drug, or the last available date in the database snapshot 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 Group 1 (or plus 30 days for participants from Treatment Group 2) who permanently discontinued study drug, or the last available date in the database snapshot 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 participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Graded laboratory abnormalities through Week 48
- 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 up to 60 days after last dosing date of BIC/LEN (or 30 days after last doing date of B/F/TAF) in the blinded phase.

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 of the study 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 BIC/LEN for participants in Treatment Group 1, or up to 30 days after the last dose of B/F/TAF for participants in Treatment Group 2, 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 blinded phase as follows:

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

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

Median (Q1, Q3) of the observed 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 takes the first study drug. Prior ARV medications will be summarized by WHO drug class (Anatomical Therapeutic Chemical [ATC] Level 2) and preferred name using the number and percentage of participants for each treatment group and overall. A participant reporting the same medication more than once within each ATC Level 2 drug class will be counted only once when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC Level 2 medical class and then by preferred name in 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 drug 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 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.

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

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

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of any study drug (and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of any study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of any study drug or with a start date after the last dosing date of all study drugs will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the stop month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the start month and year (if day is missing) or year (if day and month are missing) after all study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries 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. Other Safety Measures

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

7.6. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

Pharmacokinetic (PK) analyses will not be discussed in this SAP as this SAP only includes the analyses of primary and key secondary endpoints.

9. REFERENCES

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

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

10. SOFTWARE

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

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

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

11. SAP REVISION

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

12. APPENDICES

STUDY PROCEDURES TABLE

Table 12-1. Study Procedures Table

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

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

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

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

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

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

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

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

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

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

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

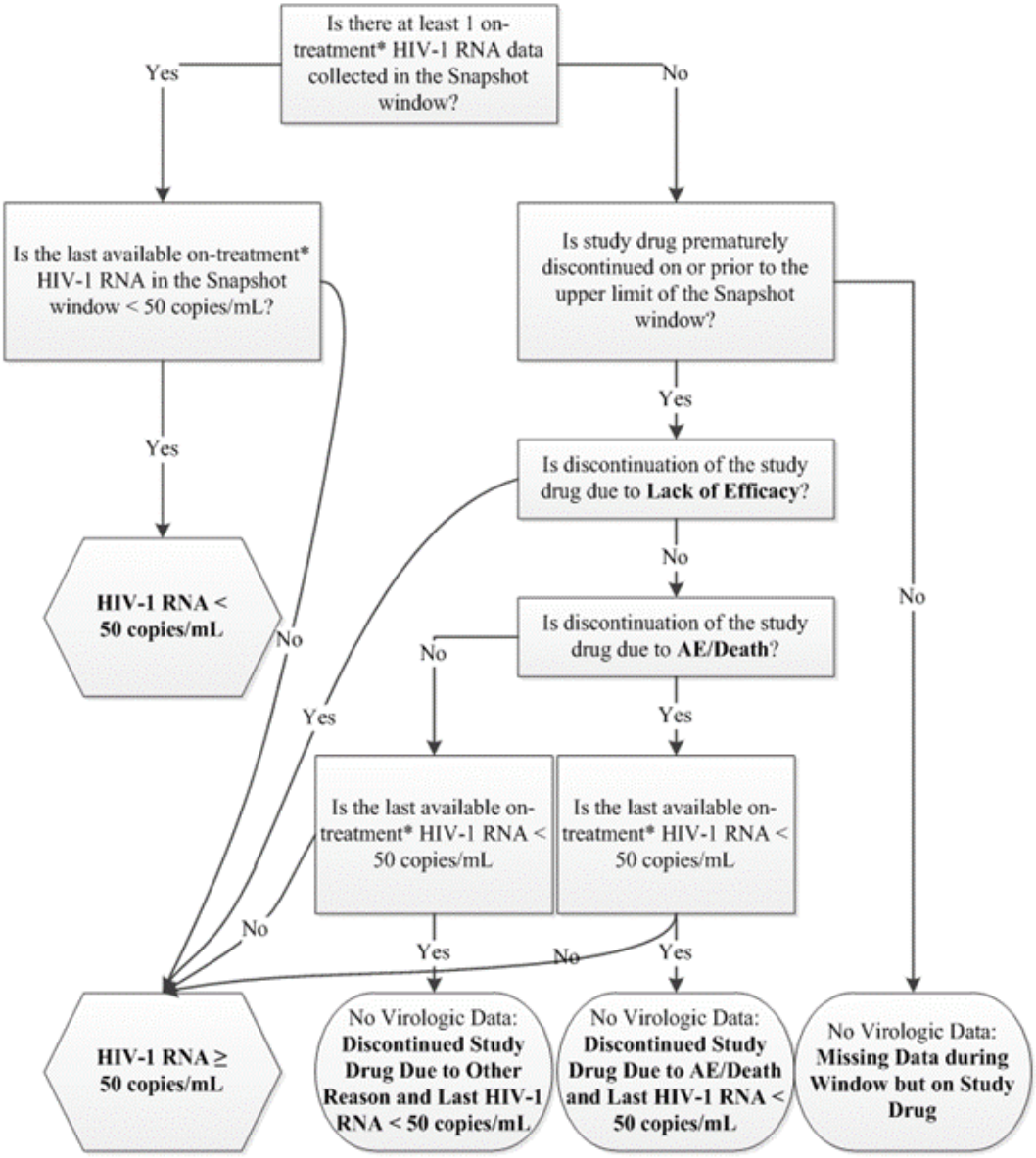
g Participants from Treatment Group 1 will receive BIC/LEN FDC through at least OL Week 48.

h At screening, details about medications taken within 30 days of the visit should be collected.
i Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
j Whole blood storage for possible proviral DNA sequencing needs to be done for all participants at Day 1. Proviral DNA sequencing will be performed on these samples in cases of virologic failure during the study. Separate consent for future research is not needed to collect this sample.
k Stored plasma samples may be used for evaluation of biomarker assays, PK analysis and virology assays (as appropriate). Separate consent for future research is not needed to collect these samples.
l HBV blood panel (HBsAg, HBsAb, and HBcAb) will be performed at screening, EBT visit, and 60-day in-clinic follow-up visit. Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study. Participants who are HBsAg positive will have a plasma HBV DNA test performed.
m HIV 1 genotype and phenotype testing for participants with confirmed virologic failure only. In case of unconfirmed virologic rebound, refer to Section 6.3.10.2. Plasma samples will be collected at all visits indicated in the notes column and at the virological failure confirmation visits.
n A single predose plasma PK sample (≤ 15 min before dose) **and** a single postdose plasma PK sample at 4 hours (± 1 hour) (relative to study drugs administration) 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 hour) (relative to study drugs administration) at Weeks 24 and 36.
o For participants who become pregnant and provide reconsent to remain on study, sparse PK samples will be collected as follows: at all specified time points described above in footnote 'n' during blinded treatment visits until Week 48. A single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12-week visit (as possible) until the EBT visit and during the OL phase. These additional trough samples will continue to be collected until the next 2 scheduled visits postdelivery or until the end of the study participation or OL phase, whichever occurs first.
p At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse PK sample.
q Participants from Treatment Group 2 who enter the OL phase will receive a 2-day oral loading dose of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2, without regard to food), in addition to the daily doses of BIC/LEN FDC starting on Day 1 of the OL phase. Please refer to Section 6.3.8 for further details.

12.1. 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.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	25-Apr-2024 16:58:02
PPD	Clinical Development eSigned	26-Apr-2024 03:15:55