THE LANCET

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: Orkin C, Ruane PJ, Hedgcock M, et al. Switch to single-tablet bictegravir–lenacapavir from a complex HIV regimen (ARTISTRY-1): a randomised, open-label, phase 3 clinical trial. *Lancet* 2026; published online Feb 25. https://doi.org/10.1016/S0140-6736(26)00307-7.

SUPPLEMENTARY APPENDIX

Switch to single-tablet bictegravir/lenacapavir from a complex HIV regimen: results from ARTISTRY-1, a randomised, open-label phase 3 clinical trial

Chloe Orkin, MD, Peter J. Ruane, MD, Malcolm Hedgcock, MD, Cyril Gaultier, MD, Marcelo H. Losso, MD, Benoit Trottier, MD, Thomas Lutz, MD, Mark O'Reilly, BMED, Mark Bloch, MBBS, MMed, Jihad Slim, MD, Moti Ramgopal, MD, Simiso Sokhela, MBChB, Karam Mounzer, MD, Hung-Chin Tsai, MD, PhD, Jorge Santana Bagur, MD, Xu Zhang, PhD, Keith Aizen, MBChB, Kwanza Price, MPH, Nicolas Margot, MA, Jairo M. Montezuma-Rusca, MD, MPH, Peter Sklar, MD, MPH, Martin Rhee, MD, Pedro Cahn, MD, PhD, on behalf of the ARTISTRY-1 Study Group

Table of Contents

Principal Investigators and Study Sites 3

Supplementary Methods 6

Study Protocol Amendments 6

ARTISTRY-1 Eligibility Criteria 8

Geographic Stratification Used for Randomisation 10

Copy of Treatment Satisfaction Questionnaires 11

Details of Statistical Analysis 15

Handling of Missing Data 15

Supplementary Results 17

Footnote to Figure 2: Definition of category 'Other' 17

Table S1: Participant disposition by region and country (all randomised analysis set) 18

Figure S1: CD4 cell count over time (full analysis set) 19

Table S2: Treatment satisfaction over time (safety analysis set) 20

Table S3: Drug-related adverse events (safety analysis set) 21

Table S4: Renal-related adverse events (safety analysis set) 22

Table S5: Laboratory abnormalities (safety analysis set) 23

Figure S2: Fasting lipid parameters at week 48 (safety analysis set) 24

Clinical Study Protocol and Statistical Analysis Plan 25

Principal Investigators and Study Sites

Geographic Region/Country or Region Principal Investigator (Site Number)	Institutional Review Board or Independent Ethics Committee
Africa/South Africa	
Sokhela, Simiso, MD	University of the Witwatersrand Human Research Ethics Committee, Houghton, South Africa
Singh, Yashna, MD	University of Cape Town Faculty of Health Sciences Research Ethics Committee, Groote Schuur Hospital Observator, Cape Town, South Africa
Asia/Japan	
Yokomaku, Yoshiyuki, MD	National Hospital Organization Nagoya Medical Center Institutional Review Board, Nagoya-shi, Japan
Shirasaka, Takuma, MD	National Hospital Organization Osaka Toneyama Medical Center IRB, Toyonaka-shi, Japan
Asia/South Korea	
Kim, Shin-Woo, MD	Kyungpook National University Hospital Institutional Review Board, Daegu, South Korea
Choi, Jun Yong, MD	Yonsei University Health System Institutional Review Board, Seoul, South Korea
Asia/Taiwan	
Lu, Po-Liang, MD	Kaohsiung Medical University, Chung-Ho Memorial Hospital Institutional Review Board, Kaohsiung City, Taiwan
Cheng, Shu-Hsing, MD	Institutional Review Board of Taoyuan General Hospital, Taoyuan City, Taiwan
Lu, Po-Liang, MD Tsai, Hung-Chin, MD	Kaohsiung Veterans General Hospital – Institutional Review Board, Kaohsiung City, Taiwan
Central America/Dominican Republic	
Adon Moreta, Carlos, MD	Consejo Nacional de Bioética en Salud – CONABIOS, Ave. Bolivar, Universidad Catolica de Santo Domingo, Santo Domingo, Dominican Republic
Central America/Puerto Rico	
Santana Bagur, Jorge L., MD Santiago, Lizette, MD	Advarra Institutional Review Board, Columbia, MD, United States
Europe/France	
Cua, Eric, MD Ghosn, Jade, MD Pourcher, Valerie, MD Rubenstein, Emma, MD	European Medicines Agency, Amsterdam, the Netherlands
Europe/Germany	
Boesecke, Christoph, MD Grunwald, Stephan, MD Hoffmann, Christian, MD Jonsson-Oldenbüttel, Celia, MD Lutz, Thomas, MD	European Medicines Agency, Amsterdam, the Netherlands
Europe/Italy	
Antinori, Andrea, MD Castagna, Antonella, MD Di Perri, Giovanni, MD Cossu, Maria Vittoria, MD Mussini, Cristina, MD	European Medicines Agency, Amsterdam, the Netherlands
Europe/Spain	
Bernardino de la Serna, José Ignacio, MD Estrada, Vicente, MD Lopez Cortes, Luis Fernando, MD Mallolas Masferrer, Josep, MD	European Medicines Agency, Amsterdam, the Netherlands

Geographic Region/Country or Region Principal Investigator (Site Number)	Institutional Review Board or Independent Ethics Committee
Moreno Guillén, Santiago, MD	
Europe / United Kingdom	
Clarke, Amanda, MD Nelson, Mark, MD Orkin, Chloe, MD Post, Frank, MD Taylor, Stephen, MD	Medicines and Healthcare products Regulatory Agency, London, United Kingdom
North America/Canada	
Wong, Alexander, MD	Saskatchewan Health Authority Research Ethics Board, Regina, Canada
Lebouche, Bertrand, MD	McGill University Health Centre-Montreal General Hospital, Biomedical D (BMD), Montreal, Canada
Brunetta, Jason, MD Hedgcock, Malcolm, MD Trottier, Benoit, MD	Advarra, Aurora, Canada
Angel, Jonathan, MD	Ottawa Health Science Network Research Ethics Board, Ottawa, Canada
North America/United States	
Mounzer, Karam, MD	Philadelphia FIGHT Institutional Review Board, Philadelphia, PA, United States
Ogbuagu, Onyema, MD	Yale University Human Investigation Committee, New Haven, CT, United States
Slim, Jihad, MD	Saint Michael's Medical Center Institutional Review Board, Newark, NJ, United States
Stang, Alexandra, MD	University and Medical Center Institutional Review Board, East Carolina University, Greenville, NC, United States
Stephens, Jeffrey L., MD	Mercer University Institutional Review Board, Macon, GA, United States
Burack, Jeffrey, MD	Sutter Health Institutional Review Board, CA, United States
Benson, Paul, DO Berhe, Mezgebe, MD Brinson, Cynthia, MD Creticos, Catherine M., MD DeJesus, Edwin, MD Gardner, Edward, MD Gathe, Joseph C., MD Gaultier, Cyril, MD Gay, Cindy, MD Gorgos, Linda, MD Hsu, Ricky K., MD Jayaweera, Dushyantha, MD Little, Susan, MD McDonald, Cheryl, MD Meissner, Eric, MD Mills, Anthony, MD Ogbuagu, Onyema, MD Oguchi, Godson, MD Osiyemi, Olayemi, MD Prelutsky, David J., MD Ramgopal, Moti N., MD Ruane, Peter J., MD Sanchez, William, MD Scribner, Anita, MD Sension, Michael, MD Shalit, Peter, MD Sims, James, MD Sinclair, Gary I., MD Stang, Alexandra, MD Stephens, Jeffrey L., MD Tellez, Marcus, MD Thedinger, Blair, MD	Advarra, Columbia, MD, United States

Geographic Region/Country or Region Principal Investigator (Site Number)	Institutional Review Board or Independent Ethics Committee
Yung, Lok, MD Zurawski, Christine, MD	
Oceania/Australia	
McMahon, James, MD	Alfred Human Research Ethics Committee, Melbourne, VIC, Australia
Bloch, Mark, MD O'Reilly, Mark, MD	Bellberry Human Research Ethics Committee, Eastwood, SA, Australia
Carr, Andrew, MD	Alfred Human Research Ethics Committee, Melbourne, VIC, Australia
South America/Argentina	
Cassetti, Isabel L., MD	Comité Independiente de Etica en Investigación Clínica Larrea, Buenos Aires, Argentina
Cahn, Pedro, MD	Comité de Bioética Fundación Huesped, Buenos Aires, Argentina
Losso, Marcelo H., MD	Comision de Bioética Comité de Docencia e Investigación Hospital General de Agudos J.M. Ramos Mejía, Buenos Aires, Argentina

Supplementary Methods

Study Protocol Amendments

SUMMARY OF PROTOCOL AMENDMENTS

Key Changes in Amendment 1 (Jul 27, 2022)

- Intensive plasma pharmacokinetic (PK) sampling was removed from the end of treatment column in the Study Procedures table and replaced with single anytime PK sampling.
- Exclusion criterion #12, which included cardiovascular-specific exclusion criteria, was removed.
- A history of significant cardiac disease, family history of long QT syndrome or unexpected death in an otherwise healthy individual aged 1–30 years, syncope, palpitations, and unexpected dizziness were added to the exclusion criterion #9.
- Text was updated to clarify that serious adverse events and special situations report will be documented by paper form, and reference to electronic collection was removed.

Key Changes in Amendment 2 (Oct 5, 2023)

- Selection of BIC 75 mg/LEN 50 mg fixed-dose combination (FDC) dose for phase 3 based on the totality of data from the phase 2 portion of Study GS-US-621-6289 and multiple cohorts/formulations evaluated in the relative bioavailability Study GS-US-621-6292.
- Updates to phase 3 secondary objectives and endpoints to evaluate the efficacy and safety of BIC/LEN FDC in participants from treatment group 1 at week 96 as determined by viral load suppression rate and CD4 cell count, and treatment-emergent adverse events.
- Modification of the phase 3 extension period to require participants in treatment group 1 to be followed-up until at least week 96.
- Updates to inclusion criteria related to HIV-1 RNA levels for the phase 3 part of the study.
- Updates to exclusion criteria to exclude participants under guardianship, curatorship, or legal protection.
- Addition of week-4 visit for participants in treatment group 3 of the phase 2 part and treatment group 2 of the phase 3 part of the study who enrol in the extension period.
- Reference to safety assessment committee was removed as it is duplicative of the data monitoring committee responsibilities.
- Addition of patient-reported outcome assessments to the phase 3 part of the study.
- Clarification of the test procedure for HIV-1 RNA ≥50 and <200 copies/mL at any post–day 1 visit.
- Clarification that the daily dose of BIC/LEN FDC should be taken in the clinic on the day of each study visit.
- Updates pertaining to demographic and baseline characteristics analysis and efficacy and safety analyses.
- Addition of randomisation by geographical region to the phase 3 part of the study.
- Clarification that hepatitis C virus serology will not be performed in the phase 3 portion of the study as this test is not required.
- Removal of rosuvastatin and pravastatin from the list of prior and concomitant medications that are prohibited or to be used with caution while taking LEN, per current understanding of LEN disposition informed by the totality of available data.
- Clarification that electronic data capture is not considered source data.
- Addition of text regarding the review of past medical history of comorbid conditions.
- Addition of information as data available on BIC in pregnant participants indicate no adverse effect on embryo-foetal development.
- EU CT number changed from 2022-500929-33-00 to 2022-500929-33 for alignment with initial EU CTR resubmission required due to technical issues with the Clinical Trials Information System.

Key Changes in Amendment 3 (Jun 18, 2024)

- Updates to primary analysis to use the estimand framework for the primary endpoint.
- Updates to secondary analysis to use the estimand framework for the key secondary endpoint.
- Clarification that plasma storage samples, including early study drug discontinuation, may be used for PK testing.

- Footnotes “r” of Study Procedures Tables 1, 3, and 4 and “q” of Table 3 were updated to provide additional information pertaining to pregnant participants taking evening doses.
- Addition of 48-week timepoint for HIV Treatment Satisfaction Questionnaire—Status 12-item (HIVTSQs-12) assessment.
- Footnotes for metabolic assessment updated to remove fasting information pertaining to food and liquid as this fasting step is not required.
- Addition of 60-day in-clinic follow-up timepoint for concomitant medications assessment.
- Addition of Subsection 3.3.1.1.1 for partial withdrawal information, per updated protocol template.
- Pandemic risks to study conduct broadened to include unanticipated events (disasters and public health emergencies).
- “Participant request to discontinue for any reason” added, per protocol template update.
- Clarifying information added for acid reducing agents/antacids/buffered medications to include 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 information was updated to reflect how the drug should be taken together with supplements or antacids containing calcium, iron, and/or zinc.
- Clarifying information added on oral hypoglycaemic agents to “refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of the study drug and metformin.”
- Deletion of information on “Participants with documented nonadherence within 72 hours of the visit may not be tested for resistance.”
- Clarification of unscheduled visits during pregnancy.
- Clarification of interim analysis timepoints.
- Updates to Safety Analysis Set to include “all participants” instead of “all randomized participants.”
- Deletion of subsections for analysis of phase 2 and phase 3 categorical and continuous demographic and baseline characteristics.
- Updates to text pertaining to publication of clinical trial as per local regulatory requirements.
- Addition of new Protocol Section 9.3.5 for data protection language.
- Updated section heading to replace “Pandemic” with “Disaster and Public Health Emergency.”
- Updated standard text to further refer to “Disaster or Public Health Emergency” as “an event,” per template.

Key Changes in Amendment 4 (Apr 3, 2025)

- Noninferiority test with a 10% noninferiority margin will not be performed for the secondary efficacy endpoint (HIV-1 RNA <50 copies/mL) in accordance with request from US Food and Drug Administration (FDA).
- Updates to frequency of participant dosing diary to fix error.
- Clarification that future research is optional and collection subject to local regulations.
- Updates to align with Protocol Clarification Letter 3.0.1.
- Addition of follow-up visits for participants who discontinue study drugs early.
- Clarifying statement added regarding metformin exposure when co-administered with BIC.
- Updates to timeframe for virologic rebound reflex testing and retesting to align with the current testing policy.
- Updates to the estimand framework for virologic outcomes and the Snapshot algorithm in accordance with the request from the US FDA.

ARTISTRY-1 Eligibility Criteria

Inclusion criteria

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

1. Willing and able to provide informed written consent
2. Aged ≥18 years at screening
3. Documented plasma HIV-1 RNA levels <50 copies/mL during treatment with the baseline complex regimen for ≥6 months before screening
4. Participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse agreed to use protocol-specified methods of contraception
5. Documented plasma HIV-1 RNA levels <50 copies/mL ≥6 months before screening
    - If plasma HIV-1 RNA measurements in the 6 months before screening are available, all levels must be <50 copies/mL
    - At least one documented plasma HIV-1 RNA level measured between 6 and 12 months (±2 months) before 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. Currently receiving a complex antiretroviral regimen due to previous antiretroviral resistance, intolerance, or contraindication to existing single-tablet regimens
8. No documented or suspected resistance to bictegravir (BIC; T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene)
9. Estimated glomerular filtration rate ≥15 mL/min (by Cockcroft-Gault equation) and not on renal replacement therapy

Exclusion criteria

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

1. Positive serum pregnancy test result at screening or a positive pregnancy test result before day 1 randomisation
2. Breastfeeding participant
3. Current alcohol or substance use judged by the investigator to potentially interfere with participant's study compliance
4. Prior use of, or exposure to, lenacapavir (LEN)
5. Active, serious infections (other than HIV-1) requiring parenteral therapy <30 days prior to randomisation
6. Active tuberculosis infection
7. Acute hepatitis <30 days before randomisation
8. Chronic hepatitis B virus (HBV) infection, as determined by either:
    - Positive HBV surface antigen and negative HBV surface antibody test result, regardless of HBV core antibody status, at the screening visit

- Positive HBV core antibody and negative HBV surface antibody test result, regardless of HBV surface antigen status, at the screening visit

9. Known hypersensitivity to the study drug, its metabolites, or formulation excipient
10. History of, or current, clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, or variceal bleeding)
11. Abnormal electrocardiogram at the screening visit that is determined to be clinically significant by the investigator
12. Active malignancy requiring acute systemic therapy
13. Any of the following laboratory values at screening:
    - Creatinine clearance <15 mL/min (by Cockcroft-Gault equation)
    - Alanine aminotransferase level >5 × upper limit of normal
    - Direct bilirubin level >1·5 × upper limit of normal
    - Platelet count <50,000/mm^3
    - Haemoglobin level <8·0 g/dL
14. Requirement for ongoing therapy with, or prior use of, any prohibited medications:
    - Antiarrhythmic agents: dofetilide
    - Anticonvulsants: phenobarbital, phenytoin, carbamazepine, oxcarbazepine
    - Antimycobacterials: rifampin, rifabutin, rifapentine
    - Any antiretroviral drug that is not part of the study treatment regimen
    - Ergot derivatives: ergotamine, ergonovine, dihydroergotamine, methylergonovine, ergometrine
    - Herbal/natural supplements: St John's wort, echinacea, milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or xiao-shai-hu-tang)
    - Systemic corticosteroids for >7 days
15. Participation or planned participation in any other clinical study (including observational studies) without prior approval from the sponsor
16. 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
17. Being under guardianship, curatorship, or legal protection

Geographic Stratification Used for Randomisation

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

Copy of Treatment Satisfaction Questionnaires

HIV Treatment Satisfaction Questionnaire status version (HIVTSQs)

The following questions are concerned with your medical treatment for HIV and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

	very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How well controlled do you feel your HIV has been recently?

	very well controlled	6	5	4	3	2	1	0	very poorly controlled

3. How satisfied are you with any side effects of your present treatment?

	very satisfied	6	5	4	3	2	1	0	very dissatisfied

4. How satisfied are you with the demands made by your current treatment?

	very satisfied	6	5	4	3	2	1	0	very dissatisfied

5. How convenient have you been finding your treatment to be recently?

	very convenient	6	5	4	3	2	1	0	very inconvenient

6. How flexible have you been finding your treatment to be recently?

	very flexible	6	5	4	3	2	1	0	very inflexible

7. How satisfied are you with your understanding of your HIV?

	very satisfied	6	5	4	3	2	1	0	very dissatisfied

8. How satisfied are you with the extent to which the treatment fits in with your life-style?

	very satisfied	6	5	4	3	2	1	0	very dissatisfied

9. Would you recommend your present treatment to someone else who is being offered this HIV treatment?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

10. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

11. How easy or difficult have you been finding your treatment to be recently?

very easy	6	5	4	3	2	1	0	very difficult

12. How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.
Thank you for taking the time to complete this questionnaire.

HIV Treatment Satisfaction Questionnaire change version (HIVTSQc)

For the past 6 months you have been taking part in an HIV treatment study. At the start of the study you may have had a change of treatment. Today we would like to know how your experience of your current treatment has changed from your experience of treatment before the study began. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

2. How well controlled do you feel your HIV has been recently?

much better controlled now	3	2	1	0	-1	-2	-3	much worse controlled now

3. How satisfied are you with any side effects of your present treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

4. How satisfied are you with the demands made by your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

5. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now

6. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now

7. How satisfied are you with your understanding of your HIV?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

8. How satisfied are you with the extent to which the treatment fits in with your life-style?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

9. How likely would you be to recommend your present treatment to someone else who is being offered this HIV treatment?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now

10. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

11. How easy or difficult have you been finding your treatment to be recently?

much easier now	3	2	1	0	-1	-2	-3	much less easy now

12. How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

Please make sure that you have circled one number on each of the scales.
Thank you for taking the time to complete this questionnaire.

Details of Statistical Analysis

CD4 cell counts were summarised using observed, on-treatment data for participants in the Full Analysis Set. Differences in changes from baseline in CD4 cell count between the treatment groups were estimated using an analysis of covariance model including baseline CD4 cell count and geographical region (US vs. non-US) as covariates and treatment (BIC/LEN vs. complex regimen) as a fixed effect. Patient-reported outcomes were summarised using descriptive statistics.

The proportion of participants with HIV-1 RNA levels ≥50 copies/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 levels ≥50 copies/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.

Treatment difference in change from baseline in fasting lipids levels at week 48 between the BIC/LEN and complex regimens groups was estimated using the mixed model with repeated measures with treatment, visit, treatment*visit, baseline value, and geographical region (US vs. non-US) as fixed effects, and participant as a random effect.

Handling of Missing Data

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

Missing last dosing date of study drug

For participants who prematurely discontinued study drug/complex regimen in the randomised period and for whom only the year of the last dosing date was known or completely missing, the latest date among the following was used: BIC/LEN or complex regimen 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). 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 (for BIC/LEN), BIC/LEN or complex regimen 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. For participants who were still on treatment at the time of an interim analysis, the data cut was used.

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 BIC/LEN) or 30 days (for complex regimen) after the last dosing date of BIC/LEN or complex regimen.

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

Footnote to Figure 2: Definition of category 'Other'

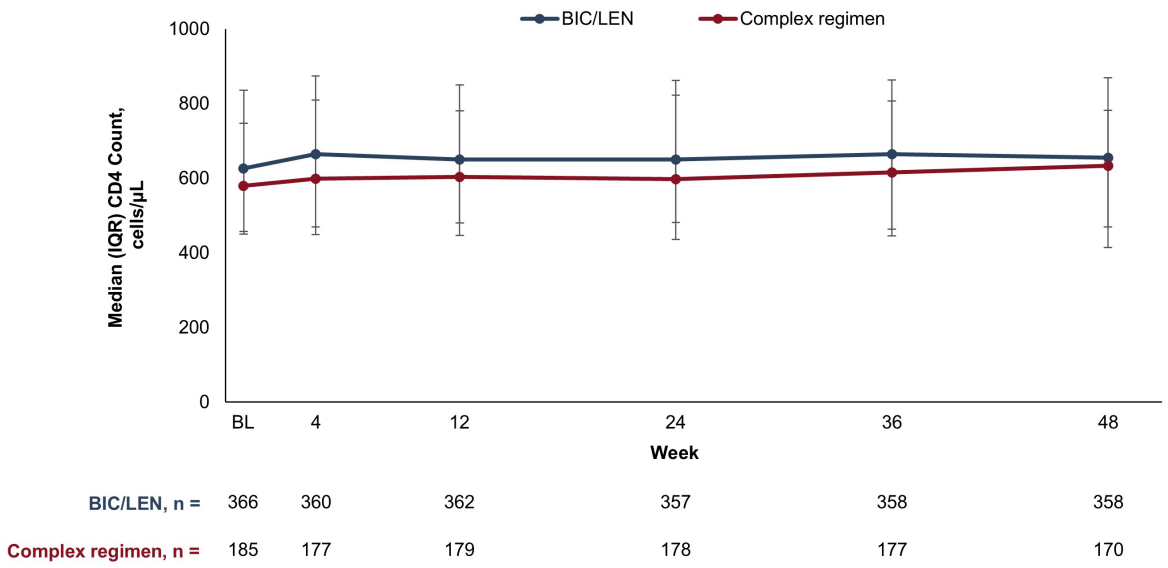
Other regimens consist of: darunavir + etravirine + maraviroc + ritonavir (n=3), lamivudine + abacavir + maraviroc (n=2), lamivudine + abacavir + raltegravir (n=2), abacavir + dolutegravir + tenofovir disoproxil fumarate (n=2), darunavir + maraviroc + ritonavir (n=2), dolutegravir + emtricitabine + tenofovir alafenamide (n=2), lamivudine + abacavir + azidothymidine (n=1), lamivudine + abacavir + darunavir + ritonavir (n=1), lamivudine + abacavir + darunavir + ritonavir + tenofovir disoproxil fumarate (n=1), lamivudine + abacavir + dolutegravir (n=1), lamivudine + abacavir + dolutegravir + tenofovir alafenamide (n=1), lamivudine + abacavir + lopinavir + ritonavir (n=1), lamivudine + abacavir + nevirapine (n=1), lamivudine + azidothymidine + dolutegravir (n=1), lamivudine + azidothymidine + maraviroc (n=1), lamivudine + azidothymidine + nevirapine (n=1), lamivudine + lopinavir + ritonavir (n=1), lamivudine + raltegravir (n=1), lamivudine + rilpivirine (n=1), abacavir + darunavir + ritonavir + tenofovir disoproxil fumarate (n=1), abacavir + dolutegravir (n=1), azidothymidine + emtricitabine + tenofovir disoproxil fumarate (n=1), bictegravir + cobicistat + doravirine + darunavir + emtricitabine + maraviroc + tenofovir alafenamide (n=1), cabotegravir + cobicistat + darunavir + maraviroc + rilpivirine (n=1), cobicistat + darunavir + dolutegravir + maraviroc + rilpivirine (n=1), cobicistat + darunavir + emtricitabine + maraviroc + tenofovir disoproxil fumarate (n=1), doravirine + emtricitabine + tenofovir alafenamide (n=1), darunavir + dolutegravir + etravirine + maraviroc + ritonavir (n=1), darunavir + emtricitabine + ritonavir + tenofovir disoproxil fumarate (n=1), dolutegravir + emtricitabine + ibalizumab + tenofovir alafenamide (n=1), emtricitabine + maraviroc + rilpivirine + tenofovir alafenamide (n=1), emtricitabine + raltegravir + tenofovir alafenamide (n=1), emtricitabine + raltegravir + tenofovir disoproxil fumarate (n=1), emtricitabine + ritonavir + tenofovir alafenamide + tipranavir (n=1).

Table S1: Participant disposition by region and country (all randomised analysis set)

Region Country, n (%)	BIC/LEN (n=373)	Complex Regimen (n=188)	Total (n=561)
Africa	4 (1)	2 (1)	6 (1)
South Africa	4 (1)	2 (1)	6 (1)
Asia	10 (3)	6 (3)	16 (3)
Japan	2 (1)	1 (1)	3 (1)
Korea	3 (1)	1 (1)	4 (1)
Taiwan	5 (1)	4 (2)	9 (2)
Central and South America	32 (9)	16 (9)	48 (9)
Argentina	31 (8)	15 (8)	46 (8)
Dominican Republic	1 (<1)	1 (1)	2 (<1)
Europe	123 (33)	62 (33)	185 (33)
Germany	35 (9)	12 (6)	47 (8)
France	19 (5)	16 (9)	35 (6)
Italy	25 (7)	11 (6)	36 (6)
Spain	25 (7)	14 (7)	39 (7)
United Kingdom	19 (5)	9 (5)	28 (5)
North America	179 (48)	90 (48)	269 (48)
United States	135 (36)	70 (37)	205 (37)
Puerto Rico	2 (1)	1 (1)	3 (1)
Canada	42 (11)	19 (10)	61 (11)
Oceania	25 (7)	12 (6)	37 (7)
Australia	25 (7)	12 (6)	37 (7)

BIC=bictegravir. LEN=lenacapavir.

Figure S1: CD4 cell count over time (full analysis set)



Difference in least-squares mean for BIC/LEN versus complex regimen at week 48, +19·0 (95% CI −11·6 to +49·5); p=0·22; from an analysis of covariance model of change in CD4 cell count from baseline using baseline CD4 cell count and geographical region (US vs. non-US) as covariates and treatment as a fixed effect. BIC=bictegravir. LEN=lenacapavir.

Table S2: Treatment satisfaction over time (safety analysis set)

	BIC/LEN (n=371)	Complex Regimen (n=186)
HIVTSQs total score at baseline	55 (10·4) n=359	55 (9·4) n=178
HIVTSQs total score at week 48	63 (6·2) n=356	55 (11·5) n=172
Change from baseline at week 48*	+7 (10·6) n=344	0 (9·6) n=165

Data are mean (SD).

*p<0·0001 for the difference in mean change in HIVTSQs total score for BIC/LEN vs. complex regimen. P-value was calculated from the mixed model for repeated measures in change from baseline with baseline value, geographical region, treatment, visit, and treatment*visit as fixed effects and participant as a random effect.

HIVTSQs total score was calculated as the sum of responses ranging from 0 to 66.

BIC=bictegravir. HIVTSQs=HIV Treatment Satisfaction Questionnaire status version. LEN=lenacapavir.

Table S3: Drug-related adverse events (safety analysis set)

	BIC/LEN (n=371)	Complex Regimen (n=186)
Grade 1 or 2		
Headache	13 (4)	0
Nausea	10 (3)	0
Diarrhoea	8 (2)	1 (1)
Abdominal pain	4 (1)	0
Constipation	4 (1)	0
Fatigue	4 (1)	0
Dizziness	3 (1)	0
Erectile dysfunction	3 (1)	0
Abnormal dreams	2 (1)	0
Dyspepsia	1 (<1)	1 (1)
Vertigo	2 (1)	0
Alopecia	1 (<1)	0
Back pain	1 (<1)	0
Change of bowel habit	1 (<1)	0
Colon dysplasia	0	1 (1)
Decreased appetite	1 (<1)	0
Dyslipidaemia	1 (<1)	0
Eczema	1 (<1)	0
Fat tissue increased	1 (<1)	0
Gingival hypertrophy	1 (<1)	0
Gynaecomastia	1 (<1)	0
Hyperhidrosis	1 (<1)	0
Hypersomnia	1 (<1)	0
Hypertension	1 (<1)	0
Hyperthyroidism	1 (<1)	0
Insomnia	1 (<1)	0
Irritability	1 (<1)	0
Myalgia	1 (<1)	0
Night sweats	1 (<1)	0
Palpitations	1 (<1)	0
Paraesthesia	1 (<1)	0
Seasonal allergy	1 (<1)	0
Sleep disorder	1 (<1)	0
Tension headache	1 (<1)	0
Tooth discoloration	1 (<1)	0
Vomiting	1 (<1)	0
Weight increased	1 (<1)	0
Wound cellulitis	0	1 (1)
Grade 3 or 4		
Diabetes mellitus	1 (<1)	0
Maculo-papular rash	1 (<1)	0

Data are n (%).
Multiple adverse events were counted once per participant for the highest-severity grade for each preferred term.
BIC=bictegravir. LEN=lenacapavir.

Table S4: Renal-related adverse events (safety analysis set)

	eGFR >15 to ≤30 mL/min		eGFR >30 to <60 mL/min		eGFR ≥60 mL/min	
	BIC/LEN (n=3)	Complex Regimen (n=3)	BIC/LEN (n=56)	Complex Regimen (n=26)	BIC/LEN (n=312)	Complex Regimen (n=157)
Any renal-related adverse event	0	1 (33)	2 (4)	7 (27)	15 (5)	7 (4)
Acute kidney injury	0	1 (33)	1 (2)	2 (8)	2 (1)	1 (1)
Chronic kidney disease	0	0	1 (2)	3 (12)	1 (<1)	1 (1)
Pollakiuria	0	0	0	1 (4)	2 (1)	0
Blood creatinine increased	0	0	0	1 (4)	0	1 (1)
Renal creatinine clearance decreased	0	0	0	0	0	2 (1)
Haematuria	0	0	0	0	1 (<1)	1 (1)
Hyperkalaemia	0	0	0	2 (8)	0	0
Hypokalaemia	0	0	0	0	2 (1)	0
Nocturia	0	0	0	0	2 (1)	0
Blood phosphate decreased	0	0	0	0	0	1 (1)
Crystalluria	0	0	0	0	0	1 (1)
Encephalopathy	0	0	0	0	1 (<1)	0
Glomerular filtration rate decreased	0	0	0	0	1 (<1)	0
Glycosuria	0	0	0	0	1 (<1)	0
Hypocalcaemia	0	0	0	0	1 (<1)	0
Hypophosphataemia	0	0	0	0	0	1 (1)
Toxic nephropathy	0	0	0	1 (4)	0	0
Oliguria	0	0	0	0	1 (<1)	0
Pericarditis	0	0	0	0	0	1 (1)
Proteinuria	0	0	0	0	1 (<1)	0

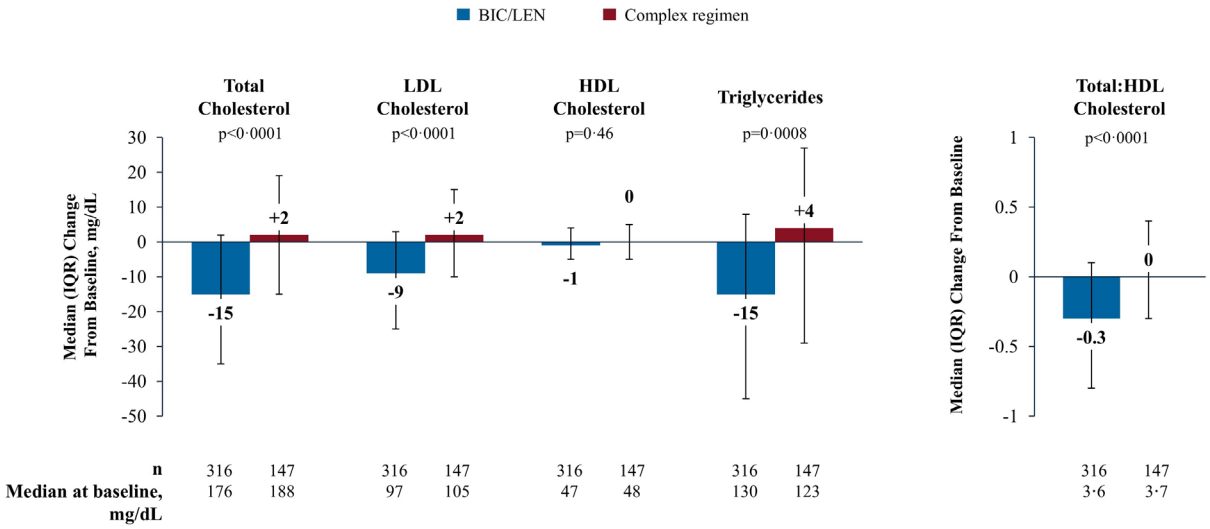
Data are n (%).
Multiple adverse events were counted once per participant for each preferred term.
BIC=bictegravir. eGFR, estimated glomerular filtration rate. LEN=lenacapavir.

Table S5: Laboratory abnormalities (safety analysis set)

	BIC/LEN (n=371)	Complex Regimen (n=186)
Laboratory abnormalities – any grade	341 (92)	178 (97); n=183
Grade ≥3	124 (33)	64 (35); n=183
Grade ≥3 laboratory abnormalities reported in ≥2% of participants in any group		
Decreased creatinine clearance	46 (12)	29 (16); n=183
Increased direct bilirubin level*	36 (10)	11 (6); n=183
Glycosuria*	21 (6); n=368	6 (3); n=182
Increased creatinine level	11 (3)	11 (6); n=183
Increased fasting triglyceride level	10 (3); n=365	6 (3); n=181
Increased fasting low-density lipoprotein cholesterol level*	8 (2); n=365	9 (5); n=181
Increased lipase level	10 (3)	5 (3); n=183
Hyperglycaemia (non-fasting)*	5 (2); n=228	2 (2); n=123
Hypercholesterolemia (fasting)*	5 (1); n=365	4 (2); n=181

Data are n (%).
*All abnormalities were grade 3 in severity.
BIC=bictegravir. LEN=lenacapavir.

Figure S2: Fasting lipid parameters at week 48 (safety analysis set)



n numbers indicate the number of participants with available data for change from baseline to week 48.
Treatment difference in change from baseline in fasting lipids at week 48 between the BIC/LEN and complex regimens groups was estimated using the mixed model with repeated measures with treatment, visit, treatment*visit, baseline value, and geographical region (US vs. non-US) as fixed effects, and participant as a random effect.
BIC=bictegravir. HDL=high-density lipoprotein. LDL=low-density lipoprotein. LEN=lenacapavir.

CLINICAL STUDY PROTOCOL

Study Title:	An Operationally Seamless Phase 2/3 Randomized, Open-label, Multicenter, Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Stable Baseline Regimen in Virologically Suppressed People With HIV-1 on Stable Complex Treatment Regimens
Study Acronym:	ARTISTRY-1
Short Title:	Study to Compare Bictegravir/Lenacapavir Versus Current Therapy in People With HIV-1 Who Are Successfully Treated With a Complicated Regimen
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	158963 2022-500929-33 NCT05502341
Indication:	HIV-1 infection
Protocol ID:	GS-US-621-6289
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 4: 03 April 2025
Amendment History:	Original: 26 April 2022 Amendment 1: 19 July 2022 Amendment 2: 05 October 2023 Amendment 3: 18 June 2024 High-level summaries of the histories of amendments are provided in Appendix 11.7

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.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

TABLE OF CONTENTS

TABLE OF CONTENTS 3
LIST OF IN-TEXT TABLES 7
LIST OF IN-TEXT FIGURES 7
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 8
PROTOCOL SYNOPSIS 11
STUDY SCHEMA 20
STUDY PROCEDURES TABLE 21
1. INTRODUCTION 34
1.1. Background 34
1.1.1. Rationale for Development of Bictegravir/Lenacapavir Fixed-Dose Combination Tablet 34
1.2. Background on Study Interventions 35
1.2.1. Lenacapavir 35
1.2.2. Bictegravir 36
1.3. Rationale for This Study 36
1.4. Rationale for Dose Selection of Study Drugs 37
1.4.1. Dose Selection for the Phase 2 Portion of the Study 37
1.4.2. Phase 2 Experience and Dose Selection for the Phase 3 Portion of the Study 40
1.5. Risk/Benefit Assessment for the Study 44
1.6. Compliance 45
2. OBJECTIVES AND ENDPOINTS 46
3. STUDY DESIGN 48
3.1. Study Design Overview 48
3.1.1. Dose Selection/Modification 48
3.2. Duration of Intervention 51
3.2.1. Phase 2 51
3.2.2. Phase 3 51
3.3. Protocol-Specific Discontinuation Criteria 52
3.3.1. Criteria for Early Discontinuation for the Individual Participants 52
3.3.2. Criteria for Early Discontinuation of the Study 53
3.3.3. Loss to Follow-up 53
3.4. Definitions for Time of Primary Endpoint and End of Study 53
3.4.1. Primary Endpoint 53
3.4.2. End of Study 54
3.5. Poststudy Care 54
3.6. Source Data 54
4. PARTICIPANT POPULATION 55
4.1. Number of Participants and Participant Selection 55
4.1.1. Participant Replacement 55
4.2. Inclusion Criteria 55
4.3. Exclusion Criteria 56
5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS 58
5.1. Randomization, Blinding, and Treatment Code Access 58

5.1.1. Randomization 58
5.1.2. Blinding 59
5.2. Description and Handling of Bictegravir, Lenacapavir, and Bictegravir/Lenacapavir Fixed-Dose Combination Study Drugs 59
5.2.1. Bictegravir Tablets 59
5.2.2. Lenacapavir Tablets 60
5.2.3. Bictegravir/Lenacapavir FDC Tablets 61
5.3. Dosage and Administration 61
5.3.1. Phase 2 61
5.3.2. Phase 3 62
5.3.3. Missed Dose Recommendations for Study Drugs in Phase 2 and 3 Portions of the Study 62
5.4. Prior and Concomitant Medications 63
5.4.1. Prior and Concomitant Medications That Are Prohibited or to Be Used With Caution 63
5.4.2. Concomitant Administration of COVID-19 Vaccines and Study Drugs 65
5.5. Accountability for Study Drugs 65
5.5.1. Study Drug Return or Disposal 66

6. STUDY PROCEDURES 67

6.1. Informed Consent 67
6.2. Screening, Participant Enrollment, and Treatment Assignment 67
6.3. Instructions for Study Procedures 67
6.3.1. Adverse Events 67
6.3.2. Concomitant Medications 68
6.3.3. Electrocardiograms 68
6.3.4. Medical History and Demography 68
6.3.5. Physical Examination 68
6.3.6. Vital Signs 69
6.3.7. Clinical Laboratory Assessments 69
6.3.8. Virtual Visits 70
6.3.9. Pharmacokinetics 71
6.3.10. Clinical Virology Analyses 74
6.3.11. Questionnaires/Patient-Reported Outcomes 75
6.3.12. Pregnancy 77
6.4. Assessments for Early Discontinuation From Study Intervention or From the Study 77
6.4.1. Assessments for Early Discontinuation From Study Intervention 78
6.4.2. Assessments for End of Study 78
6.5. Poststudy Care 78
6.6. Sample Storage 78

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT 79

7.1. Definitions of Adverse Events and Serious Adverse Events 79
7.1.1. Adverse Events 79
7.1.2. Serious Adverse Events 79
7.1.3. Serious Adverse Drug Reaction 80
7.1.4. Study Drugs and Gilead Concomitant Medications Special Situations Reports 80
7.2. Assessment of Adverse Events and Serious Adverse Events 81
7.2.1. Assessment of Causality for Study Drugs, Authorized Auxiliary Medicinal Products and Procedures 81
7.2.2. Assessment of Severity 82
7.3. Investigator Reporting Requirements and Instructions 82
7.3.1. Requirements for Collection Before Study Drug Initiation 82

7.3.2. Adverse Events 82
7.3.3. Serious Adverse Events 82
7.3.4. Study Drug Special Situations Reports 82
7.3.5. Concomitant Medications Reports 83
7.4. Reporting Process for Serious Adverse Events and Special Situations Reports 83
7.4.1. Serious Adverse Event Reporting Process 83
7.4.2. Special Situations Reporting Process 84
7.5. Gilead Reporting Requirements 87
7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events 87
7.7. Toxicity Management 88
8. STATISTICAL CONSIDERATIONS 89
8.1. Analysis Objectives and Endpoints 89
8.2. Planned Analyses 89
8.2.1. Interim Analyses 89
8.2.2. Primary Analysis 90
8.2.3. Final Analysis 90
8.3. Analysis Conventions 91
8.3.1. Analysis Sets 91
8.3.2. Data Handling Conventions 91
8.4. Demographic and Baseline Characteristics Analysis 92
8.5. Efficacy Analysis 92
8.5.1. Primary Analysis 94
8.5.2. Secondary Analyses 94
8.5.3. Exploratory Analyses 95
8.6. Safety Analysis 95
8.6.1. Extent of Exposure 95
8.6.2. Adverse Events 96
8.6.3. Laboratory Evaluations 96
8.6.4. Other Safety Evaluations 96
8.7. Adjustments for Multiplicity 97
8.7.1. Phase 2 97
8.7.2. Phase 3 97
8.8. Pharmacokinetic Analysis 97
8.8.1. Phase 2 97
8.8.2. Phase 3 98
8.9. Sample Size 98
8.9.1. Phase 2 98
8.9.2. Phase 3 98
8.10. Data Monitoring Committee 98
9. RESPONSIBILITIES 99
9.1. Investigator Responsibilities 99
9.1.1. Good Clinical Practice 99
9.1.2. Financial Disclosure 99
9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval 99
9.1.4. Informed Consent 99
9.1.5. Confidentiality 100
9.1.6. Study Files and Retention of Records 101
9.1.7. Case Report Forms 102
9.1.8. Investigator Inspections 102
9.1.9. Protocol Compliance 102

9.2. Sponsor Responsibilities 103
9.2.1. Protocol Modifications 103
9.2.2. Study Reports and Publications 103
9.3. Joint Investigator/Sponsor Responsibilities 103
9.3.1. Payment Reporting 103
9.3.2. Access to Information for Monitoring 103
9.3.3. Access to Information for Auditing or Inspections 104
9.3.4. Study Discontinuation 104
9.3.5. Data Protection 104

10. REFERENCES 105

11. APPENDICES 108

11.1. Investigator Signature Page 109
11.2. Marketing Authorization Status of Study Interventions 110
11.3. Disaster and Public Health Emergency Risk Assessment and Mitigation Plan 111
11.4. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements 114
11.5. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities 117
11.6. Management of Clinical and Laboratory Adverse Events 118
11.7. Amendment History 119
11.7.1. Amendment 4 (03 April 2025) 119
11.7.2. Amendment 3 (18 June 2024) 119
11.7.3. Amendment 2 (05 October 2023) 121
11.8. Sponsor Signature Page 122

LIST OF IN-TEXT TABLES

Table 1. Phase 2 – Treatment Groups 1, 2, and 3: Screening through Post-Endpoint Week 24 21
Table 2. Phase 2 – Treatment Groups 1, 2, and 3: ERT Visit through 60-Day In-Clinic Follow-up Visit 24
Table 3. Phase 3 – Treatment Groups 1 and 2: Screening through Post-Endpoint Week 48 27
Table 4. Phase 3 – Treatment Groups 1 and 2: ERT Visit through 60-Day In-Clinic Follow-up Visit 31
Table 5. Comparison of Projected LEN Exposures in the Oral BIC+LEN or the BIC/LEN FDC Treatment Groups Versus the Model-Estimated LEN Exposures With SC Dosing Regimens 39
Table 6. Comparison of Steady State PK parameters for BIC 75 mg Once Daily Dosing Across Studies 41
Table 7. GS-US-621-6292: Preliminary PK Parameters of BIC Following Single Dose Co-administration of BIC 75 mg + LEN 25 mg (Reference Arm) versus BIC 75 mg/LEN 50 mg FDC Under Fasted or Fed Conditions 41
Table 8. Comparison of Steady State PK parameters for LEN 25 or 50 mg Once Daily Dosing Versus SC LEN Dosing Across Studies 42
Table 9. GS-US-621-6292: Preliminary Pharmacokinetic Parameters of LEN Following Single Dose Co-administration of BIC 75 mg + LEN 25 mg (Reference Arm) versus BIC 75 mg/LEN 50 mg FDC Under Fasted or Fed Conditions 44
Table 10. Missed Daily Dose(s) Recommendation for BIC+LEN or BIC/LEN Treatment Groups 62
Table 11. Examples of Prior and Concomitant Medications That Are Prohibited or to be Used With Caution With BIC+LEN or BIC/LEN FDC Because of the Potential for Pharmacokinetic Drug-Drug Interaction or Impact on Efficacy Assessments or Participant Safety 63
Table 12. Laboratory Analytes 69
Table 13. Estimand and Handling for Intercurrent Events for Virologic Outcomes 93

LIST OF IN-TEXT FIGURES

Figure 1. Study Schema 20
Figure 2. GS-US-621-6289: Preliminary Distribution of LEN Trough Concentrations at Steady State (Weeks 16 or 24) Following QD Co-administration 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) 43

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ART	ARV therapy
ARV	antiretroviral
AUC	area under the concentration versus time curve
AUC_{0-t}	area under the concentration versus time curve from time zero to any given time 't'
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BIC	bictegravir
BLQ	below the limit of quantitation
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CD4	clusters of differentiation 4
CI	confidence interval
CL/F	apparent oral clearance
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CSR	clinical study report
C_t	concentration of drug at any given time 't'
C_{tau}	observed drug concentration at the end of the dosing interval
C_{trough}	concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme
DAIDS	Division of AIDS
DDI	drug-drug interaction
DMC	data monitoring committee

ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-3L	EuroQol 5 Dimensions, 3 Levels
ERT	end of randomized treatment
ESDD	early study drug discontinuation
EU	European Union
EU CT	European Union Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
GCP	Good Clinical Practice
Gilead	Gilead Sciences/Gilead Sciences, Inc.
PS	Patient Safety
HBV	hepatitis B virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIVTSQc-12	HIV Treatment Satisfaction Questionnaire—Change 12-item
HIVTSQs-12	HIV Treatment Satisfaction Questionnaire—Status 12-item version
HLT	high-level term
HRQOL	health-related quality of life
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
IND	investigational new drug
INSTI	integrase strand-transfer inhibitor
IRB	institutional review board
IRT	Interactive Response Technology
LEN	lenacapavir
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTR	multitablet regimen
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
PRO	patient-reported outcome
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

PK	pharmacokinetic(s)
PopPK	population PK
PT	preferred term
rBA	relative bioavailability
RNA	ribonucleic acid
SAE	serious adverse event
SBR	stable baseline regimen
SC	subcutaneous
SOC	system organ class
SSR	special situations report
STR	single-tablet regimen
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
T_{max}	time (observed time point) of C_{max}
ULN	upper limit of normal
US	United States
VR	virologic rebound
V_z	volume of distribution
V_z/F	apparent volume of distribution
WPAI - HIV	Work Productivity and Activity Impairment Questionnaire: HIV

PROTOCOL SYNOPSIS

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

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

Short Title: Study to Compare Bictegravir/Lenacapavir Versus Current Therapy in People With HIV-1 Who Are Successfully Treated With a Complicated Regimen

IND Number: 158963
EU CT Number: 2022-500929-33
ClinicalTrials.gov Identifier: NCT05502341

Study Centers Planned:

Approximately 110 centers globally.

Objectives and Endpoints:

Primary Objectives	Primary Endpoints
Phase 2: • To evaluate the efficacy of switching to a bictegravir (BIC) + lenacapavir (LEN) regimen (BIC 75 mg + LEN 25 mg or BIC 75 mg + LEN 50 mg) versus continuing on a stable baseline regimen (SBR) in virologically suppressed people with HIV-1 as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24	**Phase 2:** • Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm
Phase 3: • To evaluate the efficacy of switching to BIC/LEN fixed-dose combination (FDC) tablet regimen (BIC 75 mg/LEN 50 mg) versus continuing on a SBR in virologically suppressed people with HIV-1 as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48	**Phase 3:** • 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
Phase 2:	**Phase 2:**
• To evaluate the efficacy of the 3 treatment regimens in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count at Week 24	• Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm • Change from baseline in CD4 cell count at Week 24
• To evaluate the safety and tolerability of the 3 treatment groups through Week 24	• Proportion of participants experiencing treatment-emergent adverse events (AEs) through Week 24
• To evaluate the pharmacokinetics (PK) of BIC and LEN for participants receiving BIC 75 mg + LEN 25 mg and BIC 75 mg + LEN 50 mg	• PK parameters C_{max}, AUC_{tau}, and C_{tau} (as applicable) of BIC and LEN
Phase 3:	**Phase 3:**
• To evaluate the efficacy of the 2 treatment groups in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count at Week 48	• Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm • Change from baseline in CD4 cell count at Week 48
• To evaluate the efficacy of BIC/LEN in participants from Treatment Group 1 as determined by viral load suppression rate and CD4 cell count at Week 96	• Proportion of participants from Treatment Group 1 with HIV-1 RNA ≥ 50 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm • Change from baseline in CD4 cell count at Week 96 for participants from Treatment Group 1
• To evaluate the safety and tolerability of the 2 treatment groups through Week 48	• Proportion of participants experiencing treatment-emergent AEs through Week 48
• To evaluate the safety and tolerability of BIC/LEN in participants from Treatment Group 1 through Week 96	• Proportion of participants from Treatment Group 1 experiencing treatment-emergent AEs through Week 96

Study Design:

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

Phase 2:

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

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

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

Phase 3:

A randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of FDC tablets containing BIC 75 mg/LEN 50 mg versus SBR in people with HIV-1 who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a SBR for at least 6 months prior to screening.

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

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

Randomization will be stratified by geographic region in the Phase 3 portion of the study.

Number of Participants Planned:

Approximately 671 participants total: 125 participants in Phase 2 (50 each in Treatment Groups 1 and 2, and 25 in Treatment Group 3) and 546 participants in Phase 3 (364 in Treatment Group 1 and 182 in Treatment Group 2).

Target Population: People with HIV-1 (≥ 18 years of age), virologically suppressed for at least 6 months prior to screening on a stable complex treatment regimen.

Duration of Intervention:

Phase 2:

Participants will be treated for at least 24 weeks during the Randomized Period.

After Week 24, participants will continue to take their study drug (BIC+LEN or SBR) and attend visits every 12 weeks. Once the last participant completes Week 24 and the dose is selected for the BIC/LEN FDC tablets, all participants will attend the end of randomized treatment (ERT) visit and will be given the option to participate in an Extension Period to receive BIC 75 mg/LEN 50 mg FDC tablets, until this product becomes available, or until Gilead Sciences (Gilead) elects to discontinue the study, whichever occurs first.

Phase 3

Participants will be treated for at least 48 weeks during the Randomized Period.

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

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

Diagnosis and Main Eligibility Criteria:

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

- Documented plasma HIV-1 RNA levels must be < 50 copies/mL during treatment with the baseline regimen for a minimum period of 6 months prior to the screening visit (Phase 2 only).
- If plasma HIV-1 RNA measurements in the 6 months prior to screening are available, all levels must be < 50 copies/mL (Phase 3 only).
- At least one documented plasma 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 (Phase 3 only).
- Plasma HIV-1 RNA levels < 50 copies/mL at screening.

- Currently receiving a complex antiretroviral (ARV) regimen due to previous viral resistance, or intolerance, or contraindication to the components of existing single-tablet regimens, and on this regimen for at least 6 months prior to the screening visit. The criteria to define a complex regimen in this study are as follows:
  - A regimen containing a boosted protease inhibitor or a nonnucleos(t)ide reverse transcriptase inhibitor plus at least 1 other third agent (ie, an agent from a class other than NRTIs) (eg, bictegravir/emtricitabine/tenofovir alafenamide [coformulated; Biktarvy®; BVY] + darunavir/cobicistat, BVY + etravirine), or
  - A regimen of ≥ 2 pills/day, or a regimen requiring dosing more than once daily, or
  - A regimen containing parenteral agent(s) (excluding a complete long-acting injectable regimen, such as intramuscular cabotegravir plus rilpivirine) as well as oral agents.
- No documented or suspected resistance to BIC (mutations T66A/I/K, E92G/Q, G118R, F121Y, Y143C/H/R, S147G, Q148H/K/R, N155H/S, or R263K in the integrase gene).
- Estimated glomerular filtration rate ≥ 15 mL/min according to the Cockcroft-Gault formula for creatinine clearance who are not on renal replacement therapy.
- 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

Study Procedures/Frequency:

Phase 2:

Randomization Period: Following the Day 1 visit, participants will be required to return for study visits at Day 2 (oral loading dose for Treatment Groups 1 and 2), Weeks 4, 12, and 24. According to the participant preference, an optional visit at Week 16 may be scheduled for blood collection for the optional intensive PK substudy to facilitate study procedures scheduled for visit Week 24. Participants will be followed every 12 weeks after the Week 24 visit until the ERT visit.

The timings of efficacy and safety assessments for the Phase 2 Randomized Period are detailed in Table 1.

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

Extension Period: Participants from Treatment Groups 1, 2, and 3 who complete the ERT visit will be given the option to enter an Extension Period. Participants who received BIC+LEN tablets (ie, Treatment Groups 1 and 2) during the Randomized Period will continue treatment with BIC 75 mg/LEN 50 mg FDC tablets without any oral loading doses of LEN. Participants who received their SBR (ie, Treatment Group 3) during the Randomized Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to BIC 75 mg/LEN 50 mg FDC tablets starting on Day 1 of the Extension Period. Following the Day 1 visit, these participants will be required to return for the study visit at Day 2 (option to conduct this as a virtual visit will be available, as appropriate) and Extension Period Week 4 in addition to the regularly scheduled visits once every 12 weeks as per below.

All participants enrolled in the Extension Period will return for study visits every 12 weeks and will have a telephone visit at 30 days and a clinic visit at 60 days after the end of the Extension Period.

Participants who complete the study through the ERT visit of the Randomized Period and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit, and will be considered to have completed the Phase 2 portion of the study.

The timings of efficacy and safety assessments for the Phase 2 Extension Period are detailed in Table 2.

Phase 3:

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

The timings of efficacy and safety assessments for the Phase 3 Randomized Period are detailed in Table 3.

Sparse PK blood samples will be collected at on-treatment study visits for all participants in Treatment Group 1 at the time points specified in Table 3. An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites (Table 3).

Extension Period:

Participants from Treatment Group 1 will continue to receive BIC/LEN FDC tablets until at least Week 96. At the Week 96 or ERT visit, whichever occurs later, participants will be given the option to enter the Extension Period to continue to receive BIC/LEN FDC tablets.

Participants who do not wish to enter the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the Week 96 visit or ERT visit, whichever occurs later, and will be considered to have completed the study.

Participants from Treatment Group 2 who completed the ERT visit will be given the option to enter an Extension Period to receive BIC/LEN FDC tablets and will return for an Extension Period Week 4 visit.

Participants from Treatment Group 2 who complete the study through ERT visit and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit and will be considered to have completed the study.

All participants enrolled in the Extension Period will return for study visits every 12 weeks and will have a telephone visit at 30 days and a clinic visit at 60 days after the end of the Extension Period.

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

The timings for efficacy and safety assessments for the Phase 3 Extension Period are detailed in Table 4.

Test Product, Dose, and Mode of Administration:

Phase 2:

Bictegravir 75 mg + LEN 25 mg, once daily, orally (Treatment Group 1); BIC 75 mg + LEN 50 mg, once daily, orally (Treatment Group 2). Participants randomized to Treatment Groups 1 and 2 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily doses of BIC+LEN starting on Day 1. The study drugs will be administered without regard to food, except for participants enrolled in the intensive PK substudy who will receive study drugs under fasted conditions on Days 1 and 2, and at Weeks 16 or 24 visits.

Phase 3:

Bictegravir 75 mg/LEN 50 mg FDC (Treatment Group 1). Participants randomized to Treatment Group 1 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC tablets starting on Day 1.

Reference Therapy, Dose, and Mode of Administration: Participants in the SBR groups of Phase 2 and Phase 3 will continue on their current complex ARV drug regimen.

Statistical Methods:

The analyses of this study will be structured in 2 portions: exploratory (Phase 2) to select the appropriate doses of the individual components of BIC and LEN as part of the BIC/LEN FDC, and confirmatory (Phase 3) to evaluate the treatment effect of BIC/LEN FDC.

Unique participants will be enrolled in the Phase 2 and Phase 3 portions of the study. Data from the interim and final analyses of each phase of the study will be analyzed separately. The confirmatory analyses will only include data from participants randomized into the Phase 3 portion of the study; they will not include data from participants in the Phase 2 portion.

Results from Week 24 primary analysis of the Phase 2 portion will be used in conjunction with the results of Phase 1 rBA Study GS-US-621-6292 to select the dose of the BIC/LEN FDC tablet to be used in Treatment Group 1 of the Phase 3 portion, and the Phase 2 and Phase 3 Extension Periods of the study.

Phase 2:

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA–defined snapshot algorithm. The 2-sided 95% CIs for the difference in proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 between each of the BIC+LEN groups and SBR group will be constructed based on an unconditional exact method using 2 invert 1-sided tests.

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

The changes from baseline in CD4 cell count at Week 24 will be summarized by treatment using descriptive statistics. The differences in changes from baseline in CD4 cell count between each of the BIC+LEN groups and SBR group and the associated 95% CIs will be constructed using an analysis of covariance (ANCOVA) models, including baseline CD4 cell count as a covariate and treatment (each of the BIC+LEN groups versus SBR) as a fixed effect in the models.

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

For the general PK analyses, the PK of BIC and LEN may be evaluated using descriptive statistics and/or population analysis approaches. For the intensive PK substudy, plasma concentrations of BIC and LEN may be summarized by nominal sampling time using descriptive statistics. Also, PK parameters ($AUC_{0\text{-}t}$, AUC_{tau}, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, and C_t, as appropriate) may be listed and summarized using descriptive statistics.

The target sample size is 125 participants, with 50 participants in each of the BIC+LEN groups and 25 participants on SBR. The sample size in the Phase 2 portion of this study is determined based on practical considerations and past experience with similar types of studies. The sample size will provide an assessment of safety, efficacy, and PK to inform dose selection of BIC and LEN for the FDC tablet to be used in Phase 3 portion of the study.

Phase 3:

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

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 Full Analysis Set.

The changes from baseline in CD4 cell count at Week 48 will be summarized by treatment using descriptive statistics. The difference between the 2 treatments groups and the associated 95% CI will be constructed using ANCOVA models, including baseline CD4 cell count and geographic region as covariates and treatment (BIC/LEN FDC versus SBR) as a fixed effect in the model.

Longer term antiviral effect including proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 96 and change from baseline in CD4 cell count through Week 96 will also be assessed for participants randomized to Treatment Group 1. Antiviral effect, safety, and tolerability of BIC/LEN FDC will also be evaluated for participants switching to BIC/LEN FDC in the Extension Phase.

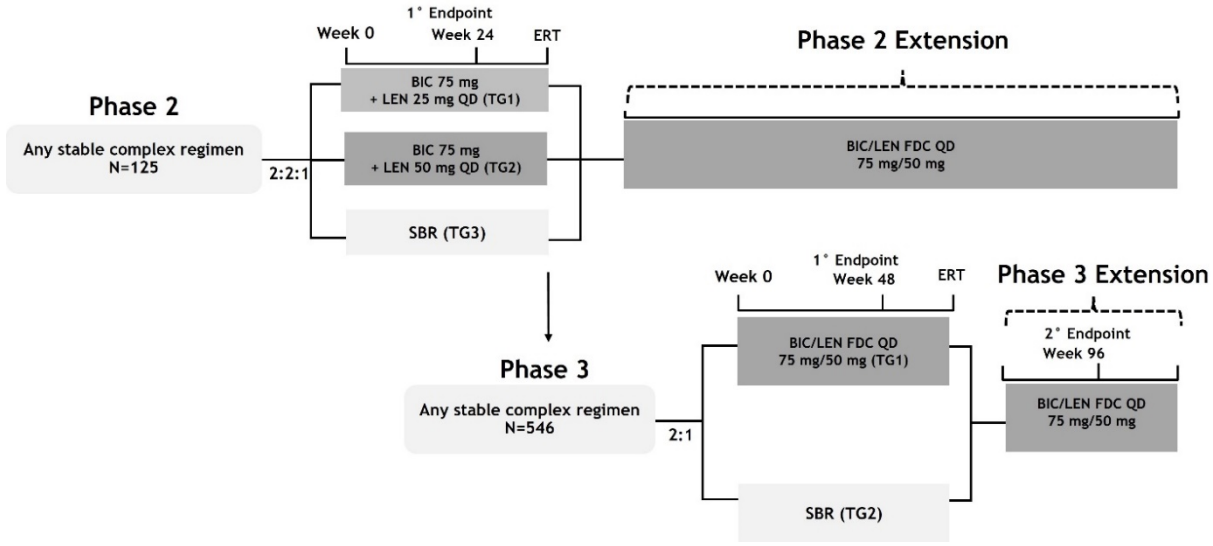
The number and proportion of participants experiencing treatment-emergent AEs (by SOC, HLT [if applicable], and PT), AEs leading to discontinuation of study drugs, and treatment-emergent laboratory abnormalities will be summarized by treatment using descriptive statistics.

For the general PK analyses, PK of BIC and LEN may be evaluated using descriptive statistics and/or population analysis approaches. For the intensive PK substudy, plasma concentrations of BIC and LEN may be summarized by nominal sampling time using descriptive statistics. Also, PK parameters (AUC_{0-t}, AUC_{tau}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, and C_t, as appropriate) may be listed and summarized using descriptive statistics.

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

STUDY SCHEMA

Figure 1. Study Schema



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

STUDY PROCEDURES TABLE

Table 1. Phase 2 – Treatment Groups 1, 2, and 3: Screening through Post-Endpoint Week 24

				Week				Post-Endpoint Week 24[d]
Study Procedures	**Screening[a]**	**Day 1[b]**	**Day 2[c]**	**4**	**12**	**16 (optional)**	**24**	**Every 12 weeks**
Visit Window		**30 days after screening visit**		**± 6 days**	**± 6 days**	**±6 days**	**± 6 days**	**± 6 days**
Informed consent	X							
Medical history	X							
Concomitant medications	X	X	X	X	X		X	X
Adverse events[e]	X	X	X	X	X	X	X	X
Complete physical exam	X	X			X		X	
Symptom-directed physical exam[f]				X				X
12-Lead ECG (performed supine)	X				X		X	
Height	X							
Vital signs[g]	X	X		X	X		X	X
Urinalysis	X	X		X	X		X	X
Urine pregnancy test[h]		X						
Serum pregnancy test[h]	X							
FSH[i]	X							
Chemistry profile[j]	X	X		X	X		X	X
Metabolic assessments[k]		X			X		X	X
Creatinine clearance	X	X		X	X		X	X
Hematology profile[l]	X	X		X	X		X	X
Plasma HIV-1 RNA	X	X		X	X		X	X
CD4 cell count	X	X		X	X		X	X
Plasma and urine storage sample[m]	X	X		X	X		X	X

Study Procedures	Screening[a]	Day 1[b]	Day 2[c]	Week 4	Week 12	Week 16 (optional)	Week 24	Post-Endpoint Week 24[d] Every 12 weeks
Visit Window		**30 days after screening visit**		**± 6 days**	**± 6 days**	**±6 days**	**± 6 days**	**± 6 days**
HCV serology[n]	X						X	
HBV blood panel[o]	X						X	
Plasma samples stored for potential HIV-1 genotype/phenotype[p]		X		X	X		X	X
Whole blood for proviral DNA sequencing		X						
Sparse PK: trough and postdose PK sample (Treatment Groups 1 and 2)[q,r,s]		X		X	X		X	X[r]
Optional intensive PK substudy (Treatment Groups 1 and 2)[s,t]		X	X			X	X	
Randomization		X						
Provide participant dosing diary to participants		X		X	X		X	X
Study drug dispensation		X		X	X		X	X
Study drug accountability				X	X		X	X

AE = adverse event; BIC = bictegravir; CD4 = clusters of differentiation 4; ECG = electrocardiogram; ERT = end of randomized treatment; FDC = fixed-dose combination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HBcAb = hepatitis B virus core antibody; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HCV Ab = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; LEN = lenacapavir; PK = pharmacokinetic(s)

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

b Initiation of the first dose of study drug is to take place in clinic following completion of study procedures at the Day 1 visit. Participants randomized to Treatment Groups 1 and 2 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily doses of BIC+LEN starting on Day 1. The study drugs will be administered without regard to food, except for participants enrolled in the intensive PK substudy who will receive study drugs under fasted conditions on Days 1 and 2, and at Weeks 16 or 24 visits.

c Day 2 visit is not applicable to participants in Treatment Group 3. Day 2 visit is to be completed the day after Day 1 visit. Day 2 visit may be a virtual visit and the participants will self-administer the study drugs and be observed by site staff to confirm dosing. Please refer to Section 6.3.8 for further details. Participants in the optional intensive PK substudy, and/or when a virtual visit cannot be performed, will dose in clinic and optional PK samples will be obtained (as applicable) as described in Section 6.3.9.

d After Week 24, all participants will return for visits every 12 weeks until the FDC is determined.

e Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

f Symptom-directed physical examination as needed.

g Blood pressure, pulse, respiration rate, temperature, and weight.

h Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.

i At screening, a FSH test is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.

j Chemistry profile per Table 12.

k Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

l Hematology profile per Table 12.

m Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate) in accordance with local regulations. Separate consent for optional future research is not needed to collect these samples unless required per local regulations and requirements.

n HCV Ab serology to be performed at screening and Week 24 of randomized treatment and at the 60-day follow-up visit. Participants who are HCV Ab positive will have an HCV RNA test performed.

o HBV blood panel (HBsAg, HBsAb, and HBcAb) will be performed at screening, Week 24 of Randomized Treatment Period and 60-day follow-up visit. **Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study.** Participants who are HBsAg positive will have a plasma HBV DNA test performed.

p HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Section 6.3.10.2).

q For participants in Treatment Groups 1 and 2 not enrolled in the intensive PK substudy, a single predose plasma PK sample (≤ 5 min before dose) **and** a single postdose plasma PK sample at 4 hours (± 1 hours) (relative to BIC+LEN dosing and oral loading dose of LEN) on Day 1. A single trough plasma PK sample approximately 23 to 24 hours after the previous dose and prior to dosing at Weeks 4, 12, and 24, **and** a single postdose plasma PK sample at 2 hours (± 1 hours) (relative to BIC +LEN dosing) at Weeks 4, 12, and 24.

r For participants who become pregnant and provide reconsent to remain on study, sparse PK samples will be collected as follows: at all specified time points described above in footnote 'p' during randomized treatment visits until Week 24. A single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12 week visit (as possible) after Week 24 until ERT visit and during Extension Period. See Section 6.3.9.1 for additional information. For pregnant participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at every 12 week visit (as possible) after Week 24 until the ERT visit and during Extension Period.

s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse/intensive PK sample (as applicable).

t An intensive PK substudy will be performed in a subset of participants in Treatment Groups 1 and 2 at selected study sites. Participants may select to participate in 1 or more visit(s). Intensive PK blood samples will be collected for the subset of participants as described below **instead of** the sparse plasma PK samples on those specific visits.
Day 1: Single PK sample predose (≤ 5 min before dose), and at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC+LEN dosing and oral loading dose of LEN).
Day 2: Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose on Day 1 and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, and 6 hours postdose (relative to BIC+LEN dosing and oral loading dose of LEN).
Week 16 or Week 24 visit: Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose that was administered the day before and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC+LEN dosing).
All participants enrolled in the intensive PK substudy on Days 1 and 2, and at Weeks 16 or 24 will receive BIC+LEN under fasted conditions.

Table 2. Phase 2 – Treatment Groups 1, 2, and 3: ERT Visit through 60-Day In-Clinic Follow-up Visit

Study Procedures	ERT Visit[a]	Phase 2 Extension Period[b] (Only for TG3 participants who enroll in the Extension Period)			Early Study Drugs DC Visit[c]	30-day Telephone Visit[d]	60-day In-Clinic Follow-up Visit
		Day 2	Week 4	Every 12 weeks			
Visit Window			± 6 days	± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Concomitant medications	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X
Complete physical exam	X				X		X
Symptom-directed physical exam[f]			X	X			
12-Lead ECG (performed supine)					X		
Vital signs[g]	X		X	X	X		X
Urinalysis	X		X	X	X		X
Urine pregnancy test[h]					X		X
Chemistry profile[i]	X		X	X	X		X
Metabolic assessments[j]	X			X			
Creatinine clearance	X		X	X	X		X
Hematology profile[k]	X		X	X	X		X
Plasma HIV-1 RNA	X		X	X	X		X
CD4 cell count	X		X	X	X		X
Plasma and urine storage sample[l]	X		X	X	X		X
HCV serology[m]							X[l]
HBV blood panel[n]							X[m]

Study Procedures	ERT Visit[a]	Phase 2 Extension Period[b] (Only for TG3 participants who enroll in the Extension Period)			Early Study Drugs DC Visit[c]	30-day Telephone Visit[d]	60-day In-Clinic Follow-up Visit
		Day 2	Week 4	Every 12 weeks			
Visit Window			± 6 days	± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Plasma samples stored for potential HIV-1 genotype/phenotype[o]	X		X	X	X		X
Sparse PK: trough and postdose PK sample (Treatment Groups 1 and 2) [p,q]				X			
Provide participant dosing diary to participants	X		X	X			
Study drug dispensation	X		X	X			
Study drug accountability	X		X	X	X		

AE = adverse event; BIC = bictegravir; CD4 = clusters of differentiation 4; DC = discontinuation; ECG = electrocardiogram; ERT = end of randomized treatment; FDC = fixed-dose combination; HBV = hepatitis B virus; HBcAb = hepatitis B virus core antibody; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HCV Ab = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1; LDL = low-density lipoprotein; LEN = lenacapavir; PK = pharmacokinetic(s); TG3 = Treatment Group 3

a Once the last participant completes the Week 24 visit and Gilead completes the Week 24 analysis, all participants will return to the clinic (preferably within 30 days) on their next follow-up visit for an ERT visit. At the ERT visit, participants will be given BIC/LEN FDC in an Extension Period until drug is available or until Gilead elects to discontinue the study, whichever occurs first. Participants who complete the study through the ERT visit, and do not wish to participate in the Extension Period, will be required to return to the clinic 60 days after the ERT visit for a 60-day follow-up visit, and will be considered to have completed the Phase 2 portion of the study.

b Participants from Treatment Group 3 who enroll in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1 of the Extension Period. Day 2 may be a virtual visit and the participants will self-administer study drugs and be observed by the site to confirm dosing. Please refer to Section 6.3.8 for further details.

c Participants who discontinue study drug early will have a telephone visit at 30 days and a clinic visit at 60 days after the early study drugs DC visit.

d Participants must complete a 30-day follow-up telephone visit after completion of the Extension Period. Participants who choose to not continue the study after the ERT visit, must return for a 30-day follow-up visit. Participants must also complete a 60-day in-clinic follow-up visit after the completion of the Extension Period.

e Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

f Symptom-directed physical examination as needed.

g Blood pressure, pulse, respiration rate, temperature, and weight.

h Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.

i Chemistry profile per Table 12.

j Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

k Hematology profile per Table 12.

l Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate) in accordance with local regulations. Separate consent for optional future research is not needed to collect these samples unless required per local regulations and requirements.

m HCV Ab serology to be performed at screening and Week 24 of randomized treatment and at the 60-day follow-up visit. Participants who are HCVAb positive will have an HCV RNA test performed.

n HBV blood panel (HBsAg, HBsAb, and HBcAb) will be performed at screening, Week 24 of Randomized Treatment Period and 60-day follow-up visit. **Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study.** Participants who are HBsAg positive will have a plasma HBV DNA test performed.

o HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Section 6.3.10.2).

p For participants who become pregnant and provide reconsent to remain on study, a single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12 week visit (as possible) during Extension Period. See Section 6.3.9.1 for additional information..

q At each on-treatment study visit, participants are to take study drug in the clinic after collection of trough sparse/intensive PK sample (as applicable).

Table 3. Phase 3 – Treatment Groups 1 and 2: Screening through Post-Endpoint Week 48

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

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

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

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

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

b Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit. Participants randomized to Treatment Group 1 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1. The study drugs will be administered without regard to food.

c Day 2 visit is not applicable to participants in Treatment Group 2. Day 2 visit is to be completed the day after Day 1 visit. Day 2 visit may be a virtual visit and the participants will self-administer the study drugs and be observed by site staff to confirm dosing. Please refer to Section 6.3.8 for further details.

d After Week 48, all participants will return for visits every 12 weeks until the ERT visit.

e Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

f Symptom-directed physical examination as needed.

g Blood pressure, pulse, respiration rate, and temperature.

h Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.

i At screening, a FSH is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.

j Chemistry profile per Table 12.

k Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

l Hematology profile per Table 12.

m Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate) in accordance with local regulations. Separate consent for optional future research is not needed to collect or use these samples unless required per local regulations and requirements.

n HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb), at Week 48 of randomized treatment, at Week 48 of the Extension Period visits, and at the 60 day in-clinic follow-up visit. **Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study.** Participants who are HBsAg positive will have a plasma HBV DNA test performed.

o HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Section 6.3.10.2).

p Proviral DNA sequencing is for research use only. Sample is to be collected for all participants on study. Separate consent is not required for this test.

q For participants in Treatment Group 1, a single predose plasma PK sample (≤ 5 min before dose) and a postdose plasma PK sample at 4 hours (± 1 hours) (relative to BIC/LEN FDC dosing and oral loading dose of LEN) will be collected on Day 1. A single trough plasma PK sample approximately 23 to 24 hours after the previous dose and prior to dosing at Weeks 4, 12, 24, 36, and 48, and a single postdose plasma PK sample at 2 hours (± 1 hours) (relative to BIC/LEN dosing) at Weeks 4, 12, 24, 36, and 48 will be collected. For participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule (except for participants enrolled in the intensive PK substudy), a PK sample prior to dosing in clinic should be collected at Weeks 4, 12, 24, 36, and 48.

r For participants who become pregnant and provide reconsent to remain on study, sparse PK samples will be collected as follows: at all specified time points described above in footnote 'q' during randomized treatment visits until Week 48. A single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12 week visit (as possible) after Week 48 until ERT visit and during Extension Period. See Section 6.3.9.2 for additional information. For pregnant participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at every 12 week visit (as possible) after Week 48 until the ERT visit and during Extension Period.

s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse intensive PK sample (as applicable).

t An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites. Participants may select to participate in either one of the visits. Intensive PK blood samples will be collected for the subset of participants as described below **instead of** the sparse plasma PK samples on those specific visits.
Week 24 or 36 or 48 visit: Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose that was administered the day before and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC/LEN FDC dosing).

u Investigators may perform a virtual visit or a phone call visit to review study drug and dosing diary adherence in between 2 in-clinic visits especially when the visits are 12 weeks apart.

v EQ-5D-3L Questionnaire will only be collected at Week 96 visit.

Table 4. Phase 3 – Treatment Groups 1 and 2: ERT Visit through 60-Day In-Clinic Follow-up Visit

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

Study Procedures	ERT Visit[a]	Phase 3 Extension[b]			Early Study Drugs DC Visit	30-day Telephone Visit[e]	60-day In-clinic Follow-up Visit[e]
		Only for TG2 participants who enroll in the Extension Period		Every 12 weeks[d]			
		Day 2	Week 4[c]				
Visit Window			± 6 days	± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Hematology profile[n]	X		X	X	X		X
Plasma HIV-1 RNA	X		X	X	X		X
CD4 cell count	X		X	X	X		X
Plasma and urine storage sample[o]	X		X	X	X		X
HBV blood panel[p]				X			X[o]
Plasma samples stored for potential HIV-1 genotype/ phenotype[q]	X		X	X	X		X
Sparse PK: trough PK sample (Treatment Group 1)[r,s]				X			
Provide participant dosing diary to participants	X		X	X			
Study drug dispensation	X		X	X			
Study drug accountability[t]	X		X	X	X		

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

a Once the last participant completes the Week 48 visit and Gilead completes the Week 48 analysis, all participants will return to the clinic (preferably within 30 days) on their next follow-up visit for an ERT visit. At the ERT visit, participants will be given BIC/LEN FDC in an Extension Period until drug is available or until Gilead elects to discontinue the study, whichever occurs first. Participants in Treatment Group 1 will continue to the Extension Period until Week 96, if they do not wish to continue in the Extension Period after Week 96, they will be required to return to the clinic 60 days after the Week 96 visit for a 60-day follow-up visit and will be considered to have completed the Phase 3 portion of the study. Participants in Treatment group 2 who complete the study through the ERT visit, and do not wish to participate in the Extension Period, will be required to return to the clinic 60 days after the ERT visit for a 60-day follow-up visit, and will be considered to have completed the Phase 3 portion of the study.

b Participants from Treatment Group 2 who enroll in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1 of the Extension Period. Day 2 may be a virtual visit and the participants will self-administer study drugs and be observed by the site to confirm dosing. Please refer to Section 6.3.8 for further details.
c Week 4 visit at the extension phase is only for participants who are previously randomized to Treatment Group 2 and then enrolled in extension phase.
d Every 12 week visits will follow the schedule of previously scheduled visits in the randomized phase and not from the ERT Visit for Treatment Group 1.
e Required for participants who enroll in the Extension Period or discontinue study drugs early. Participants who enroll in the Extension Period or discontinue study drugs early should have a 30-day telephone visit conducted. They will be required to return to clinic for a 60 day follow-up visit. For the purpose of scheduling a 60-day follow-up visit, a ± 6 days window may be used.
f Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
g Symptom-directed physical examination as needed.
h After the ERT visit, these questionnaires will only be administered to participants in Treatment Group 1 every 12 weeks until the Week 96 visit.
i During the Phase 3 Extension Period, EQ-5D-3L should only be collected at Week 96.
j Blood pressure, pulse, respiration rate, and temperature.
k Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.
l Chemistry profile per Table 12.
m Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
n Hematology profile per Table 12.
o Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate). Separate consent for optional future research is not needed to collect or use these samples unless required per local regulations and requirements.
p HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb), at Week 48 of randomized treatment, at Week 48 of the Extension Period visits, and at the 60 day in-clinic follow-up visit. **Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study.** Participants who are HBsAg positive will have a plasma HBV DNA test performed.
q HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Section 6.3.10.2).
r For participants who become pregnant and provide reconsent to remain on study, a single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12 week visit (as possible) during the Extension Period. See Section 6.3.9.2 for additional information. For participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at every 12 week visit (as possible) during the Extension Period.
s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse intensive PK sample (as applicable).
t Investigators may perform a virtual visit or a phone call visit to review study drug and dosing diary adherence in between 2 in-clinic visits especially when the visits are 12 weeks apart.

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 26 million taking antiretroviral (ARV) treatment {UNAIDS 2021}. 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 {European Aids Clinical Society (EACS) 2021, Panel on Antiretroviral Guidelines for Adults and Adolescents 2021, Saag 2020, U. S. Department of Health and Human Services (DHHS) 2019}. 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, several single-tablet regimens (STRs) exist for people with HIV-1. However, based on Gilead Sciences' (Gilead) 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). In an online survey of people with HIV-1, 8% (21/279) of respondents were taking 4 or more pills per day and 34% (94/279) of respondents were taking 2 to 3 pills per day {Dube 2020}. History of virologic failure and viral resistance is often the main reason for patients to take a complex ARV regimen. However, some patients may require a multitablet regimen (MTR) due to intolerance, toxicity or contraindications to existing STRs {Chang 2022}. Regimen simplification is recognized by healthcare providers as an unmet need for a segment of their patients.

An MTR is more difficult for people with HIV-1 to adhere to consistently over the long term and poor adherence is the most common reason for virologic failure. Low pill burden is associated with higher levels of adherence {Nachega 2014, Raboud 2011}. Additionally, people with HIV-1 receiving STRs are less likely to discontinue therapy (ie, higher persistence) compared with those receiving MTRs {Hines 2019}. In 2 meta-analyses, people with HIV-1 on an STR were more likely to achieve and maintain virologic suppression {Clay 2015, Clay 2018}. Convenience (eg, pill burden, dosing frequency, availability of FDC or STR formulations, food requirements) is one of the regimen-specific considerations in selecting an initial ARV regimen {AIDSinfo 2019}. The Food and Drug Administration (FDA) *Guidance for Industry: Human*

Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (November 2015) recognizes "convenient dosing schedule" as a desirable feature for an investigational agent. These data and recommendations highlight the continued need to simplify treatment regimens for all people with HIV-1, including those who are virologically suppressed on a complicated regimen due to their prior history of virologic failure and viral resistance, or due to intolerance, toxicity, or contraindications.

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. Collectively these qualities indicate that a BIC/LEN FDC tablet has the potential to address an important unmet medical need for virologically suppressed treatment-experienced people with HIV-1 who are on complex regimens by simplifying their treatment to 1 tablet once a day.

This study will evaluate the safety, efficacy and tolerability of switching from complex ART regimens to BIC+LEN (Phase 2 part of the study) or to BIC/LEN FDC (Phase 3 part of the study) as an option for virologically suppressed treatment-experienced people with HIV-1.

1.2. Background on Study Interventions

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

1.2.1. Lenacapavir

1.2.1.1. General Information

Lenacapavir 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 investigator's brochure (IB), including information on the following:

- Nonclinical pharmacokinetic (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.2. Bictegravir

1.2.2.1. General Information

Bictegravir, a potent inhibitor of HIV-1 integrase, is approved for the treatment of HIV infection as a component of the FDC of BIC/emtricitabine/tenofovir alafenamide (B/F/TAF).

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

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

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 on a complex ARV regimen. The majority of patients on complex regimens may have history of virologic failure due to HIV-RNA associated mutations that confer resistance to 1 or more ARV classes; however, this patient population may also include those with intolerance or contraindication to current STRs. 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 a STR alternative for treatment simplification in people with HIV-1 who are on a complex ARV regimen.

This study is an operationally seamless Phase 2/3 randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus stable baseline regimen (SBR) in virologically suppressed people with HIV-1 on a stable complex treatment regimens for at least 6 months prior to screening. In the Phase 2 portion, BIC+LEN tablets will be coadministered as single agents to provide supportive data to determine the optimal dose of LEN to be combined with BIC. Analysis of the Phase 2 primary endpoint and Phase 1 relative bioavailability (rBA) Study GS-US-621-6292 will enable dose selection and subsequent initiation of the Phase 3 portion of this study in which a single BIC/LEN FDC tablet will be administered. 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. Dose Selection for the Phase 2 Portion of the Study

1.4.1.1. Bictegravir Dose Selection

The PK/pharmacodynamic analyses in the proof-of-concept study of BIC as a single agent (Study GS-US-141-1219) supported the selection of a dose between 50 and 100 mg as the clinically efficacious oral dose of BIC for later-phase studies. Bictegravir at 75 mg coadministered with F/TAF in the BIC Phase 2 Study GS-US-141-1475 demonstrated BIC exposures that were consistent with those associated with efficacy in Study GS-US-141-1219. Furthermore, Week 24 data from Study GS-US-141-1475 supported the safety and efficacy of BIC exposures obtained with the 75 mg dose of BIC single agent.

The relative bioavailability (rBA) Study GS-US-141-1233 evaluated BIC exposures following administration of 2 doses of BIC as a component of B/F/TAF (50 or 75/200/25 mg) FDC compared to a 75 mg strength tablet of BIC and a 200/25 mg strength FDC tablet of F/TAF administered simultaneously under fasted conditions. Pharmacokinetic analysis showed that BIC exposures achieved with BIC 50 mg as a component of B/F/TAF FDC was comparable to the reference tablet of BIC 75 mg + F/TAF 200/25 mg tablet, whereas mildly higher BIC exposures were observed following administration of BIC 75 mg as a component of B/F/TAF 75/200/25 mg FDC as compared with the reference treatment (C_{max} and AUC_{inf} increases of 31% and 27%, respectively). Thus, bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®; BVY; B/F/TAF 50/200/25 mg coformulated FDC tablet), which contains 50 mg dose of BIC, was deemed acceptable for evaluation in Phase 3 clinical studies. The safety and efficacy data generated with BIC 50 mg as a component of the BVY FDC has supported its approval by global regulatory authorities, with an estimated 1,206,038 patient-years of cumulative exposure to BVY as of 06 August 2021 (estimated from sales data) since its first marketing approval in the US on 07 February 2018. Oral once-daily BIC 75 mg as a single agent is currently being evaluated in combination with subcutaneous (SC) LEN 927 mg once every 6 months in Treatment Group 2 of the Phase 2 study of LEN (Study GS-US-200-4334) because the PK of BIC 75 mg has been previously evaluated and shown to be safe and efficacious at this dose. Although DDI liability of both BIC and LEN supported by data from Studies GS-US-141-1485 and GS-US-200-4333, respectively, is suggestive of small increase in BIC exposure expected due to moderate cytochrome P450 enzyme (CYP) 3A4 inhibition potential of LEN, it is unlikely that inhibition of the CYP3A4 pathway alone will lead to clinically significant increases in BIC exposure. Indeed, slight (albeit clinically insignificant) increases (up to 1.7-fold) in mean BIC exposures were observed in the once-daily BIC 75 mg + SC LEN group (Treatment Group 2) of Study GS-US-200-4334 relative to the mean Phase 3 exposure estimates of BIC 50 mg following administration of BVY in a total of 1193 people with HIV-1 in Phase 3 registrational studies of BVY. As such, the safety and efficacy of BIC at these higher exposures are supported by the data from Study GS-US-200-4334 in conjunction with the wide range of BIC concentrations (approximately 0.4 to 2.3-fold of the mean exposures) in the aforementioned Phase 3 studies of BVY.

In the current study, once-daily oral LEN will be coadministered with oral BIC in Treatment Group 1 (BIC 75 mg + LEN 25 mg) and Treatment Group 2 (BIC 75 mg + LEN 50 mg) of the Phase 2 portion of the study (refer to Section 1.4.1.2 for the dose rationale for LEN). Guided by the totality of available data that suggest lack of a clinically significant DDI potential between BIC and LEN, the same dose of BIC as a single agent (ie, BIC 75 mg) will be administered with LEN 25 or 50 mg despite the comparatively higher LEN exposures anticipated following dosing of LEN 50 mg (Table 5). To support the clinical development of the once-daily BIC/LEN FDC tablet, Gilead is planning to evaluate 2 doses of BIC, 75 mg and a lower dose ranging from 50 to 75 mg, as part of a separate BIC/LEN rBA Study GS-US-621-6292. If the coformulation of BIC and LEN as an FDC tablet impacts BIC plasma exposure, a lower dose of BIC will be selected in an adaptive fashion and assessed as a component of the BIC/LEN FDC. The rBA study will confirm the comparability of the BIC exposure in the BIC/LEN FDC to the oral once-daily BIC 75 mg exposure profile in Treatment Groups 1 and 2 of the Phase 2 portion of the current study (based on the data from the Week 24 primary endpoint). The totality of available data will inform dose selection of BIC (ranging from 50 to 75 mg) for the BIC/LEN FDC tablet to be used in the Phase 3 portion of the study.

1.4.1.2. Lenacapavir Dose Selection

Lenacapavir oral and SC dosing has been extensively studied in Studies GS-US-200-5977, GS-US-200-4334, and GS-US-200-4625. Table 5 outlines the relevant exposure parameters (daily AUC, C_{trough}, etc) observed and/or predicted based on population PK (PopPK) modeling conducted by leveraging the data in the aforementioned studies (Regimens 1 to 4). To assist with the LEN dose selection for this study, LEN exposures were simulated for the proposed dosing regimen in Treatment Group 1 of the Phase 2 portion of the study using a previously developed PopPK model for the LEN treatment program. Preliminary observed data after 50 days of once-daily oral administration of LEN 25 mg without any loading doses of LEN (from Study GS-US-200-5977) were incorporated into the model to better delineate the LEN PK estimates following administration of once-daily oral LEN 25 mg with loading doses of LEN 600 mg on Days 1 and 2 (LEN Regimen 1). Additionally, PopPK analysis of the observed data following administration of once-daily oral LEN 50 mg with loading doses of LEN 600 mg on Days 1 and 2 from Study GS-US-200-4334 (Treatment Group 3) is suggestive of LEN exposure estimates in Treatment Group 2 in the Phase 2 portion of the current study with similar dosing regimen (LEN Regimen 2). Lenacapavir exposures from the Phase 2/3 SC regimens (GS-US-200-4334 and GS-US-200-4625 [LEN Regimens 3 and 4, respectively]) are also presented below to show comparison with efficacious LEN exposures.

Prior exposure-response analyses for LEN in heavily treatment-experienced population did not reveal any further increase in efficacy (virologic response or virologic failure) in an exposure-dependent manner within a broad range of plasma exposures (C_{trough} [9.1 to 92.6 ng/mL], and estimated average daily AUC [247.7 to 3999.7 h•ng/mL; calculated by dividing the $AUC_{Day1-15}$ values by 15]) (data on file). As shown below, LEN exposures following administration of once-daily LEN 25 mg or LEN 50 mg with oral 2-day loading doses of LEN as part of the proposed Treatment Groups (1 and 2) in the Phase 2 portion of the study are expected to be comparable or higher, respectively, than the exposures achieved

via the SC route of LEN which have been shown to be efficacious based on the data from GS-US-200-4334 and GS-US-200-4625. This dose-ranging design will further supplement the previous exposure-response data to evaluate the appropriate dose for LEN in potential BIC/LEN FDC evaluation in Phase 3.

To that end, the Week 24 primary endpoint analysis in the Phase 2 portion of this study in conjunction with the data from the rBA Study GS-US-621-6292, wherein similar doses of LEN (ie, 25 or 50 mg) are planned to be evaluated as a component in the BIC/LEN FDC, will inform final dose selection of LEN (25 or 50 mg) for the BIC/LEN FDC tablet to be used in the Phase 3 portion of the study.

Table 5. Comparison of Projected LEN Exposures in the Oral BIC+LEN or the BIC/LEN FDC Treatment Groups Versus the Model-Estimated LEN Exposures With SC Dosing Regimens

	LEN Regimen 1: Oral 600 mg on Days 1 and 2 + Once-Daily Oral 25 mg	**LEN Regimen 2: Oral 600 mg on Days 1 and 2 + Once-Daily Oral 50 mg**	**LEN Regimen 3: Oral 600 mg on Days 1 and 2, Oral 300 mg on Day 8, SC 927 mg Q26W From Day 15 Onward**	**LEN Regimen 4: Oral 600 mg on Days 1 and 2, Oral 300 mg on Day 8, SC 927 mg Q26W From Day 15 Onward**
LEN PK Parameter[a]	**Proposed BIC + LEN or BIC/LEN FDC Regimen[b]**	**GS-US-200-4334 Phase 2, Cohort 3 (N = 51)[b, c]**	**GS-US-200-4334 Phase 2, Cohorts 1 and 2 (N = 98)[c]**	**GS-US-200-4625 Phase 2/3 (N = 62)[c]**
Average daily AUC (h•ng/mL)[d]	1304 [1101, 1507]	2759 (61)	1116 (47.8)	1418 (46.7)
C_{max} (ng/mL)	75.1 [66.0, 84.1]	116 (60)	93.1 (61.9)	136.2 (75.2)
C_{last} (ng/mL)[e]	57.4 [46.3, 68.4]	113 (61)	22.5 (63.4)	35.1 (59.2)

BIC = bictegravir; CI = confidence interval; FDC = fixed-dose combination; HTE = heavily treatment-experienced; IV = intravenous; LEN = lenacapavir; PK = pharmacokinetic(s); PopPK = population PK; Q26W = every 26 weeks; SC = subcutaneous

a All data presented as mean (%CV) except for LEN Regimen 1 which is presented as predicted mean (90% CI).

b Using the PopPK model, LEN exposures were projected following Regimens 1 and 2 as proposed for BIC+LEN or the BIC/LEN FDC treatment groups.

c Post hoc LEN exposure estimates derived using the PopPK model for the Phase 2 study (GS-US-200-4334) in treatment-naive people with HIV-1 and the Phase 2/3 study (GS-US-200-4625) in HTE people with HIV-1.

d Average daily AUC = Projected $AUC_{0\text{-}Day50}$ divided by 50 for Regimen 1, the steady state AUC_{tau} for Regimen 2 (LEN HTE PopPK report CTRA-2021-1054), and $AUC_{0\text{-}Week28}$ divided by 196 for Regimens 3 and 4 (LEN HTE PopPK report CTRA-2021-1054).

e C_{last} = Projected C_{min} on Day 50 for Regimen 1, the steady state C_{min} for Regimen 2 (LEN HTE PopPK report CTRA-2021-1054), and C_{min} on Week 28 (Day 196) for Regimens 3 and 4 (LEN HTE PopPK report CTRA-2021-1054).

1.4.2. Phase 2 Experience and Dose Selection for the Phase 3 Portion of the Study

1.4.2.1. 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 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 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 to the SBR treatment group. BIC and LEN co-administered through Week 24 were safe and well tolerated as demonstrated by the low percentages of participants who had Grade 3 or higher 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) with no participants reporting 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 and LEN were consistent with historical data associated with efficacy and safety.

1.4.2.2. 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 6), 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 QD) 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 ~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 co-administration arm (Table 7) 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 6. 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)[e]
$AUC_{0\text{-}8h}$[c] (h•ng/mL)	64200 (30.6)	59600 (36.9)	72865.9 (31.0)[d]	-
AUC_{tau} (h•ng/mL)	150000 (30.9)	137000 (43.6)	167620.6 (37.6)[c]	139778.8 (27.0)[f]

BIC = bictegravir; FTC = emtricitabine; LEN = lenacapavir; PK = pharmacokinetic; 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 = 11

e N = 21

f N = 22

Table 7. GS-US-621-6292: Preliminary PK Parameters of BIC Following Single Dose Co-administration 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) Co-administration; Fasted (N=60)	BIC 75 mg/ LEN 50 mg FDC; Fasted (N=60)	FDC vs Co-administration %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)
$AUC_{0\text{-}Day8}$ (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)	-

BIC = bictegravir; CI = confidence interval; CV = coefficient of variation; 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)

1.4.2.3. 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, ~1.84-fold higher AUC_{tau} and ~1.85-fold higher C_{trough}) (Table 8). 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 ~3.8- and ~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 to 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 two LEN dose levels (25 and 50 mg QD) 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 8. 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,d]	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,d]
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_{0-8h} (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)

BIC = bictegravir; FTC = emtricitabine; LEN = lenacapavir; PK = 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.

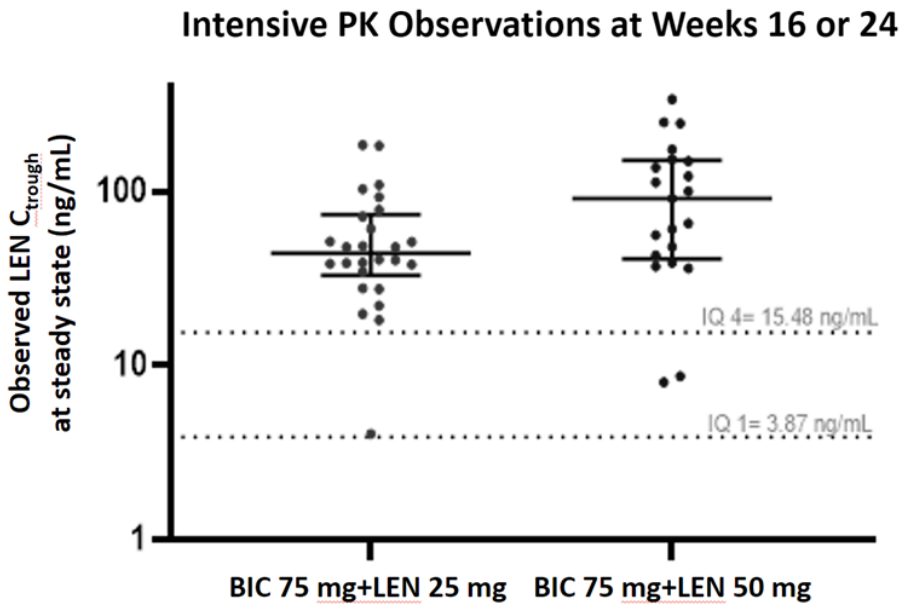
c In this Phase 2/3 study, heavily treatment experienced people with HIV-1 received oral LEN 600 mg on Days 1 and 2, and oral LEN 300 mg on Day 8 with SC LEN 927 mg dosed on Day 15 to be administered every 26 weeks thereafter.

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

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

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

Figure 2. **GS-US-621-6289: Preliminary Distribution of LEN Trough Concentrations at Steady State (Weeks 16 or 24) Following QD Co-administration 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 the with BIC 75 mg + LEN 25 mg co-administration in fasted state (Table 9; $AUC_{0\text{-}8days}$ 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 $AUC_{0\text{-}8days}$ 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 co-administration. 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 (TQT 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 9. GS-US-621-6292: Preliminary Pharmacokinetic Parameters of LEN Following Single Dose Co-administration 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) Co-admin; Fasted (N=60)	BIC 75 mg/ LEN 50 mg FDC; Fasted (N=60)	FDC vs Co-admin %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)
$AUC_{0\text{-Day8}}$ (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)	

BIC = bictegravir; CI = confidence interval; Co-admin = co-administration; CV = coefficient of variation; FDC = fixed-dose combination; GLSM = geometric least-squares mean; LEN = lenacapavir; 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 inter-individual variability and any potential for missed doses with a chronic once daily regimen.

1.5. Risk/Benefit 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 the drug. No events have been identified as ADRs in clinical studies that evaluated BIC as a single agent. Bictegravir is a component of the marketed product BVY; ADRs identified for BVY 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/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. Considering that BIC has a documented high barrier to resistance and patients with mutations associated to LEN resistance have achieved viral suppression on alternative regimens, the development of resistance to any component of the study regimen is unlikely to have an impact on a participant's future treatment options.

Potential benefits of BIC/LEN may include provision of a new 2-drug ART that is not currently available, which may have fewer side effects than alternative therapies and may be the only STR option for patients taking complex ART regimens. Participants will also be contributing to an understanding of the safety, tolerability, and PK of a novel 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 11.3 for further details on the risks and risk mitigation strategy.

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

1.6. Compliance

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints
Phase 2: • To evaluate the efficacy of switching to a BIC+LEN regimen (BIC 75 mg + LEN 25 mg or BIC 75 mg + LEN 50 mg) versus continuing on SBR in virologically suppressed people with HIV-1 as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24	**Phase 2:** • Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA–defined snapshot algorithm
Phase 3: • To evaluate the efficacy of switching to BIC/LEN FDC tablet regimen (BIC 75 mg/LEN 50 mg) versus continuing on a SBR in virologically suppressed people with HIV-1 as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48	**Phase 3:** • 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**
Phase 2: • To evaluate the efficacy of the 3 treatment regimens in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count at Week 24 • To evaluate the safety and tolerability of the 3 treatment groups through Week 24 • To evaluate the PK of BIC and LEN for participants receiving BIC 75 mg + LEN 25 mg and BIC 75 mg + LEN 50 mg	**Phase 2:** • Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the US FDA–defined snapshot algorithm • Change from baseline in CD4 cell count at Week 24 • Proportion of participants experiencing treatment-emergent AEs through Week 24 • PK parameters C_{max}, AUC_{tau}, and C_{tau} (as applicable) of BIC and LEN
Phase 3: • To evaluate the efficacy of the 2 treatment groups in virologically suppressed people with HIV-1 as determined by viral load suppression rate and CD4 cell count at Week 48 • To evaluate the efficacy of BIC/LEN in participants from Treatment Group 1 as determined by viral load suppression rate and CD4 cell count at Week 96 • To evaluate the safety and tolerability of the 2 treatment groups through Week 48 • To evaluate the safety and tolerability of BIC/LEN in participants from Treatment Group 1 through Week 96	**Phase 3:** • 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 as determined by the US FDA-defined snapshot algorithm • Change from baseline in CD4 cell count at Week 96 for participants from Treatment Group 1 • Proportion of participants experiencing treatment-emergent AEs through Week 48 • Proportion of participants from Treatment Group 1 experiencing treatment-emergent AEs through Week 96

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

3. STUDY DESIGN

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

3.1. Study Design Overview

This study is an operationally seamless Phase 2/3 randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of BIC/LEN versus SBR in virologically suppressed people with HIV-1 on a stable complex treatment regimen for at least 6 months prior to screening. In the Phase 2 portion, single agent BIC and LEN tablets (BIC+LEN) will be coadministered to determine the optimal doses to be used in subsequent portions of the study. In the Phase 3 portion of the study, a single BIC/LEN FDC tablet will be administered. Participants will be recruited from approximately 110 centers globally.

3.1.1. Dose Selection/Modification

3.1.1.1. Phase 2

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

Randomized Period

Participants who provide written consent and meet all eligibility criteria will be randomized in a 2:2:1 ratio to one of the following 3 treatment groups in which they will receive treatment for up to 24 weeks:

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

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

- **Treatment Group 3 (n = 25):** Participants will continue with their SBR as defined above.

Investigators must provide a prescription SBR to participants in Treatment Group 3. Participants in Treatment Group 3 are responsible for obtaining their SBR. The dose of BIC/LEN FDC for the Phase 2 Extension Period and Phase 3 of the study will be BIC 75 mg/LEN 50 mg.

Following the Day 1 visit, the Day 2 visit may be a virtual visit and participants in Treatment Groups 1 and 2 will self-administer the study drugs and be observed by site staff to confirm dosing. Participants in the optional intensive PK substudy, or when a virtual visit cannot be performed, will dose in clinic. All participants will be required to return for study visits at Weeks 4, 12, and 24. According to the participant preference, an optional visit at Week 16 may be scheduled for blood collection for the optional intensive PK substudy to facilitate study procedures scheduled for visit Week 24. Participants will be followed every 12 weeks after the Week 24 visit until the end of randomized treatment (ERT) visit as described in Section 3.2.

The timings of efficacy and safety assessments for the Phase 2 Randomized Period are detailed in Table 1.

Sparse PK blood samples will be collected at on-treatment study visits for all participants in Treatment Groups 1 and 2 at the time points specified in Table 1 and Section 6.3.9.1. An intensive PK substudy will be performed in a subset of participants in Treatment Groups 1 and 2 at selected study sites (Table 1 and Section 6.3.9.1).

Extension Period

During the Extension Period of the study, participants from Treatment Groups 1, 2, and 3 who complete the ERT visit will be given the option to enter an Extension Period. Participants who received BIC+LEN tablets (ie, Treatment Groups 1 and 2) during the Randomized Period will continue with BIC 75 mg/LEN 50 mg FDC tablets without any oral loading doses of LEN. Participants who received their SBR (ie, Treatment Group 3) during the Randomized Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to BIC 75 mg/LEN 50 mg FDC tablets starting on Day 1 of the Extension Period. Following the Day 1 visit, these participants will be required to return for the study visit at Day 2 (option to conduct this as a virtual visit will be available, as appropriate) and Extension Week 4 in addition to the regularly scheduled visits once every 12 weeks as per below.

All participants enrolled in the Extension Period will return for study visits every 12 weeks and will have a telephone visit at 30 days and a clinic visit at 60 days after the end of the Extension Period.

Participants who complete the study through the ERT visit of the Randomized Period and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit, and will be considered to have completed the Phase 2 portion of the study.

The timings of efficacy and safety assessments for the Phase 2 Extension Period are detailed in Section 6 and Table 2.

3.1.1.2. Phase 3

A randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of FDC tablets containing BIC 75 mg/LEN 50 mg versus SBR in people with HIV-1 who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a SBR for at least 6 months prior to screening.

Randomized Period

Participants who provide written consent and meet all eligibility criteria will be randomized in a 2:1 ratio to one of the following 2 treatment groups and will receive treatment for up to 48 weeks:

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

Randomization will be stratified by geographic region.

Investigators must provide a prescription to participants in Treatment Group 2 for their SBR. Participants in Treatment Group 2 are responsible for obtaining their SBR.

Following the Day 1 visit, participants will be required to return for study visits at Day 2 (oral LEN loading dose for Treatment Group 1), Weeks 4, 12, 24, 36, and 48. Participants will be followed every 12 weeks after the Week 48 visit until the ERT visit (Treatment Group 2) and ERT / Week 96 visit (Treatment Group 1) as described in Section 3.2.

The timings of efficacy and safety assessments for the Phase 3 Randomized Period are detailed in Table 3.

Sparse PK blood samples will be collected at on-treatment study visits for all participants in Treatment Group 1 at the time points specified in Table 3 and Section 6.3.9.2. An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites (Table 3 and Section 6.3.9.2).

Extension Period

Participants from Treatment Group 1 will continue to receive BIC/LEN FDC tablets until at least Week 96. At the Week 96 or ERT Visit, whichever occurs later, participants will be given the option to enter the Extension Period to continue to receive BIC/LEN FDC tablets.

Participants who do not wish to enter the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the Week 96 visit or ERT visit, whichever occurs later, and will be considered to have completed the study.

Participants from Treatment Group 2 who complete the ERT visit will be given the option to enter an Extension Period to receive BIC/LEN FDC tablets and will return for an Extension Period Week 4 visit.

Participants from Treatment Group 2 who complete the study through ERT visit and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit and will be considered to have completed the study.

All participants enrolled in the Extension Period will return for study visits every 12 weeks and will have a telephone visit at 30 days and a clinic visit at 60 days after the end of the Extension Period.

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

The timings for efficacy and safety assessments for the Phase 3 Extension Period are detailed in Section 6 and Table 4.

3.2. Duration of Intervention

3.2.1. Phase 2

Participants will be treated for at least 24 weeks during the Randomized Period.

After Week 24, participants will continue to take their study drug (BIC+LEN or SBR) and attend visits every 12 weeks. Once the last participant completes Week 24 and the dose is selected for the BIC/LEN FDC, all participants will attend the ERT visit and will be given the option to participate in an Extension Period to receive BIC/LEN FDC at the selected dose until this product becomes available, or until Gilead elects to discontinue the study, whichever occurs first.

3.2.2. Phase 3

Participants will be treated for at least 48 weeks during the Randomized Period.

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

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

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participants

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.
- 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 11.3 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
- Disaster or public health emergency (Appendix 11.3 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 return to the investigational site for a scheduled protocol-specific visit, sites will need to make at least 3 attempts separated by at least 2 weeks 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 Time of Primary Endpoint and End of Study

3.4.1. Primary Endpoint

The dates for the last participant visit for the primary endpoints for the Phase 2 and Phase 3 portions of the study are the dates of the last visit to perform assessments for the primary analysis for each phase.

3.4.2. End of Study

The end of this study will be the last participant's last observation (or visit).

3.5. Poststudy Care

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.

3.6. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, participant charts, central 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 671 participants in total: 125 participants in Phase 2 (50 in each of Treatment Group 1 and Treatment Group 2, and 25 in Treatment Group 3) and 546 participants in Phase 3 (364 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) Participants assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 11.4.

4) Documented plasma HIV-1 RNA levels

   a) Phase 2 only: documented plasma HIV-1 RNA levels must be < 50 copies/mL during treatment with the baseline regimen for a minimum period of 6 months prior to the screening visit.

   b) Phase 3 only:

      - 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 plasma 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.

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

6) Currently receiving a complex ARV regimen due to previous viral resistance, or intolerance, or contraindication to the components of existing STRs, and on this regimen for at least 6 months prior to the screening visit. The criteria to define a complex regimen in this study are as follows:

   a) A regimen containing a boosted protease inhibitor or a nonnucleos(t)ide reverse transcriptase inhibitor plus at least 1 other third agent (ie, an agent from a class other than NRTIs) (eg, BVY + darunavir/cobicistat, BVY + etravirine), or

   b) A regimen of ≥ 2 pills/day, or a regimen requiring dosing more than once daily, or

   c) A regimen containing parenteral agent(s) (excluding a complete long-acting injectable regimen, such as intramuscular cabotegravir plus rilpivirine) as well as oral agents.

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

8) Estimated glomerular filtration rate ≥ 15 mL/min according to the Cockcroft-Gault formula for creatinine clearance (CL_{cr}) {Cockcroft 1976} who are not on renal replacement therapy.

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 at screening or a positive pregnancy test prior to Day 1 randomization (Appendix 11.4).

2) Breastfeeding participant.

3) Current alcohol or substance use judged by the investigator to potentially interfere with participant study compliance.

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

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

6) Active tuberculosis infection.

7) Acute hepatitis < 30 days before randomization.

8) 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.

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

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

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

12) Active malignancy requiring acute systemic therapy.

13) Any of the following laboratory values at screening:

   a) $CL_{cr} < 15$ mL/min according to the Cockcroft-Gault formula {Cockcroft 1976}

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

   c) Direct bilirubin > 1.5 × ULN

   d) Platelets < 50,000/mm^3

   e) Hemoglobin < 8.0 g/dL

14) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.4.1.

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

16) 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.

17) 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

5.1.1.1. Phase 2

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 the Day 1 visit provided all screening procedures have been completed and participant eligibility has been confirmed.

Participants who meet eligibility criteria will be randomized in a 2:2:1 ratio to Treatment Group 1, Treatment Group 2, and Treatment Group 3.

The IRT will assign study drug bottle numbers of open-label study drugs at Day 1 and subsequent visits for each participant.

5.1.1.2. Phase 3

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 the Day 1 visit provided all screening procedures have been completed and participant eligibility has been confirmed.

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

Randomization will be stratified by geographic region.

The IRT will assign study drug bottle numbers of open-label study drugs at Day 1 and subsequent visits for each participant.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study. As this is an open-label study, access to certain data will be limited to mitigate bias. The details of the data access limitations will be described in a Data Access Plan.

5.2. Description and Handling of Bictegravir, Lenacapavir, and Bictegravir/Lenacapavir Fixed-Dose Combination Study Drugs

5.2.1. Bictegravir Tablets

5.2.1.1. Formulation

Bictegravir tablets are available as 75 mg strength tablets. Bictegravir tablets are round, plain-faced, film-coated yellow tablets. In addition to the active ingredient, BIC tablets contain lactose monohydrate, microcrystalline cellulose, crospovidone, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

5.2.1.2. Packaging and Labeling

Bictegravir tablets are packaged in white, high-density polyethylene (HDPE) bottles with 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 Trial Regulation (CTR), as applicable, and/or other local regulations.

5.2.1.3. Storage and Handling

Bictegravir tablets should be stored at 25 °C, excursions permitted from 15 °C to 30 °C. Storage conditions are indicated on the label.

Bictegravir tablets should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of BIC 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

5.2.2.1. Formulation

Lenacapavir tablets are available as 25, 50, and 300 mg strength tablets. Lenacapavir tablets, 25 and 50 mg, are capsule-shaped, film-coated green tablets with "GSI" debossed on one side of the tablet and "07S" debossed on the other side of the tablet. Lenacapavir tablets, 300 mg, 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, 25 and 50 mg contain copovidone, poloxamer 407, mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide black.

In addition to the active ingredient, LEN tablets, 300 mg, 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.

5.2.2.2. Packaging and Labeling

Lenacapavir 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

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

Lenacapavir 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

5.2.3.1. Formulation

BIC/LEN FDC tablets are available as BIC 75 mg/LEN 50 mg strength 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.

5.2.3.2. Packaging and Labeling

BIC/LEN FDC tablets are packaged in white, HDPE bottles with silica gel desiccant and with or without a 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.

5.2.3.3. Storage and Handling

BIC/LEN FDC 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. Dosage and Administration

5.3.1. Phase 2

Treatment Group 1: BIC 75 mg + LEN 25 mg, once daily, orally.

Treatment Group 2: BIC 75 mg + LEN 50 mg, once daily, orally.

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

Extension Period: Participants from Treatment Groups 1, 2, and 3 enrolled in the Extension Period will receive BIC/LEN FDC tablets at the selected dose, once daily, orally. Participants from Treatment Group 3 enrolled in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily BIC/LEN FDC tablet starting on Day 1 of the Extension Period.

5.3.2. Phase 3

Treatment Group 1: BIC 75 mg/LEN 50 mg FDC, once daily, orally.

Participants randomized to Treatment Group 1 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC tablet starting on Day 1.

Extension Period: Participants from Treatment Groups 1 and 2 enrolled in the Extension Period will receive BIC/LEN 75/50 mg FDC tablets, once daily, orally. Participants from Treatment Group 2 enrolled in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC tablet starting on Day 1 of the Extension Period.

The study drug will be administered without regard to food. The daily dose of BIC/LEN FDC tablet should be taken in the clinic after the predose or trough PK sample collection (as applicable) on the day of each study visit.

5.3.3. Missed Dose Recommendations for Study Drugs in Phase 2 and 3 Portions of the Study

If a participant misses the scheduled daily dose(s) of BIC+LEN or BIC/LEN FDC, recommendations for restarting the treatment are summarized below in Table 10.

Table 10. Missed Daily Dose(s) Recommendation for BIC+LEN or BIC/LEN Treatment Groups

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(s) the next day and daily thereafter.
More than 7 days (more than 7 missed daily doses)[a]	Reload by dosing the 2-day oral loading regimen of LEN (2 × 300 mg on Day 1 and on Day 2 of treatment reinitiation)[b] in addition to restarting the normal schedule of dosing by taking study drug(s) on Day 1 of treatment reinitiation and daily thereafter.

LEN = lenacapavir
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).

5.4. Prior and Concomitant Medications

5.4.1. Prior and Concomitant Medications That Are Prohibited or to Be Used With Caution

Medications in Table 11 are prohibited or should be used with caution while participants are taking BIC+LEN or BIC/LEN FDC. 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 11. Examples of Prior and Concomitant Medications That Are Prohibited or to be Used With Caution With BIC+LEN or BIC/LEN FDC Because of the Potential for Pharmacokinetic Drug-Drug Interaction or Impact on Efficacy Assessments or Participant Safety

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 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 In pregnant participants: for antacids containing aluminum and/or magnesium, the 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.	

Medication Class[a]	Use Discouraged and To Be Used With Caution[b]	Prohibited Medications[c]
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	
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	

Medication Class[a]	Use Discouraged and To Be Used With Caution[b]	Prohibited Medications[c]
	no more than 10 mg in 72 hours be coadministered	
Sedatives/hypnotics	Midazolam, triazolam	
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 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.

Investigators should refer to the package insert for the guidance on concomitant medications with ARVs included as part of the SBR of Treatment Group 3 (Phase 2 portion), and Treatment Group 2 (Phase 3 portion) of this study.

5.4.2. 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 or 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).

5.5. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drug supplies (drugs and bottles). 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 Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion) 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 9.1.4 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. Investigators are responsible for confirming participant eligibility. Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for enrollment and randomization 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.

Once the informed consent form (ICF) has been signed, all screening and eligibility tests and assessments have been assessed, and study eligibility has been confirmed, participants will be randomized to receive study drugs on Day 1.

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 serious adverse events (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. Concomitant Medications

Review of concomitant medications will occur at the time points presented in Table 1 and Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion). Further information about concomitant medications is provided in Sections 4.3 and 5.4.

6.3.3. Electrocardiograms

Participants should rest quietly in the supine position for a minimum of 10 minutes before ECG acquisition and should remain in that position until the recording is complete.

There should be no environmental distractions (including TV, radio, video games, and conversation) while the participants are resting prior to and during the recordings.

Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the aVR lead is not inverted.

The investigator or other qualified individuals at the study site will review ECGs to assess for changes in ECG intervals and morphology as compared with pretreatment ECGs. The ECG interval measurements output by the machine will be used for bedside safety monitoring. Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

6.3.4. Medical History and Demography

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

- Review medical history including HIV-1 disease-related events, available historical genotype/phenotype reports, available HIV-1 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.

6.3.5. Physical Examination

Physical examinations conducted throughout the study will be complete or symptom directed. Refer to Table 1 and Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion).

6.3.6. Vital Signs

Vital sign measurements 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. Refer to Table 1 and Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion) for vital signs and weight collection time points.

6.3.7. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined in Table 1 and Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion). Laboratory assessments are listed in Table 12.

Participants who meet the criteria for virologic failure will be managed according to the management of virologic rebound (Section 6.3.10.2.1).

Table 12. 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	Glucose 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 & clarity Specific gravity pH Glucose Protein Blood and microscopic Pregnancy test[b]	Serum pregnancy test[b] Serum FSH[c] Plasma HIV-1 RNA CD4 cell count HBV blood panel: HBcAb, HBsAg, and HBsAb Plasma HBV DNA[d] HCV serology: HCVAb (HCVAb positive participants will have an HCV RNA test performed) Plasma and urine storage samples Plasma storage sample for potential HIV-1 genotype/phenotype Whole blood for proviral DNA sequencing[e]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CD4 = cluster of differentiation 4; CL_{cr} = creatinine clearance; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus;

HCVAb = hepatitis C virus antibody; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MCV = mean corpuscular volume; RBC = red blood cell; 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 For participants who were assigned female at birth and are < 54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
d Participants who are HBsAg positive will have a plasma HBV DNA test performed.
e For all participants enrolled in Phases 2 and 3, to be done on Day 1.

6.3.8. Virtual Visits

6.3.8.1. Phase 2

Randomized Period

Participants in Treatment Groups 1 and 2 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) 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 will be conducted as a video conference or a video call to ensure the required dose has been appropriately administered. The participant must have a video-enabled device for the site to be able to conduct the virtual visit, and the investigator site must provide clear instructions on the expectations of the participant prior to the virtual visit.

The Day 2 visit will be performed in clinic when the site or participant is not able to conduct a virtual visit, or the participant has consented for the optional intensive PK substudy. Samples will be obtained as described in Section 6.3.9.

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

Extension Period

Participants in Treatment Group 3 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) 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 to be performed and documented by the site in the source documentation.

6.3.8.2. Phase 3

Randomized Period

Participants in Treatment Group 1 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) 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 to be performed and documented by site in source documentation.

Extension Period

Participants in Treatment Group 2 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) 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. Participants who wish to have the Day 2 as an in-clinic visit may do so.

A review of AEs and changes in concomitant medications 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

6.3.9.1. Phase 2: Pharmacokinetic Assessments for Treatment Groups 1 and 2

Sparse PK collection:

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

- A single predose plasma PK sample (≤ 5 min before dose) **and** a single plasma PK sample 4 (± 1) hours postdose (relative to BIC+LEN dosing and oral loading dose of LEN) on Day 1
- A single trough plasma PK sample approximately 23 to 24 hours after the previous dose and prior to dosing at Weeks 4, 12, and 24, **and** a single postdose plasma PK sample 2 (± 1) hours postdose (relative to BIC+LEN dosing) at Weeks 4, 12, and 24.

- Should a participant become pregnant and provide reconsent to remain on the study, sparse PK samples will continue to be collected as follows:

  — During the Randomized Treatment Period (until the Week 24 visit): At all the protocol-specified visits/time points (as described above).

  — After Week 24 visit (until the ERT) and during the Extension Period: A single trough plasma PK sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at once every 12 Week visit (as possible). These additional trough samples will continue to be collected until the next 2 scheduled visits postdelivery or until the end of the study participation or Extension Period, whichever occurs first.

Intensive PK Substudy:

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

Day 1: Approximately 20 evaluable participants will be enrolled (10 from Treatment Group 1 and 10 from Treatment Group 2). Intensive PK will be collected as follows:

1) Single PK sample predose (≤ 5 min before dose).

2) PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC+LEN dosing and oral loading dose of LEN).

Day 2: Approximately 20 evaluable participants will be enrolled (10 from Treatment Group 1 and 10 from Treatment Group 2). Intensive PK will be collected as follows:

1) Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose on Day 1 and before the next scheduled dose.

2) PK samples will be collected at 0.5, 1, 2, 3, 4, and 6 hours postdose (relative to BIC+LEN dosing and oral loading dose of LEN).

Week 16 or 24 visit: Approximately 40 evaluable participants will be enrolled (20 from Treatment Group 1 and 20 from Treatment Group 2). Intensive PK will be collected as follows:

1) Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose that was administered the day before and before the next scheduled dose.

2) PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC+LEN dosing).

Notes:

1) **All the participants enrolled in the intensive PK substudy on Days 1 and 2, and at Weeks 16 or 24 will receive BIC+LEN under fasted conditions.**

2) **At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse/intensive PK sample (as applicable).**

6.3.9.2. Phase 3: Pharmacokinetic Assessments for Treatment Group 1

Sparse PK collection:

Sparse PK blood samples will be collected at on-treatment study visits for all participants at the time points specified below:

- A single predose plasma PK sample (≤ 5 min before dose) and a postdose plasma PK sample at 4 (± 1) hours (relative to BIC/LEN FDC dosing and oral loading dose of LEN) on Day 1.

- A single trough plasma PK sample approximately 23 to 24 hours after the previous dose and prior to dosing at Weeks 4, 12, 24, 36, and 48, and a single postdose plasma PK sample at 2 (± 1) hours (relative to BIC/LEN FDC dosing) at Weeks 4, 12, 24, 36, and 48.

- Should a participant become pregnant and provide reconsent to remain on the study, sparse PK samples will continue to be collected as follows:

  — During the Randomized Treatment Period (until the Week 48 visit): At all the protocol-specified visits/time points (as described above).

  — After Week 48 visit (until the ERT) and during the Extension Period: A single trough plasma PK sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at once every 12 Week visit (as possible). These additional trough samples will continue to be collected until the next 2 scheduled visits postdelivery or until the end of the study participation or Extension Period, whichever occurs first.

Intensive PK Substudy:

An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites. Participants may choose to participate at either one of the visits. Intensive PK blood samples will be collected for this subset of participants as described below **instead of** the sparse plasma PK samples on those specific visits.

Week 24 or 36 or 48 visit: Approximately 30 evaluable participants from Treatment Group 1

- Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose that was administered the day before and before the next scheduled dose.

- PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC/LEN FDC dosing).

- **Note: At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse/intensive PK sample (as applicable).**

6.3.10. Clinical Virology Analyses

6.3.10.1. Virology Testing

6.3.10.1.1. Virology Samples to Address the Study Objectives

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 and Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion), including potential HIV-1 viral load retesting. Plasma and whole blood samples may be used to assess HIV-1 genotype at baseline and/or 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 whole blood and plasma samples may be used for possible future biomarker and virology-related testing, PK assessments, and evaluation of inflammatory markers. 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 participants with VR 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 study drug discontinuation

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. 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 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 who are noncompliant 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. Questionnaires/Patient-Reported Outcomes

Patient-reported outcome (PRO) assessments will be completed by participants at the visits specified in Table 3 and Table 4 for the Phase 3 portion of the study only.

6.3.11.1. Treatment Expectations Questionnaire

The treatment expectations questionnaire captures participants' satisfaction of their prior treatment, expectations of the study treatment regimen, and preference of treatment regimen. The treatment expectations questionnaire will be used for the interpretation of HIVTSQs-12 data.

6.3.11.2. PozQoL Scale

The PozQoL Scale is a 13-item PRO intended to assess the quality of life of people with HIV-1. Participants are presented with a series of statements and asked to rate each statement using a 5-point verbal descriptor scale from "Not at all" to "Extremely". The PozQoL includes psychological, social, health concerns, and functional domains. A total score is calculated as a sum when all items are complete, or an average when item responses are missing. A score for each domain can also be calculated {Brown 2018}.

6.3.11.3. HIV Treatment Satisfaction Questionnaire Status—12 item (HIVTSQs-12)

The HIVTSQs-12 is a 12-item instrument assessing participant satisfaction with HIV treatment; all items use a 7-point numeric rating scale with anchor text (eg, 6 = very satisfied to 0 = very dissatisfied and 6 = very well controlled to 0 = very poorly controlled). The HIVTSQs-12 includes a treatment satisfaction and a pain/discomfort domain. The treatment satisfaction score is obtained by finding the sum of all the responses to items 1 to 11 while the pain/discomfort score corresponds to the individual rating to item 12.

6.3.11.4. HIV Treatment Satisfaction Questionnaire Change—12 item (HIVTSQc-12)

The HIVTSQc is a 12-item instrument assessing the change in treatment satisfaction between a participant's previous and current treatment. The individual items are scored from −3 ("much less satisfied now") to 3 ("much more satisfied now"). The total score for the HIVTSQc ranges from −33 to 33, where higher scores indicate a greater improvement in treatment satisfaction with the new treatment, and lower scores indicate lower treatment satisfaction with the new treatment, and a score of zero represents no change in satisfaction {Woodcock 2006}.

6.3.11.5. Treatment Preference Questionnaire

The treatment preference questionnaire captures participants' preference for study drug regimen over prior treatment. Participants are asked to report if they prefer their previous treatment plan compared with the clinical study treatment plan.

6.3.11.6. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem v2.0 (WPAI:HIV)

The WPAI:HIV is a 6-item instrument designed to evaluate the impact of a specific health problem (HIV) on work productivity and activity. The WPAI produces 4 scores: absenteeism, presenteeism, work productivity loss, and activity impairment. The 4 scores are expressed as impairment percentages ranging from 0 to 100%: The percent of work time missed, percent of impairment while working, percent of overall work impairment, and percent of activity impairment due to participants' HIV {Reilly 1993}.

6.3.11.7. EuroQol (5 Dimensions, 3 Levels) (EQ-5D-3L) Questionnaire

The EQ-5D-3L is a standardized instrument developed by the EuroQol Group as a measure of HRQoL that can be used in a wide range of health conditions and treatments. The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels. The EQ-VAS records the participant's self-rated health on a vertical visual analogue scale where the endpoints are labeled "The best health you can imagine" and "The worst health you can imagine" {EuroQol Research Foundation 2018}.

Regarding scoring, for the first section, the participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the participant's health state. The EQ-VAS is scored from 0 to 100. EQ-5D-3L scores are converted to an index value that can be compared to country-specific value sets. The scoring manual for the EQ-5D-3L can be found here {Division of AIDS 2017}.

6.3.11.8. Patient Global Impression of Change (PGI-C): Impact Questionnaire

The PGI-C: Impact is a single item scale that measures participants' impression of change in the impact of HIV since beginning the phase 3 study. The measure uses a 5-point scale ranging from 1: "much better" to 5: "much worse."

6.3.11.9. Patient Global Impression of Severity (PGI-S): Impact Questionnaire

The PGI-S: Impact is a single item scale used to measure participants' impression of amount of impact of HIV using a 5-point scale from 1: "not at all" to 5: "very much."

6.3.12. Pregnancy

Any participant who becomes pregnant after randomization may remain in the study and continue to receive study drug(s) after a reconsent process 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 7.1.4, 7.3.4, 7.4.2.3, and Appendix 11.4). Participants who continue on study drug during pregnancy may also provide 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.

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 visit procedures. 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

Participants who discontinue study drug early will be asked to return to the investigational site within 3 days of stopping study drug to attend an early study drug discontinuation (ESDD) visit for assessments and procedures specified in Table 1 and Table 2 (Phase 2 portion) and Table 3 and Table 4 (Phase 3 portion). Participants who discontinue study drug early will have a telephone visit at 30 days and a clinic 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

All participants enrolled in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the end of the Extension Period.

Participants who complete the study through the ERT visit of the Randomized Period and do not wish to participate in the Extension Period will have a telephone visit at 30 days and a clinic visit at 60 days after the ERT visit, and will be considered to have completed the Phase 3 study.

Assessments for follow-up visits are specified in Table 2 (Phase 2 portion) and Table 4 (Phase 3 portion).

At the 60-day 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 be followed beyond the protocol-defined follow-up period.

6.5. Poststudy Care

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.

6.6. Sample Storage

The stored biological samples may be used by Gilead or its research partners 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.

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 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, and 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 (see Section 7.1.4).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the 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 one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a 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 situations reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or 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 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, Authorized Auxiliary Medicinal Products 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).

When there is a reasonable possibility that the causality of the AE/SAE can be assigned to the authorized auxiliary medicinal product (AxMP), the investigator or qualified subinvestigator will need to report the causality assessment for the authorized AxMP(s) in accordance with the eCRF.

7.2.2. Assessment of Severity

The severity of AEs and laboratory abnormalities will be graded using the Division of AIDS (DAIDS) Toxicity Grading Scale, Version 2.1 (Appendix 11.5). 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 prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs related to protocol-mandated 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 Extension Period follow-up) and report the AEs on the eCRF as instructed.

All AEs and clinically significant laboratory abnormalities should be followed up 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 informed consent) and throughout the duration of the study, including the posttreatment follow-up period (including Extension Period follow-up), must be reported on the applicable eCRFs and sent to Gilead Patient Safety (PS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if an 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 the study drug, the investigator should promptly document and report the event to Gilead PS.

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 period, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to 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 the informed consent) and throughout the duration of the study, including the posttreatment follow-up period, must be reported to Gilead 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 due to 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 Gilead 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 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 PS

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 Gilead 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 Gilead 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 the SSR information electronically, record the SSR on the paper SSR form and transmit to:

Gilead PS

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 Gilead 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 Gilead PS utilizing the paper SSR form to:

Gilead PS
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 due to a non-Gilead concomitant medication must be reported as on the AE eCRF.

7.4.2.3. Pregnancy Reporting Process

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

Gilead PS
Email: Safety_FC@gilead.com
or
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 (eg, a spontaneous abortion, an induced therapeutic abortion due to 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 poststudy must be reported to Gilead PS.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead 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 Gilead PS. Gilead PS contact information is as follows: email: Safety_FC@gilead.com and fax: +1-650-522-5477.

Refer to Appendix 11.4 for Pregnancy Precautions, Definition for Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC)/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, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC)/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.

In the intended study population, Gilead anticipates the occurrence of SAEs that are manifestations of the underlying disease, commonly occur in the study population independent of drug exposure, or are components of the study endpoints. The anticipated SAEs, unless life-threatening/fatal, will not be reported in an expedited fashion to the US FDA.

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 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, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia) not the laboratory result (eg, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS Toxicity Grading Scale, Version 2.1 (Appendix 11.5). 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

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

The analyses of this study will be structured in 2 portions: exploratory (Phase 2) to select the appropriate doses of the individual components BIC and LEN as part of the BIC/LEN FDC, and confirmatory (Phase 3) to evaluate the treatment effect of BIC/LEN FDC. Unique participants will be enrolled in the Phase 2 and Phase 3 portions of the study, respectively. Data from the interim and final analyses of each phase of the study will be analyzed separately. The confirmatory analyses will only include data from participants randomized into the Phase 3 portion of the study; they will not include data from the participants in the Phase 2 portion.

For the Phase 3 portion, at least 2 analyses will be conducted to evaluate primary and secondary objectives of the protocol, one after all participants have completed their visits at Week 48, and one after all participants in Treatment Group 1 have completed their visits at Week 96. The Week 48 analysis will be the primary analysis.

Results from Week 24 primary analysis of Phase 2 portion will be used in conjunction with the results of Phase 1 rBA Study GS-US-621-6292 to select the dose of the BIC/LEN FDC tablet to be used in Treatment Group 1 of the Phase 3 portion, and the Phase 2 and Phase 3 Extension Periods of the study.

8.2.1. Interim Analyses

Prior to the final analysis of each phase (ie, Phase 2 and Phase 3 portions) of the study, additional interim analyses may be conducted as necessary after Week 24 for Phase 2 portion and after Week 96 for Phase 3 portion, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program and to support regulatory filings. Also, interim analyses may be used for publication and presentation at scientific meetings. No interim analysis will be conducted before Week 24 primary analysis for Phase 2 portion or Week 48 primary analysis for Phase 3 portion.

8.2.1.1. Week 96 Interim Analysis (Phase 3 Portion)

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

Phase 2: There will be 1 planned data monitoring committee (DMC) analysis of safety conducted after all participants enrolled in the Phase 2 portion have completed their Week 12 visit or prematurely discontinued the study drug.

Phase 3: There will be 2 planned DMC analyses of safety conducted after approximately the first 50% of participants enrolled in the Phase 3 portion have completed their Week 12 visit or prematurely discontinued the study drug, as well as after all participants enrolled in the Phase 3 portion have completed 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.

For the Phase 2 portion, no alpha penalty will be applied for the primary analysis of the primary efficacy endpoint, given that the Phase 2 portion of the study is not adequately powered for a formal efficacy evaluation. In the Phase 3 portion, for each DMC analysis performed prior to the analysis of the primary efficacy endpoint, an alpha penalty of 0.00001 will be applied conservatively for efficacy analysis. Data from these analyses may be used to support the planning of other studies.

8.2.2. Primary Analysis

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

For the Phase 3 portion, the primary analysis of the primary endpoint for Phase 3 will be conducted after all participants enrolled in the Phase 3 portion 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 in Phase 3 will serve as the final analysis for this endpoint and will be used to evaluate the efficacy of BIC/LEN FDC in the Phase 3 portion.

8.2.3. Final Analysis

There will be a separate final analysis for each phase (ie, Phase 2 and Phase 3 portions) of the study. The final analysis for each phase of the study will be performed after all participants in each phase have completed the study or prematurely discontinue from 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

8.3.1.1. Efficacy

8.3.1.1.1. 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.

8.3.1.2. Safety

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.

All data collected during treatment plus 30 days (for participants receiving SBR) or 60 days (for participants receiving BIC+LEN or BIC/LEN) will be included in the safety summaries.

8.3.1.3. Pharmacokinetics

8.3.1.3.1. 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 under evaluation reported by the PK laboratory. The PK analysis set will be used for analyses of general PK.

8.3.1.3.2. Pharmacokinetic Substudy Analysis Set

The primary analysis set for intensive PK analyses is defined as the PK substudy analysis set, which will include all randomized participants who have received any dose of study drug, enrolled into the PK substudy, and have at least 1 nonmissing intensive PK concentration value for the analyte under evaluation reported by the PK laboratory. This is the primary analysis set for detailed PK analysis of intensive PK sampling.

8.3.2. Data Handling Conventions

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. 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 all 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, third quartile, 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, region, 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. Data from each phase of the study will be analyzed separately. The US FDA–defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be used to determine virologic outcomes mentioned in this section at the analysis visit of interest (Week 24 for Phase 2 portion, and Week 48 for Phase 3 portion). The estimand for the virological outcomes is described in Table 13.

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 analysis visit window of interest.
- 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 analysis visit window of interest, or
  b) Who do not have on-treatment HIV-1 RNA data in the analysis window of interest and
     i) Who discontinue study drug prior to or in the analysis window of interest due to lack of efficacy, or
     ii) Who discontinue study drug prior to or in analysis window of interest 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 analysis visit window of interest: this includes participants who do not have on-treatment HIV-1 RNA data in the analysis window of interest because of the following:

  a) Discontinuation of study drug prior to or in the analysis window of interest due to AE or death, or

  b) Discontinuation of study drug prior to or in the analysis window of interest 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 13. Estimand and Handling for Intercurrent Events for Virologic Outcomes

Population	People with HIV-1 who are virologically suppressed
Treatment	BIC/LEN[a] and SBR
Variable	HIV-1 RNA ≥ 50 copies/mL or HIV-1 RNA < 50 copies/mL at the analysis visit of interest (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 analysis visit window. Participants who do not have on-treatment HIV-1 RNA data for the analysis visit of interest and discontinue study drug prior to or in the 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 analysis visit window. Participants who do not have on-treatment HIV-1 RNA data for the analysis visit of interest 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 analysis visit of interest between BIC/LEN[a] and SBR.

AE = adverse event; BIC = bictegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; RNA = ribonucleic acid; SBR = stable baseline regimen; US = United States
a For Phase 2 portion, it is BIC+LEN; for Phase 3 portion, it is BIC/LEN FDC.

8.5.1. Primary Analysis

8.5.1.1. Phase 2

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA–defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The primary analysis of the efficacy will be based on the FAS.

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

8.5.1.2. Phase 3

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 FDC versus SBR, 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 SBR if the upper bound of the 2-sided 95% CI for the treatment difference (BIC/LEN FDC − SBR) 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% CI will be constructed based on stratum-adjusted Mantel-Haenszel (MH) proportion, adjusted by geographic region. 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.

8.5.2. Secondary Analyses

8.5.2.1. Phase 2

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

The changes from baseline in CD4 cell count at Week 24 will be summarized by treatment using descriptive statistics. The differences in changes from baseline in CD4 cell count between each of the BIC+LEN groups and SBR group and the associated 95% CIs will be constructed using analysis of covariance (ANCOVA) models, including baseline CD4 cell count as a covariate and treatment (each of the BIC+LEN groups versus SBR) as a fixed effect in the models.

8.5.2.2. Phase 3

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 changes from baseline in CD4 cell count at Week 48 will be summarized by treatment using descriptive statistics. The differences in changes from baseline in CD4 cell count between the 2 treatments groups and the associated 95% CIs will be constructed using ANCOVA models, including baseline CD4 cell count and geographic region as covariates and treatment (BIC/LEN FDC versus SBR) as a fixed effect in the models.

Longer term antiviral effect including proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 96, proportion of participants with HIV-1 RNA < 50 copies/mL at Week 96, and change from baseline in CD4 cell count through Week 96 will also be assessed for participants randomized to Treatment Group 1. Antiviral effect, safety, and tolerability of BIC/LEN FDC will also be evaluated for participants switching to BIC/LEN FDC in the Extension Phase.

8.5.3. Exploratory Analyses

For exploratory PRO responses collected in Phase 3 portion, summary statistics will be provided by treatment group and visit. Differences across treatment groups will be summarized and treatment comparisons may be performed.

8.6. Safety Analysis

All safety data 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 BIC/LEN FDC, or 30 days for participants receiving SBR will be summarized by treatment group (according to the study drug received) using the safety analysis set.

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.

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

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data 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 the Medical Dictionary for Regulatory Activities (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 BIC/LEN FDC) or 30 days (for SBR) 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 at the following location:
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 BIC/LEN FDC) or 30 days (for SBR) 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

8.7.1. Phase 2

No alpha level adjustments will be made for multiplicity in Phase 2, because the primary efficacy evaluation is exploratory in nature. Nominal 95% CIs and tests performed at the nominal 0.05 alpha level will be provided.

8.7.2. Phase 3

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

There 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) using the FAS 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

8.8.1. Phase 2

For the general PK analyses, the PK of BIC and LEN may be evaluated using descriptive statistics and/or population analysis approaches. For the intensive PK substudy, plasma concentrations of BIC and LEN will be summarized by nominal sampling time using descriptive statistics. Also, PK parameters ($AUC_{0\text{-}t}$, AUC_{tau}, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, and C_t, as appropriate) will be listed and summarized using descriptive statistics.

Dose proportionality may be assessed (as appropriate) using a one-way parametric (normal theory) analysis of variance model which will be fitted to the natural logarithmic transformation of PK parameters (AUC_{inf}, AUC_{last}, AUC_{tau}, and C_{max}, as appropriate) of LEN with dose as a fixed effect. The point estimate and 90% CI may be constructed for the ratio of geometric least-squares means of each PK parameter between the test dose and the reference dose (usually the lowest dose).

8.8.2. Phase 3

For the general PK analyses, PK of BIC and LEN may be evaluated using descriptive statistics and/or population analysis approaches. For the intensive PK substudy, plasma concentrations of BIC and LEN may be summarized by nominal sampling time using descriptive statistics. Also, PK parameters (AUC_{0-t}, AUC_{tau}, AUC_{last}, CL/F, $t_{1/2}$, λ_z, V_z/F, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, and C_t, as appropriate) may be listed and summarized using descriptive statistics.

8.9. Sample Size

8.9.1. Phase 2

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

8.9.2. Phase 3

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

8.10. Data Monitoring Committee

A multidisciplinary 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 AEs associated with study treatment warrant the early termination of the study in the best interests of the participants, 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.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. 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. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. 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.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the 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. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

The ICF will inform participants about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each participant participating in the study, participants will be required to document additional consent to provide additional samples and/or to allow the use of already-collected data and the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each participant participating in the study, participants will be required to document additional consent to provide additional samples for optional genomic research. 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, 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 at the screening visit, participants who become pregnant after randomization may remain on the study drugs after the reconsent process, as applicable according to local rules and regulation, where they will be informed of the benefits and risks of continuing receipt of study drug while pregnant and lactating (if applicable per local practice). If a participant becomes pregnant in the SBR groups (Treatment Group 3 of the Phase 2 portion or Treatment Group 2 of Phase 3 Portion), the participant may choose to continue in the study and reconsent after discussing risks, benefits, and contraindications of the component of the SBR drugs with the investigator.

9.1.5. 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, eCRF, 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.

9.1.6. 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.
- 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 ICH region (ie, 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.

9.1.7. 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 9.1.6.

9.1.8. Investigator Inspections

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

9.1.9. 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 may be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared for each phase portion 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 trial agreement. Study results will be made publicly available (including posted to the Clinical Trials Information System and ClinicalTrials.gov) in accordance with local regulatory requirements.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. 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.

9.3.2. 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 case report form/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.

9.3.3. 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.

9.3.4. 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.

9.3.5. 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 European Union 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.

10. REFERENCES

AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at: https://aidsinfo.nih.gov/Guidelines/HTML/1/adult-and-adolescent-treatment-guidelines/0. Accessed: 25 March 2020. Last Updated: 18 December. 2019:

Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin 2014;30 (1):89-97.

Brown G, Mikolajczak G, Lyons A, Power J, Drummond F, Cogle A, et al. Development and validation of PozQoL: a scale to assess quality of life of PLHIV. BMC Public Health 2018;18 (1):527.

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

Chang HM, Chou CH, Tsai HC. Durability of single tablet regimen for patients with HIV infection in Southern Taiwan: data from a real-world setting. BMC Infect Dis 2022;22 (1):2.

Clay PG, Nag S, Graham CM, Narayanan S. Meta-Analysis of Studies Comparing Single and Multi-Tablet Fixed Dose Combination HIV Treatment Regimens. Medicine 2015;94 (42):1-14.

Clay PG, Yuet WC, Moecklinghoff CH, Duchesne I, Tronczynski KL, Shah S, et al. A Meta-Analysis Comparing 48-Week Treatment Outcomes of Single and Multi-Tablet Antiretroviral Regimens for the Treatment of People Living with HIV. AIDS Res Ther 2018;15:17.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1. July, 2017.

Dube K, Eskaf S, Evans D, Sauceda J, Saberi P, Brown B, et al. The Dose Response: Perceptions of People Living with HIV in the United States on Alternatives to Oral Daily Antiretroviral Therapy. AIDS Res Hum Retroviruses 2020;36 (4):324-48.

European Aids Clinical Society (EACS). EACS Guidelines, Version 11.0. 2021:

EuroQol Research Foundation. EQ-5D-3L User Guide: Basic information on how to use the EQ-5D-3L instrument. Version 6.0. Available at: https://euroqol.org/publications/user-guides. Accessed: 11 May 2021. Last Updated: December. 2018:

Hines DM, Ding Y, Wade RL, Beaubrun A, Cohen JP. Treatment Adherence And Persistence Among HIV-1 Patients Newly Starting Treatment. Patient Prefer Adherence 2019;13:1927-39.

Nachega JB, Parienti JJ, Uthman OA, Gross R, Dowdy DW, Sax PE, et al. Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials. Clin Infect Dis 2014;58:1297-307.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. 16 August. 2021:

Raboud J, Li M, Walmsley S, Cooper C, Blitz S, Bayoumi AM, et al. Once daily dosing improves adherence to antiretroviral therapy. AIDS Behav 2011;15 (7):1397-409.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4 (5):353-65.

Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. JAMA 2020;324 (16):1651-69.

Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. Patient Prefer Adherence 2012;6:427-33.

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.

U. S. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologic Evaluation and Research (CBER). Pediatric HIV Infection: Drug Product Development for Treatment Guidance for Industry. March. 2019.

UNAIDS. Fact Sheet - Global HIV Statistics 2021. 2021:

Woodcock A, Bradley C. Validation of the revised 10-item HIV Treatment Satisfaction Questionnaire status version and new change version. Value Health 2006;9 (5):320-33.

11. APPENDICES

11.1. Investigator Signature Page

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

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

Protocol Amendment 4, 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 ≥ 1 ICH Country	To Be Used per Label (Marketed Products Only)
Bictegravir (BIC) 75 mg tablets	Study drug	No	No	NA
Lenacapavir (LEN) 25 mg, 50 mg, tablets	Study drug	No	No	NA
Lenacapavir (LEN) 300 mg tablets	Study drug	Yes	Yes	No
Bictegravir/Lenacapavir (BIC/LEN) FDC 75 mg/50 mg tablets	Study drug	No	No	NA
SBR[a]	AxMP/NIMP	Yes	Yes	Yes

AxMP = auxiliary medicinal product; EU = European Union; FDC = fixed-dose combination; NA = not applicable, NIMP = noninvestigational medicinal product; SBR = stable baseline regimen; TBC = to be confirmed

a Participants in this study may also continue to receive their stable baseline regimen; these regimens are not listed in this table as these encompass a multitude of treatment options which cannot be predefined.

11.3. 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 participants 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/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) Participants 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 AEs/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 and PROs have been completed and transmitted.

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) Participants 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) Participants may be unable or unwilling to attend the study visit to sign an updated 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 eCRF and described in the 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 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 BIC/LEN and BIC+LEN in study participants remains unchanged.

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

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. Investigators should refer to the prescribing information regarding pregnancy and contraception recommendations for participants randomized to SBR.

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. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for participants assigned female at birth and of childbearing potential with infrequent or irregular periods.

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

No contraception is 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.

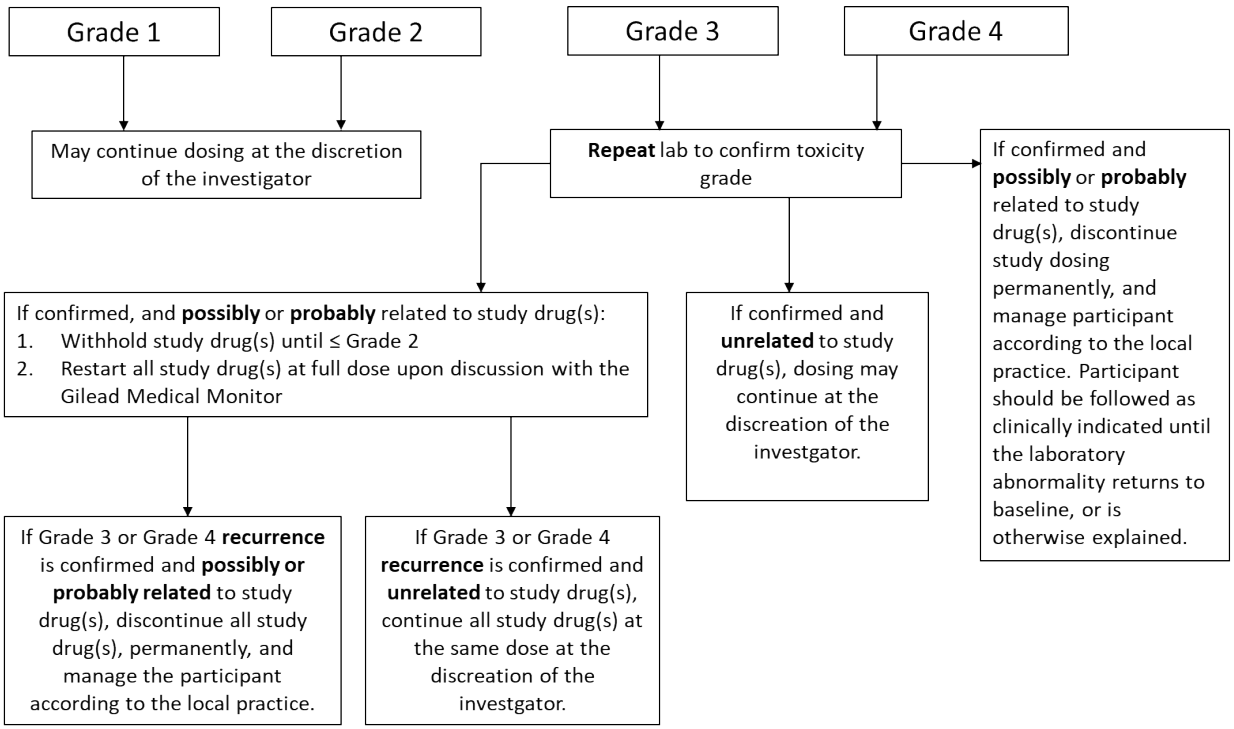
Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

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

The DAIDS Toxicity Grading Scale (Version 2.1) is available at the following location:

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

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. Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed. Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing Amendment 3 to this amendment will be made available upon the publication of this protocol.

11.7.1. Amendment 4 (03 April 2025)

Rationale for Key Changes Included in Amendment 4	Affected Sections
Noninferiority test with a 10% noninferiority margin will not be performed for the secondary efficacy endpoint (HIV-1 RNA < 50 copies/mL) in accordance with request from United States (US) Food and Drug Administration (FDA).	Synopsis, Sections 8.5.2 and 8.7.2
Frequency of participant dosing diary updated to fix error.	Study Procedures Table 3
Clarified that future research is optional and collection subject to local regulations.	Study Procedures Tables 1, 2, 3, and 4
Updates to align with Protocol Clarification Letter 3.0.1.	Study Procedures Table 3 and 4
Added follow-up visits for participants who discontinue study drugs early.	Study Procedures Tables 2 and 4, Section 6.4.1
Updated text to align with current Gilead protocol template and practices.	Study Procedures Tables 1, 2, 3, and 4, Sections 4.1, 6.2, 7.4.1.1, and 9.1.4
Clarifying statement added for metformin exposure when coadministered with bictegravir.	Table 11
Updated time frame for virologic rebound reflex testing and retesting to align with the current testing policy.	Section 6.3.10.2.1
Updated the estimand framework for virologic outcomes and the snapshot algorithm in accordance with the request from the US FDA.	Section 8.5
Minor changes to correct typographic errors.	Throughout, as needed

11.7.2. Amendment 3 (18 June 2024)

Rationale for Key Changes Included in Amendment 3	Affected Sections
Updates made on primary analysis of the study to use the estimand framework for the primary endpoint, including the addition of Table 13.	Synopsis, Section 8.5.1.2, and Table 13
Updates made on secondary analysis of the study to use the estimand framework for the key secondary endpoint, including the addition of Table 14.	Synopsis, Section 8.5.2.2, and Table 14
Updated footnote that plasma storage samples including early study drug discontinuation may be used for pharmacokinetic testing.	Study Procedures Tables 1, 2, 3, and 4

Rationale for Key Changes Included in Amendment 3	Affected Sections
Footnote "r"(and "q" of Table 3) of Study Procedures Tables 1, 3, and 4 was updated for additional information pertaining to pregnant participants taking evening doses.	Study Procedures Tables 1, 3, and 4
48 Week time point added for HIV Treatment Satisfaction Questionnaire—Status 12-item (HIVTSQs-12) assessment.	Study Procedures Table 3
Footnotes for metabolic assessment updated to remove fasting information pertaining to food and liquid as this fasting step is not required.	Study Procedures Table 3 footnote "k" and Table 4 footnote "m"
60-day in-clinic follow-up time point added for concomitant medications assessment.	Study Procedures Table 4
Subsection 3.3.1.1.1 for partial withdrawal information was added per updated protocol template.	Section 3.3.1.1.1
Pandemic risks to study conduct broadened to include unanticipated events (disasters and public health emergencies).	Section 1.5, Section 3.3.1.1, and Section 3.3.1.2
Add "Participant request to discontinue for any reason" per protocol template update	Section 3.3.1.2
Acid reducing agents/antacids/buffered medications row in Table 11 was updated 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 5.4.1, Table 11
Oral hypoglycemic agents' row in Table 11 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 5.4.1, Table 11
Information on "Participants with documented nonadherence within 72 hours of the visit may not be tested for resistance" was deleted.	Section 6.3.10.2.1
Language was added for unscheduled visits between every 12 weeks visits during pregnancy.	Section 6.3.12
Updates made for clarity on interim analysis time points.	Section 8.2.1
The Safety Analysis Set was updated to included "all participants" instead of "all randomized participants".	Section 8.3.1.2
Deletion of sub-sections for analysis of Phase 2 and Phase 3 categorical and continuous demographic and baseline characteristics.	Section 8.4
Text pertaining to publication of clinical trial as per local regulatory requirements was updated.	Section 9.2.2
New Section 9.3.5 for data protection language was added.	Section 9.3.5
Updated section heading to replace "Pandemic" with "Disaster and Public Health Emergency". Updated standard text to further refer "Disaster or Public Health Emergency" as "an event" as per template.	Appendix 11.3
Minor changes to correct typographic errors.	Throughout, as needed

11.7.3. Amendment 2 (05 October 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
BIC 75 mg/LEN 50 mg FDC dose was selected for Phase 3 based on the totality of data from the Phase 2 portion of Study GS-US-621-6289 and multiple cohorts/formulations evaluated in the rBA Study GS-US-621-6292.	Synopsis, Study Schema, and Sections 1, 2, 3, 5.3.2 and Appendix 11.2
Phase 3 secondary objectives and endpoints were updated to evaluate the efficacy and safety of BIC/LEN FDC in participants from Treatment Group 1 at Week 96 as determined by viral load suppression rate and CD4 cell count, and treatment-emergent AEs.	Synopsis and Sections 2 and 8
Phase 3 Extension Period was modified to require participants in Treatment Group 1 to be followed until at least Week 96.	Synopsis and Section 3
Inclusion criteria related to HIV-1 RNA levels were updated for the Phase 3 part of the study.	Synopsis, Section 4
Exclusion criteria were updated to exclude participants under guardianship, curatorship, or legal protection.	Section 4
Week 4 visit was added for participants in Treatment Group 3 of the Phase 2 part and Treatment Group 2 of the Phase 3 part of the study who enroll in the Extension Period	Synopsis, Tables 2 and 4, and Section 3.1.1.2
Reference to safety assessment committee was removed as it is duplicative of the data monitoring committee responsibilities.	Section 7.8
PRO assessments were added to the Phase 3 part of the study.	Tables 3 and 4, and Section 6
Test procedure for HIV-1 RNA ≥ 50 and < 200 copies/mL at any post–Day 1 visit was clarified.	Section 6.3.10.2.1
Text was added to clarify that the daily dose of BIC/LEN FDC should be taken in the clinic on the day of each study visit.	Section 5.3.2
Text was updated pertaining to demographic and baseline characteristics analysis and efficacy and safety analyses.	Section 8
Randomization by geographic region was added to the Phase 3 part of the study.	Synopsis; Sections 3.1.1, 8, and 5.1.1
HCV serology will not be performed in the Phase 3 portion of the study as this test is not required.	Tables 3 and 4
Rosuvastatin and pravastatin have been removed from the list of prior and concomitant medications that are prohibited or to be used with caution while taking LEN per our current understanding of LEN disposition informed by the totality of available data.	Table 11
Language added to clarify that electronic data capture is not considered source data.	Section 3.6
Text added regarding review of past medical history of comorbid conditions.	Section 6.3.4
Information added as data available on BIC in pregnant women indicate no adverse effect on embryo-fetal development.	Appendix 11.4
EU CT number changed from 2022-500929-33-00 to 2022-500929-33 to align with initial EU CTR resubmission required due to technical issues with Clinical Trials Information System.	Title Page; Synopsis

11.8. Sponsor Signature Page

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

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

Protocol Amendment 4, 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-621-6289 amd-4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	04-Apr-2025 16:58:33

STATISTICAL ANALYSIS PLAN

Study Title:	An Operationally Seamless Phase 2/3 Randomized, Open-label, Multicenter, Active-Controlled Study to Evaluate the Safety and Efficacy of Bictegravir/Lenacapavir Versus Stable Baseline Regimen in Virologically Suppressed People With HIV-1 on Stable Complex Treatment Regimens
Name of Test Drug:	Bictegravir/Lenacapavir (BIC/LEN)
Study Number:	GS-US-621-6289
Protocol Version (Date):	Amendment 4 (03 April 2025)
Analysis Type:	Phase 3 Portion, Week 48 Primary Analysis
Analysis Plan Version:	Final Draft
Analysis Plan Date:	02 June 2025
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 4
LIST OF IN-TEXT FIGURES 4
LIST OF ABBREVIATIONS 5
PHARMACOKINETIC ABBREVIATIONS 7
1. INTRODUCTION 8
1.1. Study Objectives and Endpoints 8
1.2. Study Design 10
1.3. Sample Size and Power 11
1.3.1. Rationale for Noninferiority Margin 11
2. TYPE OF PLANNED ANALYSES 13
2.1. Interim Analyses 13
2.1.1. Data Monitoring Committee Analyses 13
2.1.2. Week 96 Interim Analysis 14
2.2. Week 48 Primary Analysis 14
2.3. Final Analysis 14
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 15
3.1. Analysis Sets 15
3.1.1. All Randomized Analysis Set 15
3.1.2. Full Analysis Set 15
3.1.3. Per-Protocol Analysis Set 16
3.1.4. Safety Analysis Set 16
3.1.5. Pharmacokinetic Analysis Set 17
3.1.6. Pharmacokinetic Substudy Analysis Set 17
3.2. Participant Grouping 17
3.3. Strata and Covariates 17
3.4. Examination of Participant Subgroups 18
3.5. Multiple Comparisons 18
3.6. Missing Data and Outliers 18
3.6.1. Missing Data 18
3.6.2. Outliers 19
3.7. Data Handling Conventions and Transformations 19
3.8. Analysis Visit Windows 21
3.8.1. Definition of Study Day 21
3.8.2. Analysis Visit Windows 22
3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window 24
4. PARTICIPANT DISPOSITION 25
4.1. Participant Enrollment and Disposition 25
4.2. Extent of Study Medication Exposure and Adherence 26
4.2.1. Duration of Exposure to Study Drug 26
4.2.2. Duration of Exposure to SBR 27
4.2.3. Adherence to Study Drug 27

4.3. Protocol Deviations 29
5. BASELINE CHARACTERISTICS 30
5.1. Demographics and Baseline Characteristics 30
5.2. Other Baseline Characteristics 30
5.3. Medical History 31
6. EFFICACY ANALYSES 32
6.1. US FDA-Defined Snapshot Algorithm 32
6.2. Estimand 33
6.3. Primary Efficacy Endpoint 33
6.3.1. Definition of the Primary Efficacy Endpoint 33
6.3.2. Statistical Hypothesis for the Primary Efficacy Endpoint 34
6.3.3. Primary Analysis of the Primary Efficacy Endpoint 34
6.3.4. Sensitivity and Supportive Analysis of the Primary Efficacy Endpoint 35
6.3.5. Subgroup Analysis of the Primary Efficacy Endpoint 36
6.4. Secondary Efficacy Endpoints at Week 48 36
6.4.1. Definition of Secondary Efficacy Endpoints at Week 48 36
6.4.2. Primary Analysis of Secondary Efficacy Endpoints at Week 48 36
6.4.3. Sensitivity and Supportive Analysis of Secondary Efficacy Endpoints 37
6.4.4. Subgroup Analysis of the Secondary Efficacy Endpoints 37
6.5. Other Efficacy Evaluations 37
6.5.1. Proportion of Participants with HIV-1 RNA < 50 copies/mL by Visit 37
6.5.2. Change from Baseline in HIV-1 RNA Values by Visit 38
6.5.3. Change from Baseline in CD4 Cell Count by Visit 39
7. SAFETY ANALYSES 40
7.1. Adverse Events and Deaths 40
7.1.1. Adverse Event Dictionary 40
7.1.2. Adverse Event Severity 40
7.1.3. Relationship of Adverse Events to Study Drug or SBR 40
7.1.4. Relationship of Adverse Events to Study Procedure 40
7.1.5. Serious Adverse Events 41
7.1.6. Treatment-Emergent Adverse Events 41
7.1.7. Summaries of Adverse Events and Deaths 41
7.2. Laboratory Evaluations 43
7.2.1. Summaries of Numeric Laboratory Results 44
7.2.2. Graded Laboratory Values 44
7.2.3. Liver-related Laboratory Evaluations 46
7.3. Body Weight and Vital Signs 46
7.4. Prior and Concomitant Medications 47
7.4.1. Antiretroviral Medications 47
7.4.2. General Medications (Non-Antiretroviral) 48
7.5. Electrocardiogram Results 49
7.6. Other Safety Measures 49
7.7. Changes From Protocol-Specified Safety Analyses 49
8. PHARMACOKINETIC ANALYSES 50
8.1. PK Sample Collection 50
8.2. PK Analyses Related to Intensive PK Sampling 50
8.2.1. Estimation of PK Parameters 50
8.2.2. PK Parameters 50
8.2.3. Sensitivity Analyses 52
8.3. PK Analyses Related to Sparse PK Sampling 52

9. EVALUATION OF PATIENT-REPORTED OUTCOMES 53
10. REFERENCES 54
11. SOFTWARE 55
12. SAP REVISION 56
13. APPENDICES 57
13.1. Schedule of Assessments 57
13.2. US FDA-Defined Snapshot Algorithm 64
13.3. Stable Baseline Regimen Categories 65
13.4. Laboratory Values 67

LIST OF IN-TEXT TABLES

Table 3-1. Participants Excluded from Week 48 Per-Protocol Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 48 Analysis Window 16
Table 3-2. Analysis Visit Windows for Plasma HIV-1 RNA, CD4 Cell Count, Chemistry, Hematology, $eGFR_{CG}$, Weight and Vital Signs 22
Table 3-3. Analysis Visit Windows for Urinalysis Assessments 23
Table 3-4. Analysis Visit Windows for Metabolic Assessments 23
Table 3-5. Analysis Visit Windows for Safety Electrocardiogram Results 23
Table 3-6. Analysis Visit Windows for HBV Blood Panel and Hemoglobin A1c 24
Table 6-1. Estimand and Handling for Intercurrent Events for Virologic Outcomes 33
Table 8-1. Study Treatments and Associated Analytes 51
Table 8-2. PK Parameters for Each Analyte 51
Table 13-1. Schedule of Assessments in Phase 3 – Treatment Groups 1 and 2: Screening through Post-Endpoint Week 48 57
Table 13-2. Schedule of Assessments in Phase 3 – Treatment Groups 1 and 2: ERT Visit through 60-Day In-Clinic Follow-up Visit 61
Table 13-3. Stable Baseline Regimen Categories 65

LIST OF IN-TEXT FIGURES

Figure 1-1. Study Schema 10
Figure 13-1. Flowchart of US FDA-Defined Snapshot Algorithm 64

LIST OF ABBREVIATIONS

%CV	coefficient of variation
AE	adverse event
AI	Attachment Inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BIC	bictegravir
BLQ	below the limit of 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
IRT	interactive response technology
ITT	intent to treat
LEN	lenacapavir
LDL	low-density lipoprotein

LLT	lower-level term
LOQ	limit of quantification
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model with Repeated Measures
NI	noninferiority
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
SBR	stable baseline regimen
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization
WPAI-HIV	Work Productivity and Activity Impairment Questionnaire: HIV

PHARMACOKINETIC ABBREVIATIONS

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

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the primary analysis at Week 48 of the Phase 3 portion of Study GS-US-621-6289 for the primary and secondary endpoints. The analysis will be performed after all participants enrolled in the Phase 3 portion of the study complete their Week 48 visit or prematurely discontinue from the study drug.

This SAP is based on the study protocol amendment 4 dated 03 April 2025 and the electronic case report form (eCRF). This SAP will be finalized prior to data finalization for the primary analysis. Any changes made after the finalization of the SAP will be documented in the interim Week 48 clinical study report (CSR).

1.1. Study Objectives and Endpoints

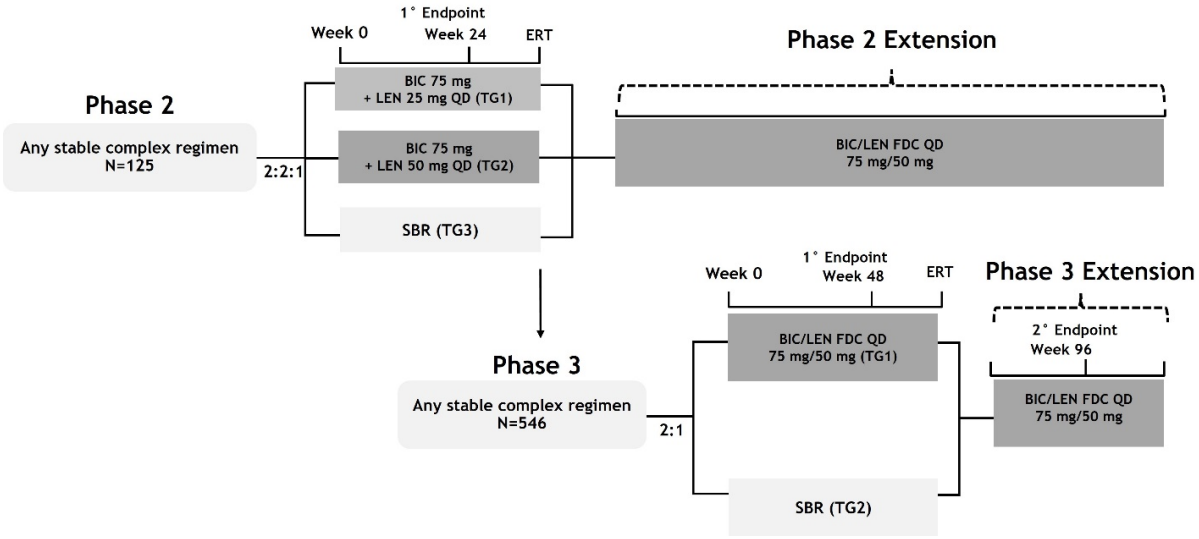
Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of switching to bictegravir/lenacapavir (BIC/LEN) fixed-dose combination (FDC) tablet regimen (BIC 75 mg/LEN 50 mg) versus continuing on a stable baseline regimen (SBR) in virologically suppressed people with HIV-1 as determined by the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

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

1.2. Study Design

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

Figure 1-1. Study Schema



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

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

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

- **Treatment Group 2 (n = 182)**: Participants continue with their SBR.

Randomization was stratified by geographic region.

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

Participants will be treated for at least 48 weeks during the Randomized Period. After Week 48, participants will continue to take their study drug (BIC 75 mg/LEN 50 mg FDC tablets or SBR)

and attend visits every 12 weeks. Once the last participant completes the Week 48 visit and the safety and efficacy of BIC/LEN FDC compared with the baseline regimen are demonstrated and the Week 48 analysis is completed, all participants will attend the end of randomized treatment (ERT) visit (preferably within 30 days).

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

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

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

Additional details regarding study assessment can be found in Table 13-1 and Table 13-2.

1.3. Sample Size and Power

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

1.3.1. Rationale for Noninferiority Margin

According to the FDA's 2015 guidance document {U. S. Department of Health and Human Services 2015}, the margin for switch trials is driven by the largest clinically tolerable virologic failure rate. Per the FDA guidance, a margin of 4% for the primary endpoint of virologic failure

rate (HIV-1 RNA ≥ 50 copies/mL) is considered clinically tolerable, with typical observed rates of virological failure seen in switch studies ranging from 1% to 3%.

2. TYPE OF PLANNED ANALYSES

This SAP describes the analyses for the primary and secondary endpoints planned for the Week 48 primary analysis of the Phase 3 portion of this study.

2.1. Interim Analyses

Prior to the final analysis of Phase 3 portion of the study, at least 2 analyses will be conducted to evaluate primary and secondary objectives of the protocol, one after all participants have completed their visits at Week 48, and the other after all participants in Treatment Group 1 have completed their visits at Week 96. The Week 48 analysis will serve as the primary analysis. Additional interim analyses may be conducted as necessary after Week 96 in order to support regulatory submission and/or publication(s).

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

2.1.1. Data Monitoring Committee Analyses

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

The Week 12 DMC analysis was conducted after approximately the first 50% of participants enrolled in the Phase 3 portion completed their Week 12 visit or prematurely discontinued the study drug. The Week 24 DMC analysis will be conducted after all participants enrolled complete their Week 24 visit or prematurely discontinue the study drug. More details are documented in the DMC charter.

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

For the Phase 3 portion, for each DMC analysis performed prior to the analysis of the primary efficacy endpoint, an alpha penalty of 0.00001 is applied conservatively for the efficacy analysis for DMC. Data from these analyses may be used to support the planning of other studies.

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

2.1.2. Week 96 Interim Analysis

For the Phase 3 portion, the Week 96 interim analysis will be conducted after all participants enrolled in Treatment Group 1 either complete their Week 96 visit or prematurely discontinue from the study drug, outstanding data queries are resolved or adjudicated as unresolvable, and the data are cleaned and finalized for the analysis.

2.2. Week 48 Primary Analysis

The primary analysis for the primary endpoint of proportion of participants with HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm will be conducted at Week 48. The Week 48 primary analysis will be conducted after all participants either complete their Week 48 visit or prematurely discontinue from the study drug, outstanding data queries are resolved or adjudicated as unresolvable, and the data are cleaned and finalized for the analysis.

2.3. Final Analysis

The final analysis for the Phase 3 portion of the study will be conducted after all participants either complete the study or prematurely discontinue from the study, outstanding data queries are resolved or adjudicated as unresolvable, and the data are cleaned and finalized for the analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The Week 48 primary analysis will include all data collected from the randomized period of the Phase 3 portion of the study. No participant will be enrolled into the extension phase before the completion of the Week 48 primary analysis.

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

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

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

3.1. Analysis Sets

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

For each analysis set, the number and percentage of participants eligible for inclusion, as well as the number and percentage of participants who 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

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

3.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** includes all randomized participants who took at least 1 dose of randomized drug (BIC/LEN FDC for Treatment Group 1, or continuing with their SBR for Treatment Group 2). This is the primary analysis set for efficacy analyses.

3.1.3. Per-Protocol Analysis Set

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

- 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 below the 2.5th percentile for active study drug BIC/LEN FDC up to Week 48.

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

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

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

3.1.4. Safety Analysis Set

The **Safety Analysis Set** includes all participants who were randomized and took at least 1 dose of randomized drug (BIC/LEN FDC for Treatment Group 1, or continuing with their SBR for Treatment Group 2). This is the primary analysis set for safety analyses.

3.1.5. Pharmacokinetic Analysis Set

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

3.1.6. Pharmacokinetic Substudy Analysis Set

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

3.2. Participant Grouping

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

In the Phase 3 portion, participants were randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 2:1 ratio using a stratified randomization schedule. Stratification was based on the geographic region as below.

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

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

Efficacy endpoints will be evaluated using stratification 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 the FAS:

- Age (< 55 years and ≥ 55 years)
- Sex (male and female)
- Race (white, all other races, and not permitted)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not permitted)
- Region (US [including US and Puerto Rico] and Ex-US)

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

3.5. Multiple Comparisons

For the Phase 3 portion, noninferiority evaluation of the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by US FDA-defined snapshot algorithm is the prespecified primary comparison.

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

There are 2 interim DMC analyses performed prior to the analysis for the primary endpoint. Conservatively, an alpha penalty of 0.00001 is 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) for both noninferiority and superiority tests to control the overall Type I error rate.

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

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

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

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

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

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters (as applicable). Values that are BLQ will be treated as 0 at all predose and postdose time points for summary purposes.

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

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

The following conventions will be used for the presentation of order statistics for intensive PK concentrations:

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

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

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

The earliest of the first dosing date of any component (ie, BIC/LEN FDC or LEN oral loading dose) is considered as the first dose date of the study drug.

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

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

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

Last Dose Date in randomized period is defined as follows:

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

If the last dose date is incomplete (ie, only year of last dose date is known) or missing, the latest date among the study drug/SBR nonmissing start date and stop date, the clinic visit dates (excluding the follow-up dates after early study drug discontinuation [ESDD]), and the laboratory sample collection dates (excluding the follow-up dates after ESDD) will be used for participants who prematurely discontinued study drug/SBR in the randomized period, 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 (for Treatment Group 1), study drug/SBR start date and stop date, and the imputed last dose date (day imputed as 15) will be used as the last dose date.

If a participant 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 randomized period is the latest date among the study drug/SBR start date and stop date, the clinic visit date (including the 30-day and 60-day follow-up visit dates), and the laboratory sample collection date, for participants who prematurely 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 randomized period for all assessments, unless otherwise specified.

3.8.2. Analysis Visit Windows

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

The analysis windows for efficacy endpoints, vital signs, weight, ECG, and safety laboratory data are provided in Table 3-2, Table 3-3, Table 3-4, Table 3-5, and Table 3-6. Analysis windows for the randomized period analysis are derived relative to Study Day 1 in the randomized period.

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 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week X* (Post-Week 96, X > 96)	7*X	7*X – 41	7*X + 42

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

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 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week X* (Post-Week 96, X > 96)	7*X	7*X – 41	7*X + 42

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

Table 3-4. Analysis Visit Windows for Metabolic Assessments

Analysis Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	168
Week 36	252	169	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week X* (Post-Week 96, X > 96)	7*X	7*X – 41	7*X + 42

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

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

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

Table 3-6. Analysis Visit Windows for HBV Blood Panel and Hemoglobin A1c

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

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

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per analysis window.

If multiple valid, nonmissing measurements (except for HIV-1 RNA) exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- For postbaseline values:

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

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

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

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

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

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

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

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

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

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

- Safety Analysis Set
- Full Analysis Set
- Per-Protocol Analysis Set
- PK Analysis Set
- PK Substudy Analysis Set
- Continuing study drug/SBR in randomized period
- Did not complete study drug/SBR in randomized period with reasons for premature discontinuation of study drug/SBR
- Completed Week 48 visit
- Continuing study

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

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

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

- Participant disposition, including treatment, date of randomization, first dose date and day, last dose date and day, end of study date and day, study drug discontinuation, study discontinuation, and reasons for study drug or study discontinuation.

- Lot number and kit ID

- Participant profile, including treatment, date of randomization, first dose date and day, last dose date and day, last visit date and day, last lab date and day, last study date and day.

4.2. Extent of Study Medication Exposure and Adherence

Extent of exposure to study drug in Treatment Group 1 will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol. The extent of exposure to SBR for participants in Treatment Group 2 will also be examined.

4.2.1. Duration of Exposure to Study Drug

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

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

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

No formal statistical testing is planned.

4.2.2. Duration of Exposure to SBR

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

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

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

4.2.3. Adherence to Study Drug

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

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

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

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.

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

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

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

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

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

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

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

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

4.3. Protocol Deviations

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

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with at least one important protocol deviations will be summarized by treatment group by deviation category for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

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

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- HIV-1 RNA level category: (a) < 50 copies/mL, (b) ≥ 50 copies/mL.
- CD4 cell count (/μL).
- CD4 cell count (/μL) category: (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500.
- CD4 percentage (%).
- eGFR (mL/min).
- HIV disease status: (a) AIDS, (b) asymptomatic, or (c) symptomatic HIV infection.
- Mode of infection (risk factors for HIV infection).
- Reasons to be on a complex regimen.
- Duration of HIV disease from diagnosis (in years): Calculated as (first dosing date of this study - date of initial diagnosis + 1 day) / 365.25. If the date of initial diagnosis is incomplete, then the following rules will be applied:
  - missing day: use the first day of the month.
  - missing month: use January.

- Duration since first HIV treatment (in years): Calculated as (first dosing date of this study - start date of the first HIV treatment + 1 day) / 365.25. If the date of first treatment start date is incomplete, rules same as above will be applied.
- Number of prior ARV medication used.
- Prior ARV medication drug class: AI, CCR5, CAI, Fusion, INI, INI/NNRTI, NRTI/INI, NRTI/NNRTI, NRTI/PI, NNRTI, NRTI, PI, PI/PKE, PKE, Post-Attachment Inhibitor, or Other.
- Antiretroviral (ARV) medication use at baseline: Defined as the ARV medications taken on or up to 14 days prior to first dosing date of study drugs for Treatment Group 1, or taken on Day 1 for Treatment Group 2. This will be grouped by composite drug class category as defined in Appendix 13.3 and summarized by PI-containing or not.
- Number of ARV medication used at baseline.
- Dosing frequency of ARVs used at baseline: once daily, twice per day, three times per day, every two weeks, once, and other.
- Number of ARV pills taken per day at baseline.
- Number of ARV pills taken per day at baseline by category: 2, 3, 4, 5, >=6
- Historical HIV-1 genotype resistance results: INSTI (Yes/No/Data Not Available), NNRTI (Yes/No/Data Not Available), NRTI (Yes/No/Data Not Available), PI (Yes/No/Data Not Available).

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

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

5.3. Medical History

Medical history data will be collected at screening for general condition 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.

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

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

6. EFFICACY ANALYSES

6.1. US FDA-Defined Snapshot Algorithm

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

"On-treatment" is defined as all data collected up to 1 day after permanent discontinuation of study drug (or SBR for Treatment Group 2), or all available data for participants who were still on study drug or SBR.

The virologic outcome will be defined as the following categories:

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

The flowchart of the US FDA-defined snapshot algorithm is provided in Figure 13-1.

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

6.2. Estimand

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

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

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

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

6.3. Primary Efficacy Endpoint

6.3.1. Definition of the Primary Efficacy Endpoint

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

6.3.2. Statistical Hypothesis for the Primary Efficacy Endpoint

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

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

vs.

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

Where the noninferiority margin θ is 4%.

6.3.3. Primary Analysis of the Primary Efficacy Endpoint

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

The treatment difference and the corresponding 2-sided 95.002% CI for the difference will be constructed based on 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 Treatment Group 1 and 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 Treatment Group 1 and Treatment Group 2 in stratum *h*, respectively.
- And $SE(P_1 - P_2) = \sqrt{\frac{\sum w \left[\frac{p^*_{1h}(1-p^*_{1h})}{n_{1h}-1} + \frac{p^*_{2h}(1-p^*_{2h})}{n_{2h}-1}\right]}{(\sum w_h)^2}}$, where $p^*_{1h} = \frac{m_{1h}+0.5}{n_{1h}+1}$ and $p^*_{2h} = \frac{m_{2h}+0.5}{n_{2h}+1}$. m_{1h} and m_{2h} are the number of participants with HIV-1 RNA ≥ 50 copies/mL in the Treatment Group 1 and Treatment Group 2 in stratum *h*, respectively.

- $\alpha = 0.04998$ for this study.
- $Z_{(1-\alpha/2)} = Z_{0.97501} = 1.9601$ is the 97.501^{th} 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 region stratification and/or low number of participants with virologic failure, combined region stratums will be used (US [including US and Puerto Rico] vs. Ex-US); if still not estimable, the primary comparison will be based on the unadjusted analysis.

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

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

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

6.3.4. Sensitivity and Supportive Analysis of the Primary Efficacy Endpoint

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

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

6.3.5. Subgroup Analysis of the Primary Efficacy Endpoint

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

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

6.4. Secondary Efficacy Endpoints at Week 48

6.4.1. Definition of Secondary Efficacy Endpoints at Week 48

The secondary efficacy endpoints are defined as follows:

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

6.4.2. Primary Analysis of Secondary Efficacy Endpoints at Week 48

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

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

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

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

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

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

6.4.3. Sensitivity and Supportive Analysis of Secondary Efficacy Endpoints

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

The modified FDA snapshot algorithm will also be performed as a sensitivity analysis for the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 48. The difference between treatment groups and the corresponding 95% CI will be calculated using the stratum-adjusted MH proportion.

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) as a sensitivity analysis 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 LS means along with 95% CIs and the p-value for the change from baseline for each treatment group, and difference in mean change from baseline in CD4 cell count at Week 48 between treatment groups from MMRM will be provided.

6.4.4. Subgroup Analysis of the Secondary Efficacy Endpoints

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

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

6.5. Other Efficacy Evaluations

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

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

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

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

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

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL Not Detectable
    - < 20 copies/mL Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL
- Missing (only applicable to M = F analysis)

The 2-sided 95% CIs for the difference in proportion of participants with HIV-1 RNA < 50 copies/mL at each postbaseline visit between treatment groups will be constructed based on the stratum-adjusted MH proportion as described in Section 6.3.3 where m_{1h} and m_{2h} are the number of participants with HIV-1 RNA < 50 copies/mL in Treatment Group 1 and Treatment Group 2 in stratum *h*, respectively.

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

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

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

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

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

6.5.3. Change from Baseline in CD4 Cell Count by Visit

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

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

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

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the Safety Analysis Set. 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 toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug or SBR

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment" for participants receiving BIC/LEN FDC in Treatment Group 1, or 'Related to SBR' for participants receiving SBR in Treatment Group 2. Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug or SBR will be considered related to study drug or SBR based on the drug received for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. 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:

- Any AEs with a start date on or after the first dose date of study drugs and up to 60 days after permanent discontinuation of the study drugs for participants in Treatment Group 1; or any AEs with a start date on or after Day 1 visit date, and up to 30 days after permanent discontinuation of SBR for participants in Treatment Group 2.

- Any AEs leading to premature discontinuation of study drugs or SBR.

7.1.6.2. Incomplete Dates

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

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

- The AE start date is the same as or before the month and year (or year alone) of the date corresponding to 60 days for Treatment Group 1 (or 30 days for Treatment Group 2) after the date of last dose of study drug (or SBR).

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

7.1.7. Summaries of Adverse Events and Deaths

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

7.1.7.1. Summaries of AE Incidence

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

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

The number and percentage of participants who experienced at least 1 TEAE during the randomized period will be provided and summarized by SOC, HLT, PT, and treatment group. For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

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

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

In addition to the above summary tables, all TEAEs, TEAEs with Grade 3 or higher, TE SAEs, TE treatment-related AEs, TE treatment-related AEs with Grade 3 or higher, TE treatment-related SAEs, and TEAEs leading to premature discontinuation of study drug or SBR during the randomized period will be summarized by PT only and by treatment group, in descending order of total frequency. These summaries will also be provided for up to Week 48 visit, as appropriate.

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

- All AEs, indicating whether the event is treatment emergent
- All AEs up to Week 48 visit, indicating whether the event is treatment emergent
- All AEs with severity of Grade 3 or higher
- All AEs with severity of Grade 2 or higher
- All SAEs
- All treatment-related AEs
- All Deaths
- All AEs leading to premature discontinuation of any study drug or SBR
- All AEs leading to premature discontinuation of study

7.2. Laboratory Evaluations

Laboratory data collected during the randomized period will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 60 days (or last dose of SBR plus 30 days) for participants who have permanently discontinued study drug (or SBR), 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 will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

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

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

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

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

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

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

7.2.2. Graded Laboratory Values

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

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities 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 SBR), 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 SBR), 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 that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities
- Marked laboratory abnormalities

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

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 60 days after last dosing date of BIC/LEN (or 30 days after last doing date of SBR) in the randomized period.

A by-participant listing of all treatment-emergent laboratory 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

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

7.3. Body Weight and Vital Signs

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

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

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug BIC/LEN for Treatment Group 1, or the date of Day 1 visit for Treatment Group 2. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

Median (Q1, Q3) of the changes from baseline for body weight and BMI will be plotted by treatment group and visit.

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

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

7.4. Prior and Concomitant Medications

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

7.4.1. Antiretroviral Medications

7.4.1.1. Prior Antiretroviral Medications

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

Prior ARV medications are defined as any ARV medications taken before a participant takes the first study drug for Treatment Group 1 or before Day 1 for Treatment Group 2. Prior ARV medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each treatment group and overall. A participant reporting the same medication more than once will be counted only once within each ATC Level 2 drug class 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 for Treatment Group 1 or before Day 1 for Treatment Group 2 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 (or Day 1 for Treatment Group 2). 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.

7.4.1.2. Concomitant Antiretroviral Medications

Current ARVs are defined as any ARV medications taken while a participant takes study drug BIC/LEN in Treatment Group 1, or any ARVs taken on or after Day 1 for Treatment Group 2.

Summary of concomitant antiretroviral will not be provided.

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

7.4.2. General Medications (Non-Antiretroviral)

7.4.2.1. Prior Medications

Prior non-ARV medications are defined as medications taken before a participant takes the first study drug for Treatment Group 1 or before Day 1 for Treatment Group 2. Any medications with a start date prior to the first dosing date of study drugs or prior to Day 1 for Treatment Group 2 will be taken as prior medications regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be taken as prior medications, unless otherwise specified.

Summary of prior medications will not be provided.

7.4.2.2. Concomitant Medications

Concomitant non-ARV medications are defined as medications taken while a participant takes study drug BIC/LEN for Treatment Group 1 or medications taken on or after Day 1 for Treatment Group 2. Use of concomitant medications will be summarized by ATC drug class Level 2 and preferred name using the number and percentage of participants for each treatment group. A participant reporting the same medication more than once within each ATC Level 2 drug class will be counted only once when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC Level 2 medical class and then by preferred name in descending overall frequency within each ATC Level 2 medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of any study drug (or Day 1 for Treatment Group 2) and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug (or SBR) will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of any study drug (or SBR) will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of any study drug (or SBR) or with a start date after the last dosing date of all study drugs (or SBR) will be excluded from the concomitant medication summary. If a partial stop date is entered, any

medication with the stop month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration (or Day 1 for Treatment Group 2) will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the start month and year (if day is missing) or year (if day and month are missing) after all study drug (or SBR) stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

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

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

7.5. Electrocardiogram Results

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

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

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

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

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

8.2. PK Analyses Related to Intensive PK Sampling

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

8.2.1. Estimation of PK Parameters

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

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

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

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

8.2.2. PK Parameters

PK parameters will be generated for all participants for whom parameters can be derived in the PK Substudy Analysis Set. The analytes presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

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

BIC = bictegravir; LEN = lenacapavir.

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

Table 8-2. PK Parameters for Each Analyte

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

BIC = bictegravir; LEN = lenacapavir.

Individual participant concentration data and individual participant PK parameters will be listed and summarized using descriptive statistics. Descriptive statistics (number of participants, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual participant concentration data by nominal time point and individual participant PK parameters for Treatment Group 1. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants in PK Analysis Set with concentration data. Any PK concentration samples not collected per protocol (e.g., planned postdose samples actually collected predose, or trough samples collected outside of the 20 - 28 hours [inclusively] postdose collection window) will be excluded from the summaries. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ, as well as an indicator if more than one-third of the participants are BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at all predose and postdose time points. If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point. Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

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

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

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

The following figures may be provided for each analyte:

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

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

8.2.3. Sensitivity Analyses

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

8.3. PK Analyses Related to Sparse PK Sampling

The sparse PK samples will be evaluated using descriptive statistics.

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

9. EVALUATION OF PATIENT-REPORTED OUTCOMES

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

10. REFERENCES

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

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

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

11. SOFTWARE

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

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

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

12. SAP REVISION

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

13. APPENDICES

13.1. Schedule of Assessments

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

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

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

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

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

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

b Initiation of the first dose of study drug is to take place in-clinic following completion of study procedures at the Day 1 visit. Participants randomized to Treatment Group 1 will receive a 2-day PK oral loading dose regimen of LEN (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1. The study drugs will be administered without regard to food.

c Day 2 visit is not applicable to participants in Treatment Group 2. Day 2 visit is to be completed the day after Day 1 visit. Day 2 visit may be a virtual visit and the participants will self-administer the study drugs and be observed by site staff to confirm dosing. Please refer to Protocol Section 6.3.8 for further details.

d After Week 48, all participants will return for visits every 12 weeks until the ERT visit.

e Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

f Symptom-directed physical examination as needed.

g Blood pressure, pulse, respiration rate, and temperature.

h Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.

i At screening, a FSH is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
j Chemistry profile per Protocol Table 12.
k Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
l Hematology profile per Protocol Table 12.
m Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate) in accordance with local regulations. Separate consent for optional future research is not needed to collect or use these samples unless required per local regulations and requirements.
n HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb), at Week 48 of randomized treatment, at Week 48 of the Extension Period visits, and at the 60 day in-clinic follow-up visit. **Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study.** Participants who are HBsAg positive will have a plasma HBV DNA test performed.
o HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Protocol Section 6.3.10.2).
p Proviral DNA sequencing is for research use only. Sample is to be collected for all participants on study. Separate consent is not required for this test.
q For participants in Treatment Group 1, a single predose plasma PK sample (≤ 5 min before dose) and a postdose plasma PK sample at 4 hours (± 1 hours) (relative to BIC/LEN FDC dosing and oral loading dose of LEN) will be collected on Day 1. A single trough plasma PK sample approximately 23 to 24 hours after the previous dose and prior to dosing at Weeks 4, 12, 24, 36, and 48, and a single postdose plasma PK sample at 2 hours (± 1 hours) (relative to BIC/LEN dosing) at Weeks 4, 12, 24, 36, and 48 will be collected. For participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule (except for participants enrolled in the intensive PK substudy), a PK sample prior to dosing in clinic should be collected at Weeks 4, 12, 24, 36, and 48.
r For participants who become pregnant and provide reconsent to remain on study, sparse PK samples will be collected as follows: at all specified time points described above in footnote ‘q’ during randomized treatment visits until Week 48. A single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12 week visit (as possible) after Week 48 until ERT visit and during Extension Period. See Protocol Section 6.3.9.2 for additional information. For pregnant participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at every 12 week visit (as possible) after Week 48 until the ERT visit and during Extension Period.
s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse intensive PK sample (as applicable).
t An intensive PK substudy will be performed in a subset of participants in Treatment Group 1 at selected study sites. Participants may select to participate in either one of the visits. Intensive PK blood samples will be collected for the subset of participants as described below **instead of** the sparse plasma PK samples on those specific visits.
Week 24 or 36 or 48 visit: Before study drug is administered on this day, a trough PK sample will be collected approximately 23 to 24 hours after the dose that was administered the day before and before the next scheduled dose. PK samples will be collected at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose (relative to BIC/LEN FDC dosing).
u Investigators may perform a virtual visit or a phone call visit to review study drug and dosing diary adherence in between 2 in-clinic visits especially when the visits are 12 weeks apart.
v EQ-5D-3L Questionnaire will only be collected at Week 96 visit.

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

Study Procedures	ERT Visit[a]	Phase 3 Extension[b]			Early Study Drugs DC Visit	30-day Telephone Visit[e]	60-day In-clinic Follow-up Visit[e]
		Only for TG2 participants who enroll in the Extension Period		Every 12 weeks[d]			
		Day 2	Week 4[c]				
Visit Window			± 6 days	± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Concomitant medications	X	X	X	X	X	X	X
Adverse events[f]	X	X	X	X	X	X	X
Complete physical exam	X				X		X
Symptom-directed physical exam[g]			X	X			
12-Lead ECG (performed supine)					X		
PozQoL[h]				X			
HIVTSQs-12[h]				X			
Treatment Preference Questionnaire[h]				X			
WPAI - HIV Questionnaire[h]				X			
EQ-5D-3L Questionnaire[h]				X[i]			
PGIC: Impact Questionnaire[h]				X			
PGIS: Impact Questionnaire[h]				X			
Weight	X			X	X		X
Vital signs[j]	X		X	X	X		X
Urinalysis	X			X	X		X
Urine pregnancy test[k]					X		X
Chemistry profile[l]	X		X	X	X		X
Metabolic assessment[m]	X			X			
Creatinine clearance	X		X	X	X		X
Hematology profile[n]	X		X	X	X		X
Plasma HIV-1 RNA	X		X	X	X		X
CD4 cell count	X		X	X	X		X

Study Procedures	ERT Visit[a]	Phase 3 Extension[b]			Early Study Drugs DC Visit	30-day Telephone Visit[e]	60-day In-clinic Follow-up Visit[e]
		Only for TG2 participants who enroll in the Extension Period		Every 12 weeks[d]			
		Day 2	Week 4[c]				
Visit Window			± 6 days	± 6 days	Within 72 hours of last dose	± 6 days	± 6 days
Plasma and urine storage sample[o]	X		X	X	X		X
HBV blood panel[p]				X			X[o]
Plasma samples stored for potential HIV-1 genotype/ phenotype[q]	X		X	X	X		X
Sparse PK: trough PK sample (Treatment Group 1)[r,s]				X			
Provide participant dosing diary to participants	X		X	X			
Study drug dispensation	X		X	X			
Study drug accountability[t]	X		X	X	X		

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

a Once the last participant completes the Week 48 visit and Gilead completes the Week 48 analysis, all participants will return to the clinic (preferably within 30 days) on their next follow-up visit for an ERT visit. At the ERT visit, participants will be given BIC/LEN FDC in an Extension Period until drug is available or until Gilead elects to discontinue the study, whichever occurs first. Participants in Treatment Group 1 will continue to the Extension Period until Week 96, if they do not wish to continue in the Extension Period after Week 96, they will be required to return to the clinic 60 days after the Week 96 visit for a 60-day follow-up visit and will be considered to have completed the Phase 3 portion of the study. Participants in Treatment group 2 who complete the study through the ERT visit, and do not wish to participate in the Extension Period, will be required to return to the clinic 60 days after the ERT visit for a 60-day follow-up visit, and will be considered to have completed the Phase 3 portion of the study.

b Participants from Treatment Group 2 who enroll in the Extension Period will receive a 2-day PK oral loading dose regimen of LEN 600 mg (2 × 300 mg LEN on Day 1 and on Day 2), in addition to the daily dose of BIC/LEN FDC starting on Day 1 of the Extension Period. Day 2 may be a virtual visit and the participants will self-administer study drugs and be observed by the site to confirm dosing. Please refer to Protocol Section 6.3.8 for further details.

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

d Every 12 week visits will follow the schedule of previously scheduled visits in the randomized phase and not from the ERT Visit for Treatment Group 1.

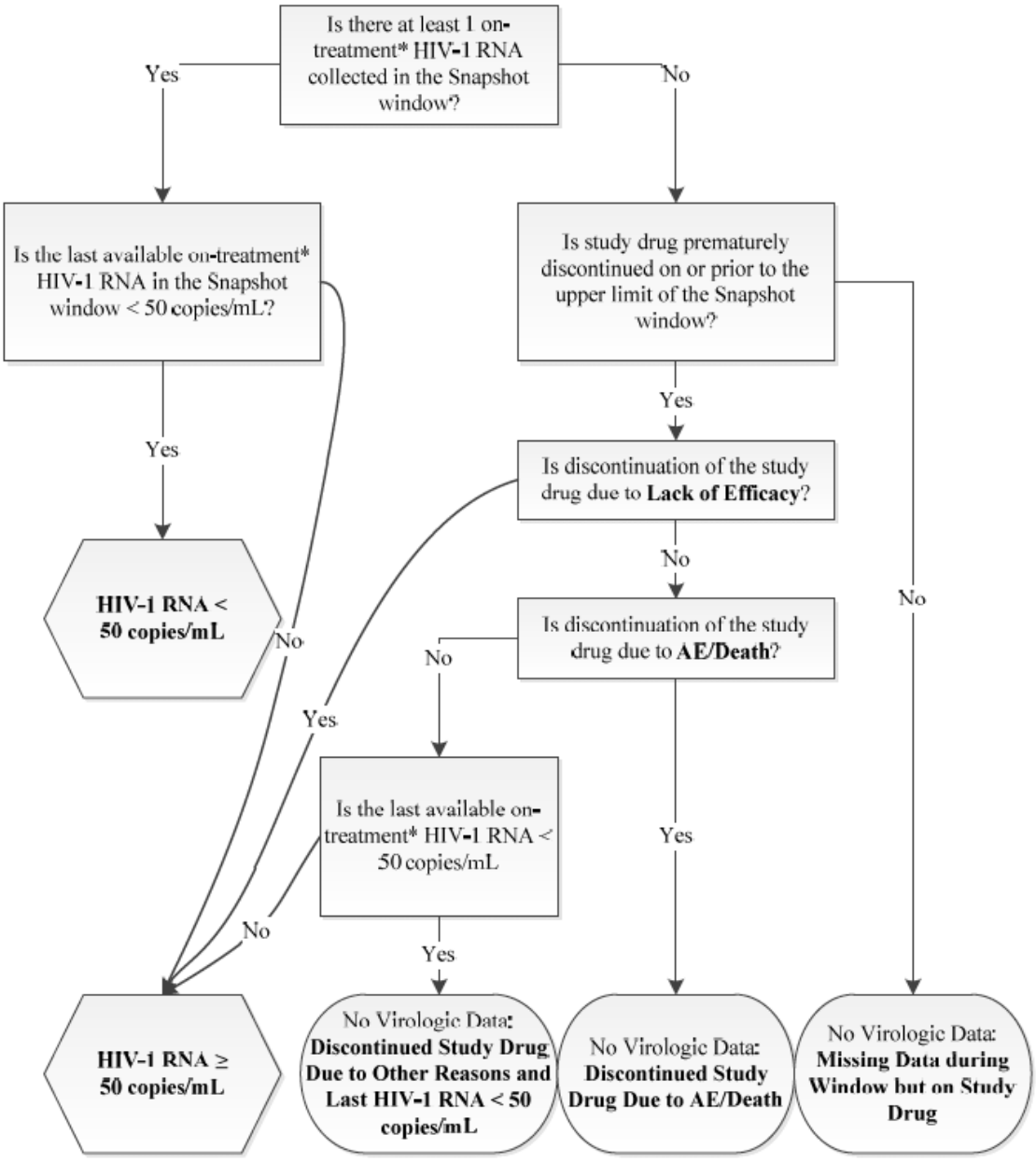
e Required for participants who enroll in the Extension Period or discontinue study drugs early. Participants who enroll in the Extension Period or discontinue study early should have a 30-day telephone visit conducted. They will be required to return to clinic for a 60 day follow-up visit. For the purpose of scheduling a 60-day follow-up visit, a ± 6 days window may be used.

f Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
g Symptom-directed physical examination as needed.
h After the ERT visit, these questionnaires will only be administered to participants in Treatment Group 1 every 12 weeks until the Week 96 visit.
i During the Phase 3 Extension Period, EQ-5D-3L should only be collected at Week 96.
j Blood pressure, pulse, respiration rate, and temperature.
k Participants assigned female at birth of childbearing potential only. A negative urine pregnancy test is required prior to randomization. Positive urine pregnancy tests will be confirmed with a serum test.
l Chemistry profile per Protocol Table 12.
m Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
n Hematology profile per Protocol Table 12.
o Stored plasma samples at all available time points may be used for evaluation of biomarker, PK, and virology assays (as appropriate). Separate consent for optional future research is not needed to collect or use these samples unless required per local regulations and requirements.
p HBV blood panel will be performed at screening (HBsAg, HBsAb, and HBcAb), at Week 48 of randomized treatment, at Week 48 of the Extension Period visits, and at the 60 day in-clinic follow-up visit. **Participants who meet the definition of HBV infection at screening will not be eligible to participate in the study.** Participants who are HBsAg positive will have a plasma HBV DNA test performed.
q HIV-1 genotype and phenotype testing for participants with confirmed virologic failure. Following unconfirmed virologic rebound, participants will be asked to return to the clinic (2 to 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype, in addition to genotypic and phenotypic Gag-Pro assays) blood draw. Note: 2 different laboratories will run resistance testing. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Protocol Section 6.3.10.2).
r For participants who become pregnant and provide reconsent to remain on study, a single trough sample will be collected approximately 23 to 24 hours after previous dose and prior to next dose at every 12 week visit (as possible) during the Extension Period. See Protocol Section 6.3.9.2 for additional information . For participants taking their daily doses in the evening, preference would be to have them change their dosing schedule to morning dosing about 3 to 4 days prior to the study visit as much as possible. For extenuating scenarios wherein the participant is not able to change their dosing schedule, a PK sample prior to dosing in clinic should be collected at every 12 week visit (as possible) during the Extension Period.
s At each on-treatment study visit, participants are to take study drug in the clinic after collection of predose or trough sparse intensive PK sample (as applicable).
t Investigators may perform a virtual visit or a phone call visit to review study drug and dosing diary adherence in between 2 in-clinic visits especially when the visits are 12 weeks apart.

13.2. US FDA-Defined Snapshot Algorithm

The flowchart of the US FDA-defined snapshot algorithm based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment {U. S. Department of Health and Human Services 2015} is provided in Figure 13-1.

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



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

13.3. Stable Baseline Regimen Categories

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

Table 13-3. Stable Baseline Regimen Categories

Unique Drug Class Combination from eCRF Options	Category
INI, PI	PI + INSTI
INI, PI, PKE	
INI, NRTI, PI	PI + INSTI + NRTIs (1 or 2)
INI, NRTI, PI, PKE	
INI, NNRTI, PI	PI + INSTI + NNRTI (+/- NRTIs)
INI, NNRTI, PI, PKE	
INI, NNRTI, NRTI, PI	
INI, NNRTI, NRTI, PI, PKE	
AI, INI, NRTI, PI	PI + INSTI + Attachment (+/- NRTIs)
AI, INI, NRTI, PI, PKE	
AI, INI, PI	
AI, INI, PI, PKE	
CCR5, INI, NRTI, PI	
CCR5, INI, NRTI, PI, PKE	
CCR5, INI, PI	
CCR5, INI, PI, PKE	
NNRTI, NRTI, PI	PI + NNRTI (+/- NRTIs)
NNRTI, NRTI, PI, PKE	
NNRTI, PI	
NNRTI, PI, PKE	
INI, NNRTI	INSTI + NNRTI (+/- NRTIs)
INI, NNRTI, NRTI	
AI, INI	INSTI + Attachment (+/- NRTIs)
AI, INI, NRTI	
CCR5, INI	
CCR5, INI, NRTI	

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

All other combinations	Other

13.4. Laboratory Values

Calcium Corrected for Albumin

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

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

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

Estimated Glomerular Filtration Rate

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

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

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

GS-US-621-6289-ph3-wk48-FDA-Final Draft-SAP-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	05-Jun-2025 22:17:16
PPD	Biostatistics eSigned	05-Jun-2025 23:30:45