CLINICAL STUDY PROTOCOL

Study Title:	A Phase 4 Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Oral B/F/TAF after Discontinuing Injectable CAB + RPV
Plain Language Short Title:	Study of B/F/TAF in Participants Switching from CAB + RPV to B/F/TAF for HIV-1 Infection.
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	125589
EU CT Number:	2023-506660-13
ClinicalTrials.gov Identifier:	~~Not Available~~ NCT06104306
Population Diagnosis or Condition:	HIV-1 infection
Protocol ID:	GS-US-380-6738
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List
Protocol Version/Date:	Original 27 July 2023
Country-Specific Requirements:	Country-specific requirements, as applicable, are listed 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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BIC, B	bictegravir
BUN	blood urea nitrogen
BVY	Biktarvy®
CAB	cabotegravir
CBC	complete blood count
CD4	clusters of differentiation 4
CFR	Code of Federal Regulations
CIs	confidence intervals
C_{max}	maximum observed concentration of drug
CSR	clinical study report
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DTG	dolutegravir
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation
ESRD	end-stage renal disease
EU	European Union
EVG	elvitegravir
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC, F	emtricitabine (Emtriva®)
GCP	Good Clinical Practice
Gilead	Gilead Sciences/Gilead Sciences, Inc.
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein

HDPE	high-density polyethylene
HIV, HIV-1	human immunodeficiency virus type 1
HIVTSQc	HIV Treatment Satisfaction Questionnaire Change
HIVTSQs	HIV Treatment Satisfaction Questionnaire Status
HLT	high-level term
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
INSTI	integrase strand-transfer inhibitor
IRB	institutional review board
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
NA	North American
NDA	new drug application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PK	pharmacokinetic(s)
PS	Patient Safety
PT	preferred term
PWH	people with HIV-1
RAL	raltegravir
RNA	ribonucleic acid
RPV	Rilpivirine
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide (Vemlidy®)
TAM	thymidine analog mutation
TDF	tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-DP	tenofovir diphosphate
ULN	upper limit of normal
US	United States
VR	virologic rebound

PROTOCOL SYNOPSIS

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

Study Title: A Phase 4 Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Oral B/F/TAF after Discontinuing Injectable CAB + RPV

Plain Language Short Title: Study of B/F/TAF in Participants Switching from CAB + RPV to B/F/TAF for HIV-1 infection.

Regulatory Agency Identifier Number(s):

IND Number: 125589
EU CT Number: 2023-506660-13
ClinicalTrials.gov Identifier: Not Available

Study Sites Planned: Approximately 19 sites; 15 study sites in the USA and Canada, 4 sites in France

Objectives and Endpoints:

Primary Objective	Co-Primary Endpoints
• To assess the safety of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in virologically suppressed participants unable/unwilling to continue on cabotegravir and rilpivirine (CAB+RPV) IM injections or wishing to switch to oral therapy through Week 12	• Proportion of participants experiencing treatment-emergent Grade 3 or 4 study drug-related adverse events (AEs) through Week 12 • Proportion of participants experiencing treatment-emergent Grade 3 or 4 laboratory abnormalities through Week 12
Secondary Objectives	**Secondary End Points**
• To assess the pharmacokinetics of bictegravir (BIC), CAB and RPV after switching to B/F/TAF from CAB+RPV • To assess the efficacy and persistence of B/F/TAF after switching from CAB+RPV • To assess the safety of B/F/TAF after switching from CAB+RPV through Week 24 • To evaluate treatment satisfaction of switching to B/F/TAF from CAB+RPV	• Plasma concentrations of BIC, CAB and RPV at Day 1, Week 4, 12, and 24, as appropriate • Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 24 (missing = excluded and discontinuation = failure) • Number and proportion of participants with B/F/TAF discontinuation by Weeks 12 and 24 • Proportion of participants experiencing treatment-emergent grade 3 or 4 laboratory abnormalities through Week 24 • Change in HIV treatment satisfaction (HIVTSQc) score at Week 4
Exploratory Objective	**Exploratory End Point**
• To understand PWH experience with injectable and oral therapies for HIV treatment • To evaluate reasons for switching to B/F/TAF from CAB+RPV	• Participant reported experiences with CAB+RPV, preferences for injectable and oral therapies • Participant reported reasons for switching to B/F/TAF

Study Design: Open-label, multicenter, single arm interventional switch study to evaluate the safety, PK, and efficacy of daily oral bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/F/TAF) fixed-dose combination (FDC) in virologically-suppressed participants ≥ 18 years who are unable/unwilling to continue on CAB+RPV IM injections or wishing to switch to oral therapy

Number of Participants Planned: A total of approximately 35 participants will be enrolled (to obtain at least 20 participants with evaluable pharmacokinetic[s] [PK] samples) including approximately 10 participants from France. French participants will not undergo PK analysis and qualitative interview.

Study Population: Virologically suppressed PWH on CAB+RPV injection (at least one dose)

Diagnosis and Main Eligibility Criteria:

Medically stable HIV-1 infected participants who meet the following criteria:

- Age ≥ 18 years
- PWH or provider decision to switch off CAB+RPV due to intolerance, inconvenience, adverse events (AEs) or willing to switch to (and intention to remain on) daily B/F/TAF.
- Currently virologically suppressed (HIV-1 RNA < 50 copies/ mL) on CAB+RPV IM injections (Q2M)
- Currently on CAB+RPV IM injections (Q2M) and received at least one dose of CAB+RPV IM injection; no missed CAB+RPV injections
- No immediate oral antiretroviral therapy (ART) bridge or use of other antiretroviral (ARV) agents before switching to B/F/TAF
- B/F/TAF to be given up to 7 days of next scheduled CAB+RPV IM injection
- Documented plasma HIV-1 RNA < 50 copies/mL during treatment for ≥ 6 months preceding the screening visit. Unconfirmed HIV-1 RNA ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable. If the lower limit of detection of the local HIV-1 RNA assay is < 50 copies/mL (eg, < 20 copies/mL), the HIV-1 RNA level cannot exceed 50 copies/mL on 2 consecutive visits.
- Estimated GFR ≥ 30 mL/min according to the Cockcroft-Gault formula
- No history of B/F/TAF intolerance
- No history of previous integrase strand-transfer inhibitor (INSTI) virologic failure including CAB+RPV
- No documented or suspected resistance to BIC, FTC, or tenofovir (TFV)
- Women who are not pregnant or breastfeeding
- In the opinion of the investigator, no history of poor adherence to oral daily medication

Test Product, Dose, and Mode of Administration: bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (B/F/TAF) FDC administered orally, once daily, without regard to food.

Reference Therapy, Dose, and Mode of Administration: None

Duration of Intervention: 24 weeks

Study Procedures/Frequency: After Screening procedures, study visits will occur at Day 1, and Weeks 4, 12, and 24. Laboratory analyses (chemistry, hematology, and urinalysis), HIV-1 RNA, assessment of AEs and concomitant medications, and complete or symptom directed physical examinations will be performed at all study visits. Clusters of differentiation (CD4+) cell count will be assessed at visits at Day 1 and Weeks 12 and 24. Sparse PK will be collected as per Table 3. Participants will be screened within 42 days before the Day 1 visit to determine eligibility for this study. Any assessments that are over 42 days will need to be repeated for the current study.

Adverse events and concomitant medications will be assessed at each visit. Patient questionnaires and qualitative interviews will be performed as per Table 3.

Statistical Methods: Descriptive statistics will summarize baseline characteristics, efficacy, safety, and patient reported outcomes data.

Safety: The proportion of participants experiencing treatment-emergent Grade 3 or 4 study drug-related AEs through Week 12 (by system organ class [SOC] and preferred term [PT]) and the proportion of participants experiencing treatment-emergent Grade 3 or 4 laboratory abnormalities through Week 12 will be summarized using the safety analysis set. The 2-sided 95% confidence intervals (CIs) of the proportion will be constructed based on the exact method. The same endpoints through Week 24 will be summarized similarly. Treatment-emergent AEs, serious adverse events (SAEs), study drug related AEs, study drug related SAE, and AEs leading to permanent study drug discontinuation will also be summarized.

Clinical laboratory assessment and vital signs will be summarized using descriptive statistics.

Efficacy: The proportion of participants with HIV-1 RNA $\geq$ 50 copies/mL at Weeks 12 and 24 using a missing=excluded [M=E] and discontinuation=failure [D=F] approach will be summarized using descriptive statistics. The 2-sided 95% CIs of the proportion will be constructed based on the exact method. The change from baseline in CD4+ cell count and percentage at Weeks 12 and 24 will be summarized using descriptive statistics.

Treatment Persistence: Number and proportion of participants who prematurely discontinued B/F/TAF will be summarized. The 2-sided 95% CIs of the proportion will be constructed based on the exact method.

Pharmacokinetics: Plasma concentrations of BIC, CAB and RPV will be presented using descriptive statistics, as appropriate.

Treatment satisfaction: HIVTSQs score at Day 1, change in HIVTSQs score from Day 1 to Weeks 12 and 24, and HIVTSQc score at Week 4 will be summarized using descriptive statistics.

Patient reported experience of CAB+RPV treatment and reason for switching: Data will be summarized using descriptive statistics, as appropriate.

Sample Size: The sample size in this study is determined based on practical considerations and past experience with similar types of studies. No sample size calculation was performed. A total sample size of approximately 35 participants (with at least 20 participants with evaluable PK) should provide a suitable assessment of the descriptive PK and safety profile (as applicable).

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type 1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 38.4 million people living with HIV worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Treatment of HIV-1 infection has been significantly advanced by the availability of combination antiretroviral therapy (ART), which has been associated with a dramatic decrease in AIDS-related morbidity and mortality {Mocroft 1998, Palella 1998, Sterne 2005}.

With the success of potent and well-tolerated ART, clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}.

For ART-naive HIV-infected patients, current treatment guidelines recommend that initial therapy for most people consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and an integrase strand-transfer inhibitor (INSTI) or a two-drug regimen of dolutegravir (DTG) plus lamivudine (3TC) {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Bictegravir (BIC; B) is a potent inhibitor of HIV-1 integrase. Antiviral testing has shown that BIC is active against a broad panel of HIV-1 viral lab strains and clinical isolates. BIC is fully active against a panel of mutant viruses with resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Integrase mutant viruses that are resistant to the INSTIs raltegravir (RAL) and elvitegravir (EVG) remain largely sensitive to BIC.

Gilead Sciences (Gilead) has coformulated BIC with the NRTI emtricitabine (FTC; F) and the NRTI TAF into a fixed dose combination (FDC) tablet that is suitable for once daily use. This B/F/TAF FDC provides a potent, convenient, well-tolerated, and practical regimen for the long-term treatment of PWH. Biktarvy® (B/F/TAF) was approved for use in adult patients in the United States (US) on 07 February 2018 and in the European Union (EU) on 21 June 2018. The B/F/TAF 50/200/25 mg tablet is currently approved for use in adult and pediatric patients weighing ≥ 25 kg in the US, EU, and several other countries, and the B/F/TAF 30/120/15 mg tablet is currently approved for use in pediatric patients weighing ≥ 14 to < 25 kg in the US and EU. The B/F/TAF FDC is a recommended initial regimen for most people with HIV-1 in the US Department of Health and Human Services {Panel on Antiretroviral Guidelines for Adults and Adolescents 2023}, International Antiviral Society – USA {Gandhi 2022}, and global treatment guidelines.

Virologically suppressed, HIV-infected patients may desire to switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}. Virologically suppressive ART has also contributed to a decline in HIV incidence in communities with high rates of virologic suppression, by reducing the transmissibility of infected individuals on treatment {Grabowski 2017, Kurth 2011}.

1.2. Background on Study Interventions

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

1.2.1. Treatment with B/F/TAF

B/F/TAF is a three-drug combination of BIC, an HIV-1 INSTI, and FTC and TAF, both HIV-1 NRTIs, and is indicated in the US as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of the regimen {BIKTARVY®. 2022}. B/F/TAF is also approved for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg in the European Union (EU) and for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg in Canada and several other countries {Biktarvy. 2023, BIKTARVY®. 2023}.

1.2.1.1. General Information

For further information on B/F/TAF, refer to the investigator's brochure (IB) for Biktarvy (BVY).

1.2.1.2. Nonclinical Data

1.2.1.2.1. Preclinical Pharmacology and Toxicology and Studies

Nonclinical pharmacology and toxicology studies are provided in the IB for BVY.

1.2.1.3. Clinical Studies of B/F/TAF

For background information on clinical studies of B/F/TAF, refer to the BVY IB.

1.2.2. Information About Auxiliary Medicinal Products/Non-investigational Medicinal Products

Auxiliary medicinal products/non-investigational medicinal products are not used in this study.

1.3. Rationale for This Study

Cabotegravir and rilpivirine IM injections (CAB+RPV) were approved in the US as a complete regimen for the treatment of HIV-1 in virologically suppressed adults in January 2021. Despite community interest in long-acting HIV treatment, implementation has been challenging, with variable use in diverse clinical settings. Clinicians recognize that patients who have initiated CAB+RPV may not stay on injectables permanently for a variety of reasons: i) short term challenges with adherence, including vacations and other conflicts with office visits; ii) intolerance (many reasons noted in clinical trials, including injection site reactions); iii) frequency of injections and/or office visits. Reports suggest that up to 20% of patients who initiate CAB+RPV switch back to daily oral therapies {Angel 2021}. Even in carefully selected clinical trial populations, rates of discontinuation have been high. In the ATLAS-2M study, through 3 years 9.8% of those on Q2M injections discontinued CAB+RPV (4.4% due to AEs and 5.4% for other reasons) {Overton 2023}.

Given the long half-life and pharmacokinetic decay of CAB (90% elimination can take approximately 38 weeks) and RPV, this prospective interventional study will assess the safety of discontinuing CAB+RPV and switching to B/F/TAF in people with HIV (PWH). At present, little data exist for long-term overlap of two different INSTIs. Specifically, initiation of B/F/TAF with residual systemic concentrations of CAB+RPV still onboard would lead to an overlap of BIC with CAB that has not been studied. While both antivirals are well tolerated, data to document the lack of any untoward interaction and combined toxicity are not available. Although several ART options are available after discontinuation of CAB+RPV, B/F/TAF is a clinician-preferred once daily oral regimen. Switch data is desirable to build clinical confidence and to reassure patients that the switch has been studied.

The objective of this study is to evaluate safety, pharmacokinetic(s) (PK), and efficacy during the extended CAB pharmacologic decline, which will inform clinical decisions for PWH who elect or require discontinuation of CAB+RPV. Additionally, qualitative and quantitative participant-reported data will help determine the net benefit of switching off an injectable requiring Q2 monthly visits. Ultimately, study data will assess if B/F/TAF is a safe and effective option after CAB+RPV discontinuation. Retrospective cohort data could answer some of the questions, but would take time to accumulate and would not provide PRO or nuanced pharmacokinetic, tolerability, and toxicity data.

1.4. Rationale for Dose Selection

B/F/TAF

The B/F/TAF FDC containing B (50 mg), F (200 mg), and TAF (25 mg), has been approved in the US and EU for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg, and in Canada for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg {Biktarvy. 2023, BIKTARVY®. 2022, BIKTARVY®. 2023}.

1.5. Benefit-Risk Assessment for the Study

All patients with HIV-1 infection should receive effective antiretroviral therapy. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, weight gain, changes in lipids and gastrointestinal symptoms. The risk of serious adverse events (SAEs) with current recommended regimens is low. All participants enrolling in this study would like to or need to switch off their current CAB+RPV IM injections and need to substitute a new regimen. As B/F/TAF is recommended by US and international guidelines and is a clinician preferred regimen, switching from CAB+RPV to B/F/TAF is an important clinical option. Providing data to characterize the PK and adverse events of two INSTIs (due to the long terminal elimination of CAB IM concentrations) would provide benefit for clinical and patient decision making. Potential benefits may include provision of an optimal switch ARV therapy which may have fewer side effects than continuing CAB+RPV, with maintenance of adherence and long-term virologic suppression.

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

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Co-Primary Endpoints
• To assess the safety of switching to B/F/TAF in virologically suppressed participants unable/unwilling to continue on CAB+RPV IM injections or wishing to switch to oral therapy through Week 12	• Proportion of participants experiencing treatment-emergent Grade 3 or 4 study drug-related adverse events through Week 12 • Proportion of participants experiencing treatment-emergent Grade 3 or 4 laboratory abnormalities through Week 12
Secondary Objectives	**Secondary Endpoints**
• To assess the pharmacokinetics of BIC, CAB, and RPV after switching to B/F/TAF from CAB+RPV • To assess the efficacy and persistence of B/F/TAF after switching from CAB+RPV • To assess the safety of B/F/TAF after switching from CAB+RPV through Week 24 • To evaluate treatment satisfaction of switching to B/F/TAF from CAB+RPV	• Plasma concentrations of BIC, CAB, and RPV at Day 1, Weeks 4, 12, and 24, as appropriate • Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 24 (missing = excluded and discontinuation = failure) • Number and proportion of participants with B/F/TAF discontinuation by Weeks 12 and 24 • Proportion of participants experiencing treatment-emergent grade 3 or 4 laboratory abnormalities through Week 24 • Change in HIV treatment satisfaction (HIVTSQc) score at Week 4
Exploratory Objective	**Exploratory Endpoints**
• To understand PWH experience with injectable and oral therapies for HIV treatment • To evaluate reasons for switching to B/F/TAF from CAB+RPV	• Participant reported experiences with CAB+RPV, preferences for injectable and oral therapies • Participant-reported reasons for switching to B/F/TAF

3. STUDY DESIGN

3.1. Study Design Overview

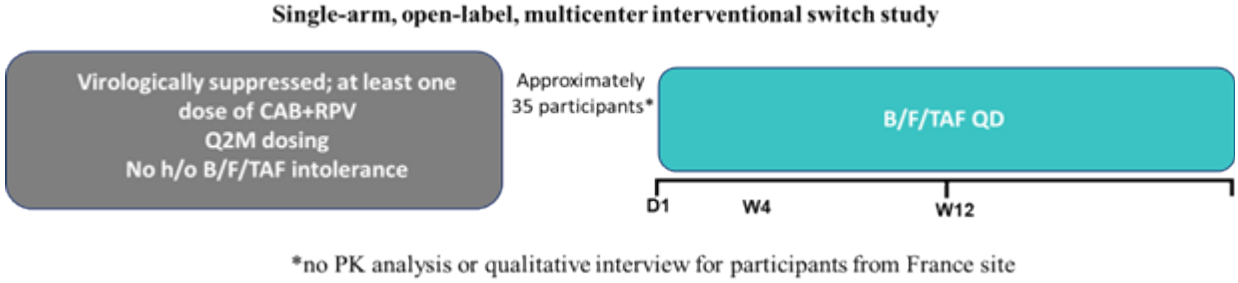
This study is a Phase 4, single-arm, open-label, multicenter interventional switch study to evaluate the safety, PK, and efficacy of daily oral B/F/TAF 50/200/25 mg in virologically suppressed adults with HIV-1 infection who are unable/unwilling to continue on CAB+RPV IM injections or wishing to switch to oral therapy. A total of approximately 35 participants (with at least 20 participants with evaluable PK) will be enrolled in the study including approximately 10 participants in France; French participants will not undergo PK analysis and qualitative interview.

This study will evaluate the PK of BIC and residual levels of CAB and RPV following initiation of B/F/TAF 50/200/25 mg once daily by means of sparse PK sampling.

The study will enroll male and nonpregnant, nonlactating female PWH ≥ 18 years of age.

An overview of the study design is described in Figure 1. Participants in North America will have safety, efficacy, and sparse PK assessments, receive quantitative questionnaires, and be eligible for qualitative interviews, while participants in France will have safety and efficacy assessments and receive quantitative questionnaires.

Figure 1. Study Schema



Abbreviations: h/o = history of; Q2M = twice monthly

3.2. Duration of Intervention

Participants who meet eligibility requirements will be treated for 24 weeks.

3.2.1. Poststudy Care

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

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participant

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

Study drug will be discontinued in the following instances:

- An adverse event (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.
- Participant noncompliance. 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 drug for an individual participant must discuss with the medical monitor prior to study drug discontinuation.
- Loss to follow-up.
- Discontinuation of the study by the sponsor.

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:

- Withdrawal of consent.
- Death.

3.3.2. Criteria for Early Discontinuation of the Study

The study will be discontinued in the following instances:

- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board/independent ethics committee (IRB/IEC)

3.3.3. Loss to Follow-up

Should the participant fail to attend a scheduled protocol-specified visit (eg, in-person, telephone, or virtual), sites will need to make at least 3 attempts by a combination of telephone and mail (electronic or physical) to contact the participant. Sites must document all attempts to contact the participant. If a participant does not respond within 5 days after the third contact, the participant will be considered lost to follow-up and no additional contact will be required.

3.4. Definitions for End-of-Study Dates

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

3.5. Source Data

The source data for this study will be obtained from Interactive Response Technology (IRT), central laboratory, electronic and paper medical records, original records (eg, hospital records, clinical charts), interview transcripts, and questionnaires. Electronic data capture is not considered source data.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

A total of approximately 35 participants will be enrolled (to obtain at least 20 participants with evaluable PK samples) including approximately 10 participants from France. French participants will not undergo PK analysis and qualitative interview. Every effort will be made to include participants of any race, gender, and across the age range described in the study inclusion and exclusion criteria provided in Section 4.2 and Section 4.3, respectively, of the protocol.

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) Participants 18 years of age or older and able to understand and give written informed consent.

2) PWH or provider decision to switch off CAB+RPV IM injections due to intolerance, inconvenience, AEs, *or* willing to switch to (and intention to remain on) daily B/F/TAF.

3) Currently virologically suppressed (HIV-1 RNA < 50 copies/mL) on CAB+RPV IM injections (Q2M).

4) Currently on CAB+RPV IM injections (Q2M) and received at least one dose of CAB+RPV IM injection; no missed CAB+RPV injections

5) Ability to receive B/F/TAF up to 7 days prior to the next scheduled dose of CAB+RPV.

6) Documented plasma HIV-1 RNA < 50 copies/mL during treatment for ≥ 6 months preceding the screening visit.

    a) Unconfirmed HIV-1 RNA ≥ 50 copies/mL (transient detectable viremia, or “blip”) prior to screening are acceptable.

    b) If the lower limit of detection of the local HIV-1 RNA assay is < 50 copies/mL (eg, < 20 copies/mL), the HIV-1 RNA level cannot exceed 50 copies/mL on 2 consecutive visits.

7) Adequate renal function
Estimated GFR ≥ 30 mL/min according to the Cockcroft-Gault formula {Cockcroft 1976}based on serum creatinine and actual body weight as measured at screening and upon admission, eg,

a) Male:

$$\frac{(140 - Age\ [years]) \times (Weight\ [kg])}{72 \times (Serum\ Creatinine\ [mg/dL])} = CLcr\ (mL/min)$$

b) Female:

$$\frac{(140 - Age\ [years]) \times (Weight\ [kg])}{72 \times (Serum\ Creatinine\ [mg/dL])} \times 0.85 = CLcr\ (mL/min)$$

8) Participants assigned female at birth of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 11.5.

9) Hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN)

10) Total bilirubin ≤ 1.5 mg/dL (≤ 26 µmol/L), or normal direct bilirubin.

11) No documented or suspected resistance to BIC, FTC, or tenofovir (TFV).

12) Must be willing and able to comply with all study requirements.

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 (Appendix 11.5) or pregnant

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

3) History of B/F/TAF intolerance

4) History of previous INSTI virologic failure including CAB+RPV

5) Requirement for ongoing therapy with any prohibited medications listed in local prescribing information for B/F/TAF starting within 30 days prior to screening until 30 days following the last dose of study drug.

6) Have been treated within 3 months of study screening or expected to receive during the study immunosuppressant therapies or chemotherapeutic agents (eg, chronic [at least 4 weeks] systemic steroids, immunoglobulins, and other immune- or cytokine-based therapies).

7) Participation in any other clinical study, including observational studies, without prior approval from the sponsor is prohibited while participating in this study

8) Need for oral ART bridge or use of other ARV agents prior to starting B/F/TAF on Day 1

9) Chronic hepatitis B virus (HBV) infection

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

11) Serious illness requiring hospitalizations within 30 days prior to screening and during the screening period.

12) 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 the dosing requirements.

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Enrollment

Participants will be assigned a screening number at the time of consent. Day 1 visit cannot occur until participant eligibility has been confirmed.

Once eligibility has been confirmed, prior to or during the Day 1 visit, the investigator or designee will enroll the participant using the Interactive Response Technology (IRT). Once a participant number has been assigned to a participant, it will not be reassigned to another participant. The participant number assignment may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed. If necessary, additional participants may be enrolled after discussion and approval from the sponsor.

Enrolled participants will be assigned study drug bottle numbers of B/F/TAF FDC at study visits by IRT.

5.2. Description and Handling of B/F/TAF

5.2.1. Formulation

B/F/TAF FDC tablets are an immediate-release oral dosage form containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide fumarate. B/F/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with “GSI” on one side of the tablet and “9883” on the other side of the tablet. In addition to the active ingredients, the tablets contain microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, and iron oxide black.

5.2.2. Packaging and Labeling

B/F/TAF tablets are packaged as 30 tablets in a 100 mL HDPE bottle. Each bottle contains 3 grams of desiccant and a polyester coil, and is capped with a white, continuous thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

5.2.3. Storage and Handling

B/F/TAF tablets should be stored at a controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label.

Until dispensed to the participants, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure stability and proper identification, study drug should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure.

5.3. Prior and Concomitant Medications

Starting from screening until the end of the study, the investigator should follow the local prescribing information for B/F/TAF in regards to concomitant medications and pay special attention to prohibited and cautionary concomitant medications and inform/instruct the participants accordingly. Participants should refrain from consumption of grapefruit juice and Seville orange juice throughout the duration of the study. Additionally, following the last dose of CAB/RPV prior to Day 1, the use of medications for the treatment of HIV, other than B/F/TAF is prohibited.

Should participants have a need to initiate treatment with any prohibited/cautionary 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.

5.4. Dosage and Administration

Following completion of screening and admission assessments, all eligible participants will be administered B/F/TAF 50/200/25 mg once daily with or without food on Day 1 through the end of Week 24.

5.5. Accountability for B/F/TAF

The investigator is responsible for ensuring adequate accountability of all used and unused B/F/TAF. This includes acknowledgment of receipt of each shipment of B/F/TAF (quantity and condition). All used and unused B/F/TAF 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 B/F/TAF
- The date, participant number, and the quantity of B/F/TAF dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.5.1. B/F/TAF Return or Disposal

Gilead recommends that used and unused study drugs be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug 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.

For both disposal options listed above, the study monitor must first perform drug accountability during a monitoring visit.

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 3 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 screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study. This assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 3 and described in the following text. Refer to Section 9.1.3 for further information regarding informed consent.

6.1.1. Informed Consent for Optional Research

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 the following, in accordance with applicable regulations:

- Additional sample for optional future research
- Permission to use the remainder of their already-collected PK and virology specimen for optional future research
- Permission to use already-collected data for optional future research

The specimens collected for optional future research and residual biologic samples consented for optional future research and research will be destroyed no later than 15 years after the end of the study or per country requirements (Section 9.1.3).

6.2. Screening, Participants Enrollment, and Pretreatment Assessment

6.2.1. Screening

Screening evaluations will be performed within 42 days before enrollment in the study to determine eligibility. Eligible participants meeting all inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage. Participants will be asked to arrive at the study center on Day −1 for admission assessments. Screening evaluations are described in Table 3.

Prospective participants should be screened no more than 42 days prior to administration of the first dose of study drug. If a participant does not begin the treatment phase within this 42 day window, all screening evaluation procedures must be repeated. Screening laboratory assessments may be repeated once within 42 days prior to administration of study drug to rule out laboratory error.

A sufficient number of participants will be screened to identify the planned number of participants for enrollment.

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

6.3. Instructions for Study Procedures

6.3.1. Adverse Events

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

Evaluation for AEs will occur at the times shown in Table 3.

In case new (nonprohibited) therapies need to be administered during the study, the benefit-risk to the participant should be carefully assessed and consideration given to the timing of any necessary introduction of new therapies.

6.3.2. Medical History and Demography

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

- Review medical history including disease specific history, disease-related events, available historical genotype/phenotype reports, available disease treatment history, substance (ie, illicit drug, tobacco) use, and medications taken within 30 days of the screening visit.
- 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 (if available).

6.3.3. Vital Signs, Weight and Height

Vital signs, weight, and height will be recorded according to the Study Procedures Table (Table 3). Vital signs will include blood pressure, heart rate, body temperature, and weight and will be recorded after the participant has been resting for at least 5 minutes.

6.3.4. Physical Examination

Physical examination will be performed according to the Study Procedures Table (Table 3).

At the screening visit, a complete physical examination should be performed that will include source documentation of general appearance, and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest; respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, and nails; musculoskeletal; and neurological. Breast, genitourinary, and reproductive examinations should only be conducted if clinically indicated. Symptom-directed physical examinations should be performed at all other visits.

6.3.5. Clinical Laboratory Assessments

The laboratory analyses will be performed at a central laboratory. Blood and urine samples for clinical laboratory assessments will be collected as specified in the Study Procedures Table (Table 3). Participants only need to be fasted on days where lipid or fasting glucose profiling is scheduled. Fasting is defined as 8 hours without food or drink (except water) prior to laboratory draw.

See Table 1 for a summary of the laboratory analytes.

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

Table 1. Laboratory Analytes

Safety Laboratory Measurements			Other Laboratory Measurements
Chemistry (Serum or Plasma)	**Hematology**	**Urinalysis**	
Alkaline phosphatase ALT AST Total bilirubin Total protein Albumin Bicarbonate BUN Calcium Chloride Serum creatinine Glucose Phosphorus Potassium Sodium Fasting lipid profile: Triglycerides Cholesterol and its subfractions (HDL and LDL)	Hematocrit Hemoglobin Platelet count RBC count RBC indices WBC count differentials (absolute and percentage), including: Leucocytes Monocytes Neutrophils Eosinophils Basophils	Appearance Blood Color Glucose Leukocyte esterase Microscopy (including crystals) Nitrites pH Pregnancy Protein Specific gravity Urobilinogen	CD4+ counts DBS HBV/HCV Serologies HIV-1 RNA HIV-1 genotype/phenotype PK blood Serum Pregnancy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CD4+ = clusters of differentiation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PK = pharmacokinetic(s); RBC = red blood cell; RF = rheumatoid factor; RNA = ribonucleic acid; TB = tuberculosis; TSH = thyroid-stimulating hormone; WBC = white blood cell
Refer to Table 3 for collection time points.

6.3.6. Pharmacokinetics

A single PK plasma sample will be collected at Day 1 prior to dose. A single trough plasma PK sample approximately 23 to 24 hours after the previous B/F/TAF dose and prior to B/F/TAF dosing on Weeks 4, 12, and 24, and a single plasma PK sample at approximately 2 hours post B/F/TAF dose, witnessed by study staff, at Weeks 4, 12, and 24 will be collected.

6.4. Virologic Failure

Virologic failure is defined as confirmed virologic rebound of HIV-1 RNA ≥ 50 copies/mL at 2 consecutive visits, or having HIV-1 RNA ≥ 50 copies/mL at the last on-treatment study visit (including early study drug discontinuation [ESDD] or key study endpoints).

6.4.1. Management of Virologic Rebound

Participants experiencing, at any post-Day 1 visit, a rebound in HIV-1 RNA to ≥ 50 copies/mL, will be considered to have virologic rebound. At any visit with HIV-1 RNA ≥ 50 copies/mL, 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, if available. If the repeat (reflex) result is < 50 copies/mL, no further action is required. If the repeat result is ≥ 50 copies/mL, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA VR) for confirmation of VR.

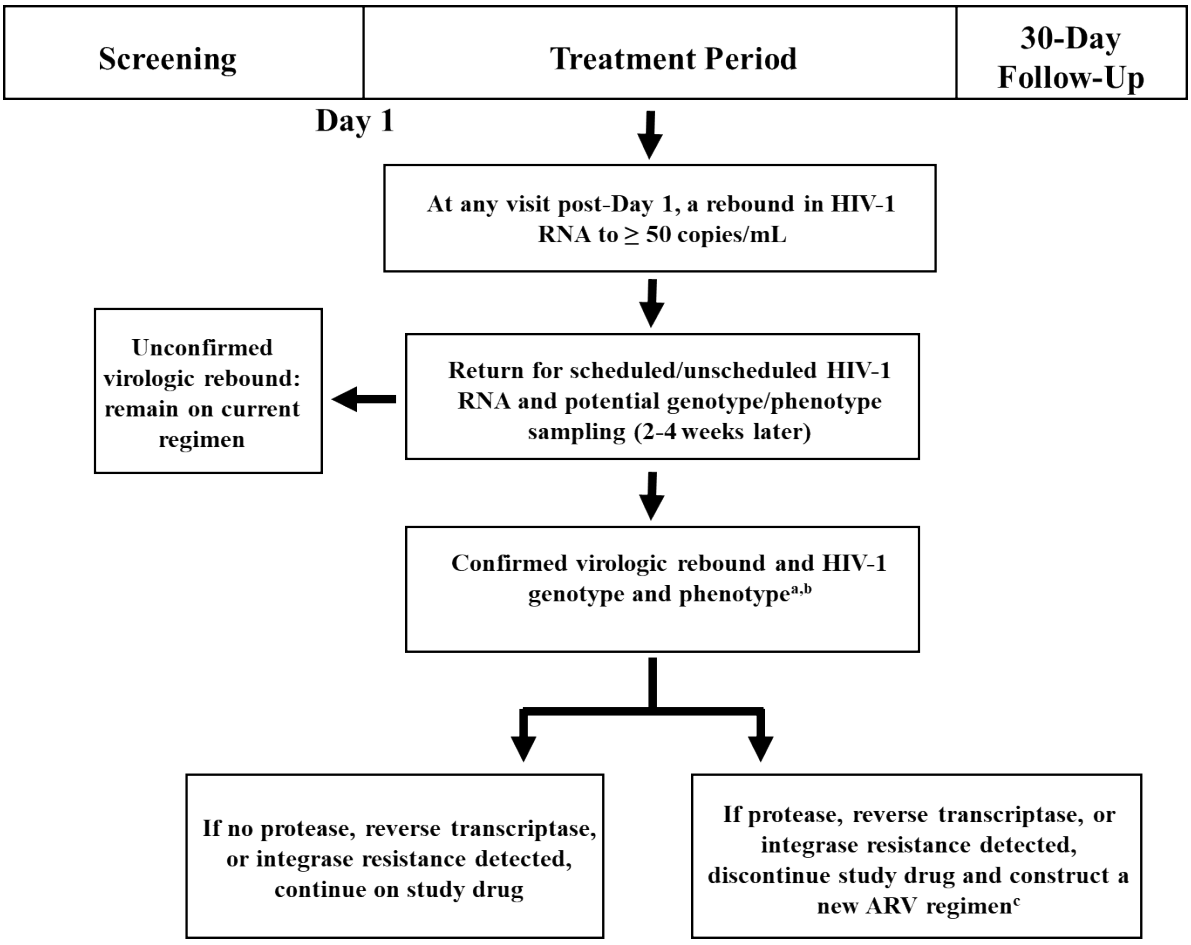
- If VR is confirmed and HIV-1 RNA is ≥ 200 copies/mL, a plasma sample from the VR confirmation visit is the primary sample tested for HIV-1 PR, RT, and IN genotypic and phenotypic resistance. After a participant's first post–Day 1 resistance test, additional testing is conducted on a case-by-case basis. Any participant may be discontinued at investigator's discretion or per local treatment guidelines.

- If no resistance to study drug is detected from the genotype or phenotype, the participant may remain on study drug and HIV-1 RNA test should be repeated at a new visit (within 2-4 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.

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

Figure 2 describes the management of participants who experience virologic rebound.

Figure 2. Virologic Rebound Schema



a If virologic rebound is confirmed, and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype and phenotype (protease, reverse transcriptase, and integrase) will be analyzed.
b Based on the results of the genotype and phenotype assays, the participant will remain on study drug or study drug will be discontinued. If genotyping or phenotyping fails, a new ARV regimen may be configured at the discretion of the investigator.
c A new ARV regimen will be configured, at the investigator's discretion, and the participants will remain on study.

6.4.1.1. Participants with HIV-1 RNA ≥ 50 copies/mL at last on-treatment study visit or at Study Endpoints

Participants with HIV-1 RNA ≥ 50 copies/mL at ESDD or last visit will be considered virologic failures. Participants with HIV-1 RNA ≥ 50 copies/mL at Week 12 or Week 24 will be asked to return for an unscheduled visit within the visit window for a retest.

Participants with HIV-1 RNA ≥ 200 copies/mL at ESDD or last visit will also have resistance testing conducted.

6.5. Participant-Reported Outcomes: Questionnaires and Qualitative Interviews

6.5.1.1. HIV Treatment Satisfaction Status (HIVTSQs)

HIVTSQs are to be completed by the participant at Day 1 and Weeks 12 and 24 (see Table 3). Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires. See Appendix 11.4.1 for questionnaire.

6.5.1.2. HIV Treatment Satisfaction Change (HIVTSQc)

HIVTSQc is to be completed by the participant at Week 4 (see Table 3). Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaire. See Appendix 11.4.1 for questionnaire.

6.5.1.3. Additional Study-Specific Questions

A study-specific questionnaire will completed by the participant on Day 1 and Week 4 to document preference for oral vs injection therapy and specific reasons for decisions to switch from CAB+RPV to oral therapy. Refer to Appendix 11.4.3 for study-specific questionnaire.

6.5.1.4. Qualitative Interviews (English only)

Among the participants who are recruited and consented to undergo qualitative interviews, a vendor will schedule face to face (or telephone) interviews with these participants in English over a video communication platform. Interviews will cover topics such as reasons for switching to B/F/TAF; experiences using CAB+RPV, including injection site reactions, side effects, time spend via clinic visits, etc; preferences for injectable and oral HIV medications; and treatment satisfaction post switch. Interviews will be recorded and transcribed for data analysis purposes. The qualitative interview will occur near the Week 4 visit (visit window range Week 3-9). Refer to Appendix 11.4.2 for qualitative interview guide.

The qualitative interviewer would be responsible for notifying the investigator of all the AE's/SAE's/SSR's identified during the interview within 24 hours of awareness. Please refer to Section 7.4 for the reporting process.

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

If a participant discontinues study medication dosing (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (Section 3.3). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study. The participant will be requested to return for an early study ESDD visit. If it is not possible or acceptable to the participant or investigator to keep the participant in the study (after discussion of the benefits/risks with the investigator), the participant may be withdrawn from the study and be required to return to the study site for a 30-day follow-up visit (Table 3).

6.6.1. Assessments for Early Discontinuation From Study Intervention

A participant who discontinues study drug early will be asked to return to the investigational site within 72 hours of stopping study drug, or within 72 hours of notifying the investigator they no longer wish to receive study drug, to attend an ESDD visit for assessments and procedures specified in Table 3.

6.6.2. Assessments for End of Study

A participant who discontinues study drug early will be asked to return to the investigational site within 30 days of stopping study drug to attend an ESDD visit for assessments and procedures specified in Table 3.

6.7. Sample Storage

The stored biological samples may be used by Gilead or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements if shorter. If participants provide additional specific consent for optional future research, residual biologic samples may be retained in storage no later than 15 years after the end of the study or per country requirements, whichever is shorter (Section 9.1.3).

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

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

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

7.1.2. Serious Adverse Events

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

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

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

7.1.3. Serious Adverse Drug Reaction

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

7.1.4. Study Drug 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 of falsified medicine, and pregnancy regardless of an associated AE.

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

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

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

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

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

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drug and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship for the study drug using clinical judgment and the following consideration:

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

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

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

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

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

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Toxicity Grading Scale, Version 2.1. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 11.6).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

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

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30 days after administration of the last dose of study drug and report the AEs on the eCRFs as instructed.

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

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the 30-day follow-up visit, must be reported on the applicable eCRFs and to Patient Safety (PS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

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

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

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

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situations Report

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

7.3.5.2. Non-Gilead Concomitant Medications Report

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

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

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

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

7.4.1. Serious Adverse Event Reporting Process

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

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

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

7.4.1.1. Electronic Serious Adverse Event Reporting Process

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

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

Gilead Patient Safety
Email: PPD
or
Fax: PPD

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

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

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

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

Gilead Patient Safety
Email: PPD
or
Fax: PPD

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

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

7.4.2.2. Reporting Process for Gilead Concomitant Medications

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

Gilead Patient Safety:
Email: PPD
or
Fax: PPD

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

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

7.4.2.3. Pregnancy Reporting Process

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

Gilead Patient Safety:
Email: PPD
or
Fax: PPD

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to PS (email: PPD and fax: PPD

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

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

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

Refer to Appendix 11.5 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 United States Food and Drug Administration Code of Federal Regulations, the European Union 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 European Union Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IR/IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

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

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

Severity of laboratory abnormalities should be recorded and graded according to the DAIDS Toxicity Grading Scale, Version 2.1. 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

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor (or designee) for treatment related Grade 3-4 AEs or SAE, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to Day −1 levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Clinical and laboratory AEs should be managed as outlined in Section 3.3 and Appendix 11.6.

Any questions regarding toxicity management should be directed to the Gilead medical monitor (or designee).

8. STATISTICAL CONSIDERATIONS

This section provides a high-level description of the planned analyses. Additional details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Study objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Before the final analysis, interim analyses may be conducted and the analyses may be submitted to conferences/journals for presentation/publication.

8.2.1.1. Planned Interim Analysis

There will be one planned interim analysis after all participants at North American (NA) Sites have completed their Week 12 visit or prematurely discontinued the study drug. Only participants enrolled at NA sites will be included in this interim analysis.

8.2.2. Final Analysis

The final analysis will be performed after all participants have completed the study or prematurely discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoints for all enrolled participants will be conducted at the time of the final analysis. This analysis will include all data collected during the study.

8.3. Analysis Conventions

8.3.1. Analysis Sets

The datasets for analyses are defined in Table 2.

Table 2. Analysis Set Definitions

Analysis Set	Description
All Enrolled Analysis Set	The All Enrolled Analysis Set includes all participants enrolled into the study after screening. This is the primary analysis set for listings.
Full Analysis Set	The primary analysis set for efficacy analyses is defined as Full Analysis Set (FAS), which will include all enrolled participants who have received at least 1 dose of study drug.
Safety Analysis Set	The primary analysis set for safety analyses, participant reported outcomes analysis is defined as the Safety Analysis Set, which will include all enrolled participants who have received at least 1 dose of study drug. All the data collected up to 30 days after participants permanently discontinue their study drug will be included in the safety and participant reported outcomes, unless specified otherwise.
PK Analysis Set	The primary analysis set for PK analyses is defined as the PK Analysis Set, which will include all enrolled participants who have received at least 1 dose of study drug), and have at least 1 non-missing PK concentration datum for any analyte of interest reported by the PK laboratory.

FAS = full analysis set; PK = pharmacokinetics

8.3.2. Data Handling Conventions

HIV-1 RNA results of "No HIV-1 RNA detected" and "< 20 copies/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purpose.

Natural logarithmic transformation of plasma concentrations and PK parameters will be applied for PK analysis.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

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

All available data for participants who do not complete the study will be included in the data listings.

8.4. Demographic and Baseline Characteristics Analysis

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

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

Baseline data will include a summary of body weight, height, body mass index, estimated glomerular filtration rate (eGFR), HIV-1 infection, and HIV therapy at study entry.

8.5. Efficacy Analysis

The analysis of the efficacy endpoints will be based on the FAS. The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 24, and the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 12 and 24 as determined by M=E and D=F approaches will be summarized using descriptive statistics. Their 2-sided 95% CIs of the proportion will be constructed based on the exact method.

The proportion of participants who prematurely discontinued B/F/TAF through Weeks 12 and 24 and their 95% CIs will be summarized similarly.

The change from baseline in CD4+ cell counts and percentages will be summarized by visit using descriptive statistics.

8.6. Safety Analysis

Safety data collected from participants in the Safety Analysis Set on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized. Data for the pretreatment period and the period post the date of last dose of study drug plus 30 days will be included in data listings for all enrolled participants.

8.6.1. Extent of Exposure

Data for a participant's extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized using the Safety Analysis Set. Duration of exposure to study drug (expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration) will be summarized. Dosing information for individual participants will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) 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 30 days. or any AE leading to study drug discontinuation.

The number and percentage of participants with treatment-emergent Grade 3 or 4 study drug-related AEs after starting oral B/F/TAF through Weeks 12 and 24 will be summarized by SOC and PT. The 2-sided 95% CIs of the proportion will be constructed based on the exact method. The number and percentage of participants with treatment-emergent AEs and SAEs after starting oral B/F/TAF through Weeks 12 and 24 will be summarized similarly.

Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drug, 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. Observed absolute value and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme referenced in Appendix 11.6.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time after baseline up to and including the date of last dose of study drug plus 30 days, will be summarized. The incidence of treatment-emergent laboratory abnormalities and Grade 3 and 4 laboratory abnormalities will also be summarized. If baseline data are missing, any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The maximum postbaseline toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study drug or after the participant has been discontinued from treatment for at least 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and weight will be summarized by visit, as appropriate (please refer to study procedures [Table 3]).

8.7. Pharmacokinetic Analysis

Plasma concentrations of BIC, CAB, and RPV will be listed and summarized using descriptive statistics for the PK Analysis Set, as appropriate. Additional population analysis approaches may be explored if needed.

8.8. Participant Reported Outcome Analysis

8.8.1. Participant Reported Experience of CAB+RPV Treatment, Preferences for Injectable and Oral Therapy from Qualitative Interview

Participant reported experience of CAB+RPV treatment and participant experience with injectable and oral therapy may be explored.

8.8.2. Participant Reported Reasons for Switching to B/F/TAF

Participant reported experience of CAB+RPV treatment will be summarized. Proportion of participants with specific reasons for switching treatment (eg, AEs, dissatisfaction with required clinic visits/copays/time, provider logistics) will be summarized by visit.

8.9. Sample Size

The sample size in this study is determined based on practical considerations and past experience with similar types of studies. No sample size calculation was performed. A total sample size of approximately 35 participants (to obtain at least 20 participants with evaluable PK) should provide a suitable assessment of the descriptive PK and safety profile.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Financial Disclosure

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

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the purpose (aims), methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved ICF for documenting written informed consent. Each ICF 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). A copy of the signed ICF will be provided to the participant or the participant's legally authorized representative.

The ICF will inform participant 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, participant will be required to document additional consent to provide additional samples and/or to allow the use of 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, whichever is shorter; but participants may at any time request that their stored samples be destroyed.

9.1.4. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead 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. 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, case report forms/eCRFs, study drug information, and any other study information, remains the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

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

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

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

- Participant identification
- Documentation that participant meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)

- Study discussed and date of informed consent
- 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, the United States, Europe, or Japan) and until there are no pending or planned marketing applications in an International Council for Harmonisation region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

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

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

9.1.6. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (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 nonelectronic data capture 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 CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or

Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigator Inspections

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

9.1.8. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicableand 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).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical study agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Regulatory and Ethical Considerations

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

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

9.3.2. Payment Reporting

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

9.3.3. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the 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.

9.3.4. Access to Information for Auditing or Inspections

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

9.3.5. Study Discontinuation

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

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11. APPENDICES

11.1. Investigator Signature Page

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

A Phase 4 Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Oral B/F/TAF after Discontinuing Injectable CAB + RPV

Original Protocol 27 July 2023

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 ≥ 1 Country Following EU Regulation No. 536/2014	Authorized in ≥ 1 ICH Country
bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg fixed-dose combination tablets	Study drug	Yes	Yes

EU = European Union, ICH = International Council for Harmonisation

11.3. Study Procedures Table

Table 3. Study Procedures Table

Study Procedures	Screening	Day 1[b]	Week 4[c]	Week 12[c]	Week 24[c]	30-Day Follow-up[d]	ESDD[e]	Notes
Informed Consent	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	At screening, concomitant medications taken within 30 days prior to screening will be recorded; at subsequent visits all medications since the last study visit will be recorded.
Adverse Events	X	X	X	X	X	X	X	
Complete Physical Examination	X							Complete physical examination (urogenital/anorectal examinations will be performed at the discretion of the investigator).
Symptom-Directed Physical Examination		X	X	X	X	X		Symptom-directed physical examination at all post-screening time points.
Vital Signs and Weight	X	X	X	X	X	X	X	
Height	X							
Urinalysis	X	X	X	X	X	X	X	
Urine Pregnancy		X	X	X	X	X	X	For participants of childbearing potential only
Serum Pregnancy	X							For participants of childbearing potential only
Chemistry Profile[f]	X	X	X	X	X	X	X	
Hematology Profile	X	X	X	X	X	X	X	CBC with differential and platelet count
CD4+ Cell Count	X	X		X	X		X	
Plasma HIV-1 RNA[g]	X	X	X	X	X	X	X	
HBV and HCV Serologies[h]	X							
Estimated GFR	X	X		X	X		X	Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
Metabolic Assessments[i]		X		X	X			
Baseline PK, Sparse PK: trough and postdose PK sample[j]		X	X	X	X			

Study Procedures	Screening	Day 1[b]	Week 4[c]	Week 12[c]	Week 24[c]	30-Day Follow-up[d]	ESDD[e]	Notes
Plasma Storage Sample		X	X	X	X		X	For optional future research
Whole Blood sample for potential HIV DNA genotyping		X						Whole blood sample for virology analysis
Plasma HIV-1 genotyping/phenotyping sample[k]			X	X	X		X	HIV-1 genotype/phenotype resistance testing for participants with unconfirmed virologic rebound with HIV-1 RNA value ≥ 200 copies/mL
Dried Blood Spot (DBS) collection			X	X	X		X	TFV-DP from DBS will be run in retrospect for participants with confirmed viral failure.
HIVTSQs		X		X	X			
HIVTSc Questionnaire			X					
Additional study specific questions		X	X					
Qualitative interview			X					Qualitative interview will explore in-depth experiences on CAB+RPV, reasons for switch B/F/TAF and satisfaction post switch. The visit window for the interview is from Week 3 to Week 9.
Study Drug Accountability		X	X	X	X	X	X	
Study Drug Dispensation		X		X				
Observed Dosing		X	X	X				Participants must take their study drug in the clinic for observed dosing on Day 1, Week 4, and Week 12.

CBC = complete blood count; CD4+ = clusters of differentiation 4; DNA = deoxyribonucleic acid; DBS = dried blood spot; ESDD = early study drug discontinuation; GFR = glomerular filtration rate calculated using the Cockcroft-Gault equation; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus type 1; HIVTSQs = HIV treatment satisfaction status questionnaire [quantitative]; HIVTSQc = HIV treatment satisfaction change questionnaire [quantitative]; RNA = Ribonucleic acid; PK = pharmacokinetic(s); TFV-DP = tenofovir diphosphate.

a Evaluations to be completed within 42 days prior to Day 1 visit.

b Participants will be dispensed study drug at the Day 1 visit; initiation of treatment with the study drug must take place in the clinic for observed dosing at Day 1 visit.

c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol-specified date through Week 12, ± 6 days of the protocol-specified date for Week 24. For the purpose of scheduling a 30-day follow-up visit, a ± 6-day window may be used. Those participants who prematurely discontinue study drug and continue in the study through at least one subsequent visit after the early study drug discontinuation visit will not be required to complete the 30-day follow-up visit.

d Only applies to participants who miss the Week 24 visit, and must be completed within 30 days of discontinuing study drug.

e Early study drug discontinuation visit to occur within 72 hours of last dose of study drug.

f Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, and sodium.

g For any post-Day -1 visit, if the HIV-1 RNA value is ≥ 50 copies/mL, a retest should be performed at a scheduled or unscheduled visit 2-4 weeks after the date of the original test.

h Hepatitis B virus surface Antigen (HBsAg), Hepatitis B core antibody (HBcAb), and Hepatitis C virus (HCV) serologies (reflex HCV RNA is performed in participants with positive HCV Ab serology)

i Metabolic Assessments: Fasting lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the pparticipant must return within 72 hours in a fasted state.\

j A single PK plasma sample will be collected at Day 1 prior to dose. A single trough plasma PK sample approximately 23 to 24 hours after the previous B/F/TAF dose and prior to B/F/TAF dosing on Weeks 4, 12, and 24, and a single postdose plasma PK sample at approximately 2 hours post B/F/TAF dose, witnessed by the study staff, at Weeks 4, 12, and 24 will be collected

k HIV-1 genotype/phenotype resistance testing (which includes protease, reverse transcriptase, and integrase testing) only conducted for participants with confirmed virologic failure with HIV-1 RNA value ≥ 50 copies/mL. Participants should be managed according to Figure 2. Following virologic rebound, participants will be asked to return to the clinic (2-4 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for an HIV-1 RNA and HIV-1 genotype and phenotype blood draw. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema (Figure 2). Participants with HIV-1 RNA ≥ 50 copies/mL at Week 12 and/or 24 will be asked to return for an unscheduled visit within the visit window for a retest. Participants with HIV-1 RNA ≥ 200 copies/mL at ESDD, last visit, or Week 12 or 24 will also have resistance testing conducted.

11.4. Questionnaires, Participant Provided Outcomes

11.4.1. Item content of the HIVTSQs and HIVTSQc

			HIVTSQs	HIVTSQc
			Instructions The following questions are concerned with your anti-HIV medicine therapy for HIV infection and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.	**Instructions** The following questions are concerned with your *present* anti-HIV medicine therapy *compared with* your experience of medicine therapy used *just before you started in the current study*. We are interested to know how, if at all, your experience of medicine therapy has changed. 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, circle "0".
Item no.	**Item label** [Suffix *(c)* denotes item label in the change version]	**Item wording**	**Response options 6–0**	**Response options 6–0**
1	*Current treatment*	How satisfied are you with your current treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to –3 much less satisfied now
2	*Control*	How well controlled do you feel your HIV has been recently?	Very well controlled 6 to 0 very poorly controlled	Much better controlled now 3 to –3 much worse controlled now
3	*Side effects*	How satisfied are you with any side effects of your present treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to –3 much less satisfied now
4	*Demands*	How satisfied are you with the demands made by your current treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to –3 much less satisfied now
5	*Convenience*	How convenient have you been finding your treatment to be recently?	Very convenient 6 to 0 very inconvenient	Much more convenient now 3 to –3 much less convenient now
6	*Flexibility*	How flexible have you been finding your treatment to be recently?	Very flexible 6 to 0 very inflexible	Much more flexible now 3 to –3 much less flexible now
7	*Understanding*	How satisfied are you with your understanding of your HIV?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to –3 much less satisfied now
8	*Lifestyle*	How satisfied are you with the extent to which the treatment fits in with your lifestyle?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to –3 much less satisfied now
9	*Recommend to others*	Would you recommend your present treatment to someone else with HIV?	Yes I would definitely recommend the treatment 6 to 0 No I would definitely not recommend the treatment	Much more satisfied now 3 to –3 much less satisfied now
10	*Continue*	How satisfied would you be to continue with your present form of treatment?	Very satisfied 6 to 0 very dissatisfied	Much more likely to recommend the treatment now 3 to –3 much less likely to recommend the treatment now
11	Easy/difficult	How easy or difficult have you been finding your treatment to be recently?	Very easy 6 to 0 very difficult	Much easier now 3 to -3 much more difficult now
12	Pain/discomfort	How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to -3 much less satisfied now
			Please make sure that you have circled one number on each of the scales.	

11.4.2. Study GS-US-380-6738 Qualitative Participant Interview Guide

Guide begins on the following page.

Study of GS-US-380-6738: B/F/TAF in Participants Switching from CAB + RPV to B/F/TAF for HIV-1 infection.

B/F/TAF Participant Interview Guide

|JULY 24, 2023 | Version 1.0

Participant ID:
Interviewer Initials:
Interview Date:

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ **Date of Interview:** (month/day/year) _____ **Interviewer Initials:** _____

PROJECT BACKGROUND AND INSTRUCTIONS *(for Interviewer only)*

The objective of this qualitative component of study GS-US-380-6738 is to understand experience with injectable and oral therapy for HIV-1 treatment for people with HIV (PWH) by exploring experiences on CAB+RPV, also known as Cabenuva, reasons for switching from CAB+RPV to B/F/TAF, also known as Biktarvy, experiences post switch on daily oral B/F/TAF, and preferences for injectable and oral therapy.

This discussion guide is designed to help focus the conversation but should not be used as a verbatim script. Probes and questions may change slightly depending on participant feedback. Additional unscripted probes to be used to gain further information or clarification may include:

- Clarification (e.g., I don't quite understand that)
- Expressing understanding (e.g., How did you cope with that?)
- Justification (e.g., What makes you say that?)
- Importance (e.g., I'm not sure I understand how these two things are linked; please could you explain this to me?)
- Extending narrative (e.g., Please tell me a bit more about that)
- Accuracy (e.g., Let me see if I understand that)

Introductory statements are in regular text; the main questions are **bolded,** and follow-up probes are in italics. Please note that instructions to the interviewer are in red font throughout this guide and should not be read to the participant.

Do not repeat questions for information that the participant has already provided unless more information is needed. Manage the conversation to complete the interview within the allotted 60 minutes.

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ **Date of Interview**: (month/day/year) _____ **Interviewer Initials**: _____

INTRODUCTION *(for Study Participant, 2-3 minutes)*

Good (***morning /afternoon/ evening***). I am <***interviewer name***>, a <***title***> with Cerner Enviza, a healthcare research group that is helping to coordinate this interview on behalf of Gilead. We are interviewing you today to understand your experience being treated with injectable CAB + RPV (Cabenuva) and oral B/F/TAF (Biktarvy). We will discuss how you learned about Cabenuva and Biktarvy, your experiences receiving the two treatments, and your thoughts on why you switched from Cabenuva to Biktarvy.

We agreed to talk for about an hour – does this time still work for you?

Before we start, I want to thank you for your participation.

What you tell me today is treated as private and confidential. Your answers will be combined into an aggregated report, and while we may use individual quotes to support findings from this research study, we will never use your real name or include any other personal information that could identify you.

We will be discussing topics that may be sensitive, and you may ask to skip any question(s). You also have the right to end this interview at any time and for any reason. There are no right or wrong answers, please answer each question to the best of your ability.

We are required to pass on to Gilead , who is a maker of medicines, details about any kind of side effects or complaints that are related to their products that are mentioned during the interview. If this happens, we will need to collect details and report the event, even if you have already reported it directly to the company or the regulatory authorities. You will be asked whether you consent to us passing your details to the client company's drug safety department for their follow up, but you may choose to remain anonymous. This will have no impact on the confidentiality and anonymity associated with the interview itself.

Are you comfortable proceeding with the interview on this basis?

[If no, thank the person for their time and end the interview.]

This interview will be recorded, and then it will be transcribed with all personally identifying information removed. For research purposes only, other Cerner Enviza team members may listen in to this interview or they may listen to the recording. Do I have your permission to record the interview?

[If no, thank the person for their time and end the interview.]

Thank you! This is <***interviewer name***> interviewing <***Patient ID***> for <***Study ID***> at <***Current Time***> on <***Date of Interview***>.

Do you have any questions before we begin?

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ Date of Interview: (month/day/year) _____ Interviewer Initials: _____

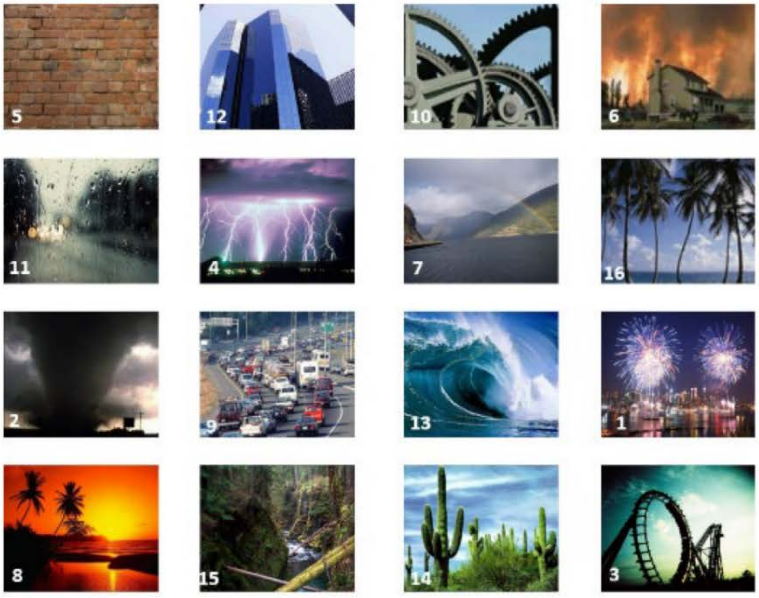
Interview Guide

Ice-breaker questions

1. First, let's start by telling me a little bit about yourself, such as your age, who you live with, and your work.
2. What do you like to do in your free time?

Discussion theme 1. Perspectives on HIV treatment overall

3. Please take a look at the images below. Which image do you think best matches how you feel about HIV treatment in general?



   a. *How did you come up with that image?*
   b. *How does HIV treatment fit into your life?*

4. What would your ideal HIV treatment look like?
   a. *How would it be administered?*
   b. *How frequently would it be taken?*

5. What are your thoughts about Biktarvy compared to Cabenuva?
   a. *Does one have advantages over the other in any way?*
   b. *Do they differ in how they make you feel about your HIV?*

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ Date of Interview: (month/day/year) _____ Interviewer Initials: _____

Discussion theme 2. Initiating Cabenuva treatment

I would like for you to think back to the time when you decided to start taking Cabenuva. I'm going to ask a few questions about your understanding of Cabenuva and what led you to begin with this treatment.

6. **How did you learn about Cabenuva?**
    a. *How did you hear about Cabenuva?*
        i. *Who did you first hear about it from?*
    b. *How was the treatment explained to you?*

7. **What factors contributed to your decision to start Cabenuva?**
    a. *Were you taking HIV treatment before starting Cabenuva?*
        i. *What factors led you to switch to Cabenuva from your previous medication?*
    b. *What information did you use to make your decision to start Cabenuva?*
    c. *Who did you talk with to help make your decision?*
    d. *To what extent was your healthcare provider involved in your decision to start Cabenuva?*

8. **What expectations did you have of Cabenuva prior to starting?**

    a. *Thinking back to before you started receiving Cabenuva, do you feel that you were provided adequate information about the treatment?*
    b. *Did you have any concerns before taking Cabenuva?*
        What did your provider do to address your concerns?
    c. *Is there any information that you wish you had known before starting Cabenuva?*
        i. *Did you feel prepared for…*
            1. *what the injections might feel like?*
            2. *frequency of visits to receive injections?*
            3. *side-effects/injection site reactions?*

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ Date of Interview: (month/day/year) _____Interviewer Initials: _____

Discussion theme 3. Cabenuva Treatment Experience and Perceptions

9. **When did you start taking Cabenuva? For how long did you take Cabenuva?**

10. **What feelings did you have starting treatment with Cabenuva?**

11. **What was your initial experience at the clinic when starting Cabenuva?**
    a. *Was there anything that you found helpful at your first visits? Was there anything that you found unhelpful at your first visits?*
    b. *How were your interactions with the provider and other staff?*

12. **How many different times did you receive Cabenuva injections?**

13. **What was your experience like receiving the Cabenuva injections?**
    a. *How did the injections make you feel at first?*
    b. *How did you feel after the injections?*
        i. *Did you experience any issues with the injections?*
    c. *Did you ever miss a Cabenuva injection appointment because you did not want the injection? For any other reasons?*
    d. *How did your experience change after your first dose or few doses (injections)?*
        i. *Were there any changes that made these injections easier? Any changes that made these injections more difficult?*

14. **Overall, how did you feel about your treatment with Cabenuva?**
    a. *What did you like about Cabenuva?*
    b. *What didn't you like about it?*

15. **How does Cabenuva compare to other HIV treatments that you've received before Cabenuva?**
    a. *To what extent were you comfortable with the way Cabenuva treatment is given? How about the 2-month schedule?*
    b. *Did taking Cabenuva affect your quality of life? In what ways?*
    c. *To what extent did treatment with Cabenuva impact your outlook for the future?*

16. **What led you to decide to stop your treatment with Cabenuva?**
    a. *Is there anything that would have made you stay on Cabenuva?*

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ Date of Interview: (month/day/year) _____Interviewer Initials: _____

Discussion theme 4. Biktarvy Treatment Experience and Perceptions

17. Now let's talk about your decision to switch to Biktarvy. How did you learn about Biktarvy?
    a. *How did you hear about Biktarvy?*
        i. *Who did you first hear about it from?*
    b. *How was the treatment explained to you?*

18. What factors contributed to your decision to start (or re-start) Biktarvy?
    a. *What factors led you to switch to Biktarvy?*
    b. *What information did you use to make your decision?*
    c. *Who did you talk with to help make your decision?*
    d. *To what extent was your healthcare provider involved in your decision to start Biktarvy?*

19. What expectations did you have of Biktarvy prior to starting?
    a. *Thinking back to before you switched to Biktarvy, do you feel that you were provided adequate information about the treatment?*
    b. *Did you have any concerns before taking Biktarvy?*
        i. *What did your provider do to address your concerns?*
    c. *Is there any information that you wish you had known before starting Biktarvy?*

20. Prior to starting Biktarvy following switching from Cabenuva, had you ever taken Biktarvy before?

21. What feelings have you had since starting (or re-starting) treatment with Biktarvy?
    a. *How does it feel to take Biktarvy?*
        i. *Do you experience any issues taking Biktarvy?*
    b. *How has your experience changed after your few doses?*
        i. *Were there any changes that made taking Biktarvy easier? Any changes that made taking Biktarvy more difficult?*

22. Overall, how do you feel about your treatment with Biktarvy?
    a. *Is there anything you like about taking Biktarvy?*

23. How does Biktarvy compare to other HIV treatments you've received?
    a. *To what extent are you comfortable with the way Biktarvy treatment is given?*
    b. *Does treatment with Biktarvy affect your quality of life? In what ways?*
    c. *How does treatment with Biktarvy impact your outlook for the future?*

24. Do you ever miss taking any doses of your HIV therapy on time? If yes, how often? Why?
    a. *What helps you to take Biktarvy on time?*

Participant Interview Guide CAB+RPV switch study

Participant ID Number: _____ Date of Interview: (month/day/year) _____Interviewer Initials: _____

25. So, we are coming to the end of our discussion. Is there anything else that you would like to share about your experience you're your HIV treatment experiences?

□□

We are finished with the interview. Thank you very much for taking the time to speak with me today.

11.4.3. Study GS-US-380-6730 Additional Study Specific Questions for Participant

Day 1 additional study specific questions begins on the following page.

Participant ID Number: _____ Date of Survey: (month/day/year) _____

GS-US-380-6738: A Phase 4 Study to Evaluate the Safety, Pharmacokinetics and of Oral B/F/TAF after Discontinuing Injectable CAB + RPV

Thank you for taking our survey. The goal of this survey to better understand your experience with your current (CAB + RPV) and new (B/F/TAF) HIV treatments.

The questions below will ask you to select **only one** option from the list **or** select **all that apply**. Some questions may also ask for you to include additional details in the space provided. Please read each question carefully and mark with an "X" the option(s) that best apply to you. Please answer all questions on each page of the survey, unless you are instructed to skip questions based on your answers.

EXAMPLE:
What is your favorite fruit to eat?

Apple	o
Banana	o
Blueberry	o
Orange	o
Raspberry	X
Strawberry	o
Some other fruit	o
I do not like to eat fruit	o

1

Participant ID Number: _____ Date of Survey: (month/day/year) _____

Day 1: Questions related to participant experience with CAB + RPV (Cabenuva)

1. How did you first hear about injectable CAB + RPV (Cabenuva)?

	*Please check the **one** best answer*	
From a doctor, nurse, social worker or other healthcare provider	O (a)	
From a friend, relative, partner, acquaintance or other patient	O (b)	
From an advertisement (TV, radio, internet, magazine, etc.)	O (c)	
Internet (search, social media, etc.)	O (d)	
Another source *(please describe in the box below)*	O (y)	→ ***DESCRIBE BELOW***
Don't remember	O (z)	

If you selected "Another source", please describe that here:

2

Participant ID Number: _____ Date of Survey: (month/day/year) _____

2. Which of the following factors led you to decide to take injectable CAB + RPV (Cabenuva)?

	*Please check **all** answers that apply*
A friend, relative, partner, acquaintance or other patient recommended it	☐ (a)
A doctor, nurse, social worker or other health practitioner	☐ (b)
Research I did on my own (such as internet searches)	☐ (c)
Advertisement (TV, radio, internet, magazine, etc.)	☐ (d)
Wanting to reduce or stop side effects from daily oral medication	☐ (e)
Fear of stigma or negative feelings from taking HIV medication every day	☐ (f)
Fear that others will be more likely to know I have HIV with daily oral medication	☐ (g)
Not needing to remember to take daily oral medication	☐ (h)
Fear of missing doses of daily oral HIV medications	☐ (i)
Wanting to forget about having HIV for a while (no reminder every day)	☐ (j)
More convenient than oral treatment	☐ (k)
I think injections would work better than daily oral medication	☐ (l)
It is a new and exciting HIV treatment	☐ (m)
Want to have more in-person contact with healthcare system	☐ (n)
Another reason *(please describe in the box below)*	☐ (y) → ***DESCRIBE BELOW***

If you selected "Another reason", please describe that here:

3

Participant ID Number: _____ Date of Survey: (month/day/year) _____

3. **Of the reasons you checked in question number 2 above, which would you rank as the TOP reason you started injectable CAB + RPV (Cabenuva)?**

	*Please check the **one** best answer*
A friend, relative, partner, acquaintance or other patient recommended it	☐ (a)
A doctor, nurse, social worker or other health practitioner	☐ (b)
Research I did on my own (such as internet searches)	☐ (c)
Advertisement (TV, radio, internet, magazine, etc.)	☐ (d)
Wanting to reduce or stop side effects from daily oral medication	☐ (e)
Fear of stigma or negative feelings from taking HIV medication every day	☐ (f)
Fear that others will be more likely to know I have HIV with daily oral medication	☐ (g)
Not needing to remember to take daily oral medication	☐ (h)
Fear of missing doses of daily oral HIV medications	☐ (i)
Wanting to forget about having HIV for a while (no reminder every day)	☐ (j)
More convenient than oral treatment	☐ (k)
I think injections would work better than daily oral medication	☐ (l)
It is a new and exciting HIV treatment	☐ (m)
Want to have more in-person contact with healthcare system	☐ (n)
Other reason *(described in the box below Question 2)*	☐ (y)

4. **During your time taking CAB + RPV (Cabenuva), how inconvenient was it to go to the clinic/doctor's office to receive CAB + RPV (Cabenuva) injections as directed?**

	*Please check the **one** best answer*
Not at all inconvenient	O (a)
A little inconvenient	O (b)
Moderately inconvenient	O (c)
Very inconvenient	O (d)
Extremely inconvenient	O (e)

4

Participant ID Number: _____ Date of Survey: (month/day/year) _____

5. **Did you reschedule any appointments for getting your CAB + RPV (Cabenuva) injections in the past 6 months?**

	*Please check the **one** best answer.*
I did not reschedule any appointments	O (a)
I rescheduled 1-2 appointments	O (b)
I rescheduled 3-4 appointments	O (c)
I rescheduled 5 or more appointments	O (d)

6. **Did you miss any appointments entirely for getting your CAB + RPV (Cabenuva) injections in the past 6 months?**

	*Please check the **one** best answer.*	
I did not miss any appointments	O (a)	*Skip to Question 8*
Missed 1-2 appointments	O (b)	
Missed 3-4 appointments	O (c)	
Missed 5 or more appointments	O (d)	

5

Participant ID Number: _____ Date of Survey: (month/day/year) _____

7. Did missing appointments in the last 6 months lead to receiving CAB + RPV (Cabenuva) injections late or outside of the window when you were supposed to receive them?

	*Please check the **one** best answer.*
Yes	O (a)
No	O (b)
I don't know	O (c)

8. Which of the following side effects did you experience while on CAB + RPV (Cabenuva)?

	*Please check **all** answers that apply*	
Pain from the injection	☐ (a)	
Soreness from the injection	☐ (b)	
Lump, bump or nodule from the injection	☐ (c)	
Swelling around the injection site	☐ (d)	
Redness around injection site	☐ (e)	
Itching at the injection site	☐ (f)	
Muscle aches	☐ (g)	
Headache	☐ (h)	
Nausea / Upset stomach	☐ (i)	
Diarrhea	☐ (j)	
Sleep problems	☐ (k)	
Dizziness	☐ (l)	
Allergic reaction (rash, fever, blisters, tiredness, trouble breathing)	☐ (m)	
Fatigue / Tiredness	☐ (n)	
Another side effect *(please describe in the box below)*	☐ (y)	→ ***DESCRIBE BELOW***
I did not experience any side effects while on CAB + RPV (Cabenuva)	O (z)	→ ***SKIP TO QUESTION 11***

If you selected "Another side effect", please describe that here:

6

Participant ID Number: _____ Date of Survey: (month/day/year) _____

9. Did you experience any side effects that affected your ability to do your daily activities?

	*Please check the **one** best answer.*
Yes	☐ (a)
No	☐ (b)

10. How much did the side effects experienced while on CAB + RPV (Cabenuva) bother you?

	*Please check the **one** best answer*
They don't bother me at all	○ (a)
I am a little bothered by them	○ (b)
I am moderately bothered by them	○ (c)
I am very bothered by them	○ (d)
I am extremely bothered by them	○ (e)

7

Participant ID Number: _____ Date of Survey: (month/day/year) _____

11. Why did you decide to switch from CAB + RPV (Cabenuva) to daily oral medication B/F/TAF (Biktarvy)?

	*Please check **all** answers that apply*	
I didn't like the side effects of CAB + RPV (Cabenuva)	☐ (a)	
Visits to the clinic were too frequent	☐ (b)	
Waiting time in the office to get injections	☐ (c)	
Difficulty with insurance or cost	☐ (d)	
Difficulty scheduling appointments for injections	☐ (e)	
I want to have less in-person contact with the healthcare system	☐ (f)	
I have anxiety about receiving injections	☐ (g)	
I prefer oral medication over injections	☐ (h)	
A doctor, nurse, social worker or other health practitioner said I should switch	☐ (i)	
A friend, relative, partner, acquaintance or other patient said I should switch	☐ (j)	
I already take on other daily oral medication, so taking one more wouldn't make a difference	☐ (k)	
Concern that the medication in the injection might not last 2 months	☐ (l)	
Concern about developing resistance with CAB + RPV (Cabenuva)	☐ (m)	
I want to be in more control of my HIV medication	☐ (n)	
I took B/F/TAF (Biktarvy) before and I had a good experience with it	☐ (o)	
I think B/F/TAF (Biktarvy) is more effective than CAB + RPV (Cabenuva)	☐ (p)	
I think B/F/TAF (Biktarvy) has less side effects than CAB + RPV (Cabenuva)	☐ (q)	
Another reason *(please describe in the box below)*	☐ (y)	→ ***DESCRIBE BELOW***

If you selected "Another reason", please describe that here:

8

Participant ID Number: _____ Date of Survey: (month/day/year) _____

12. Of all the reasons you checked in question 10, which would you rank as the TOP reason you decided to switch from CAB + RPV (Cabenuva) to daily oral medication B/F/TAF (Biktarvy)?

	*Please check the **one** best answer*
I didn't like the side effects	O (a)
Visits to the clinic were too frequent	O (b)
Waiting time in the office to get injections	O (c)
Difficulty with insurance or cost	O (d)
Difficulty scheduling appointments for injections	O (e)
I want to have less in-person contact with the healthcare system	O (f)
I have anxiety about receiving injections	O (g)
I prefer oral medication over injections	O (h)
A doctor, nurse, social worker or other health practitioner said I should switch	O (i)
A friend, relative, partner, acquaintance or other patient said I should switch	O (j)
I already take on other daily oral medication, so taking one more wouldn't make a difference	O (k)
Concern that the medication in the injection might not last 2 months	O (l)
Concern about developing resistance with CAB + RPV (Cabenuva)	O (m)
I want to be in more control of my HIV medication	O (n)
I took B/F/TAF (Biktarvy) before and I had a good experience with it	□ (o)
I think B/F/TAF (Biktarvy) is more effective than CAB + RPV (Cabenuva)	O (p)
I think B/F/TAF (Biktarvy) has less side effects than CAB + RPV (Cabenuva)	O (q)
Another reason *(described in the box below Question 10)*	O (y)

13. How hopeful do you feel about starting Biktarvy in terms of successfully treating your HIV?

	*Please check the **one** best answer*
Very hopeful	O (a)
Hopeful	O (b)
Somewhat hopeful	O (c)

9

Participant ID Number: _____ Date of Survey: (month/day/year) _____

Not hopeful at all	○ (d)

THANK YOU, YOU ARE FINISHED WITH THE SURVEY.

10

The Week 4 additional study specific questions begins on the following page.

Participant ID Number: _____ Date of Survey: (month/day/year) _____

GS-US-380-6738: A Phase 4 Study to Evaluate the Safety, Pharmacokinetics and of Oral B/F/TAF after Discontinuing Injectable CAB + RPV

Thank you for taking our survey. The goal of this survey to better understand your experience with your current HIV treatment.

The questions below will ask you to select only **one option** from the list **or** select **all that apply**. Some question may also ask for you to include additional details in the space provided. Please read each question carefully and mark with an "X" the option(s) that best apply to you.

EXAMPLE:
What is your favorite fruit to eat?

Apple	o
Banana	o
Blueberry	o
Orange	o
Raspberry	X
Strawberry	o
Some other fruit	o
I do not like to eat fruit	o

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Participant ID Number: _____ Date of Survey: (month/day/year) _____

Week 4: Questions related to participant experience after switching to oral B/F/TAF

1. **Which of the following side effects have you experienced with B/F/TAF (Biktarvy) since switching from CAB + RPV (Cabenuva)?**

	*Please check **all** answers that apply*	
Headache	O (a)	
Nausea / Upset stomach	O (b)	
Diarrhea	O (c)	
Sleep problems	O (d)	
Fatigue / Tiredness	O (e)	
Dizziness	□ (f)	
Abdominal swelling or bloating	□ (g)	
Another side effect *(please describe in the box below)*	□ (y)	→ ***DESCRIBE BELOW***
I have not experienced any side effects with B/F/TAF (Biktarvy)	O (z)	→ ***SKIP TO QUESTION 5***

If you selected "Another side effect", please describe that here:

2. **Are you still experiencing any of these side effects? Please select all the side effects that still bother you at least a little.**

	*Please check **all** answers that apply*	
Headache	O (a)	
Nausea / Upset stomach	O (b)	
Diarrhea	O (c)	
Sleep problems	O (d)	
Fatigue / Tiredness	O (e)	
Dizziness	□ (f)	
Abdominal swelling or bloating	□ (g)	
Other side effect (described in the box below Question 1)	□ (y)	
I am not still experiencing any side effects with B/F/TAF (Biktarvy)	O (z)	→ ***SKIP TO QUESTION 5***

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Participant ID Number: _____ Date of Survey: (month/day/year) _____

3. **If you are still experiencing side effects from B/F/TAF (Biktarvy), have any of these side effects affected your ability to do your daily activities?**

Yes	O (a)
No	O (b)

4. **If you are still experiencing side effects from B/F/TAF (Biktarvy), please rate how much the side effects bother you.**

	*Please check the **one** best answer*
They don't bother me at all	O (a)
I am a little bothered by them	O (b)
I am moderately bothered by them	O (c)
I am very bothered by them	O (d)
I am extremely bothered by them	O (e)

5. **Since you started B/F/TAF (Biktarvy), have you missed any doses? In other words, were there any days you did not take B/F/TAF (Biktarvy)?**

	*Please check the **one** best answer*
I did not miss any doses	O (a)
Missed 1-2 doses	O (b)
Missed 3-4 doses	O (c)
Missed 5-6 doses	O (d)
Missed 7-8 doses	O (e)
Missed 9 or more doses	O (f)

THANK YOU, YOU ARE FINISHED WITH THE SURVEY.

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11.5. 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 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 with medical documentation.

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

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Biktarvy data on pregnant participants are limited. Data from nonclinical toxicity studies of Biktarvy have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that Biktarvy has demonstrated there is no reduction in the clinical efficacy of hormonal contraception. Refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

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. 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.

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 the 30-day follow-up visit.

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 (IUD)
- 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 measures are needed.

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 to 4 days after the last Biktarvy dose.

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

The Division of AIDS (DAIDS) scale is available at the following location:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

11.7. Country-Specific Requirements

Not applicable.

11.8. Sponsor Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404
USA

A Phase 4 Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Oral B/F/TAF after Discontinuing Injectable CAB+RPV

Original Protocol 27 July 2023

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

APPROVAL OF CLINICAL STUDY PROTOCOL

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

	[See appended electronic signature]
Name (Printed) [Responsible Person's Title]	Signature
[See appended electronic signature]	
Date	

protocol GS-US-380-6738

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Medical Affairs eSigned	29-Jul-2023 18:03:45