NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY SURVEILLANCE STUDY PROTOCOL

Study Title	Multi-country, non-interventional, cohort study of the effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adult patients receiving Bictegravir/ Emtricitabine/Tenofovir alafenamide (B/F/TAF)
Protocol ID	GS-EU-380-4472
Protocol Version/Date:	Final: Version 1.0 [19 December 2017]
EU PAS Register No	EUPAS22185
Clinical Trials.gov Identifier	Not Applicable
Active substances	ATC Code: J05AR20, Antivirals for systemic use; antivirals for treatment of HIV infections, combinations. Bictegravir, Emtricitabine, Tenofovir Alafenamide
Medicinal Product	Bictegravir/ Emtricitabine/Tenofovir Alafenamide fixed dose combination
Product reference	To be completed after market authorization of B/F/TAF
Procedure number	Not Applicable
Joint PASS	No
Research Question and Objectives	To assess the effectiveness and safety of B/F/TAF in treatment naive and treatment experienced HIV-1 infected adult patients, including adherence, resource utilization, quality of life, health status, and treatment satisfaction during its daily routine use.
Country (-ies) of study	As a minimum, the following countries are likely to be included: Germany, Netherlands, Ireland, France, Italy and Spain.

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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ABC	Abacavir
ADR	Adverse Drug Reaction
AE	Adverse Event
ART	Antiretroviral Therapy
BIC	Bictegravir
B/F/TAF	Bictegravir/ Emtricitabine/Tenofovir alafenamide
CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
DTG	Dolutegravir
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	(United States) Food and Drug Administration
FDC	Fixed Dose Combination
FTC	Emtricitabine
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	European Medicines Agency Guidelines on Good Pharmacovigilance Practices
HIV	Human Immunodeficiency Virus
HIVSI	HIV Symptom Index
HIVTSQs	HIV Treatment Satisfaction Questionnaire Status version
HIVTSQc	HIV Treatment Satisfaction Questionnaire Change version
HMA	Heads of Medicines Agencies
HRQoL	Health Related Quality of Life
IEC	Independent Ethics Committee
INSTI	Integrase Strand-Transfer Inhibitor
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
NRTI	Nucleoside Reverse-Transcriptase Inhibitor
N(t)RTI	Nucleotide Reverse Transcriptase Inhibitor
PAS	Post-Authorization Study
PRO	Patient Reported Outcome
PVE	Pharmacovigilance and Epidemiology
QPPV	Qualified Person for Pharmacovigilance
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SF-36	Health Survey Short Form
SmPC	Summary of Product Characteristics
SSR	Special Situation Report
SUSAR	Serious Unexpected Suspected Adverse Reaction
TAF	Tenofovir Alafenamide
TAFNES	**N**on-Interventional Real-Life Study of **E**ffectiveness, **S**afety, Adherence, and Health-Related Quality of Life in Adult Patients receiving Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (E/C/F/**TAF**) or Emtricitabine/Tenofovir alafenamide (F/**TAF**) or Rilpivirine/Emtricitabine/Tenofovir alafenamide (R/F/**TAF**) for HIV-1 Infection in Germany
US, USA	United States, United States of America
VAS	Visual Analog Scale

3. RESPONSIBLE PARTIES

Table 3-1. Table of Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
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4. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences Europe Ltd
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Study Title:	Multi-country, non-interventional, cohort study of the effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adult patients receiving Bictegravir/ Emtricitabine/Tenofovir alafenamide (B/F/TAF)
Rationale and Background:	Current treatment guidelines recommend that patients initiate antiretroviral therapy (ART) at time of diagnosis, leading to the requirement for lifelong treatment. Accordingly, there is a need for new HIV-1 therapies that improve the current standard of care so that lifelong ART is more effective, more tolerable, and safer for patients. Bictegravir (BIC) is a novel unboosted integrase strand-transfer inhibitor (INSTI) with potent activity against HIV-1 integrase and an enhanced resistance profile. Gilead Sciences has co-formulated BIC with the NRTI emtricitabine (FTC; F) and the N(t)RTI tenofovir alafenamide (TAF) into a single tablet that is suitable for once-daily use. This B/F/TAF single tablet regimen may provide a potent, convenient, tolerable, and practical regimen for the life-time treatment of people living with HIV. While large Phase 3 clinical trials are necessary to support the registration of new drugs, these studies are performed in highly selected patients under controlled conditions. Thus, data derived from observational cohorts that reflects a more heterogeneous patient population are important in helping physicians better understand the use of new drugs in real-life healthcare settings. The aim of this non-interventional, multi-country, cohort study is to evaluate the effectiveness and safety of B/F/TAF in ART-naive and ART-experienced HIV-1 infected adult patients as well as adherence, resource utilization, quality of life, health status, and treatment satisfaction during its daily routine use.

Research Question and Objectives:

This non-interventional cohort study will evaluate the effectiveness, safety, adherence, resource utilization and patients' health condition via Patient Reported Outcome (PRO) questionnaires, during treatment with B/F/TAF in routine clinical care.

The primary objective of this study is as follows:

- To evaluate HIV-1 RNA suppression, defined as HIV-1 RNA <50 copies/mL, at 12 months after initiating or switching to B/F/TAF

The secondary objectives of this study are as follows:

- To evaluate HIV-1 RNA suppression (<50 copies/mL) at months 3, 6 and 24 after initiating or switching to B/F/TAF
- To evaluate changes in CD4 cell count and CD4/CD8 ratio at months 3, 6, 12 and 24 after initiating or switching to B/F/TAF
- To assess rates of adverse events (AEs) and serious AEs (SAEs)

Additional exploratory objectives:

- To describe the reasons for ART initiation in ART-naïve patients and for switching to B/F/TAF in ART-experienced patients
- To assess time to treatment initiation in ART-naïve patients
- To evaluate adherence to treatment with B/F/TAF using a Visual Analog Scale (VAS) Adherence Questionnaire
- To evaluate persistence on B/F/TAF and to describe the reasons for B/F/TAF discontinuation during the study
- To describe physical and mental health-related quality of life, health status, and treatment satisfaction using standardized Patient Reported Outcomes (PRO) questionnaires: Health Survey Short Form (SF-36), HIV Symptom Index (HIVSI), and HIV Treatment Satisfaction Questionnaire (HIVTSQ)
- To describe health care resource utilization (e.g., number of hospitalizations, number of physician visits)

The above parameters may be evaluated in various subgroups, e.g., ART-naïve patients versus ART-experienced patients, by baseline viral load ≥ or <100,000 copies/mL, age, presence of specific comorbidities, gender, as well as comparing between participating countries.

Study Design:	Prospective, non-interventional cohort study. Patient enrollment and data will be collected using an electronic case report form (eCRF) by the participating sites. Each enrolled patient will be followed-up for 24 months.
Population:	The study population will be comprised of ART-naïve and ART-experienced HIV-1 infected adults aged ≥18 years initiating treatment with B/F/TAF in routine clinical care. As a minimum, the following countries are likely to be included: Germany, Netherlands, Ireland, France, Italy and Spain.
Variables:	Baseline and follow-up variables are specified in section 9.3 and include amongst others: demographics, clinical characteristics (i.e., comorbidities), laboratory measurements, medications (i.e., prior ARV and concomitant medications), adherence and PROs.
Data Sources:	Electronic data capture (EDC) at each participating site will collect study variables gathered from routine standard care.
Study Size:	At least 1400 patients starting treatment with B/F/TAF (to include both ART-naïve and ART-experienced patients) are planned to be enrolled into the study. Assuming an HIV RNA response rate of at least 90% (<50 copies/ mL via the U.S. FDA-defined Snapshot algorithm), a sample size of 1400 patients will provide a 95% confidence interval around the point estimate of less than 2.2% (i.e., 90 +/- 2.2%). Additionally, assuming there are 30% of patients over age 50 years (similar to the E/C/F/TAF TAFNES study), then with 980 patients <50 years and 420 patients 50 years or older, there is more than 90% power to detect a difference in HIV RNA response rate between the age groups of at least 7%, assuming a 90% response rate in older patients (versus 83% in younger patients) and a two-sided alpha of 0.05 and a continuity corrected test of two proportions. With a target of at least 200 patients per country, there is 80% power to determine a 7% difference in HIV RNA response rates between any country and the remaining countries, assuming a 90% response rate in the overall countries. In addition, assuming a 90% response rate in one country with 200 patients, there is more than 80% power to determine an 11% difference in HIV RNA response rates compared to any country including the same sample size.

Data Analysis:

For categorical variables, numbers and percentages of patients will be reported including the according 95% confidence intervals.

For continuous variables, mean, standard deviation (SD), minimum, first and third quartile (Q1, Q3), median, maximum and 95% confidence intervals will be calculated, together with the total number of observations and the number of missing values.

Descriptive statistics will summarize demographics and baseline characteristics.

The questionnaires scores will be calculated according to the algorithms elaborated for these questionnaires.

Visit windows will be defined only in the statistical analysis plan to group data in order to generate descriptive statistics across time to assess potential trends in patient reported outcome questionnaires, safety data or CD4 cell count. P-values and confidence intervals (95% two-sided) will be calculated when considered relevant.

Multivariate logistic regression models will be used to model binary outcome variables (HIV-1 RNA suppression, categorical CD4 cell count, i.e.>500, adherence and persistence of B/F/TAF).

Multivariate Poisson regression models will be used to model questionnaires scores (SF-36, HIV Symptom Index, and HIV Treatment Satisfaction Questionnaires) and rates of AEs and SAEs.

Multivariate analyses will also be conducted to compare ART-naïve and ART-experienced groups. Longitudinal analysis will be performed using mixed models.

Further details of the data analysis will be provided in the Statistical Analysis Plan.

Milestones:

EU PAS Registration	Q1 2018
Start of data collection: B/F/TAF	Q2 2018 or upon EMA approval of
End of data collection:	Q2 2022
Interim report:	Q1 2020
Final report:	Q4 2022

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

5. AMENDMENTS AND UPDATES

- **Protocol Modifications**

Protocol modifications may only be made by Gilead.

6. MILESTONES

Milestone	Planned Date
EU PAS Registration	Q1 2018
Start of data collection	Q2 2018 or upon EMA approval of B/F/TAF
End of data collection	Q2 2022
Interim report	Q1 2020
Final report of study results	Q4 2022

7. RATIONALE AND BACKGROUND

Current treatment guidelines recommend that patients initiate antiretroviral treatment (ART) earlier, thereby requiring lifelong treatment, potentially for 50 years or more. Accordingly, there is a need for new HIV-1 therapies that improve the current standard of care so that lifelong ART is more effective, more tolerable, and safer for patients.

Bictegravir (BIC) is a novel unboosted integrase strand-transfer inhibitor (INSTI) with potent activity against HIV-1 integrase and an enhanced resistance profile {Tsiang 2016}. Gilead Sciences has co-formulated BIC with the NRTI emtricitabine (FTC; F) and the N(t)RTI tenofovir alafenamide (TAF) into a single tablet that is suitable for once-daily use. This B/F/TAF fixed dose combination (FDC) may provide a potent, convenient, tolerable, and practical regimen for the life-time treatment of people living with HIV.

In a phase 2, double-blind, randomized controlled trial, ART-naïve patients were randomly assigned to receive BIC (as the single agent) or dolutegravir (DTG), both with F/TAF. At 48 weeks, 97% of the BIC treated patients and 91% of the DTG treated patients achieved HIV-1 RNA of <50 copies/mL, with no treatment emergent resistance in either arm {Sax 2017a}.

Based on the results of the phase 2 study, two large, ongoing, phase 3, double-blind, randomized-controlled trials in ART-naïve patients compared B/F/TAF FDC to either coformulated abacavir, DTG and lamivudine (ABC/DTG/3TC) (GS-US-380-1489) or DTG with F/TAF (GS-US-380-1490). Both studies demonstrated that virological suppression with B/F/TAF was non-inferior to the DTG-based regimen in ART-naive patients. At 48 weeks, 92% on B/F/TAF vs. 93% on ABC/DTG/3TC {Gallant 2017} and 89% on B/F/TAF vs. 93% on DTG plus F/TAF {Sax 2017b} achieved HIV-1 RNA <50 copies/mL. There was no treatment emergent resistance to any component of either regimen. The fixed-dose combination of B/F/TAF was safe and well tolerated compared with the DTG-based regimens.

Two further ongoing phase 3 studies are evaluating B/F/TAF in virologically suppressed patients switching from an existing antiretroviral regimen containing either DTG (GS-US-380-1844) or a boosted protease inhibitor (GS-US-380-1878). In study GS-US-380-1878, switching to B/F/TAF was non-inferior to continuing a boosted darunavir- or atazanavir-based regimen with 92% vs. 89% of patients achieving HIV-1 RNA <50 copies/mL at 48 weeks and no patients treated with B/F/TAF developed resistance {Daar 2017}.

While large phase 3 clinical trials are fundamental to supporting the registration of new drugs, these studies are performed in highly selected patients under well controlled conditions. The results of such trials may be limited in terms of their generalizability to the wider HIV-infected population. Thus, there is a need for data derived from more heterogeneous patient populations, such as in observational cohorts, in order to help physicians gain a better understanding of the use of new drugs in real-life healthcare settings.

The aim of this non-interventional, multi-country, cohort study is to evaluate the effectiveness and safety of B/F/TAF in ART-naive and ART-experienced HIV-1 infected adult patients as well

as adherence, resource utilization, quality of life, health status, and treatment satisfaction during routine clinical practice.

8. RESEARCH QUESTIONS AND OBJECTIVES

This non-interventional cohort study will evaluate the effectiveness, safety, adherence, resource utilization and PROs of B/F/TAF use in routine clinical care.

The primary objective of this study is:

- To evaluate HIV-1 RNA suppression, defined as HIV-1 RNA <50 copies/mL, at 12 months after initiating or switching to B/F/TAF.

The secondary objectives of this study are:

- To evaluate HIV-1 RNA suppression (<50 copies/mL) at months 3, 6 and 24 after initiating or switching to B/F/TAF
- To evaluate changes in CD4 cell count and CD4/CD8 ratio at months 3, 6, 12 and 24 after initiating or switching to B/F/TAF.
- To assess rates of adverse events (AEs) and serious AEs (SAEs)

Additional exploratory objectives:

- To describe the reasons for ART initiation in ART-naïve patients and for switching to B/F/TAF in ART-experienced patients
- To assess time to treatment initiation in ART-naïve patients
- To evaluate adherence to treatment with B/F/TAF using a Visual Analog Scale (VAS) Adherence Questionnaire
- To evaluate persistence on B/F/TAF and to describe the reasons for B/F/TAF discontinuation during the study
- To describe physical and mental health-related quality of life, health status, and treatment satisfaction using standardized Patient Reported Outcomes (PRO) questionnaires: Health Survey Short Form (SF-36), HIV Symptom Index (HIVSI), and HIV Treatment Satisfaction Questionnaire (HIVTSQ)
- To describe health care resource utilization (e.g., number of hospitalizations, number of physician visits)

The above parameters may be evaluated in various subgroups, e.g., ART-naïve patients versus ART-experienced patients, by baseline viral load ≥ or <100,000 copies/mL, age, presence of specific comorbidities, gender, as well as comparing between participating countries.

9. RESEARCH METHODS

9.1. Study Design

This non-interventional study will be a prospective cohort comprised of HIV-1 infected adults who initiate B/F/TAF therapy in accordance with the approved Summary of Product Characteristics (SmPC).

Patients can be enrolled in this study after the physician has independently decided to treat a specific patient with B/F/TAF and after patient´s Informed Consent Form (ICF) is obtained. Although the study will not define which therapy a patient will receive, only patients starting or switching to B/F/TAF will be enrolled.

Patient data will be collected prospectively according to clinical practice from initial enrollment into the study (Day 1/Baseline) and thereafter (Follow-up period) until study completion at Month 24, loss to follow-up, withdrawal of consent, or death, whichever occurs sooner.
Day 1/Baseline will be defined as the time at which patients either start (ART-naïve) or switch to (ART-experienced) B/F/TAF.

9.1.1. Early Study Drug Discontinuation

In case of B/F/TAF discontinuation, the date of discontinuation, reasons for discontinuation (e.g., patient choice, adverse reaction, lack of efficacy) and patients' new ART will be collected. The patient will remain in the study and will be followed-up with the new ART until premature end of documentation (e.g., due to lost to follow up) or until reaching the defined end of the study (24 months after enrollment). If the patient has subsequent changes in therapy, all ARV changes will be recorded until the patient completes the study.

9.2. Setting

The study population will consist of HIV-1 infected adults aged ≥18 years receiving B/F/TAF who will be enrolled across participating countries (as a minimum likely to include Germany, Netherlands, Ireland, France, Italy and Spain). The start of enrolment will be determined by the availability of B/F/TAF in each of the participating countries based on national reimbursement timelines.

All treatments will be prescribed according to local treatment guidelines and/or routine clinical practice. There will be no additional diagnostic or laboratory monitoring procedures required by the study.

9.2.1. Inclusion Criteria

1. HIV-1 infection
2. Signed informed consent
3. Age ≥ 18 years old
4. Initiating treatment with B/F/TAF in accordance with the SmPC

9.2.2. Exclusion Criteria

1. Participation in any other observational or interventional clinical trial without prior approval from the Medical Monitor

9.3. Variables

	On-Treatment Period			
	Baseline/Day 1	**3 Months**	**6, 12, 24 Months**	**B/F/TAF Discontinuation[j]**
Informed consent	X	-	-	-
Demographics	X	-	-	-
Weight	X	-	X	X
Date of HIV diagnosis	X	-	-	-
CDC classification[a]	X	-	-	-
New AIDS-defining events	-	X	X	X
Co-morbidities	X	-	-	-
ART History	X	-	-	-
Concomitant medications	X	X	X	X
Plasma HIV-1 RNA	X	X	X	X
CD4 cell count	X	X	X	X
CD4/CD8 ratio	X	X	X	X
Chemistry profile[b]	X	-	X	X
Metabolic assessments[c]	X	-	X	X
Urinalysis[d]	X	-	X	X
Reasons for ART initiation or switch to B/F/TAF	X	-	-	-
AEs and SAEs		X	X	X
Resistance status	X	-	X	-
VAS	X[e]	-	X	-
HIVSI	X	-	X	-
HIVTSQs	X[f]	X[g]		-
HIVTSQc	-	X[h]	X[i]	-
SF-36	X	-	X	-
Health Utilization Assessment	-	-	X	-
Date and reason for B/F/TAF discontinuation	-	-	-	X

a Selik RM, et al. Morbidity and Mortality Weekly Report (MMWR). Revised Surveillance Case Definition for HIV Infection - United States 2014. Centers for Disease Control and Prevention, 2014.
b Chemistry profile: AST, ALT, Total/direct bilirubin, albumin, serum glucose, serum phosphate, serum creatinine.
c Metabolic assessments: Lipid panel (Total cholesterol, HDL, LDL, triglycerides).
d To include dipstick test (glucose, leukocytes, protein) and urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR).
e For ART-experienced patients only.
f For ART-experienced patients only.
g For ART-naïve patients only.
h For ART-experienced patients only.
i For all patients.

j The evaluations should be done at the time of B/F/TAF discontinuation visit. After the B/F/TAF discontinuation visit, the subject should follow the same schedule of clinical routine evaluations, but only record data listed in this column until study completion.

9.3.1. Unscheduled Visit Assessments

For patients requiring follow-up outside of the normal routine clinic visits, the variables collected will be according to local medical practice.

9.3.2. Patient Reported Outcomes

In order to assess treatment impact on Health-Related Quality of Life (HRQoL), HIV-related symptoms, medication related beliefs, medication adherence, and resource utilization, patients will be asked to complete the following paper questionnaires at the clinic according to the schedule outlined in Section 9.3. Questionnaires are self-administered and are recommended to be completed prior to any other study assessments/procedures. Patients are to record all answers and complete every question.

- Short Form-36 (SF-36)
  - A generic 36-item questionnaire which assesses eight health domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health).
- HIV Symptom Index (HIVSI)
  - A 20-item questionnaire which assesses signs and symptoms associated with HIV with a recall period of the past four weeks.
- HIV Treatment Satisfaction Questionnaire: status (HIVTSQs) and change (HIVTSQc) versions
  - Each is a 10-item questionnaire regarding current treatment regimen to assess satisfaction with HIV-treatment at baseline (HIVTSQs) and during study follow-up (HIVTSQc).
- Visual Analog Scale (VAS) Adherence questionnaire
  - Adherence to treatment is assessed using a 10-centimeter VAS which assesses treatment adherence over the past 30 days.
- Health Utilization Assessment
  - Patients will receive a questionnaire on which they will be asked to document any hospitalizations (number and duration) and number of appointments with other physician types (e.g., renal or bone specialists).

9.4. Data Sources

Data will be collected from participating countries (as a minimum, likely to include Germany, Netherlands, Ireland, France, Italy and Spain).

Each investigator at the participating sites will offer the study to potentially eligible patients, for whom, the independent decision to prescribe B/F/TAF has been made. The decision to prescribe B/F/TAF should be made by a patient's primary HIV care provider and should not be related to study entry. Potential participants will be asked to sign an ICF for the collection of retrospective and prospective data. Patients will not have to attend any additional visits or undergo any procedures above their standard of care.

Data collection will be performed by manual entry of data from the patient's medical file and questionnaires to a computer based eCRF. No patient initials will be included and only anonymized data will be entered.

9.5. Study Size

At least 1400 patients starting treatment with B/F/TAF (to include both ART-naïve and ART-experienced patients) are planned to be enrolled into the study.

Assuming an HIV RNA response rate of at least 90% (<50 copies/ mL via the U.S. FDA-defined Snapshot algorithm), a sample size of 1400 patients will provide a 95% confidence interval around the point estimate of less than 2.2% (i.e., 90 +/- 2.2%). Additionally, assuming there are 30% of patients over age 50 years (similar to the E/C/F/TAF TAFNES study), then with 980 patients <50 years and 420 patients 50 years or older, there is more than 90% power to detect a difference in HIV RNA response rate between the age groups of at least 7%, assuming a 90% response rate in older patient (versus 83% in younger patients) and a two-sided alpha of 0.05 and a continuity corrected test of two proportions.

With a target of at least 200 patients per country, there is 80% power to determine a 7% difference in HIV RNA response rates between any country and the remaining countries, assuming a 90% response rate in the overall countries. In addition, assuming a 90% response rate in one country with 200 patients, there is more than 80% power to determine an 11% difference in HIV RNA response rates compared to any country including the same sample size.

The study will not have strict enrollment goals for specific strata of patient types. However, the protocol team will monitor enrollment into specific strata of interest (e.g., age > 50, treatment naïve) and may close enrollment to a strata in order to preserve statistical power to evaluate sub-groups of interest.

9.6. Data Management

After finalization and approval of the protocol, an electronic case report form (eCRF) will be built in a commercial EDC system to collect the data listed in the Variables section (9.3).

Personal identifying data such as names, health record identifiers, and social security numbers will not be collected.

Site users will receive a unique username and password from the EDC system administrator following completion of the EDC system training. Receipt of username, password and successful completion of EDC training, will allow site to enter data into the EDC system. Investigators will electronically sign the eCRFs to confirm responsibility for the data following completion of data entry and data quality activities. Study data will be stored on secure network drives with access restricted to authorized personnel only.

After reviewing the questionnaires for completeness, the questionnaires will be returned to the Contract Research Organisation for data entry into the EDC system.

9.7. Data Analysis

For categorical variables, numbers and percentages of patients will be reported including the according 95% confidence intervals.

For continuous variables, mean, standard deviation (SD), minimum, first and third quartile (Q1, Q3), median, maximum and 95% confidence intervals will be calculated, together with the total number of observations and the number of missing values.

Descriptive statistics will summarize demographics and baseline characteristics (including the type of regimen at enrolment). Once data is available from more than one country, descriptive analyses by country will be done to determine if patient heterogeneity exists across countries and sites.

The questionnaires scores will be calculated according to the algorithms elaborated for these questionnaires.

Visit windows will be defined in the Statistical Analysis Plan (SAP) to group data in order to generate descriptive statistics across time to assess potential trends in patient reported outcome questionnaires, safety data or CD4. P-values and/or confidence intervals (95% two-sided) will be calculated when considered relevant.

Following descriptive analysis, a multiple imputation approach will be used to carry out multivariate analyses in case the assumptions of missing at random (MAR) are met. If this assumption doesn't hold, a complete case (subjects with all variables present) or regression approach may be used dependent on the results of a sensitivity analysis. Patterns of missing data will be determined using the methodology outlined by Rubin {Rubin 1976}. Imputation methods will be used to account for missing values in the dataset adhering to current ENCePP guidelines {European Medicines Agency 2010}.

Multivariate logistic regression models will be used to model binary outcome variables (HIV-1 RNA suppression, change in CD4 cell count category (e.g. CD4 > 500 at week 48), HIV RNA suppression, adherence and persistence of B/F/TAF).

Multivariate Poisson regression models will be used to model questionnaires scores (SF-36, HIV Symptom Index, and HIV Treatment Satisfaction Questionnaire s) and rates of ADRs and SADRs, adjusted for confounding.

Multivariate analyses will be also conducted to compare treatment-naïve and non-naïve treatment groups. In order to maximize homogeneity between groups and reduce the impact of treatment-selection bias, an inverse probability of treatment weighted (IPTW) approach will be applied (Rosenbaum and Rubin 1983, Thoemmes and Ong 2016,{Austin 2011b} {Austin 2011a}),. Demographics and baseline measures would be potential confounders/effect modifiers for multivariate analyses. Confounders/effect modifiers and respective adjustments will be addressed in the SAP. For multivariate analyses, significantly skewed data will be transformed using the fractional polynomial approach (Royston et al. 1999). Longitudinal analysis will be done using mixed models. Further details of the data analysis will be provided in the SAP.

9.8. Quality Control

In order to ensure the quality and integrity of the study results, the EDC tool will include automatic data validation checks and the sponsor and/or contracted third party will perform remote manual data quality review in accordance with the study data quality and monitoring documents. In addition, monitors will engage with sites regarding data quality and completeness via telephone calls and onsite visits, as documented in the study monitoring plan. Study monitors must have direct access to patients' source data in order to verify the accuracy of the data recorded into the EDC tool during onsite visits. The investigator agrees to respond to the resulting queries in a timely manner to enable the timely collation of the analysis datasets.

Representatives of regulatory authorities or of 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 medical monitor(s) 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.

9.9. Limitations of the Research Methods

This study has the characteristic limitations of observational studies, for example selection bias, information bias and missing values.

In order to reduce selection bias, patient's eligibility criteria have been well defined. However, this is not a type of bias easy to prevent or measure. A selection bias introduced by the choice of sites that contribute patient data cannot totally be avoided. However, a selection of sites in multiple countries will help to reduce this kind of bias.

This study is a non-comparative, non-interventional study, and as a result, confounding by indication (i.e., confounding indicated by study drug) should be a minimal issue in the absence of a comparator. Multivariate analyses will aim to minimize potential confounding by indication by including disease assessment and according details of treatment in the analyses.

Information bias can be prevented by using standard measurement instruments, like eCRF and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patient' medical records.

As documentation of the study variables is not obligatory, the extent to which missing data occurs is unpredictable. Patterns of missing data will be determined using the methodology outlined by Rubin et al {Rubin 1976}. Here, it has to be determined if the "Missing At Random" (MAR) criterion is fulfilled. If the assumptions of MAR or missing completely at random (MCAR) are met then a multiple imputation approach will be used. If this assumption doesn't hold, a full case or regression approach may be used.

Multiple imputation by chained equations (MICE) also referred to as sequential regression multiple imputation, is a validated statistical method for the handling of missing data {Azur 2011}. Using MICE, missing values are imputed based on the observed values for a given individual and the relationships within the data for other participants.

9.10. Other Aspects

9.10.1. Joint Investigator/Gilead Responsibilities

9.10.1.1. Access to Information for Monitoring

The study monitor is responsible for review of the eCRFs as documented in the study monitoring plan for completeness, consistency, and accuracy of the data being entered. The investigator may provide the study monitor with access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.10.1.2. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and IRBs/ IECs, where applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. Independent Ethics Committee (IEC) Review

The investigator will submit this protocol and any accompanying material to be provided to the patient (such as patient information sheets, or descriptions of the study used to obtain informed consent) to an IEC as required. The investigator will not begin any study patient activities until approval from the IEC has been documented and provided as a letter to the investigator as required.

Any subsequent modifications made to the protocol or any accompanying material to be provided to the patient after initial IEC approval will also be submitted for IEC approval as required prior to use, with the exception of those necessary to reduce immediate risk to study patients.

10.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and alternatives of the study prior to study participation and before performing any study-related activities. The investigator must utilize the most current IEC approved ICF for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the patient and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements.

10.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, CRFs, and any other study information, remain 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 study site to any third party or otherwise into the public domain.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

This study is a post-authorization safety study and will collect all required safety information in line with requisite global requirements. Details for the Gilead global pharmacovigilance system through which all safety data are being managed are described in the Pharmacovigilance Masterfile, particularly in the PSMF Module on PV processes.

11.1. Investigator Instructions for Collecting and Reporting Selected Safety Information to Gilead

The following safety information is required to be collected and reported for this study from the time of the patient's consent to participate in the study (i.e., signing informed consent) until study completion at Month 24, loss to follow-up, withdrawal of consent, or death, whichever occurs sooner - this applies even if patients prematurely discontinue B/F/TAF.

- All fatal events (regardless of causality)
- All serious adverse events (SAEs)
- All non-serious adverse events (AEs)
- Special Situation Reports (SSRs)

Timelines for reporting to Gilead are as follows:

- Within 3 calendar days of investigator's knowledge of all fatal events (regardless of causality) and all SAEs
- Within 30 calendar days of investigator's knowledge of non-serious AEs
- Within 30 calendar days of investigator's knowledge for SSRs

11.1.1. Process for Reporting to Gilead

- Site personnel must record all deaths, AEs, SAEs, and SSRs in the eCRF database and transmit them to Gilead Pharmacovigilance and Epidemiology within the timelines shown above. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the safety information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the event on the paper report form (i.e. the Non-Interventional Study AE/SAE Report Form or Non-Interventional Study Special Situations Report Form) and submit by e-mail or fax to:

Gilead Pharmacovigilance and Epidemiology:	Fax:	1-650-522-5477
	E-mail:	Safety_FC@gilead.com

- As soon as it is possible to do so, any safety event reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If a safety event has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

11.1.2. Instructions for Reporting Pregnancies

The following information is required to be collected and reported for this study if a patient becomes pregnant while taking B/F/TAF:

- Information on all pregnancies

- The outcome of the pregnancy, including any premature termination (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons)

Timelines for reporting to Gilead are as follows:

- Within 30 calendar days of knowledge of the pregnancy

- Within 3 calendar days of knowledge of all pregnancy related serious events (regardless of causality, e.g., a spontaneous abortion, hospitalization, etc.)

If reporting of pregnancies is by electronic submission via eCRF, this method must always be used unless the eCRF system cannot be accessed.

Pregnancy information should also be reported on the paper pregnancy report form, and the outcome should be reported on pregnancy outcome report form. However, if the event qualifies as an SAE then an SAE form should be reported.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) or SAE occurring as an adverse pregnancy outcome post-study must be reported within the 3-calendar-day timelines.

11.2. Gilead Reporting Requirements to Regulatory Authorities

Gilead is responsible for analyzing reports of all safety information and reporting to regulatory agencies as determined by country-specific legislation or regulations.

Assessment of expectedness for all safety reports will be determined by Gilead using reference safety information specified in the product label.

11.3. Definitions

11.3.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study patient administered a pharmaceutical product, which 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 medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

11.3.2. Adverse Drug Reactions

An adverse drug reaction (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

11.3.3. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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 patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

11.3.4. Serious Adverse Drug Reaction

A SADR is defined as any SAE that is considered causally related to the medicinal product at any dose administered.

11.3.5. Special Situations Reports

Special situation reports include reports of pregnancy; medication error, abuse, misuse, overdose, lack of effect; AE in infants following exposure from breastfeeding, off-label use, product complaints with AE and occupational exposure with an AE.

A pregnancy report is used to report any pregnancy that occurs during the study, whether or not maternal or paternal exposure to the product occurred.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product 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 medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product label.

Off-label use is defined as the intentional use of licensed medicinal product by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

11.4. Clinical Laboratory Abnormalities

Laboratory abnormalities without clinical significance are not recorded as safety events. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation and considered to be causally associated with the medicinal product must be recorded as an ADR, or an SADR, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an ADR or SADR if they meet the definition of an ADR or SADR as described in Section 11.3. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

11.5. Assessment of Causality for Study Drugs

The investigator or qualified sub-investigator is responsible for assessing the causal relationship to drug therapy for each event and using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes:** There is a reasonable possibility that the event may have been caused by the medicinal product (and thus reported as an ADR or an SADR).

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

A non-interventional study report will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on GVP Module VIII. Note that an abbreviated report may be prepared in certain cases. The final study report will be submitted within 12 months of study completion.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites.

- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

Gilead shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

13. ACCESS TO INFORMATION FOR AUDITING OR INSPECTIONS

Representatives of regulatory authorities or of 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 medical 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.

14. REFERENCES

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15. APPENDICES

Appendix 1. ENCePP Checklist for Study Protocols
Appendix 2. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)
Appendix 3. Gilead Signature Page
Appendix 4. Investigator Signature Page

Appendix 1. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 3)

Doc.Ref. EMA/540136/2009

Study title: Multi-country, non-interventional, cohort study of the effectiveness, safety, adherence, and health-related quality of life in HIV-1 infected adult patients receiving Bictegravir/ Emtricitabine/Tenofovir alafenamide (B/F/TAF)

Study reference number: GS-EU-380-4472

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4, 6
1.1.2 End of data collection[2]	☒	☐	☐	4, 6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6, 12.1

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.5
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.1
3.2. Primary and secondary data will be collected.				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	4, 7.1, 9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.9
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	9.3

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3 Covariates?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates?	☐	☒	☐	

9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.7, 9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9

Section 12: Limitations	Yes	No	N/A	Section Number
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10.4

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

Name of the main author of the protocol: David Thorpe

Date: 19/December/2017

Signature: PPD

Appendix 2. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis of esophagus
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis, extrapulmonary
6. Cryptosporidiosis, chronic intestinal (> 1 month duration)
7. Cytomegalovirus disease (other than liver, spleen or nodes)
8. Cytomegalovirus retinitis (with loss of vision)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis oresophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (> 1 month duration)
13. Kaposi's sarcoma
14. Lymphoma, Burkitt's (or equivalent term)
15. Lymphoma, immunoblastic (or equivalent term)
16. Lymphoma, primary, of brain
17. *Mycobacterium avium* complex or *Myobacterium kansasii*, disseminated or extrapulmonary
18. *Mycobacterium tuberculosis*, of any site, pulmonary, disseminated or extrapulmonary
19. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
20. Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*) pneumonia
21. Pneumonia, recurrent
22. Progressive multifocal leukoencephalopathy
23. Salmonella septicemia, recurrent
24. Toxoplasmosis of brain
25. Wasting syndrome attributed to HIV infection

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 {Selik 2014}

Appendix 3. Gilead Signature Page

GILEAD SCIENCES EUROPE LTD
2 ROUNDWOOD AVENUE, STOCKLEY PARK, UXBRIDGE UB11 1AF, UK

MULTI-COUNTRY, NON-INTERVENTIONAL, COHORT STUDY OF THE EFFECTIVENESS, SAFETY, ADHERENCE, AND HEALTH-RELATED QUALITY OF LIFE IN HIV-1 INFECTED ADULT PATIENTS RECEIVING BICTEGRAVIR/ EMTRICITABINE/TENOFOVIR ALAFENAMIDE (B/F/TAF)

ORIGINAL – 19/DECEMBER/2017

This protocol has been approved by Gilead Sciences Europe, Ltd The following signatures document this approval

DAVID THORPE
Gilead Study Director (Printed)
Author

PPD
Signature

10th Jan 2018
Date

Gilead Study Director (Printed)
Author

Signature

Date

PPD
Gilead EU QPPV (Printed)

Signature

Date

Appendix 3. Gilead Signature Page

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ORIGINAL – 19/DECEMBER/2017

This protocol has been approved by Gilead Sciences Europe, Ltd. The following signatures document this approval.

Gilead Study Director (Printed) Author	Signature
Date	
Marion Heinzkill	PPD
Gilead Study Director (Printed) Author	Signature
08/Jan/2018	
Date	
PPD	
Gilead EU QPPV (Printed)	Signature
Date	

Appendix 3. Gilead Signature Page

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ORIGINAL – 19/DECEMBER/2017

This protocol has been approved by Gilead Sciences Europe, Ltd. The following signatures document this approval.

Gilead Study Director (Printed) Author	Signature
Date	
Gilead Study Director (Printed) Author	Signature
Date	
PPD Gilead EU QPPV (Printed)	PPD
12 Jan. 2018 Date	

Appendix 4. Investigator Signature Page

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 Europe. I will discuss this material with them to ensure that they are fully informed about the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number