NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	Non-Interventional Real-Life Study of Effectiveness, Safety, 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	
Protocol ID	GS-DE-292-1912	
Protocol Version/Date:	Original	24 Sept 2015
	Amendment 1	14 April 2016
	Amendment 2	12 April 2019
EU PAS Register No	ENCEPP/SDPP/11010	
Clinical Trials.gov Identifier	Not applicable	
Active substances	Elvitegravir Rilpivirine Cobicistat Emtricitabine Tenofovir alafenamide	
Medicinal Products	Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) as single tablet formulation Emtricitabine/Tenofovir alafenamide (F/TAF) as single tablet formulation Rilpivirine/Emtricitabine/Tenofovir alafenamide (R/F/TAF) as single tablet formulation	
Product reference	EU/1/15/1061/001 EU/1/15/1061/002 EU/1/16/1099/001 EU/1/16/1099/002 EU/1/16/1112/001 EU/1/16/1112/002	

Procedure number	Not applicable
Joint PASS	No
Research Question and Objectives	To assess effectiveness, safety, adherence, resource utilization, and patient reported outcomes for quality of life for the use of E/C/F/TAF, F/TAF and R/F/TAF in routine care.
Country (-ies) of study	Germany
Gilead Study Director / Author/Contact Person:	Name: PPD Telephone: PPD Fax: PPD
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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

(e)CRF	(Electronic) Case report form
ADR	Adverse drug reaction
AE	adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
AMG	Arzneimittelgesetz (German Drug Act)
ART	Anti-retroviral therapy
AST	Aspartate transaminase
BMD	Bone mineral density
BUN	Blood urea nitrogen
CDC	Centers for Disease Control
E/C/F/TAF	Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide
EU	European Union
FDA	(United States) Food and Drug Administration
FDC	Fix-dose combination
Gamma-GT	Gamma-glutamyl transferase
F/TAF	Emtricitabine/Tenofovir alafenamide
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GVP	Good Pharmacovigilance Practices (guidelines for)
HDL	High-density lipoprotein
HIV-1	Human immunodeficiency virus, type 1
ICH	International Conference on Harmonization
IEC	Independent ethics committee
INSTI	Integrase inhibitor
LDL	Low-density lipoprotein
NRTI	Nucleoside reverse-transcriptase inhibitors
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PVE	Pharmacovigilance & Epidemiology
R/F/TAF	Rilpivirine/Emtricitabine/Tenofovir alafenamide
RNA	Ribonucleic acid
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SSR	Special situation report
SUSAR	Serious Unexpected Suspected Adverse Reaction

UACR	Urine albumin/creatinine ratio
UPCR	Urine protein/creatinine ratio
US, USA	United States, United States of America
Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cases	Group of individuals with the condition of interest
Cohort	Group of people characterized by a common experience (eg, occurrence of a specified disease, exposure to a given medication)
Confounder	Extraneous factor that accounts for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders
Confounding by indication	A patient characteristic that is related to the outcome of interest and which influences treatment choice (exposure)
Controls	Group of individuals without the condition of interest but are otherwise similar to cases, or unexposed to or not treated with the agent of interest
Date at which a study commences	Date of the start of data collection
Effect modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier
End of data collection	The date from which the analytical dataset is completely available
Exposure	A variable whose effect is of interest and is being studied
External validity	Whether or not the results from the study can be generalized to other populations
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
Odds	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Prevalence	Proportion of persons with the exposure/outcome at a specific point in time
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Relative Risk (RR)	A general term that can refer to the ratio of 2 risks or the ratio of 2 rates
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Start of data collection	Date from which information on the first study subject is first recorded in the study dataset

3. RESPONSIBLE PARTIES

Table Responsible Parties

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

Gilead Sciences GmbH
Fraunhoferstr. 17
82152 Martinsried
Germany

Title:

Non-Interventional Real-Life Study of Effectiveness, Safety, 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

Rationale and Background:

Background:

HIV-1 infection remains a life-threatening and serious disease of major public health significance. There are now approximately 35 million people infected worldwide. Globally, incidence continues to grow, with 2.2 million people newly infected with HIV-1 in 2011 alone. The prevalence of people living with HIV-1 infection is also increasing. Patients are being diagnosed earlier, and are living longer due to the success of highly active antiretroviral (ARV) therapy (ART).

Morbidity and mortality of HIV-1 infected patients is increasingly driven by non-AIDS associated comorbidities such as kidney, liver, and heart disease. Even with ART, patients with HIV-1 infection experience more age-related comorbidities, such as renal and bone disease, which manifest earlier than their age-matched HIV-uninfected peers. Moreover, the prevalence and incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is expected to rise as the prevalence of HIV-1 infection continues to rise{22553}.

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

Tenofovir (TFV) is a nucleotide analog that inhibits HIV-1 reverse transcription. While tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NRTI for initial therapy, nephrotoxicity is an identified risk, and reductions in bone mineral

density (BMD) have been shown that are larger than those seen with other NRTIs. Tenofovir alafenamide (TAF) is also an oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV DP), and approximately 90% lower circulating levels of TFV relative to TDF at the clinical doses. These characteristics of TAF are associated with effective suppression of viral replication, and an improved tolerability and safety profile of TAF compared to TDF.

Gilead has coformulated TAF with the HIV-1 integrase inhibitor (INSTI) elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the NRTI emtricitabine (FTC; F) into a fixed dose combination (FDC) tablet that is suitable for once-daily use. Furthermore Gilead has coformulated TAF with the NRTI emtricitabine (FTC; F) into a fixed dose combination (FDC) tablet for once-daily use with other ARV agents and coformulated TAF with the HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV; R) and the NRTI emtricitabine (FTC; F) into a fixed dose combination (FDC) tablet for once-daily use. Thus E/C/F/TAF FDC, F/TAF FDC, and R/F/TAF FDC provide potent, convenient, tolerable, and practical regimens for the long-term treatment of patients with HIV-1 infection.

Rationale:

In this non-interventional observational German study we are aiming to describe effectiveness and safety of E/C/F/TAF, F/TAF and R/F/TAF in treatment-naive and treatment-experienced HIV-1 infected adult patients as well as adherence, resource utilization, patient reported outcome data about quality of life, health status, and treatment satisfaction during daily routine use.

Research Question and Objectives:

To describe effectiveness, safety, adherence, resource utilization, and patient reported outcomes of E/C/F/TAF, F/TAF and R/F/TAF use in routine care.

The primary objective of this study is:

- To evaluate HIV-1 RNA and CD4 cell count changes for patients using E/C/F/TAF, F/TAF or R/F/TAF within a time period of 24 months

The secondary objectives of this study are:

- To describe rates adverse drug reactions (ADRs) and serious ADRs (SADRs)
- To describe the motivation for ART initiation in treatment-naïve subjects and factors driving the ART switch to E/C/F/TAF, F/TAF or R/F/TAF in treatment-experienced subjects
- To describe adherence and reasons for E/C/F/TAF, F/TAF or R/F/TAF discontinuation during the study
- To describe physical and mental health-related quality of life, health status, and treatment satisfaction using standardized questionnaires Health Survey Short Form (SF-36), HIV Symptom Index, and HIV Treatment Satisfaction Questionnaire
- To describe health care resource utilization (eg, number of hospitalizations, number of physician visits)

The above parameters will be evaluated in the overall cohort and in various subgroups (eg, treatment-naïve subjects versus treatment-experienced subjects, age (< 50 years, ≥ 50 years), presence of specific comorbidities, sex).

The collection of ADR/SADR reflects the real-life situation, in which the treating physician with best knowledge of his patient assesses whether an observed event could be related to a given treatment. In this way, the study will collect safety data that is reflective of the real-life setting in which it is conducted.

Study Design: Prospective, non-interventional, observational cohort study. Enrolled subjects will be documented using an electronic case report form (eCRF) by the participating sites. Each enrolled subject will be followed for 24 months (irrespective of regimen changes).

Population: The study will enroll 900 adult (age ≥ 18) treatment-naive and treatment-experienced HIV-1 infected subjects initiating treatment with E/C/F/TAF, F/TAF or R/F/TAF in routine care.

E/C/F/TAF arm: 150 treatment-naïve and 150 treatment-experienced subjects, at least 20% of the total 300 subjects will be ≥ 50 years of age at enrollment

F/TAF arm: 150 treatment-naïve and 150 treatment-experienced subjects, all 150 treatment-experienced subjects will be ≥ 50 years of age at enrollment

R/F/TAF arm: 150 treatment-naïve and 150 treatment-experienced

subjects, at least 20% of the total 300 subjects will be ≥ 50 years of age at enrollment

Participating study sites (hospitals and private practitioners) are specialized on treating HIV patients. All study sites are located in Germany.

Variables:

Prior to E/C/F/TAF, F/TAF or R/F/TAF treatment initiation (baseline):

Gender, year of birth, body weight and height

Race

Date of HIV-1 diagnosis

CDC stage

Co-morbidities as available from medical records

Laboratory parameters as available from medical records:

- HIV-1 RNA and limit of detection of the used assay
- CD4 cell count
- AST, ALT, gamma-GT
- Albumin
- Urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR)
- Serum total protein
- Triglycerides
- Total cholesterol
- HDL, LDL
- Serum glucose
- Serum phosphate
- Serum creatinine
- Serum uric acid
- Blood urea nitrogen (BUN)
- Calcium, chloride, magnesium, potassium, sodium
- Urine dipstick parameters (glucose, leukocytes, nitrite, protein, pH, ketone bodies)
- Urine quantitative protein, albumin, and creatinine

- Hematology profile (complete blood count with differential and platelet count)
- Bone mineral density

History of anti-retroviral therapy

CD4 nadir

Blood pressure

Historic serum creatinine, quantitative urine creatinine, quantitative urine albumin, quantitative urine protein, and body weight within the last 2 years prior to E/C/F/TAF, F/TAF or R/F/TAF treatment initiation

Co-medications as available from medical records

Resistance status as available from medical records

Motivation for ART initiation in treatment-naïve subjects and factors driving the ART switch to E/C/F/TAF, F/TAF or R/F/TAF in treatment-experienced subjects

Cardiovascular and renal risk factors (family history of angina/heart attack, smoking status, intravenous drug use, prior use of atazanavir, tenofovir disoproxil fumarate (TDF), indinavir or lopinavir)

HIV Symptom Index

HIV Treatment Satisfaction Questionnaire (only for treatment-experienced subjects)

SF-36

During follow-up (approximately 3 months, 6 months, 12 months, 18 months, and 24 months after starting E/C/F/TAF, F/TAF or R/F/TAF therapy):

Anti-retroviral therapy adherence (VAS scale and number of missed doses during the last 4 and 30 days)

In case of E/C/F/TAF, F/TAF or R/F/TAF discontinuation: date and reason for discontinuation and new ART (patients will be documented up to 24 months even after therapy switch)

Changes in co-medications as available from medical records

Body weight

Laboratory parameters: see baseline

New AIDS-defining events (CDC class C, excluding CD4 cell count < 200 cells/µL)

New co-morbidities/co-infections

ADRs and SADRs

Special situations reports as appropriate

Only approximately 12 months and 24 months after starting E/C/F/TAF, F/TAF or R/F/TAF therapy:
Blood pressure and cardiovascular and renal risk factors (eg, family history of angina/heart attack, smoking status, intravenous drug use)

HIV Symptom Index

HIV Treatment Satisfaction Questionnaire (only for treatment-experienced subjects approximately 3 months, 6 months, and 12 months after starting E/C/F/TAF, F/TAF or R/F/TAF therapy)

SF-36

In case of virologic failure: resistance status as available

Health care resource utilization (number and duration of hospitalizations, number of appointments with HIV-treating physician and with other physician types)

Data Sources: Collection of routine visit data and questionnaires via eCRF

Study Size: The study will enroll 900 adult (age ≥ 18) treatment-naive and treatment-experienced HIV-1 infected subjects initiating treatment with E/C/F/TAF, F/TAF or R/F/TAF in routine care. Each study arm will enroll 150 treatment-naive and 150 treatment-experienced subjects.

Data Analysis:	For categorical variables, numbers and percentages of patients will be reported including according 95% confidence intervals. For continuous variables, mean, standard deviation (SD), minimum, first and third quartile (Q1, Q3), median, and maximum 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 enrollment). The questionnaires scores will be calculated according to the algorithms elaborated for these questionnaires. Visit windows will be defined (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. P-values and/or confidence intervals (95% two-sided) will be calculated when considered relevant. Multivariate analyses will be conducted to compare the treatment-naïve and non-naïve treatment groups in each arm to estimate adjusted rates and proportions. Longitudinal analysis will be done using mixed models.
Milestones:	Start of data collection : January 2016 End of Data collection: 4th quarter 2019 Final Study report: 3rd quarter 2020

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

5. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	14 April 2016	various	Amendment	Adding 300 subjects treated with F/TAF and 300 subjects treated with R/F/TAF, adding blood pressure, CD4 nadir, adding historic creatinine and urine parameters, allowing full 24 months documentation even if subjects switch therapies, adding cardiovascular and renal risk factors, changes to Medical Monitor, updated study timelines
2	12 April 2019	various	Amendment	Addition of product references, update of MAH, update of EU QPPV contact details, update of definitions of special situations

- **Protocol Modifications**

Protocol modifications may only be made by Gilead. Approval must be obtained before changes can be implemented.

6. MILESTONES

Milestone	Planned Date
Start of data collection	4th Jan 2016
End of data collection	4th quarter 2019
Registration in the EU PAS register	5th Oct 2015
Final report of study results	3rd quarter 2020

7. RATIONALE AND BACKGROUND

7.1. Rationale for the Current Study

HIV-1 infection remains a life-threatening and serious disease of major public health significance. There are now approximately 35 million people infected worldwide {27071}. Globally, incidence continues to grow, with 2.2 million people newly infected with HIV-1 in 2011 alone. The prevalence of people living with HIV-1 infection is also increasing. Patients are being diagnosed earlier, and are living longer due to the success of highly active antiretroviral (ARV) therapy (ART).

Morbidity and mortality for HIV-1 infected patients is increasingly driven by non-AIDS associated comorbidities such as kidney, liver, and heart disease {19947}, {19948}, {22552}. Even with ART, patients with HIV-1 infection experience more age-related comorbidities, such as renal and bone disease, which manifest earlier than their age-matched HIV-uninfected peers {19946}. Moreover, the prevalence and incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is expected to rise as the prevalence of HIV-1 infection continues to rise {22553}.

Current treatment guidelines recommend that patients initiate therapy earlier, thereby requiring lifelong treatment, potentially for 50 years or more {19967}. Accordingly, there is a need for new HIV therapies that improve on the current standard of care so that lifelong ART is more effective, more tolerable, and safer for patients.

Tenofovir (TFV) is a nucleotide analog that inhibits HIV-1 reverse transcription. While tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NRTI for initial therapy, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs. Tenofovir alafenamide (TAF) is also an oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV DP), and results in approximately 90% lower circulating levels of TFV relative to TDF at the clinical doses. These characteristics of TAF are associated with effective suppression of viral replication, and an improved tolerability and safety profile of TAF compared to TDF.

Gilead has coformulated TAF with the HIV-1 INSTI elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the NRTI emtricitabine (FTC; F) into an FDC tablet that is suitable for once-daily use. Thus E/C/F/TAF FDC provide**s** a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV-1 infection. Findings from two randomized, double-blind, Phase 3 trials of TAF versus TDF, both coformulated with elvitegravir, cobicistat, and emtricitabine, demonstrated non-inferior efficacy of TAF versus TDF, with a significantly improved effect of TAF compared to TDF on eGFR, proteinuria, albuminuria, and bone mineral density {34827}.

Furthermore Gilead has coformulated TAF with the NRTI emtricitabine (FTC; F) into a fixed dose combination (FDC) tablet for once daily use (in combination with other ARV agents) and

coformulated TAF with the HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV; R) and the NRTI emtricitabine (FTC; F) into a fixed dose combination (FDC) tablet for once daily use.

In this non-interventional observational German study we are aiming to describe effectiveness and safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) or Emtricitabine/Tenofovir alafenamide (F/TAF) or Rilpivirine/Emtricitabine/Tenofovir alafenamide (R/F/TAF) in treatment-naive and treatment-experienced HIV-1 infected adult patients as well as adherence, resource utilization, patient reported outcome data about quality of life, health status and treatment satisfaction of E/C/F/TAF, F/TAF or R/F/TAF treated patients during daily routine use.

8. RESEARCH QUESTIONS AND OBJECTIVES

To describe effectiveness, safety, adherence, resource utilization, and patient reported outcomes of E/C/F/TAF, F/TAF or R/F/TAF use in routine care.

The primary objective of this study is as follows:

- To evaluate HIV-1 RNA and CD4 cell count changes for patients using E/C/F/TAF, F/TAF or R/F/TAF within a time period of 24 months

The secondary objectives of this study are as follows:

- To describe rates of ADRs/SADRs for E/C/F/TAF, F/TAF and R/F/TAF
- To describe the motivation for ART initiation in treatment-naïve subjects (eg, early treatment according to guidelines, treatment as prevention, patient wish) and factors driving the ART switch to E/C/F/TAF, F/T/AF or R/F/TAF in treatment-experienced subjects (eg, simplification of ART, patient preference, side effects of current ART)
- To describe adherence (number of missed E/C/F/TAF, F/T/AF or R/F/TAF doses) and reasons for E/C/F/TAF, F/TAF or R/F/TAF discontinuation during the study
- To describe physical and mental health-related quality of life, health status, and treatment satisfaction using standardized questionnaires (Health Survey Short Form (SF-36), HIV Symptom Index, and HIV Treatment Satisfaction Questionnaire (only for treatment-experienced subjects)
- To describe health care resource utilization (eg, number of hospitalizations, number of physician visits)

The above parameters will be evaluated separately per treatment arm and in various subgroups (eg, treatment-naïve subjects versus treatment-experienced subjects, age (< 50 years, ≥ 50 years), presence of specific comorbidities, sex).

The collection of ADR/SADR reflects the real-life situation, in which the treating physician with best knowledge of his patient assesses whether an observed event could be related to a given treatment. In this way, the study will collect safety data that is reflective of the real-life setting in which it is conducted.

9. RESEARCH METHODS

9.1. Study Design

This non-interventional study does not influence the treatment decisions made by the participating physicians. Subjects can be enrolled in this study after the physician has decided to treat a specific subject with E/C/F/TAF, F/TAF or R/F/TAF in accordance with the approved respective SmPCs. All treatments will be prescribed according to local treatment guidelines and/or routine clinical practice. The treating physician will make all treatment decisions and will provide prescriptions for his/her patients. There will be no study-specific procedures.

The study is designed as a multicenter, non-interventional observational cohort study, in accordance with the German Drug Act (§63f AMG). It is planned to enrol a total of 900 adult (age ≥ 18) HIV-1 infected subjects initiating treatment with E/C/F/TAF (n=300), F/TAF (n=300) or R/F/TAF (n=300) in routine care. The study will enroll approximately 150 treatment-naïve and 150 treatment-experienced subjects in each arm.

Data collection will be performed by manual entry of data from the patient's medical file and questionnaires to a computer-based electronic case report form (eCRF). No patient initials will be included.

Data will be prospectively collected for each enrolled subject for approximately 24 months. In case of E/C/F/TAF, F/TAF or R/F/TAF discontinuation the date of discontinuation, reasons for discontinuation (eg, patient wish, adverse reaction, insufficient efficacy) and subject's new ART will be collected. The subject will remain in the study and will be continuously documented with the new ART until premature end of documentation (eg, due to lost to follow up) or until reaching the defined end of documentation approximately 24 month after enrollment.

9.2. Setting

9.2.1. Study Time Period

Data will be documented at the following time points:

Baseline (start of E/C/F/TAF, F/TAF or R/F/TAF therapy) – at baseline the historic data on serum creatinine, quantitative urine parameters and body weight will be documented.

Follow-up: approximately 3 months, 6 months, 12 months, 18 months, and 24 months after E/C/F/TAF, F/TAF or R/F/TAF therapy initiation (baseline) according to clinical practice.

9.2.2. Population

The study will enroll approximately 900 adult (age ≥ 18) treatment-naïve and treatment-experienced HIV-1 infected subjects initiating treatment with E/C/F/TAF, F/TAF or R/F/TAF (300 subjects per arm) in accordance with the respective SmPC in routine care.

To evenly represent treatment-naive and treatment-experienced patients the study will enroll in each arm approximately 150 treatment-naive and 150 treatment-experienced subjects.

The total study size of 300 subjects per arm has been chosen to allow the evaluation of collected parameters also within several subgroups per arm (eg, treatment-naïve subjects versus treatment-experienced subjects, age (< 50 years, ≥ 50 years), presence of specific comorbidities, sex), assuming that such subgroups are represented in substantial numbers. Details of subgroup definition will be documented in the Statistical Analysis Plan.

Participating study sites (hospitals and private practitioners) are specialized on treating HIV patients. All study sites are located in Germany.

9.2.3. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for documentation in this study:

9.2.3.1. Arm 1 (E/C/F/TAF)

- HIV-1 infection
- Signed informed consent
- ≥ 18 years old
- Initiating treatment with E/C/F/TAF in accordance with the E/C/F/TAF SmPC

9.2.3.2. Arm 2 (F/TAF)

- HIV-1 infection
- Signed informed consent
- treatment-naïve subjects ≥ 18 years old
- treatment-experienced subjects ≥ 50 years old
- Initiating treatment with F/TAF (in combination with other ARV medication) in accordance with the F/TAF SmPC

9.2.3.3. Arm 3 (R/F/TAF)

- HIV-1 infection
- Signed informed consent
- ≥ 18 years old
- Initiating treatment with R/F/TAF in accordance with the R/F/TAF SmPC

9.3. Variables

Prior to E/C/F/TAF, F/TAF or R/F/TAF therapy initiation (baseline):

Gender, year of birth, body weight and height

Race

Date of HIV-1 diagnosis

CDC stage

Co-morbidities as available from medical records (eg, cardiovascular diseases, asthma, COPD, hypertension, hyperlipidemia, neuropsychiatric disorders, osteopathic disorder, diabetes mellitus, nephropathy, chronic hepatitis B, chronic hepatitis C)

Laboratory parameters as available from medical records:

- HIV-1 RNA and limit of detection of the used assay
- CD4 cell count
- AST, ALT, gamma-GT
- Albumin
- Urine albumin/creatinine ratio (UACR), urine protein/creatinine ratio (UPCR)
- Serum total protein
- Triglycerides
- Total cholesterol

- HDL, LDL
- Serum glucose
- Serum phosphate
- Serum creatinine
- Serum uric acid
- Blood urea nitrogen (BUN)
- Calcium, chloride, magnesium, potassium, sodium
- Urine dipstick parameters (glucose, leukocytes, nitrite, protein, pH, ketone bodies)
- Urine quantitative protein, albumin, and creatinine
- Hematology profile (complete blood count with differential and platelet count)
- Bone mineral density

History of anti-retroviral therapy

CD4 nadir

Blood pressure

Historic serum creatinine, quantitative urine creatinine, quantitative urine albumin, quantitative urine protein, and body weight within the last 2 years prior to E/C/F/TAF, F/TAF or R/F/TAF treatment initiation

Co-medications as available from medical records

Resistance status as available from medical records

Motivation for ART initiation in treatment-naïve subjects (eg, early treatment according to guidelines, treatment as prevention, patient wish) and factors driving the ART switch to E/C/F/TAF, F/TAF, or R/F/TAF in treatment-experienced subjects (eg, simplification of ART, patient preference, side effects of current ART)

Cardiovascular and renal risk factors (family history of angina/heart attack, smoking status, intravenous drug use, prior use of atazanvir, tenofovir disoproxil fumarat (TDF), indinavir or lopinavir)

HIV Symptom Index

HIV Treatment Satisfaction Questionnaire (only for treatment-experienced subjects)

SF-36

During follow-up (approximately 3 months, 6 months, 12 months,18 months, and 24 months after starting E/C/F/TAF, F/TAF, or R/F/TAF therapy):

Anti-retroviral therapy adherence (VAS scale and number of missed doses during the last 4 and 30 days). The questionnaire with the VAS scale and the questions about the missed doses will be handed to the patients, filled in by the patients and the patient will put the questionnaire into an envelope. Only the closed envelope will be returned to the site staff. The closed envelope which only contains the subject number as identifier will be sent by the site to the CRO for data entry. The site will not know any information the patient entered into the questionnaire.

In case of E/C/F/TAF, F/TAF or R/F/TAF discontinuation: date of discontinuation, reasons for discontinuation (eg, patient wish, adverse reaction, insufficient efficacy) and subject's new ART. The subject will remain in the study and will be continuously documented with the new ART until premature end of documentation (eg, due to lost to follow up) or until reaching the defined end of documentation approximately 24 month after enrollment.

Changes in co-medications as available from medical records

Laboratory parameters: see baseline

New AIDS-defining events (CDC class C, excluding CD4 cell count < 200 cells/µL)

Changes in co-morbidities/co-infections

ADRs and SADRs for all ARV drugs used in the study

Special situations reports as appropriate

Only approximately 12 months and 24 months after starting E/C/F/TAF, F/TAF, or R/F/TAF therapy: Blood pressure and cardiovascular and renal risk factors (eg, family history of angina/heart attack, smoking status, intravenous drug use)

HIV Symptom Index

HIV Treatment Satisfaction Questionnaire (only for treatment experienced subjects and only approximately 3 months, 6 months and 12 months after E/C/F/TAF, F/TAF or R/F/TAF therapy initiation)

SF-36

In case of virologic failure: resistance status as available

Resource Utilization (number and duration of hospitalizations, number of appointments with HIV-treating physician and with other physician types between the documented visits)

9.4. Health Care Resource Utilization Data Sources

Subjects will receive a questionnaire on which they will be asked to document any hospitalizations (number and durations) and number of appointments with other physician types (eg, renal or bone specialists).

The site will document the number of visits of the subject at the site between the visits documented in the eCRF.

9.5. Study Size

Previous studies showed percentages of viral suppression (< 50 copies/mL):

Treatment	after 48 weeks	after 96 weeks
E/C/F/TAF	92% treatment-naïve {34827} 97% treatment-experienced {38028}	87% treatment-naïve {39846} not available yet
F/TAF	94% treatment-experienced {39786}	not available yet
R/F/TAF	90% treatment-naïve* {20441}	84% treatment-naïve* {20441}

* these data are estimates for R/F/TAF based on data for Eviplera (rilpivirine/emtricitabine/tenofovir disoproxil fumarate): viral suppression rates for treatment-naïve patients with baseline viral load of ≤ 100,000 copies/mL after 48 (89.6%) and 96 weeks (83.7%) as R/F/TAF data are not available yet

Due to missing data rates after 96 weeks compared to 48 seem to be decreasing with less pronounced differences between treatment-naïve and treatment-experienced patients.

A sample size of 300 subjects per arm will provide 80% power to detect a difference in the treatment-naïve and treatment-experienced group means when the expected effect size is 0.26.

9.6. Data Management

The study will use an eCRF and all users will receive specific access codes to enable them to enter their data. The electronic data entry system will contain automatic checks for data completeness and to identify inconsistent data. Participating sites will enter available data from subject's medical records into the eCRF.

9.7. Data Analysis

Data will be analysed per arm. 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, and maximum will be calculated, together with the total number of observations and the number of missing values.

Missing values will not be imputed but classified as an own category to keep them for multivariate analyses.

Descriptive and multivariate data analysis will be done per treatment arm. Some cross arm comparisons according to sub groups (age ≥ 50 years) might be conducted depending on group size.

Descriptive statistics will summarize demographics and baseline characteristics (including the type of regimen at enrollment).

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

Visit windows will be defined (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. P-values and/or confidence intervals (95% two-sided) will be calculated when considered relevant.

Multivariate analyses per arm (logistic regression) will be conducted to compare treatment naïve and non-naïve treatment groups adjusting for covariates. Longitudinal analysis will be done using mixed models.

Demographics and baseline measures would be potential confounders/effect modifiers for multivariate analyses. Confounders/effect modifiers and respective adjustments will be addressed in the Statistical Analysis Plan.

ADRs/SADRs and comorbidities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

9.8. Quality Control

The electronic data entry system will contain automatic checks for data completeness and to identify inconsistent data and respective queries will be generated when necessary. Data and queries will be remotely monitored for consistency and completeness.

9.9. Limitations of the Research Methods

As documentation of study variables is not obligatory missing data of unpredictable extent can occur.

Depending on the selection of sites selection bias cannot be excluded.

9.10. Other Aspects

9.10.1. Joint Investigator/Sponsor Responsibilities

9.10.1.1. Access to Information for Monitoring

The study monitor is responsible for routine remote review of the eCRFs at regular intervals throughout the study to verify the completeness and consistency of the data being entered on the forms.

Onsite monitoring visits can also be done at selected sites. For such onsite monitoring visits the investigator will provide the study monitor with access to any subject records needed to verify the entries in the eCRF. 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 the sponsor 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 IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

Gilead will ensure that this study is conducted in accordance with the principles of the International Conference on Harmonization (ICH) Pharmacovigilance Planning E2E guidelines, and with the laws and regulations of the country in which the research is conducted.

The investigator will conduct this study in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. Independent Ethics Committee (IEC) Review

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

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

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 consent form for documenting written informed consent. Each informed consent form will be appropriately signed and dated by the subject or the subject's legally authorized representative 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 subjects' 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 will collect related adverse events (also known as adverse drug reactions, ADRs), related serious adverse events (also known as serious adverse drug reactions, SADRs), and special situation reports (SSRs); general definitions and means of reporting of subsets of events are described hereafter. ADRs, SADRs and SSRs will be collected for all ARV drugs used during the study.

The collection of ADR/SADR reflects the real life situation, in which the treating physician with best knowledge of his patient assesses whether an observed event could be related to a given treatment. In this way, the study will collect safety data that is reflective of the real life setting in which it is conducted.

11.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a clinical study subject 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 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.

- Situations where an untoward medical occurrence has not occurred (eg, 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).

11.1.1. Adverse Drug Reactions /Serious 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 also arise from medication errors, uses outside what is foreseen in the protocol or in prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure. ADRs which meet the criteria for a serious adverse event (see below) are defined as **serious adverse drug reaction** (SADR).

11.1.2. 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 subject 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 subject 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.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. Therefore, if death occurred, the event that led to death needs to be reported as an SAE.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, is life-threatening, or meets any of the other definitions of an SAE, then it is an SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis (and not the individual signs/symptoms) should be documented as the AE and/or SAE.

A distinction should be drawn between seriousness and severity of AEs. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed for severity. An AE is defined as "serious" when it meets one of the predefined outcomes described above.

11.2. Assessment of Adverse Events and Serious Adverse Events

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

11.2.1. Assessment of Causality for Study Drugs

Study drugs in this context include E/C/F/TAF, F/TAF, R/F/TAF or any other Gilead or non-Gilead ARV used during the study. The investigator or qualified sub-investigator is responsible for assessing the relationship to drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the event has an etiology other than the drug.
- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

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

11.3. Special Situations Reports

11.3.1. Definitions of Special Situations

Special situation reports (SSR) for study drugs (study drugs in this context include E/C/F/TAF, F/TAF, R/F/TAF or any other Gilead or non-Gilead ARV used during the study) include reports of abuse, drug interactions, counterfeit or falsified medicine, exposure via breastfeeding, lack of effect, medication error, misuse, occupational exposure, off-label use, overdose, pregnancy, product complaints, transmission of infectious agents via the product, and unexpected benefit. Definitions are examples are provided below:

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.
- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.
- Counterfeit or falsified medicine: Any medicinal product with a false representation of: a) its identity, b) its source, or c) its history.
- Exposure via breastfeeding: Reports of any exposure to a medicinal product during breastfeeding.

- Lack of effect: A report of a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.

- Medication error: Any unintentional error in the prescribing, dispensing, preparation for administration or administration of a medicinal product while the medication is in the control of a healthcare professional, patient or consumer.

- Misuse: Use of a medicinal product that is intentional and inappropriate not in accordance with its authorized product information.

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

- Off-label use: Where a medicinal product is intentionally used 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).

- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose in the product labelling.

- Pregnancy reports (maternal pregnancy and partner pregnancy): Reports of pregnancy following maternal or paternal exposure to the product.

- Product complaint: Complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

- Unexpected benefits: An unintended therapeutic effect where the results are judged to be desirable and beneficial.

- Transmission of infectious agents via the product: Any suspected transmission of an infected agent through a Gilead medicinal product.

11.3.2. Instructions for Reporting Special Situations

11.3.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur while exposed to the study drugs (study drugs in this context include E/C/F/TAF, F/TAF, R/F/TAF or any other Gilead or non-Gilead ARV used during the study) and the outcome of the pregnancy are to be reported to Gilead PVE using the pregnancy report form within 3 calender days of becoming aware of the pregnancy.

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

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 3 calender days as an SAE. 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 11.4. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The outcome should be reported to Gilead PVE using the pregnancy outcome report form.

11.4. Investigator Requirements and Instructions for Reporting ADRs, SADRs, and SSRs to Gilead

All fatal events (regardless of causality) and all related non-serious AEs (ie, ADRs), and related SAEs (ie, SADRs) occurring after the subject consents to participate in the study (ie, signing informed consent) until study completion, loss to follow-up, withdrawal of consent, death or 4 weeks after discontinuation of study drugs (study drugs in this context include E/C/F/TAF, F/TAF, R/F/TAF or any other Gilead or non-Gilead ARV used during the study), whichever comes first, will be reported on the AE/SAE electronic case report form (eCRF). Special situations reports (SSRs) will be recorded on the Gilead Special Situation Report Form. Pregnancy reports will be recorded on the pregnancy eCRF.

Timelines for reporting ADRs, SADRs, and SSRs to Gilead are as follows:

- Within 3 calendar days of knowledge of all fatal events and SADRs
- Within 30 calendar days of knowledge of the ADRs and SSRs

Details of the methods for reporting ADRs, SADRs, and SSRs to Gilead PVE will be described in the CRF completion Guidelines.

If reporting of events is by electronic submission via eCRF, this method must always be used unless the eCRF system is not functioning at which time site personnel should record details of the ADR, SADR, or SSR on the appropriate paper reporting form (the *Non-Interventional Study AE/SAE Report Form* or the *Non-Interventional Study Special Situation Report Form*) and submitted by fax or e-mail, within the timelines given above, to:

PPD

Fax: PPD

11.5. Gilead Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all ADRs and SADRs or suspected unexpected serious adverse reactions (SUSARs) for Gilead drugs as determined by country-specific legislation. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for ADRs and SADRs for Gilead drugs will be determined by Gilead using reference safety information specified in the product label.

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

A clinical study report (CSR) 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 Good Pharmacovigilance Practices (GVP) Module VIII. Note that an abbreviated report may be prepared in certain cases. The final CSR will be submitted within 12 months of study completion.

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14. APPENDICES

Annex 1. Study Acknowledgement

Annex 2. ENCePP Checklist for Study Protocols

Annex 1. Study Acknowledgement

GILEAD SCIENCES GMBH
FRAUNHOFERSTR. 17
82152 MARTINSRIED, GERMANY

Non-Interventional Real-Life Study of Effectiveness, Safety, 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

Original – 24 SEP 2015
Amendment 1 – 14 APR 2016
Amendment 2 – 12 April 2019

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

PPD

Gilead Study Director (Printed)
Author

PPD

Signature

April - 18 - 2019

Date

PPD

Gilead EU QPPV (Printed)

PPD

18 Apr 2019

Date

Annex 2. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Doc.Ref. EMA/540136/2009

Study title:
Non-Interventional Real-Life Study of Effectiveness, Safety, 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

Study reference number:
GS-DE-292-1912

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	16
1.1.2 End of data collection[2]	☒	☐	☐	16
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	16
1.1.6 Final report of study results.	☒	☐	☐	16

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	17, 18
2.1.2 The objective(s) of the study?	☒	☐	☐	19
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20, 21
2.1.4 Which formal 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:

No formal hypothesis testing, comparisons between various subgroups will be done using logistic or longitudinal models.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	20
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	20, 21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	20
4.2.2 Age and sex?	☒	☐	☐	21, 22
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	21, 22
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	

Comments:

Subjects will be enrolled by sites as E/C/F/TAF, F/TAF or R/F/TAF is initiated in a patient and this patient consents to participate. 900 subjects will be enrolled and each subject documented for max. 24 months. No limitations in regard to sex, country of origin, or co-morbidities.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	20
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the	☒	☐	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
outcome occurred, use of validation sub-study)				
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	20
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	21, 22
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	24

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	26

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	26
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	26

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	20
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	22-25

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.3 Covariates?	☒	☐	☐	22-24
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	20
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	22-24
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	22-24
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	26
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	26
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

linkage between data sources not applicable

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	25

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	25
10.3 Are descriptive analyses included?	☒	☐	☐	25
10.4 Are stratified analyses included?	☒	☐	☐	21
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Potential confounders/effect modifiers for multivariate analyses and respective adjustments will be addressed in the Statistical Analysis Plan

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25, 26
11.3 Are methods of quality assurance described?	☒	☐	☐	26
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	25, 26
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	25
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20-22
12.3 Does the protocol address other limitations?	☒	☐	☐	27

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	27

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	27

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	35
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

Name of the main author of the protocol: PPD

Date: 04/18/2019

Signature: PPD