NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	A Prospective, Observational Drug Utilization Study of Cobicistat in Adults with HIV-1 Infection
Protocol ID	GS-US-216-1230
Protocol Version/Date:	Original: 12 September 2014
EU PAS Register No	To be registered prior to start of data collection
Clinical Trials.gov Identifier	NA
Active substance	Cobicistat 150mg
Medicinal Product	Tybost®
Joint PASS	No
Research Question and Objectives	To investigate the effectiveness of routine risk minimization measures by determining the rate of off-label use to boost protease inhibitors other than atazanavir or darunavir once-daily, the rate of concurrent use with contraindicated medications, the outcomes of such use, and to obtain information on potential drug interactions with COBI to investigate the effectiveness of these routine risk minimization measures by determining the rate of off-label use and concurrent use with contraindicated medications, the outcomes of such use, and to obtain information on potential drug interactions with COBI
Country (-ies) of study	Europe (anticipated to include Austria, Germany, the UK, Denmark, Ireland, Finland, Norway, Sweden, the Netherlands, Belgium, Iceland, and Spain) and Switzerland.
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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
ART	Antiretroviral therapy
AST, ALT	Asparatate aminotransferase, alanine aminotransferase
ATV	Atazanavir
CI	Confidence interval
COBI	Cobicistat, Tybost®
CPT	Child Pugh Turcotte
CRF/eCRF	Case report form/Electronic case report form
DRV	Darunavir
DSPH	Drug Safety & Public Health
DUS	Drug utilization study
EMA	European Medicines Agency
EU	European Union
FDA	(United States) Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices (guidelines for)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IRB	Institutional review board
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PI	Protease inhibitor
RMP	Risk Management Plan
RTV	Ritonavir
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SSR	Special situation report
SUSAR	Serious Unexpected Suspected Adverse Reaction

1. RESPONSIBLE PARTIES

Table of Responsible Parties

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

Gilead Sciences International, Ltd.
Cambridge, CB21 6GT
United Kingdom

Title:	A Prospective, Observational Drug Utilization Study of Cobicistat in Adults with HIV-1 Infection
Rationale and Background:	In the Tybost® (cobicistat; COBI) Summary of Product Characteristics (SmPC), COBI is indicated as a pharmacokinetic enhancer of atazanavir (ATV) 300 mg once daily or darunavir (DRV) 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults. Tybost is intended for once daily dosing of HIV-1-infected subjects for whom a regimen containing either ATV or DRV is considered to be suitable. In the Tybost SmPC, co-administration with the following drugs is contraindicated: • Drugs with a narrow therapeutic index that are highly dependent on CYP3A for their clearance as their plasma concentration may be increased when co-administered with COBI, which may result in serious and/or life-threatening reactions. • Potent CYP3A inducers as they may significantly decrease the plasma concentrations of COBI and the COBI-boosted antiretroviral (ARV) agent, which may result in loss of therapeutic effect and development of resistance to the COBI-boosted ARV agent. Areas that have been identified as important potential risks in the COBI European Union (EU) Risk Management Plan (RMP) are (a) Concurrent use of drugs whose co-administration with COBI is contraindicated; and (b) Off-label use of COBI to boost protease inhibitors other than ATV or DRV once-daily. In addition, information on drug interactions with COBI has been identified as an area of missing information. Routine risk minimization measures by way of information in the SmPC and Package Leaflet are in place in order to advise physicians and patients to prevent the important potential risks for COBI. As part of the COBI EU-RMP, this observational drug utilization study is planned 1) to investigate the effectiveness of these routine risk minimization measures by determining the rate of use to boost PIs other than ATV or DRV once-daily and concurrent use with contraindicated medications, and the outcomes of such use, and 2) to obtain information on potential drug interactions with COBI.

Research Question and Objectives:	This observational, prospective drug utilization study will evaluate compliance with routine risk minimization measures for COBI, and provide information on drug interactions with COBI. In HIV-1 infected patients ≥ 18 years of age who are prescribed COBI, the objectives of this study are as follows: Primary: To assess the rate of off-label use of COBI to boost PIs other than ATV or DRV once-daily To assess the rate of concurrent use of COBI with contraindicated medications Secondary: To describe outcomes, where possible, following either off-label use of COBI to boost PIs other than ATV or DRV once-daily, or concurrent use of COBI with contraindicated medications To describe rate of use of identified and potential interacting medications with COBI, and where possible, the rate of suspected drug interactions during use of COBI and the rate of related AEs during use of COBI with identified and potential interacting medications To describe the frequency of COBI utilization by patients with baseline conditions, including severe hepatic impairment, renal impairment, or cardiac conduction disorders, and outcomes of such use where possible Further details are provided in the body of this protocol.
Study Design:	Prospective observational study of HIV-1 infected adults taking COBI.
Population:	The study population will be comprised of HIV-1 infected adults aged ≥ 18 years who initiate treatment with COBI and are patients in clinics across several European countries (anticipated to include: Austria, Germany, the UK, Denmark, Ireland, Finland, Norway, Sweden, the Netherlands, Belgium, Iceland, and Spain) and Switzerland.

Variables:	The following variables will be collected on an electronic case report form (eCRF) at enrollment: • demographic factors (month and year of birth, sex at birth, ethnic origin, geographic region/country) • body size measures (weight, height) • date of HIV-1 diagnosis • date of enrollment • date of COBI initiation • HBV/HCV co-infection (yes/no) and diagnosis date • prior renal disease (yes/no) and diagnosis date • prior hepatic impairment (Child-Pugh class C, yes/no) and diagnosis date • prior cardiac conduction disorder (yes/no) and diagnosis date • medications (including COBI and other antiretroviral therapy) taken in the period from COBI initiation to enrollment, including such details as dose and dates of initiation and discontinuation. Should include all concurrent medications, including self-prescribed over-the-counter and herbal products • available laboratory values and date(s) of test(s), including: • most recent bilirubin • most recent and nadir CD4 count • most recent HIV viral load • most recent AST level • most recent ALT level • most recent serum creatinine level

	The following variables will be collected on an eCRF during follow-up from medical records of routine visits to the clinic for up to three years following study entry: • medications (including COBI and other antiretroviral therapy) taken since enrollment, including such details as dose and dates of initiation and discontinuation. Should include all concurrent medications, including self-prescribed over-the-counter and herbal products. • available laboratory values and date(s) of test(s), including: — CD4 count — HIV viral load • Reason and date of COBI discontinuation, if applicable The following variables will be collected on an eCRF throughout the follow-up period for each patient, and up to 30 days after end of treatment, if applicable: • Physician reports of related adverse events (AEs)/serious adverse events (SAEs), and date(s) of onset • Special situation reports (SSRs), including physician suspected lack of drug effect, and date(s) of onset • Physician reports of suspected drug interactions and date(s) of onset Data collection stop date
Data Sources:	The data source for this study is a prospective cohort of HIV-1 positive subjects treated in European clinics. This study will be conducted utilizing a common case report form and central data coordination center. Final datasets will be structured in a common data model structure for further manipulation and analysis.
Study Size:	The expected sample size of 500 subjects is determined by ability to address the primary objectives of this descriptive study, which are dependent on COBI utilization. The total duration of this study is 3 years, with recruitment during the first 2 years. With a total of 500 subjects taking COBI and assuming an even rate of recruitment and a 20% annual loss to follow-up (including discontinuation of COBI), this yields a total of 810 person-years of COBI exposure. With 810 years of person time, event rates as low as 0.37 per 100 person years can be distinguished from zero with 95% confidence.

	For comparison, rates of use of the contra-indicated medications triazolam, sildenafil citrate (for pulmonary arterial hypertension), and rifampin while on RTV, were 0.6, 0.4, and 0.4 per 100 person years, respectively, in an *ad hoc* analysis of US commercial medical claims data (IMS Pharmetrics). These medications are contra-indicated for both RTV and COBI. Comparable EU datasets that include large numbers of HIV-1 infected patients, with detailed prescribing data at the level of individual medications, are not available; however, there is no evidence to suggest that rates of contra-indicated medication use among RTV users would be markedly different in the EU vs. the US. Expected rates of the potential off-label use of COBI to boost PIs other than ATV or DRV are unknown and cannot realistically be approximated using data for RTV, as RTV is indicated for boosting many PIs in addition to ATV and DRV. However, applying the rule of three, with 810 person years, the study will be able to observe one such erroneous combination event with 95% confidence if it occurs at a rate of 0.37 per 100 person years. In summary, the proposed sample size will yield adequate power to detect rates of primary outcome events as low as 0.37 per 100 person years with 95% confidence.
Data Analysis:	All statistical summaries and analyses will be conducted using SAS® software (SAS Institute, Cary, North Carolina, USA) or other standard software tools including STATA® (StataCorp LP, College Station, Texas, USA). Primary analysis: • Rates and 95% confidence intervals (CIs) of both (a) off label use of COBI with protease inhibitors other than ATV or DRV once-daily, and (b) concomitant use of COBI with contraindicated medications, will be determined using Poisson regression models, taking into account person time of COBI exposure. Secondary analysis: • Dependent on the frequency of off-label use to boost PIs other than ATV or DRV and concomitant use with contraindicated medications multivariable Poisson regression models that take into account person-time of exposure will be used to assess the rate of related AEs, SSRs, and suspected lack of effect, associated with either (a) off label use with PIs other than ATV or DRV once-daily, or (b) concomitant use of contraindicated medications. • Poisson regression models that take into account person-time of exposure will be used to describe the rate of physician reports of suspected drug interactions and the rate of new prescriptions of identified or potential interacting medications during COBI use. Dependent on the amount of joint exposure to COBI and identified or potential interacting medications, Poisson regression models will also be used to describe the rate of related AEs during such joint exposure.

	• The frequency of COBI utilization by patients with specific pre-existing conditions will be assessed using observed numbers and percentages. Where possible, rates of related AEs and SSRs among these patient subgroups will be described using Poisson regression models.
Milestones:	This study is expected to take 3 years, including 2 years of subject recruitment and between 1 and 3 years of follow-up data collection per patient. Start of recruitment/data collection: Q1 2015 End of recruitment: Q4 2016 End of data collection: Q4 2017 Final report: Q1 2018

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.

3. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
NA	NA	NA	NA	NA

- **Protocol Modifications**

Protocol medications may only be made by Gilead Sciences International Ltd. Approval must be obtained before changes can be implemented.

4. MILESTONES

This study is expected to take 3 years, including 2 years of subject recruitment and between 1 and 3 years of follow-up data collection. Registration in the EU PAS Register will be completed prior to start of data collection.

Milestone	Planned Date
Start of recruitment/data collection	Q1 2015
End of recruitment	Q4 2016
End of data collection	Q4 2017
Final report	Q1 2018

5. RATIONALE AND BACKGROUND

5.1. Background

The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that there were 35.2 million individuals living with HIV infections worldwide with approximately 2.3 million new infections occurring in 2012 {27071}. Given that HIV-1 prevalence and incidence remain high despite considerable prevention efforts and that no vaccine is available, the need for novel, effective approaches to achieve durable viral suppression in HIV-infected patients using antiretroviral therapy (ART) is timely and important.

Atazanavir (ATV) and darunavir (DRV) are protease inhibitors (PIs) approved for the treatment of HIV-1 infected subjects. Both are cytochrome P450 (CYP) 3A substrates. They are co-administered with low-dose ritonavir (RTV), a CYP inhibitor which functions as a pharmacokinetic booster at low doses. However, low-dose RTV is associated with gastrointestinal adverse events (AEs) such as nausea, vomiting, and diarrhea, and the potential for metabolic complications, including elevations in serum cholesterol and triglycerides {11025}, and insulin resistance. As a stand-alone boosting agent, low-dose RTV creates complexities for patients who are already managing other medications needed to treat their HIV-1 infection and other comorbidities.

Cobicistat (COBI), a structural analogue of RTV, is a selective mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5). In contrast to RTV, COBI is devoid of inherent anti-HIV activity and may have less adverse biochemical effects (e.g., effect on adipocyte functions such as lipid accumulation). COBI is intended for once daily dosing of HIV-1-infected subjects for whom a regimen containing either ATV or DRV is considered to be suitable. It is indicated as a pharmacokinetic enhancer of ATV 300 mg once daily with food or DRV 800 mg once daily with food as part of combination ART in HIV-1 infected adults. Marketing authorization for COBI in the European Union (EU) was received on 25 September 2013.

5.2. Rationale

5.2.1. Overview of safety concerns

In the COBI EU-RMP, areas that have been identified as important potential risks are:

a) Concurrent use of drugs whose co-administration with COBI is contraindicated; and

b) Off-label use of COBI to boost protease inhibitors other than ATV or DRV once-daily.

In addition, the COBI EU RMP listed areas of missing information. Among those listed are:

a) drug-drug interactions with COBI

b) safety in patients with certain baseline conditions, including severe hepatic impairment, renal impairment, and cardiac conduction disorders.

These are described in more detail below.

5.2.2. Important potential risks

Off-label use. As noted in the COBI EU RMP, there is potential for off-label use of COBI to boost PIs other than ATV and once-daily DRV. These other PIs include saquinavir, fosamprenavir or tipranavir, or twice-daily DRV. The boosting dose of COBI with these PIs and others that are administered twice daily has not been established, and may result in insufficient plasma levels of the PI to achieve the desired antiviral effect.

Contra-indicated medications. Relevant information on the potential for interactions with COBI is included in the COBI SmPC. COBI is a strong mechanism-based inhibitor of CYP3A and is a CYP3A substrate. Thus, co-administration of COBI with drugs that are primarily metabolized by CYP3A is expected to result in increased plasma concentrations of such drugs which can result in increased or prolonged therapeutic effects or adverse reactions including severe, life-threatening or fatal events. Co-administration of COBI with drugs that inhibit CYP3A may decrease the clearance of COBI, resulting in increased plasma concentration of COBI. Drugs that induce CYP3A activity are expected to increase the clearance of COBI, resulting in decreased plasma concentration of COBI, and thus that of the antiretroviral agent boosted by COBI, which may lead to loss of therapeutic effect of the antiretroviral agent and development of resistance.

In light of the above, in the COBI SmPC, co-administration of COBI with the following drugs is contraindicated:

- Drugs with a narrow therapeutic index that are highly dependent on CYP3A for their clearance as their plasma concentration may be increased when co-administered with COBI, which may result in serious and/or life-threatening reactions. These drugs include:
    - alpha 1-adrenoreceptor antagonists: alfuzosin
    - antiarrhythmics: amiodarone, quinidine
    - ergot derivatives: dihydroergotamine, ergometrine, ergotamine
    - gastrointestinal motility agents: cisapride
    - 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG Co-A) reductase inhibitors: lovastatin, simvastatin

— neuroleptics: pimozide

— phosphodiesterase (PDE)-5 inhibitors: sildenafil for the treatment of pulmonary arterial hypertension

— sedatives/ hypnotics: orally administered midazolam, triazolam.

- Potent CYP3A inducers as they may significantly decrease the plasma concentrations of COBI and the COBI-boosted antiretroviral agent, which may result in loss of therapeutic effect and development of resistance to the COBI-boosted antiretroviral agent. These drugs include:

  — antimycobacterials: rifampicin

  — anticonvulsants: carbamazepine, phenobarbital, phenytoin

  — herbal products: St. John's wort (*Hypericum perforatum*)

5.2.3. Missing information

Drug interactions

Information on medications with identified and potentially significant interactions for COBI is provided in the COBI EU RMP and in the COBI SmPC. Medications listed under Identified or Potentially Significant Drug Interactions (COBI EU- RMP, Table 7-4) are listed below:

- antiretrovirals: efavirenz (600 mg single dose), etravirine, nevirapine, maraviroc
- anti-infectives: ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, boceprevir, telaprevir, rifabutin (150 mg every other day), clarithromycin
- anti-neoplastics: dasatinib, nilotinib, vinblastine, vincristine
- glucocorticoids: fluticasone
- oral anti-diabetics: metformin
- oral contraceptives: norgestimate/ethinyl estradiol
- anti-arrhythmics: disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone, digoxin (0.5 mg single dose)
- anti-hypertensives: metoprolol, timolol, amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil
- endothelin receptor agonists: bosentan

- anti-coagulants: rivaroxaban, warfarin, dabigatran
- inhaled β agonists: salmeterol
- HMG CoA reductase inhibitors: atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin (10 mg single dose)
- phosphodiesterase 5 (PDE5) inhibitors: sildenafil, tadalafil , vardenafil
- anti-depressants: trazodone
- immunosuppressants: cyclosporine, sirolimus, tacrolimus
- neuroleptics: perphenazine, risperidone, thioridazine
- sedatives/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem
- anti-gout: colchicine

Safety in patients with certain baseline conditions

The COBI SmPC contains the information that no meaningful differences in COBI pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of COBI. No dose adjustment of COBI is required for patients with renal impairment, including those with severe renal impairment. COBI has not been studied in patients receiving dialysis, and therefore no recommendations can be made for these patients. COBI has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. COBI should not be initiated in patients with creatinine clearance less than 70 mL/min if any co-administered agent requires dose adjustment based on creatinine clearance. As described in the COBI EU RMP, safety of COBI in patients with renal impairment will be determined through routine pharmacovigilance and an ongoing Phase 3 study that will provide additional information on the safety of DRV/co and ATV/co in HIV-1 infected adults with mild to moderate renal impairment (GS-US-236-0118).

As described in the EU RMP, COBI has not been studied in patients with severe hepatic impairment (Child-Pugh-Turcotte [CPT] score C) and therefore the use of COBI is not recommended in these patients. No dose adjustment of COBI is required in patients with mild (CPT score A) or moderate hepatic impairment (CPT score B). The safety of COBI in patients with severe hepatic impairment (CPT score C) is presented as a category of 'missing information' in the COBI EU RMP.

As described in the EU RMP, animal studies suggested that COBI may slightly prolong the PR interval at concentrations at least 11-fold higher than the human exposure at the 150 mg daily dose of COBI. However, clinical study data from the COBI studies (GS-US-216-0105, GS-US-216-0114 and GS-US-216-0130) and the additional supporting data from the Stribild® studies (GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104) with 150 mg dose of COBI do not support an increased risk of cardiac conduction disorders associated with the use of COBI

in patients with preexisting non-clinically significant ECG abnormalities. Subjects with abnormal ECG findings at screening that were determined by the investigator to be clinically significant were excluded from these studies. Therefore, safety in patients with cardiac conduction disorders is considered to be missing information for COBI.

5.2.4. Rationale for the study

Routine risk minimization measures by way of information in the COBI SmPC and Package Leaflet are in place in order to advise physicians and patients to prevent the important potential risks for COBI. Included as a pharmacovigilance activity in the COBI EU RMP and in conjunction with routine pharmacovigilance surveillance activities, this observational study is planned to investigate the effectiveness of these routine risk minimization measures by determining the rate of off-label use of COBI to boost PIs other than ATV or DRV once-daily and concurrent use of COBI with contraindicated medications.

In addition, the study has a number of secondary objectives. These include description of the outcomes of such off-label use and concurrent use with contraindicated medications, where possible; description of the frequency of use with identified and potential interacting medications and outcomes of such use, where possible; and description of the frequency of use by patients with certain baseline conditions including renal impairment, severe hepatic impairment, and cardiac conduction disorders, as well as outcomes of such use, where possible.

6. RESEARCH QUESTIONS AND OBJECTIVES

This observational, prospective drug utilization study will evaluate compliance with routine risk minimization measures for COBI, and provide information on drug interactions with COBI.

This study will examine HIV-1 infected patients ≥ 18 years of age who take COBI.

The primary objectives of this study are:

- To assess the rate of off-label use of COBI to boost PIs other than ATV or DRV once-daily
- To assess the rate of concurrent use of COBI with contraindicated medications

The secondary objectives of this study are:

- To describe outcomes, where possible, including related adverse events and special situation reports, following either off-label use of COBI to boost PIs other than ATV or DRV once-daily, or concurrent use of COBI with contraindicated medications
- To describe rate of use of identified and potential interacting medications with COBI, and where possible, the rate of suspected drug interactions during use of COBI and the rate of related AEs during use of COBI with identified and potential interacting medications
- To describe the frequency of COBI utilization by patients with baseline conditions, including severe hepatic impairment, renal impairment, or cardiac conduction disorders, as well as outcomes of such use, including related adverse events and special situation reports, where possible.

7. RESEARCH METHODS

7.1. Study Design

The study will be a prospective, observational cohort comprised of HIV-1 infected adults who take COBI. Subjects who meet these criteria and are seen at a participating clinical site will be followed for the duration of the study. The primary outcomes of interest will be the rates of off-label use and the rates of use with contra-indicated medications. Secondary outcomes of interest will be rates of related adverse events during off-label use and use of contra-indicated medications, frequency of potential drug interactions with COBI, and frequency of use among subgroups of the patient population who have certain baseline conditions.

7.2. Setting

The study population will consist of HIV-1 infected adults aged ≥18 years who take COBI up to one month prior to enrollment during Q1 2015 to Q1 2017 and are seen at one of approximately 40 clinical sites in Europe (anticipated to include Austria, Germany, the UK, Denmark, Ireland, Finland, Norway, Sweden, the Netherlands, Belgium, Iceland, and Spain) and Switzerland. It is anticipated that these are the European countries in which COBI will be marketed and reimbursement will be sought; thus, these countries represent the areas in which COBI will be available. Clinical sites in these countries will be selected from a range of practices types, representing variability across regions and practice types (local clinics, major referral centers, and university/research centers).

The data collected will be obtained from medical records, and include information on demographics, diagnoses, medications, and laboratory tests. Data will be collected prospectively from initial enrollment into the study (baseline) and followed thereafter (follow-up period) at routine visits to the study site until study completion, loss to follow-up, withdrawal of consent, or death, whichever occurs first. Subjects that discontinue COBI will be followed for related adverse events and drug interactions for up to one month after discontinuation.

7.3. Variables

Exposure:

- COBI medication use, in which the duration of exposure will be defined as (exposure end date – exposure initiation date + 1), regardless of temporary interruptions in exposure (<30 days), and will be expressed in days (recorded in whole days, e.g., 41 days). Exposure starts the first day the medication is known to have been taken. A subject may have multiple exposures defined as the re-initiation of therapy after a period of stoppage that is greater than 30 days. Person time exposed is defined as the number of days that the subject is known to have been exposed to COBI. Person time may also be expressed in person years ((number of person days)/365.25).

Primary Outcomes:

- Off-label use of PIs other than ATV or DRV during COBI medication use will be determined from prescriptions noted in the medical record, based on drug name, date of initiation and quantity/refills. Such exposure will be defined as new prescriptions of PIs other than ATV and DRV once-daily, either at COBI initiation or during COBI treatment.

- Concurrent use of COBI with contra-indicated medications will be determined from prescriptions noted in the medical record, based on drug names and quantity/refills. Such exposure will be defined as contra-indicated medications either started at COBI initiation or during COBI treatment.

Secondary Outcomes:

- Related AEs and SSRs occurring during use of COBI either off-label or concurrently with contraindicated medications will be determined from physician reports during such use and up to 30 days after discontinuation of such use.

  Exposure to a) off label COBI use with PIs other than ATV and DRV once-daily, and b) concurrent use of COBI with individual contra-indicated medications, is the time of joint exposure to COBI and the other medication. Thus, exposure time will be defined as (joint exposure end date – joint exposure initiation date + 1), regardless of temporary interruptions in joint exposure (<30 days), and will be expressed in days (recorded in whole days, e.g., 41 days). Joint exposure starts the first day the two medications are known to have been taken. A subject may have multiple such exposures defined as re-initiation after a period of stoppage that is greater than 30 days. Person time exposed is defined as the number of days that the subject is known to have been jointly exposed to COBI and the co-administered medication. Person time may also be expressed in person years ((number of person days)/365.25).

- Potential drug interactions will be described as follows:

  — Concurrent use of COBI with medications listed under Important or Potentially Significant Drug Interactions (COBI EU RMP, Table 7-4) will be determined from drugs noted in the medical record, based on drug names and quantity/refills. Such exposure will be defined as the rate of new drug exposures, either at the time of COBI prescription start, or during COBI exposure.

  — Rates of suspected drug interactions occurring during use of COBI will be determined from physician reports of suspected drug interactions during COBI use and up to 30 days after discontinuation of COBI.

— Related AEs and SSRs occurring during use of COBI with medications listed under Important or Potentially Significant Drug Interactions will be determined from physician reports during such use and up to 30 days after discontinuation of such use.

The time of joint exposure to COBI and the other medication will be defined as (joint exposure end date – joint exposure initiation date + 1), regardless of temporary interruptions in joint exposure (<30 days), and will be expressed in days (recorded in whole days, e.g., 41 days). Joint exposure starts the first day the two medications are known to have been taken. A subject may have multiple such exposures defined as re-initiation after a period of stoppage that is greater than 30 days. Person time exposed is defined as the number of days that the subject is known to have been jointly exposed to COBI and the other medication. Person time may also be expressed in person years ((number of person days)/365.25).

- Frequency of use of COBI by patients with severe hepatic impairment, renal impairment, or cardiac conduction disorders at baseline will be determined using reports of these conditions from the patients' medical history. Related AEs and SSRs during use of COBI by these subgroups will be determined from physician reports during COBI use and up to 30 days after discontinuation of COBI.

To define the exposures and outcomes above, the following variables and co-variables will be collected where available from the medical and prescribing records for participating patients.

The following variables will be collected on an eCRF at enrollment:

- demographic factors (month and year of birth, sex at birth, ethnic origin, geographic region/country)
- body size measures (weight, height)
- date of HIV-1 diagnosis
- date of enrollment
- date of COBI initiation
- HBV/HCV co-infection (yes/no) and diagnosis date
- any renal disease in the 6 months prior to enrollment (yes/no), type of renal disease, and diagnosis date
- any hepatic impairment in the 6 months prior to enrollment (CPT class C, yes/no) and diagnosis date
- prior cardiac conduction disorder (yes/no) and diagnosis date

- medications (including COBI and other antiretroviral therapy) taken in the period from COBI initiation to enrollment, including such details as dose and dates of initiation and discontinuation. Should include all concurrent medications, including self-prescribed over-the-counter and herbal products

- available laboratory values and date(s) of test(s), including:

  — most recent bilirubin

  — most recent and nadir CD4 count

  — most recent HIV viral load

  — most recent AST level

  — most recent ALT level

  — most recent serum creatinine level

The following variables will be collected on a follow-up basis from medical records of routine visits using an eCRF, for up to three years following study entry during treatment with COBI:

- medications (including COBI and other antiretroviral therapy) taken since enrollment, including such details as dose and dates of initiation and discontinuation. Should include, but not be limited to, the following:

  Contraindicated medications: alfuzosin, amiodarone, quinidine, dihydroergotamine, ergometrine, ergotamine, cisapride, lovastatin, simvastatin, pimozide, sildenafil, orally administered midazolam, triazolam, rifampicin, carbamazepine, phenobarbital, phenytoin, St. John's wort (as reported by the patient or the treating physician)

  Important and potential interacting medications: efavirenz (600 mg single dose), etravirine, nevirapine, maraviroc, ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, boceprevir, telaprevir, rifabutin (150 mg every other day), clarithromycin, dasatinib, nilotinib, vinblastine, vincristine, fluticasone, metformin, norgestimate/ethinyl estradiol, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone, digoxin (0.5 mg single dose), metoprolol, timolol, amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil, bosentan, rivaroxaban, warfarin, dabigatran, salmeterol, atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin (10 mg single dose), sildenafil, tadalafil , vardenafil, trazodone, cyclosporine, sirolimus, tacrolimus, perphenazine, risperidone, thioridazine, buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem, colchicine

- available laboratory values and date(s) of test(s), including:
  - CD4 count
  - HIV viral load
- Reason and date of COBI discontinuation, if applicable

The following variables will be collected on an eCRF throughout the follow-up period for each patient, and up to 30 days after end of treatment, if applicable:

- Physician reports of related AEs/SAEs and date(s) of onset
- SSRs, including physician suspected lack of drug effect, and date(s) of onset
- Physician reports of suspected drug interactions and date(s) of onset
- Data collection stop date

7.4. Data Sources

Data will be collected from up to 40 centers in several European countries. Each investigator at the participating clinical sites will offer the study to all patients receiving COBI, and potential participants will be asked to sign a consent form for the collection of retrospective medical history and prospective data. The participants will not have to attend any additional visits or undergo any procedures above their standard of care. The data from the clinics will be prospectively collected at each patient visit using eCRFs and sent to and retained at a centralized data coordinating center.

7.5. Study Size

The expected sample size of 500 subjects is determined by ability to address the primary objectives of this descriptive study, which are dependent on COBI utilization.

The total duration of this study is 3 years, with recruitment during the first 2 years. With a total of 500 subjects taking COBI and assuming an even rate of recruitment and a 20% annual loss to follow-up (including discontinuation of COBI), this yields a total of 810 person-years of COBI exposure. With 810 years of person time, event rates as low as 0.37 per 100 person years can be distinguished from zero with 95% confidence.

For comparison, rates of use of the contra-indicated medications triazolam, sildenafil citrate, and rifampin while on RTV, were 0.6, 0.4, and 0.4 per 100 person years, respectively, in an ad hoc analysis of US commercial medical claims data (IMS Pharmetrics). These medications are contra-indicated for both RTV and COBI. Comparable EU datasets that include large numbers of HIV-1 infected patients, with detailed prescribing data at the level of individual medications, are not available; however, there is no evidence to suggest that rates of contra-indicated medication use among RTV users would be markedly different in the EU vs. the US. Expected rates of the

potential off-label use of COBI to boost PIs other than ATV or DRV are unknown and cannot realistically be approximated using data for RTV, as RTV is indicated for boosting many PIs in addition to ATV and DRV. However, applying the rule of three, with 810 person years, the study will be able to observe one such erroneous combination event with 95% confidence if it occurs at a rate of 0.37 per 100 person years.

In summary, the proposed sample size will yield adequate statistical power to detect rates of primary outcome events as low as 0.37 per 100 person years with 95% confidence.

7.6. Data Management

All individual data will be collected on eCRFs using a commercial web-based electronic data capture (EDC) system deployed at each participating site. Data will be retrieved, managed, and prepared for analysis from the EDC system. Data will be stored on a secure network drive or a secure and validated commercial cloud-based data storage system, with access to only authorized personnel. Data will be transferred to Gilead for analysis. The datasets will be transformed into a common data model structure for further manipulation and analysis.

All statistical summaries and analyses will be conducted using SAS® software (SAS Institute, Cary, North Carolina, USA) or other standard software tools including STATA® (StataCorp LP, College Station, Texas, USA).

7.7. Data Analysis

Baseline information on subject demographics (i.e., age, sex, race/ethnicity, and BMI) and other clinical characteristics will be summarized using descriptive statistics (i.e., sample size, mean, standard deviation, median, interquartile range, minimum and maximum) for continuous data and by the numbers and percentages of subjects for categorical data. Summaries will be provided for subjects overall.

Primary analyses:

Multivariable Poisson regression models that account for COBI exposure time will be used to calculate rates and 95% confidence intervals (CIs) of new prescriptions of both (a) non-DRV and non-ATV PIs and (b) contra-indicated medications during exposure to COBI.

Secondary analyses:

Rates of related AEs/SAEs and SSRs during either off-label use with non-DRV and non-ATV PIs or use with contra-indicated medications will be assessed using Poisson regression models that account for time of such off-label COBI use or time of such joint exposure to contra-indicated medications and COBI.

The rates of new prescriptions of medications identified as Important or Potentially Significant Drug Interactions while exposed to COBI will be described using Poisson regression models. Where possible, rates of 1) physician reported drug interactions while exposed to COBI, and

2) related AEs and SSRs while jointly exposed to COBI and medications identified as Important or Potentially Significant Drug Interactions, will be described using Poisson regression models.

The frequency of baseline history of renal impairment, severe hepatic impairment, and cardiac conduction disorders among patients taking COBI will be assessed using observed numbers and percentages. Where possible, rates of related adverse events and SSRs among patients with such histories at baseline will be described using Poisson regression models.

7.8. Quality Control

Electronic data capture will provide an unmonitored subset of existing source data that will not be subject to source data validation. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process.

7.9. Limitations of the Research Methods

Limitations of this study are those common to observational studies. Selection bias may be present, as the sites may elect to enroll patients in the study that may either have a better or worse health status, or are more likely to be compliant, compared with the general HIV-positive population to which COBI will be available. In terms of the primary objectives, which are intended to characterize prescribing and utilization patterns contrary to the SmPC and the Package Leaflet, participating physicians and patients, aware of the scrutiny of the study, may behave differently than physicians and patients who do not participate in the study.

This study is adequately powered to address the primary objectives of this study. However, study's ability to address the secondary objectives, which are intended to be descriptive and exploratory, will depend on 1) number of physician suspected drug interactions, 2) observed amount of joint exposure time to COBI and a second medication (i.e., non-ATV and non-DRV PIs, contra-indicated medications), or 3) exposure time among subgroups of the patient population who have certain conditions at baseline. Since these situations are expected to be uncommon, and since the amount of observed exposure time for the latter two conditions is expected to be low, this study will be able to detect only very common events for the secondary objectives.

7.10. Other Aspects

7.10.1. Joint Investigator/Sponsor Responsibilities

7.10.1.1. 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.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The sponsor/designee and investigator 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), and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) including archiving of essential documents.

8.2. Independent Ethics Committee (IEC) Review

The investigator will submit this protocol and any accompanying material to be provided to the subject (such as advertisements, 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.

8.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims and methods 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 will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion as required by IEC or local requirements.

Study subjects may withdraw consent at any time with no penalty.

8.4. Confidentiality and Data Protection

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.

9. 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.

9.1. 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 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).

9.1.1. 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.

9.1.2. Serious Adverse Events

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

- Death
- Life-threatening event (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.

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 9.1**.** 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).

9.2. 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.

9.2.1. Assessment of Causality/Relatedness for Adverse Events

The investigator or qualified sub-investigator is responsible for entering only those AEs that are related to COBI utilization, as determined using clinical judgment and the following considerations:

- No evidence exists that the AE has an etiology other than the drug (e.g., preexisting condition, underlying disease, inter-current illness, concomitant medication).
- There is a reasonable possibility that the event may have been caused by the medicinal product.
- Ineffective treatment should not be considered as causally related in the context of AE reporting

9.3. Special Situations Reports

9.3.1. Definitions of Special Situations

Special situation reports include reports of pregnancy; medication error, abuse, misuse, or overdose; lack of effect; adverse reactions in infants following exposure from breastfeeding; and adverse reactions associated with product complaints and occupational exposure.

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 labeling.

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.

9.3.2. Instructions for Reporting Special Situations

9.3.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur while exposed to the drug and the outcome of the pregnancy are to be reported to the Gilead Drug Safety and Public Health (DSPH) department using the Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. These should be submitted by fax or email, within the timeframes given above, to:

Gilead Sciences DSPH: Fax: +44 (0) 208 587 2386
E-mail: Safety_fc@gilead.com

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 (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) and related to a Gilead product must be reported to Gilead DSPH within 3 calendar days as an SADR as described in Section 9.4. Furthermore, any SADR occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH. The underlying medical reason should be recorded as the AE term.

9.4. Investigator Requirements and Instructions for Reporting Adverse Events and Special Situation Reports to Gilead

All related non-serious AEs and related SAEs, also known as adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs), occurring from time of informed consent until study completion, loss to follow-up, withdrawal of consent, death or one month after discontinuation of COBI (whichever occurs first) will be reported to Gilead DSPH.

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

- Within 30 calendar days of knowledge of the event for ADRs
- Within 3 calendar days of knowledge of the event for SADRs

Special Situations will be reported to Gilead DSPH within 30 calendar days of knowledge of the event.

Details of the methods for reporting ADRs, SADRs, and SSRs to Gilead DSPH will be described in the CRF Completion Guidelines. If reporting via electronic case report form (eCRF) is established, this method must always be used unless the eCRF system is not functioning.

If reporting of an ADR, SADR or SSR via eCRF is not possible (because eCRF reporting is not yet established or not functioning for the report type), site personnel should record 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 submit it by fax or email, within the timeframes given above, to:

Gilead Sciences DSPH: Fax: +44 (0) 208 587 2386
E-mail: Safety_fc@gilead.com

9.5. Investigator and Sponsor Reporting Requirements

Gilead is responsible for reporting and analyzing reports of ADRs, SADRs, and SSRs as determined by country-specific legislation or regulations where the study is conducted and other applicable countries. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for events will be determined by Gilead using reference safety information specified in the COBI EU SmPC.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Study Report and Publications

The final (end of study) report will be submitted to the EMA based on the timelines provided in Section 4. 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.

Future publications in the form of abstracts and manuscripts have not been planned to date. Authorship of these publications will follow the guidelines proposed by the International Committee of Medical Journal Editors (2006). All designated authors will meet the criteria for authorship and potential conflicts of interest will be disclosed.

11. REFERENCES

11025 Shafran SD, Mashinter LD, SE. R. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. HIV Med 2005;6 (6):421-5.

27071 Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2013. 2013.

12. APPENDICES

Number	Document Reference Number	Date	Title
1	NA	12 September 2014	ENCePP Checklist for Study Protocols
2	NA	12 September 2014	Study Acknowledgement

Appendix 1. ENCePP Checklist for Study Protocols

Study title: A Prospective, Observational Drug Utilization Study of Cobicistat in Adults with HIV-1 Infection

Study reference number: GS-US-216-1230

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]	☒	☐	☐	14
1.1.2 End of data collection[2]	☒	☐	☐	14
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	14
1.1.6 Final report of study results.	☒	☐	☐	14

Comments:

Registration in the EU PAS register is pending.

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)	☒	☐	☐	18
2.1.2 The objective(s) of the study?	☒	☐	☐	20
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	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?	☐	☐	☒	

Comments:

The study is descriptive, it is not testing any hypotheses.

[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.

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g., cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	21
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)	☒	☐	☐	21

Comments:

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

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how the exposure is defined and measured? (e.g., operational details for defining and categorizing exposure)	☒	☐	☐	21
5.2 Does the protocol discuss the validity of exposure measurement? (e.g., precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☒	☐	☐	21
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Exposure is prospectively determined in terms of person-time; the outcome is rate of events per person time.

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?	☒	☐	☐	22
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)	☐	☐	☒	

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)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Study is descriptive, no associations are being tested

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.)	☒	☐	☐	23-25
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.)	☒	☐	☐	23-25
8.1.3 Covariates?	☒	☐	☐	23-25
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)	☒	☐	☐	23-25
8.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	23-25
8.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23-25
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g., International Classification of Diseases [ICD]-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities [MedDRA] for adverse events)	☐	☒	☐	
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:

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?	☒	☐	☐	26
10.3 Are descriptive analyses included?	☒	☐	☐	26
10.4 Are stratified analyses included?	☒	☐	☐	26
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

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?	☐	☒	☐	
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)?	☐	☒	☐	
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?	☒	☐	☐	26-27
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)	☒	☐	☐	26-27
12.3 Does the protocol address other limitations?	☐	☒	☐	

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?	☒	☐	☐	28-29
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	28-29

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?	☒	☐	☐	13

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?	☒	☐	☐	35

Comments:

Name of the main author of the protocol: ____Anand Chokkalingam _____

Date: 12 September 2014

Signature: _____

Appendix 2. Study Acknowledgement

Gilead Sciences International Ltd.
Cambridge
CB21 6GT
United Kingdom

A Prospective, Observational Drug Utilization Study of Cobicistat in Adults with HIV-1 Infection
Original Version 1.0 dated 12 September 2014

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

Gilead Study Director (Printed) Author	Signature
Date	
Gilead EU QPPV (Printed)	Signature
Date	

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. I will discuss this material with them to ensure that they are fully informed about the medication(s) and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number