NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	A Prospective, Observational Drug Utilization Study of Stribild® in Adults with HIV-1 Infection
Protocol ID	GS-EU-236-0141
Protocol Version/Date:	Original: 17 April 2014
EU PAS Register No	To be registered
Clinical Trials.gov Identifier	N/A
Active substance	Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil
Medicinal Product	Stribild® 150 mg/150 mg/200 mg/245 mg film-coated tablets Stribild®
Marketing Authorization Numbers	EU/1/13/830/001 EU/1/13/830/002
Procedure number	EMEA/H/C/002574
Joint PASS	No
Research Question and Objectives	To assess renal risk minimization measures among Stribild®-treated patients and factors associated with the risk of proximal renal tubulopathy, and its reversibility, including event rates.
Countries of study	Europe (Belgium, France, Germany, Italy, Spain, and the United Kingdom)
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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
ATV/r	ritonavir-boosted atazanavir
CI	confidence interval(s)
CKD	chronic kidney disease
CL_{cr}	creatinine clearance
CRF, eCRF	case report form, electronic case report form
COBI	cobicistat (Tybost®)
DSPH	Drug Safety and Public Health
DUS	Drug Utilization Study
eGFR, GFR	estimated glomerular filtration rate, glomerular filtration rate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EVG	elvitegravir (Vitekta®)
FDA	(United States) Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GS	Gilead Sciences
GVP	Good Pharmacovigilance Practices
HIPPA	Health Insurance Portability and Accountability Act
HIV, HIV-1	Human Immunodeficiency Virus, Human Immunodeficiency Virus Type 1
HMA	Heads of Medicines Agencies
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
KDIGO	Kidney Disease: Improving Global Outcomes
MD	Doctor of Medicine
NEAT-ID	European AIDS Treatment Network Infectious Disease Foundation
PRT	proximal renal tubulopathy
RMP	risk management plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild®)
TDF	tenofovir disoproxil fumarate (Viread®)
TVD	emtricitabine/tenofovir disoproxil fumarate (Truvada®)
UNAIDS	Joint United Nations Program on HIV/AIDS
US, USA	United States (of America)

3. RESPONSIBLE PARTIES

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

Gilead Sciences
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Title: A Prospective, Observational Drug Utilization Study of Stribild® in Adults with HIV-1 Infection

Rationale and Background: The single tablet regimen, Stribild® (STB), is a fixed-dose combination of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate. The safety and tolerability of STB has been demonstrated in 2 Gilead-sponsored Phase 3 investigational, double-blind controlled studies in HIV-1 infected, antiretroviral treatment–naïve subjects (Studies GS-US-236-0102 and GS-US-236-0103). Among the subjects in those studies over 144 weeks, 13 (1.9%) in the STB group (n=701) and 8 (2.3%) in the ritonavir-boosted atazanavir plus Truvada (ATV/r+TVD) group (n=355) discontinued study drug due to a renal adverse reaction. The renal adverse reactions seen with STB were consistent with previous experience with tenofovir disoproxil fumarate. Four subjects who received STB (0.6%) developed renal laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of STB during the first 48 weeks. No additional proximal renal tubular dysfunction cases were reported from Week 48 to Week 144. Two of the 4 subjects had renal impairment (ie, CL_{cr} <70 mL/min) at baseline. The observed renal events were identifiable through routine laboratory monitoring. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of STB but did not completely resolve in all subjects. Three subjects who received ATV/r+TVD (0.8%) developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of ATV/r+TVD after Week 96.

A drug utilization study is included as a pharmacovigilance activity in the STB European Union (EU) Risk Management Plan (RMP) to investigate the effectiveness of renal minimization measures for Stribild, the factors associated with the risk of proximal renal tubulopathy (PRT), and the reversibility of PRT.

Research Question and Objectives:	This Drug Utilization Study will assess renal risk minimization measures for Stribild and factors associated with the risk of PRT, including event rates and its reversibility. The objectives of this study are as follows: • To assess the pattern of renal monitoring and patient management in the clinical setting among subjects treated with STB and compare it to key renal messages in the STB SmPC • To evaluate baseline characteristics that may be associated with risk of proximal renal tubulopathy • To prospectively evaluate the risk of proximal renal tubulopathy associated with the use of concomitant medications of nephrotoxic potential • To establish the rates of proximal renal tubulopathy and STB discontinuation due to PRT and to document reversibility. • To document laboratory markers of tubular and glomerular damage, where available.
Study Design:	Prospective, observational cohort study of HIV-1 infected subjects who initiate treatment with Stribild.
Population:	The study population will be comprised of HIV-1 infected adults aged ≥18 years receiving Stribild who are enrolled in clinics across several European countries.
Variables:	Baseline and follow-up variables include but are not limited to the following: demographics, clinical characteristics (ie, HBV / HCV coinfection, prior renal disease), laboratory measurements (ie, CD_4 count, HIV viral load, creatinine, creatinine clearance [eGFR], glucose, phosphate, total protein, and albumin) and medications (ie, prior antiretroviral therapy and concomitant medications with nephrotoxic potential and dosages).
Data Sources:	Prospective cohort of HIV-1 positive adult subjects within the European AIDS Treatment Network (NEAT) collaboration for clinical research in HIV/AIDS. Electronic data capture at each participating clinic will collect retrospective and prospective study variables gathered from standard care.
Study Size:	Dependent on the uptake of the drug in the European Union (EU), approximately 1000 subjects, who are estimated to accrue ~1500 person-years, are projected to be enrolled by end of study.

Data Analysis:	Descriptive analysis will be conducted on enrolled subjects and for subjects with incident PRT and reversibility events. Event rates and 95% confidence intervals (CIs) adjusted for potential baseline confounders will be estimated using a multivariate Poisson regression model. The association of baseline characteristics and event rates will also be established using a Poisson regression model and 95% CIs.
Milestones:	Start of data collection: July 2014
	End of data collection: September 2016
	Interim report: January 2016
	Final report: January 2017

This study will be conducted 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.

5. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	17 April 2014	Sections 9.3 and 9.5	Update	Incorporated minor changes to draft protocol based on CHMP recommendations

6. MILESTONES

Milestone	Planned Date
Start of data collection	July 2014
End of data collection	September 2016
Interim report 1	January 2016
Final report of study results	January 2017

7. RATIONALE AND BACKGROUND

7.1. Rationale for the Current Study

The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that there were 35.2 million individuals living with human immunodeficiency virus (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 approaches to stabilize HIV-1 rates with durable viral suppression using simplified antiretroviral therapy (ART) is timely and important.

The single tablet regimen, Stribild® (STB), is a fixed-dose combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF) used in the treatment of human immunodeficiency virus type-1 (HIV-1) infection. Elvitegravir is a strand transfer inhibitor of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Cobicistat, a structural analogue of ritonavir with no antiretroviral activity, is a selective mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5). Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI), is a synthetic analogue of the naturally occurring nucleotide, 2′ deoxycytidine, a pyrimidine nucleoside, which is structurally similar to lamivudine. TDF, the oral prodrug of tenofovir, is a nucleotide reverse transcriptase inhibitor (NtRTI). Stribild was approved by the European Commission in May 2013 for adults who are antiretroviral treatment-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agent components of STB.

The safety and tolerability of STB has been demonstrated in two Gilead-sponsored Phase 3 investigational, double-blind controlled studies in HIV-1 infected, antiretroviral treatment–naïve subjects (Studies GS-US-236-0102 and GS-US-236-0103). Among the subjects in those studies across 144 weeks, 13 (1.9%) in the STB group (n=701) and 8 (2.3%) in the ritonavir-boosted atazanavir plus Truvada (ATV/r+TVD) group (n=355) discontinued study drug due to a renal adverse reaction (ie, Fanconi syndrome, renal failure, or increased serum creatinine).
Four subjects who received STB (0.6%) developed renal laboratory findings consistent with proximal renal tubular dysfunction (primarily hypophosphatemia, with increased urinary fractional excretion of phosphorus, glycosuria and proteinuria) leading to discontinuation of STB during the first 48 weeks. No additional proximal renal tubular dysfunction cases were reported from Week 48 to Week 144. Two of the 4 subjects had renal impairment (ie, creatinine clearance (CL_{cr}) < 70 mL/min) at baseline. The observed renal events were identifiable through routine laboratory monitoring. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of STB but did not completely resolve in all subjects. Three subjects who received ATV/r+TVD (0.8%) developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of ATV/r+TVD after Week 96.

In Study GS-US-236-0130, there were no clinically meaningful changes in markers of glomerular or tubular function when COBI and TDF were given alone, in combination, or as

components of STB, with the only notable effect consistent with the inhibition of tubular secretion of creatinine by COBI, which results in a modest decrease in estimated glomerular filtration rate (eGFR) without affecting actual glomerular filtration rate. In the GS-US-236-0102 and GS-US-236-0103 studies, decreases in estimated creatinine clearance occurred early in treatment with STB, after which they stabilized. The mean change in estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault method after 48 weeks of treatment was -13.9 ± 14.9 mL/min for STB, -1.6 ± 16.5 mL/min for Atripla, and -9.3 ± 15.8 mL/min for ATV/r+TVD. After 144 weeks of treatment, the mean change in estimated eGFR was -14.0 ± 16.6 mL/min for STB, -1.9 ± 17.9 mL/min for Atripla, and -9.8 ± 19.4 mL/min for ATV/r+TVD.

Analysis of postmarketing spontaneous adverse event (AE) reports has indicated that TDF therapy may cause renal adverse reactions including renal failure, acquired Fanconi syndrome, and other proximal renal tubulopathies (PRT) {9341}, {12249}, {12302}, {14062}, {14108}, {14110}, {14592}, {15373}, {15373}, {19273}. In an evaluation of AE surveillance data from the TDF expanded access program (EAP), the observed frequency of reported proximal renal tubulopathy (including Fanconi syndrome) was 0.04% (2/5686) {10921}. In a cumulative review of the reversibility of renal tubulopathy in HIV-1 and HBV adult patients from clinical trials, postmarketing surveillance, and existing literature, data from the various sources were consistent in indicating that, based on abnormalities such as low serum phosphate and glycosuria, renal tubulopathy fully resolves in the majority of patients and usually within 4 months of discontinuing TDF. From clinical study and postmarketing reports, increases in serum creatinine/decreases in creatinine clearance and proteinuria resolved (or were resolving) in 81 to 93% of patients, although some patients had not returned to their baseline renal function at the last follow-up recorded. This may reflect an insufficient duration of follow-up, as well as other factors contributing to renal impairment and decreased $CL_{cr,}$ such as underlying renal disease, AIDS, hypertension, diabetes and inhibition of tubular creatinine secretion by certain antiretrovirals. Decreases in eGFR have been observed in patients prior to starting TDF, in which case renal function would not be anticipated to return to pre-TDF levels {22608}.

Within the TDF EAP, observed risk factors for increases in serum creatinine included low CD_4 cell count, older age, low baseline weight, higher baseline serum creatinine, and concomitant nephrotoxic medications {10921}. In the EuroSIDA observational cohort, older age, hypertension, HCV coinfection, lower baseline eGFR and CD_4 count were found to be independently associated with an increased risk of chronic kidney disease (CKD) among patients who initiated TDF therapy {15280}. Also, in the D:A:D study, a prospective multi-cohort study of HIV-1 infected patients in Europe, Australia and the US, atazanavir/ritonavir use was independently associated with increased rates of confirmed eGFR $\leq$ 70 mL/min (adjusted incidence rate ratio [aIRR]: 1.20 [95% CI: 1.09-1.32]), but not with CKD (confirmed eGFR of $\leq$ 60 mL/min). However, lopinavir/ritonavir use was associated with both endpoints (aIRR: 1.11 [95% CI: 1.05-1.17] and 1.22 [95% CI: 1.16-1.28], respectively) {20067}, {20068}. In addition, analysis of data from observational cohorts have indicated that the most frequently identified predictors for development of renal dysfunction in patients receiving TDF were pre-existing renal disease, concurrent administration of nephrotoxic agents, and advanced HIV disease with low CD_4 cell counts {6772}, {7625}, {7672}, {7725}, {7987}, {8056}, {8715} ,{9023}, {9161}, {9334}, {10394}. In Study GS-US-104-353, a case-control study of Fanconi syndrome, prior and/or concomitant use of LPV/r and a lower pre-TDF CL_{cr} were significantly associated

with development of Fanconi syndrome by multivariate analysis, although the association with lopinavir/ritonavir (LPV/r) may have been confounded by prescription bias given the long median time since HIV-1 diagnosis and long duration of HIV treatment in subjects with Fanconi syndrome, which were longer compared with controls. Finally, patients who have previously experienced renal events while receiving other nucleotide analogues, such as adefovir dipivoxil, may be at an increased risk of developing renal toxicity on TDF given the similar structure of these drugs and renal toxicity profiles (Expert report by Paul Klotman MD "Adefovir dipivoxil-related nephrotoxicity" 15 June 1999).

TDF associated renal toxicity is thought to be mainly due to an effect on proximal renal tubules. Although the molecular mechanism is not fully understood at the present time, findings to date suggest a role of both the drug pharmacokinetics and renal cell physiology regulation in the rare development of Fanconi syndrome in patients chronically treated with TDF.

Appropriate guidance on patient management with Stribild therapy is provided in the Summary of Product Characteristics (SmPC) to reduce the risk for development of renal events, which includes that patients who have previously discontinued treatment with TDF due to renal toxicity should not be treated with STB and that creatinine clearance (CL_{cr}) should be calculated and urine glucose and urine protein should be determined in all patients prior to initiating therapy with STB and subsequently monitored thereafter, and CL_{cr} thresholds for the initiation and discontinuation of STB. The key renal messages for STB from the SmPC, which are included in the STB EU-RMP, are also provided to prescribers in a renal educational brochure. Included as a pharmacovigilance activity in the STB EU-RMP and in conjunction with routine pharmacovigilance surveillance activities, this drug utilization study will investigate the effectiveness of renal minimization measures for Stribild, the event rate and factors associated with the risk of PRT, and its reversibility following the discontinuation of Stribild treatment.

8. RESEARCH QUESTIONS AND OBJECTIVES

This Drug Utilization Study (DUS) will assess renal risk minimization measures for Stribild and factors associated with the risk of proximal renal tubulopathy, including event rates and its reversibility.

The objectives of this study are as follows:

- To assess the pattern of renal monitoring and patient management in the clinical setting among subjects treated with STB and compare it to key renal messages in the STB SmPC
- To evaluate baseline characteristics that may be associated with risk of proximal renal tubulopathy
- To prospectively evaluate the risk of proximal renal tubulopathy associated with the use of concomitant medications of nephrotoxic potential
- To establish the rates of proximal renal tubulopathy and STB discontinuation due to proximal renal tubulopathy and to document reversibility.
- To document laboratory markers of tubular and glomerular damage, where available.

9. RESEARCH METHODS

9.1. Study Design

The study will be a prospective, observational cohort comprised of HIV-1 infected adults who initiate Stribild therapy in Europe. Subjects who meet the inclusion criteria will be followed for the duration of the study at each recruiting center. The primary outcome of interest will be the rate of proximal renal tubulopathy, with a secondary outcome being the rate of reversibility among subjects with a PRT event.

The strengths of the study include a sample size adequate for the evaluation of the primary outcome, and the availability of sufficient information to assess the pattern of risk minimization measures implemented as per the SmPC. In addition, the European AIDS Treatment Infectious Disease Network (NEAT-ID) collaboration represents a good cross-section of the HIV-positive treated patients in Europe.

9.2. Setting

The study population will consist of HIV-1 infected adults aged ≥18 years receiving Stribild therapy that are enrolled in up to 50 participating European clinics participating in the NEAT-ID Foundation across several countries (ie, Belgium, France, Germany, Italy, Spain, and the United Kingdom) from 01 July 2014 to 30 September 2016. Confirmed diagnosis of HIV-1 infection is required in subjects who are antiretroviral treatment-naïve.

Data will be collected from subjects prospectively from initial enrollment into the study (baseline) and followed thereafter (follow-up period) until study completion, loss to follow-up, or death, whichever occurs first. Subjects that discontinue STB will be followed until PRT reversibility has occurred for up to 6 months from date of the observed PRT event.

The objective of the NEAT project is to create a durable European collaboration for Clinical Research in HIV/AIDS therapeutic approaches towards the goal of defining optimal strategies for management of HIV infection in adults and children. NEAT was designed to leverage the wealth of existing but dispersed European expertise, resources and capacities in order to make concerted efforts to have a crucial impact in the fight against AIDS. The data will contain medical records, and information on demographics, diagnoses, procedures, medications, and laboratory tests.

9.3. Variables

Exposure:

- STB medication use in which the duration of exposure will be defined as (exposure end date – exposure initiation date), regardless of temporary interruptions in exposure (<30 days), and will be expressed in days (recorded to one decimal place, eg, 40.5 days). Exposure starts the first day the medication is known to have been taken. A subject may have multiple exposures defined as the reinitiation of therapy after a period of stoppage that is greater than 30 days.

All reasons for stoppage will be collected. Person time exposed is defined as the number of days that the subject is known to have been exposed to STB.

Outcomes:

- Proximal renal tubulopathy (PRT) defined as the presence of two or more of the following within a month during the follow-up period:

  — Hypophosphatemia (serum phosphorus <0.8 mmol/L or <2.5 mg/dL) or a 1-grade level increase in fractional excretion of phosphate compared to baseline,

  — Normoglycemic glycosuria (high urine glucose vs. normal blood glucose levels, or a 1-grade level increase from baseline), or

  — Proteinuria (a 2-grade level increase in urine protein from baseline),

and the following:

  — An increase in serum creatinine [SCr] by ≥0.4 mg/dL (≥26.5 µmol/L); or an increase in SCr to ≥1.5 times baseline, at two consecutive visits based on the most recent Kidney Disease: Improving Global Outcomes [KDIGO] guideline recommendations {21645}

Onset date is defined as the earliest diagnosis date according to the respective tests. For the purposes of event rate computation, the subject is considered to be censored at the onset date of the event, irrespective of the continuation or stoppage of the medication.

- Proximal renal tubulopathy reversibility upon discontinuation of Stribild medication use defined as the improvement of laboratory markers (ie, improvements in serum creatinine and in tested tubular markers) during the follow-up period within six months. Reversibility lag and rate will be computed using the reversibility onset date. Administrative censoring will occur at the end of the follow up period for the purposes of computing reversibility rates.

The following variables will be collected, if available, at baseline and during each follow-up visit:

Demographics:

- Age
- Gender
- Race/ethnicity
- Geographic region/country
- Body Mass Index (BMI)

- Weight
- Height

Clinical Comorbid Conditions (six months prior to baseline and concurrent diagnoses):

- Diabetes
- Hepatitis B Virus coinfection
- Hepatitis C Virus coinfection
- Cardiovascular Disease
- Hypertension
- Cancer (excluding non-melanoma skin cancers)
- Muscular disorders (rhabdomyolysis, myopathy, and muscular weakness)
- Bone disorders
- Hepatic disorders (cirrhosis, hepatic failure)
- Hypercholesterolemia
- Other renal disorders including prior history of:
  - Acute Renal Injury/Failure
  - Chronic Renal Injury/Failure
  - Interstitial Nephritis
  - Nephrogenic Diabetes Insipidus

Laboratory Measurements:

- CD_4 cell counts (cells/µL)
- HIV viral load (copies/mL)
- Creatinine (serum; µmol/L)
- Creatinine clearance = estimated glomerular filtration rate (eGFR; mL/min/1.73m^2) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation {20404}.

The older Cockcroft-Gault method used in the STB SmPC recommendations also will be calculated as a comparison.

[$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.]

- Phosphate (serum; mg/dL or mmol/L)
- Glucose (serum, urine; mg/dL or mmol/L)
- Total Protein (serum, urine; g/dL)
- Albumin (serum, urine; g/dL)
- Potassium (serum; mmol/L)
- Blood Urea Nitrogen (BUN; mg/dL)
- Calcium (serum; mg/dL or mmol/L)
- Sodium (serum; mmol/L)
- Urinary alpha- and/or beta-microglobulin neutrophil gelatinase-associated lipocalin (NGAL; if available)
- Retinal binding protein (if available)

Concomitant Medications (any, and dosage), including but not limited to the following:

- Antiretroviral therapies (including prior exposure)
- Antimicrobials (ie, aminoglycosides, amphotericin B, and sulfadiazine)
- Antivirals (ie, acyclovir, foscarnet, valaciclovir, and penciclovir)
- Analgesics (ie, nonsteroidal anti-inflammatory drugs [NSAIDs], selective COX-2 inhibitors such as celecoxib, etoricoxib, diclofenac, and phenacetin)
- Other medications with nephrotoxic potential, such as angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), cepalotin, and zoledronate.

Other Variables:

- Exposure to lead, cadmium, mercury, copper, uranium, and bismuth

- Adverse events reported with STB medication use

9.4. Data Sources

Data will be collected from up to 50 centers in several European countries (ie, Belgium, France, Germany, Italy, Spain, and the UK). Each investigator at the participating clinics will offer the study to all patients receiving Stribild, and potential participants will be asked to sign a consent form for the collection of retrospective 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 electronic case reporting forms (eCRFs) and sent to and retained at a centralized data coordinating center.

9.5. Study Size

The expected sample size for this study is 1,000 subjects. This sample size has been projected based on estimates of the uptake of STB in the EU during the enrollment phase of the study. This sample size has 80% power at an alpha level of 0.05 to detect a 25% difference in the rate for proximal renal tubulopathy as compared to the expected rate. The expected rate of PRT among subjects exposed to tenofovir is 3.3 events per 1,000 person years (95% CI: 2.97 – 3.56). The expected amount of person time for this study is ~ 1,500 person years allowing for staggered entry into the study. The study can detect a rate of proximal renal tubulopathy as low as 1 per 1,000 person years with a 95% confidence interval of 0.16 to 4.80.

The estimated sample size can also detect with 80% power and the same alpha level an expected rate of STB discontinuation of 15%. If we assume that the expected discontinuation rate is 2% based on previous study findings, then the available sample size allows us to detect a rate as low as 0.8%. The number of recruited subjects will be assessed across the study duration and adjustments may be made, if determined as necessary.

9.6. Data Management

All individual data will be collected using a commercial web-based electronic data capture tool deployed at each participating site. The data coordinating center will retrieve, manage, and prepare the datasets for analysis from electronic CRFs. Data will be stored on a secure network drive with access to authorized personnel from the investigator's biometrics team only. A log of authorized personnel will be stored with the master file. Data then will be transferred to Gilead for analysis. The datasets will be transformed into a Common Data Model structure as proposed by the US Food and Drug Administration's (FDA) Sentinel Project for further manipulation {22284}.

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).

9.7. Data Analysis

Baseline information on subject demographics (ie, age, sex, race/ethnicity, and BMI) and other clinical characteristics will be summarized using descriptive statistics (ie, 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, and for those with incident PRT and reversibility events.

Changes in serum creatinine and creatinine clearance (eGFR) at baseline and during follow-up will be assessed using descriptive statistics (ie, sample size, mean, standard deviation, median, interquartile range, minimum and maximum) and by the categories outlined in the SmPC (ie, < 70 and ≥ 70 mL/min). Descriptive analyses also will be performed to assess patient management and monitoring per the STB SmPC at baseline and upon STB discontinuation (ie, the frequency of laboratory measurements and the values for creatinine clearance, serum phosphate, serum/blood glucose, and serum potassium when available). The risk factors for PRT associated with the use of STB and potentially nephrotoxic concomitant medications will be evaluated by comparing patients with PRT events to those without events.

The number and proportion of subjects with Stribild discontinuation due to PRT will be reported with 95% confidence intervals (CIs). The rate of STB discontinuation in these patients will be estimated using person-time at risk as the denominator and reported with 95% CIs. The nearest available eGFR measurement (and/or serum phosphate) also will be reported among these subjects. Reversibility, as measured by serum creatinine and other renal tubular markers, will be assessed by numbers and proportions of those with STB discontinuation, along with the median time to reversibility.

A multivariate Poisson regression model will be built to estimate the adjusted PRT incidence rate and 95% CIs given potential baseline confounders.

9.8. Quality Control

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

9.9. Limitations of the Research Methods

Limitations of this study are those common to non-randomized observational studies. There may be residual confounding in the computation of the PRT rates or the discontinuation rates that is not completely addressed by adjusting for demographics or other covariates. Selection bias may also be present, as the sites may elect to enroll patients in the study that may either have a better or worse health status compared with the general HIV-positive treated population. Specifically, channeling bias may also be present as health care providers may enroll subjects without prior, or with less severe renal disease in the cohort.

9.10. Other Aspects

9.10.1. Joint Investigator/Sponsor Responsibilities

9.10.1.1. Study Discontinuation

Both the sponsor and the NEAT collaboration 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, IRBs, 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

The sponsor 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.

10.2. 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.

10.3. Informed Consent

The investigator will be responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards and alternatives of the study prior to study participation and before performing any study-related activities. The investigator will utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) 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 investigators will 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 investigators agree 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

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 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 (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 eCRF (if applicable).

11.1.1. 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.

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.

11.1.3. 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 (eg, 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 (eg, 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 11.1**.** If the laboratory abnormality is part of a

syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator 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 and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to drug therapy using clinical judgment and the following considerations:

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

- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

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

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

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

11.3. Special Situations Reports

11.3.1. 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.

11.3.2. Instructions for Reporting Special Situations

11.3.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur while exposure 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 5 calendar 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 24 hours 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 11.5. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

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

11.4. Gilead Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all AEs and SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs) as

determined by country-specific legislation or regulations where the study is conducted. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for AEs and SAEs will be determined by Gilead using reference safety information specified in the relevant local label.

11.5. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

All serious and non-serious events will be recorded on the Gilead Observational AE/SAE Study Report Form. Special Situation Reports (SSRs) will be recorded on the Gilead Special Situation Report Form. All Serious Adverse Events will be reported to Gilead DSPH within 3 calendar days of knowledge of the event and all Nonserious Adverse Events/ Special Situation Reports will be reported to Gilead DSPH within 5 calendar days of knowledge of the event.

Such AE/SSR reports should be forwarded to the DSPH contact below:

Gilead Sciences DSPH: Fax: +1 (650) 522-5477
E-mail: Safety_fc@gilead.com

11.6. Investigator and Sponsor Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all AEs and SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs), and special situation reports (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 AEs, SAEs and SSRs will be determined by Gilead using reference safety information specified in the EU SmPC Label.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

Interim and final (end of the study) reports will be submitted to the EMA based on the timelines provided in Section 6. 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.

No future publications in the form of abstracts and manuscripts have 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.

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14. APPENDICES

Number	Document Reference Number	Date	Title
1	NA	17 April 2014	ENCePP Checklist for Study Protocols
2	NA	17 April 2014	Study Acknowledgement

Appendix 1. ENCePP Checklist for Study Protocols

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

Study reference number: GS-EU-236-0141

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]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	10
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	10

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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	15
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 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)	☒	☐	☐	15
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
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)	☒	☐	☐	20

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	19
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	15
4.2.2 Age and sex?	☒	☐	☐	15
4.2.3 Country of origin?	☒	☐	☐	15
4.2.4 Disease/indication?	☒	☐	☐	15
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)	☒	☐	☐	15

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)	☒	☐	☐	15
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)	☒	☐	☐	15
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:

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?	☐	☐	☒	
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)	☒	☐	☐	16 – 19
7.2 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

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.)	☐	☐	☒	19
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.)	☐	☐	☒	19
8.1.3 Covariates?	☐	☐	☒	19
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)	☒	☐	☐	16 – 19
8.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	16 – 19
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?	☒	☐	☐	19

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?	☒	☐	☐	20
10.3 Are descriptive analyses included?	☒	☐	☐	20
10.4 Are stratified analyses included?	☒	☐	☐	20
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	20
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)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☐	☒	☐	
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?	☒	☐	☐	20
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)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	20

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?	☒	☐	☐	22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	22

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?	☒	☐	☐	9

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)?	☒	☐	☐	29
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	29

Comments:

Name of the main author of the protocol: Robertino Mera

Date: 17/04/2014

Signature: _____

Appendix 2. Study Acknowledgement

GILEAD SCIENCES INTERNATIONAL, LTD.
333 LAKESIDE DRIVE, FOSTER CITY, CA 94404 US

A Prospective, Observational Drug Utilization Study of Stribild® in Adults with HIV-1 Infection
Version 1.0, 17 April 2014

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

Robertino Mera

Gilead Study Director (Printed)
Author

Signature

17 April 2014

Date

Anne-Ruth van Troostenburg de Bruyn

Gilead EU QPPV (Printed)

Signature

17 April 2014

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 International, Ltd. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Antoni L Pozniak
Principal Investigator Name (Printed)

Signature

29th April 2014.
Date

Site Number