FINAL STUDY REPORT

Study Title:	An Observational Drug Utilization Study of Stribild® in Adults with HIV-1 Infection
Study ID:	GS-EU-236-0141
Report Version/Date:	Interim: 23 March 2016 Final: 15 September 2017
EU PAS Register No:	ENCEPP/SDPP/6524
Active Substance:	Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (150 mg/150 mg/200 mg/300 mg)
Medicinal Product:	Stribild®
Marketing Authorization Numbers:	EU/1/13/830/001 EU/1/13/830/002
Procedure Number:	EMEA/H/C/002574
Joint PASS:	N/A
Research Question and Objectives:	To assess renal risk minimization measures among Stribild®-treated subjects 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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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1. ABSTRACT

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Title:	An Observational Drug Utilization Study of Stribild® in Adults with HIV-1 Infection
Keywords:	Stribild, HIV, observational, renal
Rationale and Background:	The safety and tolerability of the single tablet regimen, Stribild® (STB) has been demonstrated in the clinical trial program and subsequently through post-marketing surveillance activities. Tenofovir disoproxil fumarate (TDF), a component of STB, has been associated with proximal renal tubulopathy (PRT). The drug utilization study (DUS) is included as a pharmacovigilance activity in the STB European Union (EU) Risk Management Plan (RMP) to investigate the effectiveness of renal risk-minimization measures for STB, the factors associated with the risk of PRT, and the reversibility of PRT.
Research Question and Objectives:	The objectives of this study were 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 Summary of Product Characteristics (SmPC) • To evaluate baseline characteristics that may be associated with risk of PRT • To evaluate the risk of PRT associated with the use of concomitant medications of nephrotoxic potential • To establish the rates of PRT and STB discontinuation due to PRT and to document reversibility • To document laboratory markers of tubular and glomerular damage, where available.
Study Design:	An observational cohort study of HIV-1 infected subjects who initiated treatment with STB.

Setting:	The study population was comprised of HIV-1 infected adults aged ≥ 18 years who have received STB and enrolled in clinics across several European countries.
Study Size:	There were 1593 subjects that were enrolled from March 2015 to September 2016 and contributed 1627.3 person-years with STB utilization.
Variables and Data Sources:	Electronic data capture at each participating clinic within the European Treatment Network for HIV, Hepatitis and Global Infectious Diseases (NEAT-ID) collected retrospective and prospective study variables gathered from standard care on a cohort of HIV-1 positive adult subjects. Baseline (STB initiation) and follow-up variables included demographics, clinical characteristics (e.g., HBV/HCV co-infection and prior renal disease), laboratory measurements (e.g., CD4 count, HIV viral load, serum creatinine, and creatinine clearance [eGFR]) and medications (i.e., prior antiretroviral therapy and concomitant medications).
Results:	There were 1593 enrolled subjects with STB utilization from March 2015 to September 2016 at 35 HIV clinics from Belgium, France, Germany, Italy, Spain, and the UK. The mean STB exposure duration during the study follow-up period was 1.02 (SD ± 0.78) years. The median number of visits with laboratory testing was 3 (IQR: 2 – 5) during the first year of treatment, with serum creatinine tested a median of 2 (IQR: 1 – 3) times. There were 89 subjects (5.6%) with a follow-up visit within the first month of STB initiation and 254 (15.9%) subjects with a follow-up visit within the first quarter. Accounting for potential baseline confounders and varying time across visits, adjusted mean serum creatinine levels increased and eGFR and CL_{cr} decreased shortly after the initiation of STB and stabilized after the initial quarter. Two subjects were reported with PRT during treatment and both discontinued STB. The observed incidence rate of PRT development was 1.23 per 1000 person-years (95% CI: 0.15 – 4.44). Due to the low number of PRT cases, risk factors for renal toxicity were indeterminate and PRT reversibility was not fully evaluated due to the short time period between STB discontinuation after PRT development and the end of the study data collection period in the affected subjects.

Discussion:	Subjects from six EU countries contributed data across the study period. Over the follow-up period, the mean serum creatinine,eGFR, and CL_{cr} levels varied over time. The changes were primarily attributed to the initial period of treatment and consistent with the known effect of cobicistat, a component of STB, on the inhibition of tubular secretion of creatinine. Although routine subject visits and renal testing appeared be different from the SmPC recommendations and were infrequent, the observed incidence of PRT and other renal events was low and similar to previous findings from the controlled clinical trials with STB and other observational studies. No new safety concerns emerged in this study. Patients with PRT were managed in accordance with the SmPC guidance to discontinue treatment.
Marketing Authorisation Holder:	Gilead Sciences International Ltd.
Names and Affiliations of Principal Investigators:	NEAT-ID President – PPD Gilead Study Director – PPD Gilead Qualified Person Responsible for Pharmacovigilance – PPD