Combined Clinical and Cross Disciplinary Team Leader Review

Date	January 04, 2017
From	Mark Needles, MD
Through	Prabha Viswanathan, MD
Subject	Clinical Review
NDA #/ Supplement#	203100/S-25
Applicant	Gilead Sciences, Inc.
Date of Submission	July 28, 2016
PDUFA Goal Date	January 28, 2016
Proprietary Name / Established (USAN) names	Stribild; Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF)
Dosage forms / Strength	Fixed-dose combination tablet containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF
Proposed Indication(s)	A complete regimen for the treatment of HIV-1 infection in pediatric patients 12 year of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild
Recommended:	Approval

1. Introduction

This review summarizes the data used to support Gilead's supplemental NDA seeking approval for Stribild (STB) for treatment of HIV-1 infection in pediatric patients ages 12 years and older. STB is a fixed dose combination antiviral product that provides a complete antiretroviral drug regimen for the treatment of HIV-1 infection. The product contains elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF). EVG is an integrase strand transfer inhibitor (INSTI) and provides antiviral activity by inhibiting the integration of HIV-1 genetic material into the host genome. COBI is a CYP3A inhibitor devoid of antiviral activity and included in STB to serve as a pharmacokinetic enhancer for EVG. Both FTC and TDF are nucleos[t]ide reverse transcriptase inhibitors (NRTIs) and provide antiviral activity by targeting the HIV-1 reverse transcriptase enzyme necessary for viral replication.

STB is currently approved in the United States as a once daily, single tablet regimen for the treatment of HIV-1 infection in adults. The approved indication includes use as an initial regimen in those who have no antiretroviral treatment (ART) history, and use to replace the

current ART regimen in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ART regimen for ≥6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STB.

This supplemental NDA was submitted by Gilead Sciences to support inclusion of adolescent patients ≥12 years of age and weighing at least 35 kg in the approved indication for STB. The submission contains pharmacokinetic, safety, and efficacy data through Week 48 from one pivotal Phase 2/3 study (Study GS-US-236-0112) of STB in HIV-1 infected, ART-naïve adolescents. Although other one-pill once-a-day regimens are approved and available for adolescents, approval of this efficacy supplement would provide an additional option for this age group.

2. Background

STB was initially approved in the United States on August 27, 2012 for the treatment of HIV-1 infection in ART-naïve adults. The approved indication was extended on December 17, 2014 to include use as a replacement for the current ART regimen in virologically suppressed, ART-experienced adults. This supplemental NDA was submitted by the applicant to support inclusion of HIV-1 infected pediatric patients ≥12 years of age, and weighing ≥35 kg to the approved indication for STB.

EVG, COBI, FTC, and TDF are available as single drug products: Vitekta (EVG), Tybost (COBI), Emtriva (FTC), and Viread (TDF). The individual components of STB are also available in eight other fixed dose combination (FDC) products: Genvoya (EVG, COBI, FTC, and tenofovir alafenamide fumarate [TAF]), Evotaz (COBI and atazanavir), Prezcobix (COBI and darunavir), Atripla (FTC, TDF, and efavirenz), Complera (FTC, TDF, and rilpivirine), Truvada (FTC and TDF), Descovy (FTC and TAF), and Odefsey (FTC, TAF, and rilpivirine). Four of these fixed dose combination products - Genvoya, Atripla, Complera, and Odefsey - are single tablet regimens. Genvoya is of particular relevance because it contains the same dosages of EVG, COBI, and FTC as STB. The only difference between Genvoya and STB is the former product contains the TAF rather than TDF. Both TDF and TAF are prodrugs of the active ingredient, tenofovir diphosphate. The main difference between the two drugs is that TDF is converted to tenofovir in the blood, whereas TAF is largely metabolized intracellularly, resulting in lower serum concentrations of tenofovir.

The fixed dose combination product Genvoya (EVG/COBI/FTC/TAF) is approved for use in adolescents at the same dose as adults. The other products containing EVG and/or COBI (i.e., Vitekta, Tybost, Evotaz, and Prezcobix) are not approved for use in adolescents. FTC and TDF as individual products and components of combination products (Atripla, Complera, and Truvada) are approved for use in adolescents at the same dose as adults. Hence, there is a significant amount of historical data supporting the safety, tolerability, and antiviral activity of the components of STB at the doses proposed in the current efficacy supplement.

There are many benefits to having FDC products available for treatment of HIV infection in children, particularly single-tablet regiments that can be administered once daily. Most

importantly, FDC products reduce pill-burden and thus increase the likelihood of adherence; adherence is an important factor in achieving HIV viral suppression, especially for adolescents. While there are single-tablet regimens already approved for adolescents (Atripla, Genvoya, Complera, and Odefsey), the approval of STB for this age group would provide an additional one-pill, once-a-day regimen from the list of Recommended Regimens in the Department of Health and Human Services Treatment Guidelines for ART-naïve patients [Panel on Antiretroviral Guidelines for Adults and Adolescents, 2016].

3. CMC/Device

Currently, the only approved STB formulation is the fixed-dose combination tablet containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF. The marketed formulation was used in trial GS-US-236-0112. The applicant did not present new chemistry or manufacturing information in this pediatric submission.

4. Nonclinical Pharmacology/Toxicology

Nonclincal pharmacology/toxicology studies were performed for each of the 4 active ingredients in STB and have been reviewed in prior submissions. No new nonclinical pharmacology/toxicology studies were submitted in the current sNDA.

5. Clinical Pharmacology/Biopharmaceutics

Analyses of the PK data are an essential part of this supplemental NDA because efficacy is extrapolated from adults if the pediatric PK exposures match the adult exposures deemed safe and effective. Intensive pharmacokinetic (PK) samples were collected from 14 subjects ages 12 to <18 years enrolled in Part A of Study GS-US-236-0112. Samples were collected on Day 10 at the following timepoints: pre-dose (0), 2, 4, 4.5, 5, 8, and 12 hours post-dose. The PK data observed in this trial of HIV-infected adolescents were compared to the historical data in HIV-infected adults administered STB (Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104).

EVG AUC_{tau} was the primary PK endpoint; C_{max} and C_{trough} for EVG and AUC_{tau}, C_{max} and C_{trough} for COBI, FTC, and tenofovir (TFV) were the secondary PK endpoints. EVG exposure was selected as the primary endpoint by the applicant because the study was developed when there were no other EVG containing products approved to treat HIV-1 infection in adolescents. COBI exposure was a secondary endpoint because it serves as a pharmacokinetic enhancer for EVG and lacks antiviral activity. FTC and TDF exposures were also secondary endpoints because the doses for each in STB are consistent with the approved pediatric doses: 200 mg of FTC for patients weighing >33 kg and 300 mg of TDF for patients weighing >35 kg).

Table 5-1 summarizes the geometric least-squares mean (GLSM) PK exposures from the 14 adolescents who participated in the intensive PK evaluations in GS-US-236-0112 versus the combined adult data in the historical studies. EVG AUC_{tau} and C_{max} were increased by 30.29%

and 41.5%, respectively, in adolescents in Study GS-US-236-0112 compared with adults in Phase 2 and Phase 3 studies. The 90% confidence intervals (CIs) of the GLSM ratios for the EVG PK parameters extended beyond the predefined equivalence boundaries of 70% to 143%. The increased EVG exposure was not considered clinically relevant based on the favorable safety profile observed in this study. Exposure-safety analyses performed by the clinical pharmacology reviewer did not demonstrate a relationship between EVG exposures (C_{max}, C_{trough}, AUC_{tau}) and the occurrence of clinical adverse events. Please refer to the Clinical Pharmacology review by Amal Ayyoub for additional details regarding the EVG exposure safety analysis.

Overall, the COBI, FTC, and TFV PK exposures were increased in adolescents in Study GS-US-236-0112 compared with adults in Phase 2 and Phase 3 studies. The observed exposures for COBI (AUC_{tau} and C_{max}) and FTC (AUC_{tau}, C_{max}, and C_{trough}) in adolescents met the criteria for equivalence (predefined equivalence boundary of 70% to 143%). TFV AUC_{tau} and C_{max} were increased by 37.46% and 30.78%, respectively, but the exposures were in range of those observed historically in TDF-containing boosted-protease inhibitor regimens. Please refer to Clinical Pharmacology review by Amal Ayyoub, Ph.D. for complete details.

Table 5-1: Intensive Pharmacokinetic Results from Adolescents in Study GS-US-236-0112 Compared to Adults from Historical Studies

	GLSM		
PK Parameter	**Adolescent (GS-US-236-0112)**	**Adult (Historical Studies)**	**%GLSM Ratio (90% CI) Adolescents/Adults**
Elvitegravir	**N = 14**	**N = 419[a]**	
AUC_{tau} (ng•h/mL)[b]	28,529.11	21,896.87	130.29 (104.79, 162.00)
C_{max} (ng/mL)	2390.01	1689.04	141.50 (116.06, 172.52)
C_{trough} (ng/mL)	410.08	387.42	105.85 (69.99, 160.09)
Cobicistat	**N = 14**	**N = 483[c]**	
AUC_{tau} (ng•h/mL)[b]	9200.48	8728.69	105.41 (78.12, 142.22)
C_{max} (ng/mL)	1275.17	1178.59	108.20 (84.00, 139.36)
C_{trough} (ng/mL)	18.93	17.72	106.86 (65.92, 173.21)
Emtricitabine	**N = 14**	**N = 61[d]**	
AUC_{tau} (ng•h/mL)	14,508.95	12,106.32	119.85 (103.27, 139.08)
C_{max} (ng/mL)	2124.40	1813.97[f]	117.11 (100.69, 136.21)
C_{trough} (ng/mL)	98.48	104.44	94.29 (78.77, 112.88)
Tenofovir	**N = 14**	**N = 419[a]**	
AUC_{tau} (ng•h/mL)	4281.03	3114.36	137.46 (121.01, 156.14)
C_{max} (ng/mL)	409.41	313.05	130.78 (110.31, 155.05)
C_{trough} (ng/mL)	83.83	68.21	122.89 (109.33, 138.14)

[a] Combined data from HIV-infected adults who received STB in historical studies GS-US-236-0103 and GS-US-236-0104, and Study GS-US-236-0102 (PK Substudy)

[b] The predose concentration was used as a surrogate for the 24-hour postdose concentration for the purpose of estimating AUC_{tau}

[c] Combined data from HIV-infected adults who received STB in historical studies GS-US-236-0103 and GS-US-236-0104, and Study GS-US-236-0102 (PK Substudy) and adults who received COBI-boosted atazanavir plus FTC/TDF in Studies GS-US-216-0105 and GS-US-216-0114

[d] Combined data from HIV-infected adults who received STB and participated in the PK substudy in historical studies in historical studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

[f] N = 62 for C_{max}

Source: Adapted from Clinical Overview, Module 2, Section 2.5, Table 2.

Although higher EVG and TFV exposures were observed in adolescents compared to historical studies in adults, the favorable safety data in this study support the dose.

6. Clinical Microbiology

Post-baseline genotypic and phenotypic resistance testing was performed during study GS-US-236-0112 if virologic rebound or suboptimal virologic response was detected. Virologic rebound was defined as the occurrence of any of the following at two consecutive visits: HIV-1 RNA ≥ 400 c/mL after achieving HIV-1 RNA <50 c/mL or a > 1 $\log_{10}$ increase in HIV-1 RNA. Subjects were considered to have a suboptimal virologic response if they had HIV-1 RNA ≥ 400 c/mL and < 1 $\log_{10}$ reduction from baseline at the Weeks 8 and 12 visits. A total of 3 subjects (all having confirmed virologic rebound) were eligible for post-baseline resistance testing by Week 48 and none of these subjects developed treatment-emergent genotypic or phenotypic resistance to EVG, FTC, or TDF. Please refer to the clinical virology review by

Sung S. Rhee, Ph.D. for further details. No changes to the microbiology section of the label were proposed.

7. Clinical/Statistical- Efficacy

Efficacy Summary

As discussed in Section 5, pharmacokinetic data provide the pivotal data to support approval of the currently marketed STB formulation for adolescent patients. This section summarizes the Week 48 virologic results for study GS-US-236-0112, which provide supportive evidence of efficacy. Extrapolation of efficacy for antiretroviral drugs such as STB can be made based on the presumption that the course of HIV disease and the effects of the drugs are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease, noting that the routes of transmission may be different [Domachowske, 1996]. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age, in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. Once infected, the pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections as well as opportunistic infections similar to those observed in HIV-infected adults.

For both children and adults, treatment of HIV-1 infection is monitored by the same two parameters: CD4 cell count (a marker of immune status) and HIV-1 RNA viral load (a marker of viral burden). Antiretroviral drugs have been shown to lower HIV viral load, improve CD4 counts, and improve general clinical outcomes in adult and pediatric subjects. Consequently, treatment recommendations are very similar across all age groups [Panel on Antiretroviral Guidelines for Adults and Adolescents, 2016, Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2016].

Study GS-US-236-0112 is a Phase 2/3, multi-center, open-label, non-comparative study to evaluate the pharmacokinetics, safety, and antiviral activity of STB in HIV-1 infected, ART-naïve adolescents. Fifty subjects were enrolled and treated with STB: 14 in Part A and 36 in Part B. The subjects in Part A participated in an intensive PK evaluation on Day 10. EVG AUC_{tau} was increased by 30.29% compared to historical studies in adults but this modestly increased exposure in adolescents is not considered clinically relevant.

Based on FDA's snapshot analysis, the proportion of subjects with HIV-1 RNA <50 copies/mL was 88% (44/50) at both Weeks 24 and 48. The proportion of subjects with virologic success at Week 48 was greater among subjects with a baseline HIV-1 RNA ≤100,000 c/mL and males compared to those with baseline HIV-1 RNA >100,000 c/mL and females, respectively. The small sample size for these relevant subgroups may confound findings from the sub-group analysis. The CD4 count increased over the 48 week period and no subjects developed genotypic or phenotypic resistance to STB.

7.1 Summary of Trial Design

Study GS-US-236-0112 (236-0112) was the pivotal trial submitted to support approval of STB for treatment of HIV-1 infection in adolescent patients ≥12 year of age and weighing at least 35 kg. The study was a Phase 2/3, multi-center, open-label, non-comparative study designed to evaluate the pharmacokinetics, safety, and antiviral activity of STB in HIV-1 infected, ART-naive adolescents. Subjects were enrolled at 19 sites consisting of 7 located in the USA, 7 located in South Africa, and 5 located in Thailand.

The primary objectives of the study were to: (1) evaluate the steady state pharmacokinetics (PK) and confirm the dose of STB, and (2) evaluate safety and tolerability of STB through Week 48. A key secondary objective was to evaluate the antiviral activity of STB through Week 48.

Key inclusion criteria were age (12 to <18 years), weight (≥35 kg) and being ART-naïve (i.e., no prior use of any anti-HIV-1 drug other than that given for prevention of mother-to-child transmission). Subjects were required to have the following parameters at screening: HIV-1 RNA ≥1000 copies/mL, CD4+ cell count >100 cells/μL, genotype showing sensitivity to FTC and TDF, estimated glomerular filtration rate (eGFR) ≥ 90 ml/min/1.73m^2 calculated using the Schwartz formula, and clinically normal ECG (or if abnormal, determined to be not clinically significant by the investigator).

Key exclusion criteria included a diagnosis of a new AIDS-defining condition (with the exception of CD4 count and percentage criteria) within 30 days prior to screening, or evidence of active tuberculosis disease within 3 months of screening. Subjects were also excluded if they had any serious or active medical or psychiatric illness that in the opinion of the investigator would interfere with subject treatment, assessment, or compliance (i.e., any uncontrolled disorders).

The STB dose proposed for adolescents weighing at least 35 kg was the same as the approved dose for HIV-1 infected adults: a single tablet that contains 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF, administered once daily. . Adolescents received the adult STB tablets because the safety, efficacy, and PK of the individual agents in the adult STB tablets were anticipated to be comparable between adolescents and adults. In addition, the doses of FTC and TDF in the adult STB tablet are consistent with approved pediatric doses (200 mg of FTC for patients >33 kg; 300 mg of TDF for patients ≥35 kg).

The main phase of the study consisted of 50 subjects enrolled into one of two sequential parts. Enrollment began in Part A, and these subjects participated in an intensive PK evaluation on Day 10. The purpose of Part A was to confirm the appropriateness of the proposed STB dose (1 STB tablet once daily) for adolescents weighing at least 35 kg. The STB dose was confirmed if any of the following intensive PK criteria were met: adolescent vs. adult EVG exposures within the 90% confidence interval bounds of 70-143% or adolescents maintain EVG C_{trough} above 44.5 ng/ml (the protein-binding adjusted concentration required to produce 95% inhibition against HIV-1 integrase). Subjects were discontinued if they had EVG exposures <44.5 ng/mL (<2.5th percentile of the adult exposure) despite compliance with study treatment. Additional subjects were enrolled into Part B following confirmation of adequate

EVG exposure from at least 12 subjects in Part A. Intensive PK samples were not collected in Part B because the purpose of this part was to assess the safety and efficacy (antiviral activity) of STB over a 48 week period. Subjects in Part A that continued STB after the Day 10 intensive PK visit were also evaluated for safety and efficacy for a minimum of 48 weeks.

All enrolled subjects received one STB tablet once daily with food for 48 weeks. Subjects returned for study visits at Week 1, Day 10 (Part A only), Weeks 2, 4, 8, 12, 16, and 24, and then every 8 weeks through Week 48. All subjects who completed 48 weeks of study treatment were given the option to continue to receive STB in an extension phase of the study. During the extension phase, subjects returned for study visits every 12 weeks until: a) the subject turned 18 years old and STB was commercially available for adults in the country in which the subject was enrolled; b) STB became commercially available for adolescents in the country in which the subject was enrolled; or c) Gilead Sciences elected to terminate development of STB in the applicable country.

The following PK parameters were assessed for EVG, COBI, FTC, and tenofovir (TFV) following administration of STB: area under the concentration vs. time curve over the dosing interval (AUC_{tau}), maximum observed concentration of drug (C_{max}), concentration at the end of the dosing interval (C_{trough}), time to C_{max} (T_{max}), apparent oral clearance after administration of the drug (CL/F), and apparent volume of distribution of the drug (V_z/F). In Part A, the primary PK endpoint was AUC_{tau} for EVG. The secondary PK endpoints in Part A were C_{trough} and C_{max} for EVG, and AUC_{tau}, C_{max}, and C_{trough} for COBI, FTC, and TFV. Subjects in Part A had intensive PK samples collected over a single day (Day 10) and at the following time points: pre-dose (0), 2, 4, 4.5, 5, 8, and 12 hours after a witnessed dose. All enrolled subjects had trough (20 to 24 hours post-dose) and random single PK samples collected over the course of the study. Trough PK samples were collected at Weeks 1, 2, 24, and 48; random single PK samples were collected at Weeks 4, 8, 12, 16, 32, 40, and early study discontinuation (if applicable).

Safety assessments for all subjects included monitoring of adverse events (AEs) and serious adverse events (SAEs), bone mineral density (BMD) from dual energy x-ray absorptiometry (DEXA) scans, physical examinations including vital signs, and safety laboratory parameters including chemistry, hematology, fasting lipid profile, urinalysis, and serum bone biomarkers. The primary safety endpoint was incidence of treatment-emergent SAEs and all treatment-emergent adverse events.

Efficacy assessments included evaluation of virologic outcomes based on HIV-1 RNA values at Weeks 24 and 48. Virologic outcomes were calculated according to the FDA's Snapshot algorithm or the Missing, Switch or Discontinuation = Failure (MSDF) algorithm with a cutoff of HIV-1 RNA < 50 c/mL. Genotypic and phenotypic resistance testing were performed in those with suboptimal virologic response, virologic rebound, and/or at Week 48 or early study discontinuation if HIV-1 RNA ≥ 400 c/mL.

7.2 Demographics and Baseline Characteristics

A total of 50 subjects were enrolled in Study 236-0112. Part A consisted of 14 and Part B consisted of 36 subjects. The investigators in South Africa enrolled 22 subjects (44%) and the investigators in the US and Thailand enrolled 14 subjects (28%), each. All subjects received STB single tablet regimen, and EVG exposures were confirmed from all 14 subjects in Part A.

Table 7.2-1 summarizes the demographic characteristics for the subjects enrolled in Study 236-0112. There were 35 males (70%) and 15 females (30%). The median age was 16 years (range 12 -17). Sixty-eight percent of subjects were Black. All subjects weighed ≥35 kg. The median eGFR at baseline was 139.5 ml/min/1.73m^2 and 97.8 ml/min/1.73m^2 when calculated using the Schwartz formula and modified Schwartz formula, respectively.

Table 7.2-1: Demographics

Demographics	**STB N=50**
Sex, n (%)	
Male	35 (70)
Female	15 (30)
Age (years)	
Median (Q1 –Q3)	16 (15 – 17)
Min, Max	12, 17
Race, n (%)	
Black	34 (68)
Asian	14 (28)
White	1 (2)
Mixed race	1 (2)
Weight in kg	
Median (Q1- Q3)	56.4 (47.1 – 64.8)
Min, Max	35.1, 91.2
Height in cm	
Median (Q1- Q3)	163.3 (155 – 170.7)
Min, Max	125, 184
Body Mass Index (kg/m^2)	
Median (Q1 – Q3)	20.9 (18.5 – 23.0)
Min, Max	15.9, 28.5
Estimated Glomerular Filtration Rate by Schwartz Formula (mL/min/1.73 m^2)	
Median (Q1 – Q3)	139.5 (128.0 – 161.0)
Min, Max	102.0, 198.0
Estimated Glomerular Filtration Rate by Modified Schwartz Formula (mL/min/1.73 m^2)	
Median (Q1 – Q3)	97.8 (94.5 – 111.2)
Min, Max	83.2, 132.0

Source: Adapted from clinical study report for GS-US-236-0112, Table 4; Clinical reviewer's calculations.

As summarized in Table 7.2-1, the majority of subjects were male sex and/or Black race. All subjects fulfilled the minimum age, weight, and eGFR (calculated by Schwartz formula) criteria at baseline. Although eGFR values by the modified Schwartz formula were lower than by the Schwartz formula, median baseline eGFR values were ≥ 90 ml/min/1.73m^2 using either formula.

Baseline Disease Characteristics

Table 7.1-2 summarizes the baseline characteristics for the study population. Eighty percent (40/50) and 96% (48/50) of the subjects had a baseline HIV-1 RNA of ≤100,000 copies/mL and a baseline CD4 count of ≥200 cells/μL, respectively. At baseline, 74% (37/50) of subjects had asymptomatic HIV-1 infection. One subject was HBsAg positive, and no subject was HCV antibody positive.

Table 7.2-2: Baseline Characteristics

	STB N=50
HIV-1 RNA (copies/mL)	
Median (Q1 – Q3)	35,850 (20,950 – 72,500)
Min – Max	1,520 - 532,000
HIV-1 RNA category, n (%)	
≤100,000	40 (80)
>100,000	10 (20)
CD4 count (cells/μL)	
Median (Q1 – Q3)	402 (297 - 486)
Min – Max	133 – 734
CD4 count category, n (%)	
<200	2 (4)
200 - 499	38 (76)
≥500	10 (20)
HIV Disease Status, n (%)	
Asymptomatic	37 (74)
Symptomatic	12 (24)
AIDS	1 (2)

Source: Adapted from clinical study report for GS-US-236-0112, Table 5; Clinical reviewer's calculations.

Overall, most of the subjects had a baseline HIV-1 RNA ≤100,000 copies/mL, had a baseline CD4 count ≥200 cells/μL, and were not CDC HIV Category C or Stage 3.

7.3 Subject Disposition

There were 48 subjects (96%) who completed the main phase of the study and received at least 48 weeks of study treatment. Two subjects prematurely discontinued study treatment in the main phase: 1 subject discontinued at Week 12 due to pregnancy and 1 subject discontinued at Week 40 due to non-adherence with study drug. Forty subjects participated in the extension phase of the study, and 35 of these subjects remain on study drug at the time of this submission. Please see Section 8.3.3-1 for information regarding dropouts in Study 236-0112.

7.4 Analysis of Efficacy Endpoints

The primary efficacy analysis focused on the steady-state PK of STB in ART-naïve adolescents. The PK data were relied upon to extrapolate efficacy and the clinical efficacy (antiviral activity) data were presented as supportive data. Intensive PK data were collected during Part A to determine whether STB had comparable exposures to the adult dose for each of the four drugs. The primary PK endpoint was AUC_{tau} for EVG and the secondary PK endpoints were C_{trough} and C_{max} for EVG and AUC_{tau}, C_{max}, and C_{trough} for COBI, FTC, and TFV. Please see Section 5 (Table 5-2) for the results of this analysis.

Table 7.4-1 summarizes the results from the applicant's clinical efficacy analysis of virologic outcomes at Weeks 24 and 48. The proportion of subjects with virologic success (HIV-1 RNA <50 copies/mL) was 88% (44/50) at each time point. No subject prematurely discontinued study treatment due to lack of efficacy or adverse event; however, 2 subjects prematurely discontinued study treatment for other reasons. One of the subjects had an HIV-1 RNA <50 c/mL and the other subject an HIV-1 RNA ≥50 c/mL at the time of discontinuation (Week 12 and Week 40, respectively).

Ninety-five percent (42/44) of the subjects with virologic success at Week 24 and 60% (3/5) of the subjects with virologic failure (HIV-1 RNA ≥50 c/mL) at Week 24 had the same virologic outcome at Week 48. Two subjects with virologic failure at Week 24 and 2 subjects with virologic success at Week 24 became virologic successes and virologic failures, respectively, by Week 48. Overall, similar proportions of subjects were categorized as virologic successes or virologic failures at Weeks 24 and 48.

Table 7.4-1: Virologic Outcomes at Weeks 24 and 48 (Snapshot Algorithm)

	STB (N=50)	
	Week 24[a]	**Week 48**[b]
Virologic Success HIV-1 RNA <50 c/mL	**44 (88%)**	**44 (88%)**
Virologic Failure	**5 (10%)**	**5 (10%)**
HIV-1 RNA ≥50 c/mL	5 (10%)	4 (8%)
Discontinued for other reasons[c] while HIV-1 RNA ≥50 c/mL	0	1 (2%)
No Virologic Data Discontinued for other reasons[d] while HIV-1 RNA <50 c/mL	**1 (2%)**	**1 (2%)**

[a] The Week 24 analysis window was between Days 140 and 195 (inclusive).
[b] The Week 48 analysis window was between Days 308 and 377 (inclusive).
Source: Adapted from Summary of Clinical Efficacy, Module 2, Section 2.7.3, Tables 3 and 4; Clinical reviewer's calculations.

7.5 Subpopulations

The proportion of subjects with virologic success (HIV-1 RNA <50 c/mL) at Week 48 is summarized in Table 7.5-1 by baseline category. Virologic success at Week 48 was documented in 90% (36/40) and 80% (8/10) of subjects with baseline HIV-1 RNA ≤100,000 and >100,000 c/mL, respectively. Virologic success at Week 48 was also documented in more than 90% of males, subjects ages 12 to 14 years, non-Black race, and those in the US or Thailand regions. However, these trends should be regarded cautiously because the small sample size for these relevant subgroups may confound the results.

Table 7.5-1:
Proportion (%) With HIV-1 RNA <50 c/mL at Week 48 by Baseline Category

Baseline Category	STB N=50
Overall	88% (44/50)
Baseline HIV-1 RNA	
≤ 100,000 c/mL	90% (36/40)
> 100,000 c/mL	80% (8/10)
Sex	
Male	91% (32/35)
Female	80% (12/15)
Sex	
Male	91% (32/35)
Female	80% (12/15)
Age	
12 – 14 yrs	92% (11/12)
15 – 17 yrs	87% (33/38)
Race	
Black	85% (29/34)
Non-Black	94% (15/16)
Region	
South Africa	82% (18/22)
USA	93% (13/14)
Thailand	93% (13/14)

Source: Adapted from clinical study report for GS-US-236-0112; Clinical reviewer's calculations.

7.7 Additional Efficacy Issues/Analyses

Overall, a favorable immunological effect was observed through Week 48 with a positive median change in CD4 cell count at Weeks 24 and 48: the median change from baseline CD4 cell count was +152 cells/mm^3 at Week 24, and +163 cells/mm^3 at Week 48. The resistance analysis consisted of 3 subjects who all had confirmed virologic rebound. None of the subjects had treatment-emergent genotypic or phenotypic resistance to any of the study drugs.

8. Safety

Safety Summary

Safety data from 50 subjects enrolled in GS-US-236-0112 support the safety and tolerability of STB in the adolescent population. The majority of treatment emergent adverse events were non-serious, mild or moderate in severity, and self-limited. There were no deaths or adverse events leading to withdrawal. There was a low incidence of serious adverse events, and none of the serious adverse events were considered related to study drug. No notable changes in

standard or height-age spine and total body less head (TBLH) BMD Z-scores were observed between baseline and Week 48. Median changes from baseline serum creatinine and eGFR were similar to those observed for adults. One subject had treatment-emergent laboratory abnormalities consistent with proximal renal tubulopathy and was ultimately lost to follow up. Overall, the adverse reaction profile in adolescents was similar to that for adults. No new or unexpected toxicities were observed.

8.1 Approach to the Safety Review

All safety data reviewed in this submission came from a single trial, GS-US-236-0112. As described in Section 7.1, study GS-US-236-0112 is a Phase 2/3, open label, multicenter, single-arm trial designed to evaluate the PK, safety, and efficacy of STB in HIV-1 infected ART-naïve adolescents. The safety population included all subjects who received at least one dose of study medication (n=50). Safety data were analyzed by the clinical reviewer using JReview software.

The primary safety endpoint was incidence of treatment-emergent SAEs and all treatment-emergent adverse events. Treatment-emergent adverse events (TEAEs) included all events that began on or after the first day of study treatment and through 30 days post-permanent discontinuation (if applicable). Laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) were only recorded as AEs (adverse events) or SAEs (serious adverse events) if they were associated with signs and/or symptoms. In addition, laboratory abnormalities independent of the underlying medical condition that required medical or surgical intervention or led to study interruption, modification, or discontinuation were recorded as AEs or SAEs. Because the study did not have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences, descriptive statistics are used to describe the observed findings.

The STB prescribing information contains Warnings and Precautions for renal impairment and decreases in bone mineral density. Therefore, additional focused analyses were performed to identify and characterize renal and bone adverse events in adolescents. Neuropsychiatric adverse events were also a focus of this review, based on the findings of pivotal trials GS-US-236-0102 and GS-US-236-0103 in adults; although neuropsychiatric events occurred at lower frequency in the adult trials, the potentially serious nature of these events warrants thorough consideration.

8.2 Adequacy of Safety Assessments

8.2.1 Routine Clinical Testing

The safety assessments were considered sufficient. Routine clinical testing consisted of both clinical and laboratory evaluations. Evaluations occurred at screening, Day 1 (trial entry within 35 days of screening), and Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48. Subjects who discontinued the study early had routine clinical testing at 72 hours after stopping therapy (early study discontinuation visit; ESDD) and at 30 days post therapy (30-Day Follow-Up Visit). After 48 weeks of study treatment, subjects who elected to participate in the extension phase returned for routine clinical testing every 12 weeks until reaching the age where STB is

commercially available in the country they were enrolled or Gilead Sciences elects to terminate development of STB in the applicable country.

8.2.2 Evaluation of Potential Adverse Events for Similar Drugs in Drug Class

The known safety profile of EVG, COBI, FTC, and TDF were taken into consideration for this submission. All four drugs are approved for adolescents at the same doses present in STB. As previously mentioned, adverse events of special interest included bone safety, renal safety, and neuropsychiatric events. Please see Section 8.3.5 for Submission Specific Primary Safety Concerns.

8.3 Major Safety Results

8.3.1 Deaths

No deaths have occurred during Study 236-0112.

8.3.2 Nonfatal Serious Adverse Events

Table 8.3.2-1 summarizes all nonfatal serious adverse events (SAEs) reported during Study 236-0112 through October 23, 2015. There were 4 subjects who experienced serious clinical events. Each SAE was reported in no more than one subject (2%). None of the SAEs were considered related to STB treatment, resulted in permanent discontinuation of the study drug, or were responsible for subject withdrawal from the trial.

Table 8.3.2-1:
Nonfatal Serious Adverse Events

SAE by Preferred Term	STB N=50 n (%)
Number of Subjects Experiencing Any SAE	4 (8)
Asthma	1 (2)
Acute kidney injury	1 (2)
Dehydration	1 (2)
Disseminated tuberculosis	1 (2)
Food poisoning	1 (2)
Gastroenteritis Shigella	1 (2)
IRIS	1 (2)
Oral candidiasis	1 (2)
Pneumonia	1 (2)
Suicidal behavior	1 (2)

Source: Adapted from clinical study report for GS-US-236-0112.

Narratives for the 4 subjects who had SAEs are summarized below:

- Subject 2880-1001
  The subject is an 18 year old male who experienced multiple SAEs after starting STB treatment. Approximately 18 weeks after starting the study drug, the subject experienced Grade 3 suicidal behavior. The subject had a history of a prior suicidal attempt related to

social stressors. The suicidal behavior while on study drug was precipitated by the following acute environmental stressors: the subject's mother did not return his call on Mother's Day and his partner revealed the subject's HIV status in the community. The case narrative mentions that the subject took 20-30 Tylenol 500 mg pills and was hospitalized that day. No toxicities were reported. The suicidal behavior was reported as resolved that day and the subject discharged from the hospital 1 week later. STB therapy was continued throughout. Grade 1 affective disorder was reported as a non-serious adverse event, with onset the same day as the suicidal behavior and the outcome ongoing.

The subject also experienced Grade 2 acute kidney injury and Grade 3 gastroenteritis from *Shigella* as SAEs starting approximately 39 weeks after the first dose of study drug. The subject at that time presented to an emergency department with symptoms consistent with gastroenteritis associated with bloody diarrhea. The subject was admitted for hydration and noted to have a positive stool sample for *Shigella* . His serum creatinine on admission was 2.5 mg/dL (Grade 2) and was thought to be related to dehydration. Serum creatinine improved with hydration and was reported as 1.2 mg/dL at the time of discharge (reference range: 0.45 – 1.2 mg/dL). Normal values were reported at subsequent study visits as well as at the preceding study visits in this subject. STB treatment was continued throughout. This reviewer agrees with the investigator's assessment that the SAEs experienced in this subject were not related to study treatment.

- Subject 7521-1025:
  The subject is a 15 year old female who experienced Grade 1 oral candidiasis and Grade 2 immune reconstitution inflammatory syndrome (IRIS) 18 days after starting STB treatment. The subject was diagnosed with a lower respiratory tract infection and hospitalized for 5 days. She was treated symptomatically and recovered by 3 months. This reviewer agrees with the investigator's assessment that the SAEs experienced in this subject were not related to study treatment.

- Subject 7546-1010:
  The subject is an 18 year old female who experienced multiple SAEs after starting STB treatment. She had a history of asthma (ongoing) and pulmonary tuberculosis (resolved by 15 years old) prior to enrollment. After starting the study drug, the subject was hospitalized twice for community acquired pneumonia associated with asthma exacerbation at approximately 55 weeks and again at approximately 65 weeks. Both pneumonia and asthma were reported as Grade 2 SAEs and resolved by 3 weeks. Grade 2 disseminated tuberculosis and Grade 2 dehydration were additional SAEs reported during the first and second hospitalizations, respectively. Anti-tuberculosis treatment with isoniazid plus vitamin B6, ethambutol, levofloxacin, and pyrazinamide was started during the first hospitalization because the subject had chest radiographic findings consistent with tuberculosis and a history of weight loss. The disseminated tuberculosis event is ongoing and has an expected stop date in one year per treatment plan. The subject's dehydration at the second hospitalization resolved after 2 days. Both hospitalizations in this subject lasted less than 1 week and STB treatment continued throughout all of the SAEs. This reviewer agrees with the investigator's assessment that the SAEs experienced in this subject were not related to study treatment.

  The subject also had Grade 3 weight decreased reported as a non-serious treatment-emergent adverse event at approximately 32 weeks after starting STB treatment. Her baseline weight was 51.1 kg and weight decrease was initially reported as Grade 2 at Week 24 (-4.9 kg decrease from baseline). The event is ongoing and the last reported weight was 44.8 kg at Week 120 (-6.6 kg decrease from baseline). STB treatment was continued throughout and the investigator did not believe the event was related to study treatment. This reviewer agrees with the investigator's assessment and the event may be related to her tuberculosis diagnosis.

- Subject 8570-1041:
  The subject is a 16 year old male who experienced Grade 2 food poisoning approximately 28 weeks after starting STB treatment. The event resulted in a 1 day hospitalization for oral rehydration and was reported as resolved when the subject was discharged. STB therapy was continued throughout. This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study treatment.

8.3.3 Dropouts and Discontinuations

The median total exposure to study drug was 61.6 weeks (range 12 to 132.1 weeks). Thirty-five subjects (70%) remained on the study drug at the time of this submission. The most frequent reason for discontinuation was "completed main phase" and occurred in 16% of the subjects. The most frequent reason for premature discontinuation was "non-adherent with study treatment" and this reason was reported in 3% of the subjects. Table 6.1.3-1 summarizes the subject disposition in Study 236-0112.

Table 8.3.3-1: Subject Disposition
(All Available Data as of October, 23 2015)

Population	STB N=50 n (%)
Ongoing at time of report	35 (70)
Completed Week 48	48 (96)
Off Study Drug	15 (30)
Completed Main Phase Treatment[a]	8 (16)
Completed Extension Phase Treatment[b]	3 (6)
Non-adherent with Study Drug	3 (6)
Pregnancy	1 (2)

[a] "Completed Main Phase Treatment" includes subjects who discontinued the study drug upon completion of 48 weeks of study treatment.
[b] "Completed Extension Phase Treatment" includes subjects who discontinued the study drug study in the extension phase because they turned 18 years old and the study drug is commercially available for adults.
Source: Adapted from clinical study report for GS-US-236-0112, Table 2.

Two subjects discontinued the study drug prior to the Week 48 Visit. One subject withdrew at Week 40 because of non-adherence to study treatment and the other subject withdrew at Week 12 due to pregnancy. Subject 7521-1006 is a 17 year old who had a positive pregnancy test at Week 12. The study drug was discontinued and the subject remained in the study through Week 48. The pregnancy was complicated by pre-term labor at 34 weeks of gestation requiring hospitalization. She later delivered at 38 weeks by cesarean delivery.

8.3.4 Significant Adverse Events

Please see Section 8.3.5 for Submission Specific Primary Safety Concerns and Section 8.4.1 for Common Adverse Events. No other significant adverse events were identified.

8.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest included bone, renal, and neuropsychiatric events. Bone safety was of interest because decreases in BMD, increases in biochemical markers of bone metabolism, and cases of osteopenia, osteoporosis, and osteomalacia have been reported with TDF containing antiretroviral regimens. Renal safety was of interest because reports of proximal renal tubular dysfunction (i.e., Fanconi syndrome), increased serum creatinine, and acute renal failure have been noted with TDF use. The proximal tubule appears to be the most vulnerable to TDF-related renal injury and evidence of tubular dysfunction (i.e., proteinuria, normoglycemic glycosuria, and hypophosphatemia) may precede the decline of renal function. COBI usage can lead to increased serum creatinine; however, the finding is due to inhibition of tubular secretion of creatinine and COBI is not thought to affect the actual glomerular filtration rate. Neuropsychiatric events were analyzed in the study because suicidal ideation and depression have been noted with EVG as well as other drugs in the INSTI drug class. Headache, dizziness, abnormal dreams, insomnia, depression, suicidal ideation, and suicide attempt have also been reported with STB.

Bone safety:
Safety assessments for the effects on bone included analysis of preferred terms related to fracture in the Musculoskeletal and Connective Tissue Disorders System Organ Class (SOC). Bone mineral density (BMD) was assessed by serial dual energy x-ray absorptiometry (DEXA) scans of the lumber spine and total-body-less-head (TBLH). Percentage changes from baseline in spine and TBLH BMD were assessed. Changes from baseline in standard and height-age-adjusted BMD Z-scores for spine and TBLH were also assessed. Standard BMD Z-scores were calculated based on a chronological age-matched population of the same sex and ethnicity. Height-age-adjusted spine and TBLH BMD Z-scores were calculated by substituting height-age for chronological age, where height age was the age at which the subject's height was the median on the Centers for Disease Control and Prevention Year 2000 stature-for-age growth charts (boys and girls) for the US. Serum markers of bone resorption (N-telopeptide and C-telopeptide [CTx]) and bone formation (osteocalcin, bone specific alkaline phosphatase, parathyroid hormone, and 25-OH vitamin D) were also collected.

No bone fracture events were identified from the analysis of preferred terms in the Musculoskeletal and Connective Tissue Disorders SOC. .

Median baseline values for lumbar spine and TBLH BMD, and percent change at Weeks 24 and 48 are summarized in Table 8.3.5-1. Small non-progressive declines in BMD were observed at Week 24, and measurements stabilized at Week 48. Seven of 46 subjects (15.2%) at Week 48 and 2 of 48 subjects (4.2%) at Week 48 had a ≥4% decrease from baseline in spine BMD and TBLH BMD, respectively. Overall, the observed changes through Week 48 in spine and TBLH BMD were consistent with the previous studies with TDF in adolescents. The impact of TDF-related changes in BMD on long-term bone health and risk for fractures is unknown.

Table 8.3.5-1: Lumbar Spine and Total Body-Less-Head Bone Mineral Density and Bone Mineral Density Z-scores (Standard and Height-age) at Baseline, and Change from Baseline at Weeks 24 and 48

	Time point	SPINE		TBLH	
		N	Median (Q1, Q3)	N	Median (Q1, Q3)
BMD (g/cm²)	Baseline	47	0.93 (0.77, 1.06)	49	0.88 (0.82, 0.96)
	Week 24	47	0.92 (0.75, 1.06)	49	0.87 (0.82, 0.94)
	%Change from Baseline		-0.99 (-3.57, +0.94)		-0.49 (-1.52, +0.85)
	Week 48	46	0.96 (0.77, 1.04)	48	0.89 (0.82, 0.95)
	%Change from Baseline		+1.07 (-2.31, +3.37)		+0.43 (-0.86, +2.25)
BMD Z-score (Standard[a])	Baseline	47	-0.72 (-2.06, -0.01)	49	-1.58 (-2.35, -0.68)
	Week 24	47	-1.14 (-2.14, -0.18)	49	-1.78 (-2.51, -0.79)
	Change from Baseline		-0.24 (-0.46, -0.06)		-0.15 (-0.25, -0.05)
	Week 48	46	-1.14 (-2.00, -0.11)	48	-1.82 (-2.52, -0.72)
	Change from Baseline		-0.21 (-0.47, -0.02)		-0.19 (-0.37, -0.07)
BMD Z-score (Height-age[b])	Baseline	38	0.09 (-0.97, 0.98)	39	-0.67 (-1.36, 0.29)
	Week 24	38	-0.03 (-1.23, 0.80)	39	-0.71 (-1.41, 0.21)
	Change from Baseline		-0.14 (-0.31, -0.02)		-0.10 (-0.21, +0.00)
	Week 48	37	0.06 (-1.12, 0.98)	38	-0.79 (-1.54, 0.35)
	Change from Baseline		-0.02 (-0.28, +0.14)		-0.10 (-0.37, +0.07)

[a] Standard spine and TBLH BMD Z-scores are based on a chronological age-matched population of the same sex and ethnicity.

[b] Height-age adjusted spine and TBLH Z-scores substituted height-age for chronological age, where height-age was determined as the age at which a subject's height was the median on the CDC Year 2000 stature-for-age growth charts (boys and girls) for the US. Some subjects had missing height-age Z-scores because their heights were outside the median height in the CDC growth chart, or the height-ages were outside the BMD reference data for Z-scores.

Source: Adapted from clinical study report for GS-US-236-0112, Tables 37.1, 37.2, 38.1, 38.2, 38.3, and 38.4; Clinical reviewer's calculations.

Table 8.3.5-1 also presents the median baseline spine and TBLH BMD Z-scores (standard and height-age), and change from baseline at Weeks 24 and 48. A greater number of subjects had standard BMD Z-scores calculated because height-age BMD Z-scores were not calculated if the subject's height was outside the median height for 20 year old boys (> 177 cm) and girls (>163 cm) on the CDC stature-for-age growth chart or outside the BMD reference data for Z-scores. Overall, there were less prominent decreases observed in the spine and TBLH height-age BMD Z-scores than the standard BMD Z-scores by Week 48. Height-age BMD Z-scores were suggested by the applicant to be critical for interpretation because the study population was shorter than average for age.

The number of subjects with normal standard or height-age baseline Z-scores (Z-score > -2) and either stable or worsening changes at Weeks 24 and/or 48 are summarized in Table 8.3.5-2. A worsening post-baseline Z-score was defined as a change from > -2 to ≤ -2. There were 6 subjects at Week 48 with worsening spine and/or TBLH standard or height-age Z-scores. Overall, the majority of subjects with a normal Z-score at baseline did not exhibit worsening changes by Week 48.

Table 8.3.5-2: Post-baseline Lumbar Spine and Total Body-Less-Head (TBLH) Standard and Height-age BMD Z-scores in Subjects with Baseline Z-scores > -2

	SPINE		TBLH	
	Baseline Status		Baseline Status	
	Standard Z-score > -2 (N=35)	Height-age Z-score > -2 (N=36)	Standard Z-score > -2 (N=31)	Height-age Z-score > -2 (N=37)
Week 24				
Z-score > -2	35 (100%)	35 (97.2)	30 (96.8%)	35 (94.6%)
Z-score ≤ -2	0	1 (2.8%)	1 (3.2%)	2 (5.4%)
Week 48				
Z-score > -2	33 (94.3%)	34 (97.1%)	30 (96.8%)	33 (91.7%)
Z-score ≤ -2	2 (5.7%)	1 (2.9%)	1 (3.2%)	3 (8.3%)
Missing	0	1	0	1

Source: Adapted from clinical study report for GS-US-236-0112, Tables 39.1, 39.2, 39.3, and 39.4.

A >10% increase from baseline was observed in the median values for N-terminal telopeptide, osteocalcin, bone-specific alkaline phosphatase, and PTH at Weeks 24 and 48. The median percent change from baseline was -2.3% for C-telopeptide at Week 48 and 0% for 25-OH vitamin at Week 48. Increases in serum bone biomarkers have been observed in the previous studies with TDF and the long-term clinical significance of these changes is unknown.

Renal safety:
Key safety assessments for the effects on renal safety included serial measurements of serum creatinine, estimated glomerular filtration rate (eGFR) calculated using the Schwartz and modified Schartz formulae, urine protein by dipstick, serum phosphorus, and urine glucose. Urine protein to creatinine ratio (UPCR), urine retinol binding protein (RBP) to creatinine ratio, urine beta-2-microblogulin to creatinine ratio, ratio of maximum renal tubular phosphate reabsorption rate to glomerular filtration rate (TmP/GFR), fractional excretion of phosphate ($FEPO_4$), and fractional excretion of uric acid (FEUA) were also assessed. There was no established definition to report cases of proximal renal tubulopathy. This reviewer used the following definition (established in the original NDA review) for cases of proximal renal tubulopathy:
Presence of ≥2 of the following criteria at the same visit

- Normoglycemic glycosuria (≥1+ urine glucose on urinalysis)
- New onset or substantive increase (relative to baseline) in proteinuria
- Hypophosphatemia and/or increase (relative to baseline) in $FEPO_4$

Increase in serum creatinine or declines in eGFR are not included in this definition because tubulopathy may be evident before declines in renal function appear.

The applicant reported one clinically significant renal adverse event. The event, Grade 2 acute kidney injury, occurred in subject 2880-1001 and was thought to be secondary to dehydration from *Shigella* dysentery. The onset was approximately 39 weeks after starting STB and resolved after 6 days. The event was considered a SAE because the patient was hospitalized. It was not considered to be related to STB treatment and the study drug was continued throughout. Intermittent Grade 1 proteinuria by dipstick was also reported in this subject, but

no graded abnormalities in urine glucose, urine RBCs, serum phosphate, or serum creatinine were reported at any visit. Please see Section 8.2 for further details related to this serious renal event.

The applicant did not report cases of proximal renal tubulopathy, but this reviewer identified one subject (subject 7521-1013) who developed treatment-emergent laboratory abnormalities consistent with proximal renal tubulopathy. The subject had persistent proteinuria with normoglycemic glycosuria starting at Week 32 (baseline urine protein trace without glycosuria). Both Grade 1-2 proteinuria and Grade 1-2 normoglycemic glycosuria were reported at Weeks 32, 40, 48, 60, 72, 84, and 96. The subject also had Grade 1 hypophosphatemia at a single visit (2.9 mg/dL at Week 60) that was associated with concurrent Grade 1 proteinuria and Grade 2 normoglycemic glycosuria. There were no graded abnormalities in serum creatinine at any visit. STB treatment was continued throughout because the subject was virologically suppressed and the investigator did not attribute the persistent proteinuria and glycosuria to study drug. Although not disclosed by the subject, the investigator suspected this subject was visiting a traditional healer and attributed the renal laboratory abnormalities to be from use of traditional medicines. The subject received counseling at each visit to avoid use of traditional medicine while on study drug. Grade 1 proteinuria with trace urine glucose was reported at the last two visits (Weeks 108 and 120) within the Week 48 data cut-off.

The applicant, in response to an information request, provided additional information for subject 7521-1013 who had one more visit after the Week 48 data cut-off (October 23, 2015). Worsening renal labs were reported at this visit (Week 132), including concurrent Grade 2 proteinuria, Grade 2 normoglycemic glycosuria, and Grade 2 hypophosphatemia. The subject subsequently moved to live with relatives in a different province and was lost to follow up after Week 132. It is the opinion of this clinical reviewer that this subject's renal laboratory abnormalities may have been related to study drug. A comment mentioning this subject who had laboratory abnormalities consistent with proximal renal tubulopathy was added to the label.

There was one subject (subject 2880-1040) who had multiple episodes of increased serum creatinine after initiating the study drug (baseline serum creatinine 1.24 mg/dL). The subject had Grade 1 increased serum creatinine at Weeks 2 and 8 with no associated proteinuria by dipstick, hematuria by quantitative analysis, hypophosphatemia, or normoglycemic glycosuria. The elevated serum creatinine values at these visits were between 1.52 – 1.55 mg/dL. Subsequent serum creatinine values were normal and the subject continued STB treatment throughout.

Changes in renal function for the study population as whole were also assessed. Median baseline values for serum creatinine and eGFR calculated by Schwartz and modified Schwartz formulae are summarized in Table 8.3.5-3. The changes in these measurements at Weeks 24 and 48 are also listed. Over time, small non-progressive changes in serum creatinine and eGFR were observed.

Table 8.3.5-3:
Serum Creatinine and eGFR using Schwartz and Modified Schwartz formulae at Baseline, and Change from Baseline at Weeks 24 and 48

	Time point	N	Median (Q1, Q3)
Serum Creatinine	Baseline	50	0.77 (0.62, 0.89)
	Week 24	49	0.85 (0.69, 0.94)
	Change from Baseline		+0.08 (+0.01, +0.14)
	Week 48	48	0.88 (0.72, 1.00)
	Change from Baseline		+0.11 (+0.05, +0.16)
eGFR (Schwartz[a])	Baseline	50	139.5 (128.0, 161.0)
	Week 24	49	129.0 (118.0, 142.0)
	Change from Baseline		-14.0 (-25.0, -1.0)
	Week 48	48	125.5 (115.0, 138.0)
	Change from Baseline		-15.0 (-29.5, -8.0)
eGFR (Modified Schwartz[b])	Baseline	50	97.8 (94.5, 111.2)
	Week 24	49	97.0 (90.4, 102.2)
	Change from Baseline		-4.2 (-9.9, +0.8)
	Week 48	48	95.4 (91.9, 102.3)
	Change from Baseline		-3.6 (-9.2, +2.7)

Source: Adapted from clinical study report for GS-US-236-0112, Tables 42, 43.1, and 43.2.

Table 8.3.5-4 summarizes the notable renal laboratory events including proteinuria as assessed by dipstick analysis, hematuria as assessed by quantitative RBCs, hypophosphatemia, normoglycemic glycosuria, and serum creatinine increase. The majority of these events were Grade 1 and 2. Proteinuria by dipstick analysis was the most common renal laboratory abnormality and was reported in 22 subjects (44%). Post-baseline, Grade 1 or Grade 2 proteinuria was generally an isolated and transient finding.

Table 8.3.5-4: Treatment-Emergent Renal Laboratory Abnormalities by Worst Grade Toxicity

Renal Laboratory Abnormality	STB N=50			
	Maximum Toxicity Grade			Total Number of Subjects with Event n (%)
	1 n (%)	2 n (%)	3 n (%)	
Proteinuria (dipstick)	15 (30)	7 (14)	0	22 (44)
Hematuria (quantitative, RBCs)	2 (4)	7 (14)	3 (6)	12 (24)
Hypophosphatemia	1 (2)	1 (2)	0	2 (4)
Normoglycemic Glycosuria	0	1 (2)	0	1 (2)
Serum Creatinine increased	1 (2)	0	0	1 (2)

Source: Adapted from clinical study report for GS-US-236-0112, Table 21; Clinical Reviewer's calculations.

There were 3 subjects (all female) who experienced Grade 3 hematuria by quantitative analysis. One subject (subject 7521-1007) had Grade 3 hematuria at Weeks 16, 32, and 84 that was associated with concurrent Grade 1 proteinuria at the former two visits. There was no concurrent hypophosphatemia, normoglycemic glycosuria, or increased serum creatinine associated with hematuria and proteinuria in this subject. The other two subjects with Grade 3 hematuria did not have concurrent renal laboratory abnormalities (i.e., proteinuria by dipstick, hypophosphatemia, normoglycemic glycosuria, or increased serum creatinine) and their hematuria resolved at subsequent visits. All three subjects with Grade 3 hematuria continued STB treatment throughout. The Sponsor concluded that hematuria was caused by menstrual contamination and was therefore non-renal in origin. This conclusion cannot be verified with the available information.

The median serum phosphorus values were within normal age-based ranges through Week 48. There were 2 subjects who had graded hypophosphatemia. Subject 7521-1013, mentioned earlier, had Grade 1 hypophosphatemia at Week 60 (2.9 mg/dL) that was associated with concurrent Grade 1 proteinuria and Grade 2 normoglycemic glycosuria. Besides Week 60, the subject did not have graded hypophosphatemia at the other visits within the Week 48 data cut-off. Subject 8570-1049 had multiple episodes of hypophosphatemia after initiating the study drug (baseline serum phosphate 2.5 mg/dL). The hypophosphatemia was Grade 1 at Week 1 (2.1 mg/dL), Grade 2 at Week 4 (1.9 mg/dL), and Grade 1 at Week 48 (2.0 mg/dL). This subject did not have hypophosphatemia with concurrent proteinuria by dipstick, glycosuria, or increased serum creatinine. Both subjects with graded hypophosphatemia continued STB treatment throughout the trial.

This reviewer did not note any clinically meaningful observations from the analyses of the other renal laboratory assessments (i.e., proteinuria by quantitative assessment, urine retinol binding protein to creatinine ratio and beta-2 microglobulin to creatinine ratio). TmP/GFR, $FEPO_4$, and FEUA remained relative stable from baseline through Week 48.

Neuropsychiatric events:
Neuropsychiatric events in Study 236-0112 were identified using the Nervous System Disorders or Psychiatric Disorders SOCs. A total of 19 subjects (38%) experienced treatment-emergent neuropsychiatric events. Eighteen of these subjects had adverse events in the Nervous System Disorders SOC and 3 of these subjects had adverse events in the Psychiatric Disorders SOC. Table 8.3.5-5 summarizes the treatment-emergent neuropsychiatric events in Study 236-0112. The most frequently reported neuropsychiatric events were headache (13 subjects, including 1 case of migraine) and dizziness (4 subjects). A serious neuropsychiatric event was reported in 1 subject (Subject 2880-1001) with Grade 3 suicidal behavior. The subject had a prior history of suicidal attempt before study enrollment. Please see Section 8.2 for further details related to this serious neuropsychiatric event. All of the other neuropsychiatric events in Study 236-0112 were Grade 1 or Grade 2 in severity and non-serious. None of the ≥ Grade 2 neuropsychiatric events were considered related to STB treatment or led to discontinuation of treatment.

Table 8.3.5-5:
Treatment-Emergent Neuropsychiatric Events by Worst Grade Toxicity

Neuropsychiatric Event by System Organ Class and Preferred Term	STB N=50			
	Maximum Toxicity Grade			Total Number of Subjects with Event n (%)
	1 n (%)	2 n (%)	3 n (%)	
Nervous system disorders				
Headache[a]	10 (20)	3 (6)	0	13 (26)
Dizziness	3 (6)	1 (2)	0	4 (8)
Somnolence	1 (2)	0	0	1 (2)
Psychiatric disorders				
Affective disorder	1 (2)	0	0	1 (2)
Stress	1 (2)	0	0	1 (2)
Depression	0	1 (2)	0	1 (2)
Sleep disorder	0	1 (2)	0	1 (2)
Suicidal behavior	0	0	1 (2)	1 (2)

[a] Includes: headache, migraine.
Source: Adapted from clinical study report for GS-US-236-0112, Table 18; Clinical Reviewer's calculations

8.4 Supportive Safety Results

8.4.1 Common Adverse Events

Forty-five subjects (90%) reported one or more treatment-emergent clinical adverse events. Upper respiratory tract infection (28%), headache (26%), and vomiting (18%) were the most frequently reported clinical adverse events. Table 8.4.1-1 summarizes the common clinical adverse events reported by at least 3 subjects in Study 236-0112. All of the common clinical adverse events were reported as mild or moderate (Grade 1 or Grade 2).

Table 8.4.1-1: Summary of Treatment-Emergent Adverse Events (Incidence ≥ 3 subjects)

TEAE by System Organ Class and Preferred Term	STB N=50 n (%)
Gastrointestinal disorders	
Vomiting	9 (18)
Diarrhea	7 (14)
Nausea	7 (14)
Hemorrhoids	3 (6)
Toothache	3 (6)
General disorders and administration site conditions	
Pyrexia	3 (6)
Infections and infestations	
Upper respiratory tract infection	14 (28)
Pharyngitis	5 (10)
Bronchitis	4 (8)
Nasopharyngitis	4 (8)
Oropharyngeal gonococcal infection	3 (6)
Proctitis gonococcal	3 (6)
Secondary syphilis	3 (6)
Injury, poisoning and procedural complications	
Skin abrasion	3 (6)
Investigations	
Weight decreased	4 (8)
Metabolism and nutrition disorders	
Vitamin D deficiency	6 (12)
Musculoskeletal and connective tissue disorders	
Myalgia	3 (6)
Nervous system disorders	
Headache[a]	13 (26)
Dizziness	4 (8)
Skin and subcutaneous tissue disorders	
Acne	6 (12)
Rash	4 (8)
Dermatitis	3 (6)
Dermatitis contact	3 (6)

[a] Includes: headache, migraine.
Source: Adapted from clinical study report for GS-US-236-0112, Table 18.

8.4.2 Laboratory Findings

All 50 subjects (100%) reported one or more treatment-emergent laboratory abnormalities. The most common abnormalities reported were proteinuria by dipstick analysis (44%), hypercalcemia (36%), and decreased absolute neutrophil count (28%). The majority of abnormalities were categorized as Grade 1 or Grade 2 in severity. None of the laboratory abnormalities were reported as SAEs. Please see Section 8.3.5 regarding the one subject who

developed treatment-emergent sustained proteinuria and normoglycemic glycosuria that was consistent with proximal renal tubulopathy.

Grade 3 or Grade 4 laboratory abnormalities were reported in 5 subjects (8%) who had either hematuria by quantitative analysis, increased creatinine kinase (CK), and/or increased aspartate aminotransferase (AST). None of the Grade 3/Grade 4 laboratory abnormalities were reported as adverse events. Please see Section 8.3.5 for additional information related to the 3 subjects who experienced Grade 3 hematuria. The 2 subjects with Grade 3-4 laboratory abnormalities besides hematuria are summarized below:

- Subject 2880-1004 experienced transient Grade 4 increased CK (10650 U/L) at Week 40. The subject was asymptomatic at the time of the Grade 4 CK elevation and the applicant reported the elevation may have been due to physical exertion. No changes were made to study drug and no subsequent graded elevations in CK were observed. The same subject also experienced transient Grade 3 increased AST (254 U/L) associated with Grade 2 increased ALT at a single visit (Week 40). No changes were made to the study drug and subsequent levels noted resolution of both events.

- Subject 7409-1045 experienced transient Grade 3 increased CK at Week 16 and Week 40. The highest CK level (3301 U/L) was at Week 16. No changes were made to the study drug and levels both before and after these visits were normal.

Besides subject 2880-1004 who as mentioned above had Grade 3 increased AST associated with Grade 2 increased ALT, this reviewer did not identify other subjects with notable liver enzyme elevations in relation to normal ranges. No subjects, including subject 2880-1004, had elevations > 3 x ULN in AST or ALT in addition to >2 x ULN in total bilirubin and <2 x ULN in alkaline phosphatase. Therefore, no cases fulfilled criteria for Hy's law of drug-induced liver injury.

No clinically relevant changes from baseline in median values for hematology, fasting glucose and lipid parameters were noted by this reviewer. Graded abnormalities in hematologic and metabolic parameters were infrequent, and all were Grade 1 or Grade 2.
Please see Section 8.3.5 for additional information related to bone and renal laboratory evaluations.

In conclusion, no new safety signal was appreciated in HIV-1 infected, ART-naïve adolescents.

8.4.3 Pediatrics and Assessment of Effects on Growth

The applicant did not conduct a formal assessment on the effects of STB on growth and development. No specific adverse event profile has been identified which would have major impact on growth of pediatric subjects. Interpretation of growth data in Study 236-0112 was limited by the lack of robust longitudinal data.

9. Advisory Committee Meeting

An advisory committee meeting will not be held for this efficacy supplement.

10. Pediatrics

This application is in response to PREA PMR 1919-1 to study STB in the adolescent patient population:

1919-1 Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to < 18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

Final Protocol Submission: September 2012
Trial Completion: March 2016
Final Report Submission: November 2016

The pediatric assessment will be presented to the PeRC on January 25, 2017.

The PREA PMR for pediatric patients 6 years to less than 12 years of age (PMR 1919-2) remains outstanding, and no studies are required in children under 6 years of age for this FDC drug product.

11. Other Relevant Regulatory Issues

11.1 Inspections

The Office of Study Integrity and Surveillance (OSIS) is conducting bioanalytic inspections of the pharmacokinetic data, which are pivotal to the approvability of this application. The final OSIS report was not available at the time this review was finalized.

11.2 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 203100

Submission Date(s): 7/28/2016

Applicant: Gilead Sciences, Inc

Product: Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [EVG/COBI/FTC/TDF]; STB)

Reviewer: Mark Needles, M.D.

Date of Review: 01/04/2017

Covered Clinical Study (Name and/or Number): GS-US-236-0112

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 21		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from applicant)

The applicant adequately disclosed information related to financial interest/arrangements from the investigators in Study GS-US-236-0112. One of the investigators, [redacted] (b) (6), had a disclosable financial interest and enrolled [redacted] (b) (6) of total subjects in Study GS-US-236-0112. The investigator received payments from Gilead of greater than $25,000 USD (cumulative), exclusive of the costs of conducting the clinical research. Bias from this investigator was minimized by using objective efficacy endpoints that were determined by laboratory results. All data, including adverse events and laboratory data, were also verified by a Clinical Research Associate (CRA) who was able to investigate if the investigator was under-reporting the incidence of adverse events and report findings to Gilead. These actions as well as the small number of subjects enrolled from this investigator make it unlikely that inclusion of these subjects will bias the study results.

12. Labeling

Labeling negotiations were ongoing at the time this review was finalized. Below are some of the preliminary proposed modifications to the clinically-relevant sections of the label.

1 INDICATIONS AND USAGE

STRIBILD® is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation and During Treatment with STRIBILD

Prior to initiation of STRIBILD, patients should be tested for hepatitis B virus infection *[see Warnings and Precautions (5.2)]*.

It is recommended that serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating STRIBILD and during therapy in all patients as clinically appropriate *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage

STRIBILD is a four-drug fixed dose combination product containing 150 mg of elvitegravir, 150 of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir DF. The recommended dosage of STRIBILD is one tablet taken orally once daily with food in adults and pediatric patients 12 years of age and older with a body weight at least 35 kg (at least 77 lbs) and creatinine clearance greater than or equal to 70 mL per minute *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Clinical Trials in Pediatric Subjects

The safety of STRIBILD in 50 HIV-1-infected, treatment-naïve pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg (77 lbs) was evaluated through 48 weeks in an open label clinical trial (Study 112) *[see Clinical Studies (14.4)]*. In this study, the safety profile of STRIBILD was similar to that in adults. Twenty-two subjects (44%) had treatment-emergent proteinuria (Grades 1−2). One subject met laboratory criteria for proximal renal tubulopathy, evidenced by sustained proteinuria and normoglycemic glycosuria beginning at Week 32. The subject continued to receive STRIBILD and was ultimately lost to follow-up.

Among the 50 pediatric subjects receiving STRIBILD for 48 weeks, mean BMD increased from baseline to Week 48, + 0.68% at the lumbar spine and + 0.77% for total body less head. Mean changes from baseline BMD Z-scores (height-age adjusted) to Week 48 were −0.09 for lumbar spine and −0.12 for total body less head. At Week 48, 7 STRIBILD subjects had

significant (greater than or equal to 4%) lumbar spine BMD loss and 2 had significant total body less head BMD loss.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The pharmacokinetics, safety, and virologic and immunologic responses were evaluated in 50 treatment-naïve, HIV-1-infected subjects aged 12 to less than 18 years weighing at least 35 kg (77 lbs) receiving STRIBILD through 48 weeks in an open-label trial (Study 112). The safety and efficacy of STRIBILD in these subjects was similar to that in antiretroviral treatment-naïve adults *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

Safety and effectiveness of STRIBILD in pediatric patients less than 12 years of age or weighing less than 35 kg (77 lbs) have not been established.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Pediatric Patients

Exposures (AUC) of elvitegravir and tenofovir in 14 pediatric subjects aged 12 to less than 18 years who received STRIBILD in Study 112 were increased by 30% and 37%, respectively, compared with exposures achieved in adults following administration of STRIBILD, but were deemed acceptable based on the overall safety profile of these agents and exposure-safety assessments. The other components of STRIBILD had similar exposures in adolescents compared with adults *[see Use in Specific Populations (8.4)]*.

Emtricitabine has been studied in pediatric subjects from 3 months to 17 years of age. Tenofovir DF has been studied in pediatric subjects from 2 years to less than 18 years of age. The pharmacokinetics of elvitegravir or cobicistat in pediatric subjects less than 12 years of age have not been established *[see Use in Specific Populations (8.4)]*.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of STRIBILD were evaluated in the studies summarized in Table 11.

Table 11 Trials Conducted with STRIBILD in Subjects with HIV-1 Infection

Trial	Population	Study Arms (N) [a]	Timepoint (Weeks)
Study 102 [b,c]	Adults with no antiretroviral treatment history	STRIBILD (348) ATRIPLA (352)	144
Study 103 [b,c]		STRIBILD (353) TRUVADA+atazanavir+ritonavir (355)	
Study 115 [c,d]	Virologically suppressed adults without a history of virologic failure [f]	STRIBILD (293) TRUVADA+PI+ritonavir (140)	48
Study 121 [c,d]		STRIBILD (291) TRUVADA+NNRTI (143)	
Study 112 [e]	Treatment-naïve adolescents between the ages of 12 to less than 18 years	STRIBILD (50)	48

a. Randomized and dosed.
b. Randomized, double blind, active-controlled trial.
c. Patients had estimated creatinine clearance grater than or equal to 70 mL/min at screening.
d. Randomized, open label, active-controlled trial.
e. Open label trial.
f. HIV-1 RNA less than 50 copies per mL.

14.4 Clinical Trial Results in HIV-1 Treatment-Naïve Adolescent Subjects Aged 12 to Less than 18 Years

In Study 112, the efficacy, safety, and pharmacokinetics of STRIBILD were evaluated in a single group, open-label trial in HIV-1-infected treatment-naïve adolescents aged 12 to less than 18 years of age and weighing at least 35 kg (77 lbs) (N=50). Mean age was 15 years (range, 12−17); 70% were male, 68% black, and 28% Asian. At baseline, mean plasma HIV-1 RNA was 4.60 $\log_{10}$ copies per mL (range, 3.18−5.73), mean CD4+ cell count was 399 cells per mm3 (range, 133−734), and mean CD4+ percentage was 20.9% (range, 4.5%−41.1%). Twenty percent had baseline plasma HIV-1 RNA >100,000 copies per mL.

At Week 48, 44 of 50 (88%) adolescent patients treated with STRIBILD achieved HIV-1 RNA <50 copies per mL and 4 had HIV-1 RNA ≥50 copies per mL; 1 patient discontinued study drug; 1 had no virologic data at Week 48. The mean decrease from baseline in HIV-1 RNA was −3.16 $\log_{10}$ copies per mL; mean increase from baseline in CD4+ cell count was 229 cells per mm^3. No emergent resistance to STRIBILD was detected through Week 48.

13. Recommendations/Risk Benefit Assessment

- I recommend approval of this efficacy supplement.

- Recommended Regulatory Action:
  It is the opinion of this clinical reviewer that the results from Week 48 for Study 236-0112 support approval of STB as a complete regimen for the treatment of HIV-1 infection in pediatric patients 12 year of age and older weighing at least 35 kg

who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.

- Risk Benefit Assessment
  The efficacy results from Study 236-0112 demonstrated potent antiviral activity through Week 48, and the PK data support the doses of EVG, COBI, FTC, and TDF present in STB. No new safety signals for STB were detected in HIV infected adolescents. Bone and renal safety profiles in ART-naïve adolescents were consistent with findings in adults. Small non-progressive declines in BMD were observed in ART-naïve adolescents at Week 24 and measurements stabilized at Week 48. The long-term clinical significance of these declines is unknown. Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effects of COBI on renal tubular secretion of creatinine. Overall, no new safety signals were detected in HIV-infected adolescents.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  Postmarket Risk Evaluation and Mitigation Strategy (REMS) will not be required. The applicant will continue to submit Periodic Adverse Drug Experience Reports (PAERs) and Development Safety Update Reports (DSURs) for review.

- Recommendation for other Postmarketing Requirements and Commitments
  No additional PMRs or PMCs will be issued in response to this submission.

14. References

Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; *Clin. Microbiol. Rev*. 9(4) 448-468.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Table 6: Recommended, Alternative, and Other Antiretroviral Regimens Options for Treatment-Naïve Patients. Section accessed January 3, 2016.

Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed January 3, 2016.

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MARK S NEEDLES
01/04/2017

PRABHA VISWANATHAN
01/04/2017