NDA/SDN	203100 S 25/481
Submission Type	Efficacy Supplement
Applicant Name	Gilead
Submission Dates	07/28/2016
Generic Name	Elvitegravir (EVG)/ cobicistat (COBI)/ emtricitabine (FTC)/ tenofovir disoproxil fumarate (TDF)
Dosage Form (Strength)	Tablet/150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF once daily
Indication	Treatment of HIV-1 infection in pediatric patients 12 years of age and older weighing ≥ 35 kg
Review Team	Amal Ayyoub, PhD, Islam R. Younis, PhD

1 Contents

2 Executive Summary 2
2.1 Recommendations 3
2.2 Labeling Recommendations 3
3 Individual Study Review 4
3.1 Comparison of Stribild® Exposure between Adult and Adolescent HIV-Infected Patients 4
4 Appendix 10
4.1 Criteria for Evaluation of Bioanalytical Methods and Study Sample Analyses. 10
4.2 Statistical Summary of EVG, COBI, FTC, and TFV Plasma Pharmacokinetic Parameter Estimates Following Administration of Stribild to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies. 10

2 Executive Summary

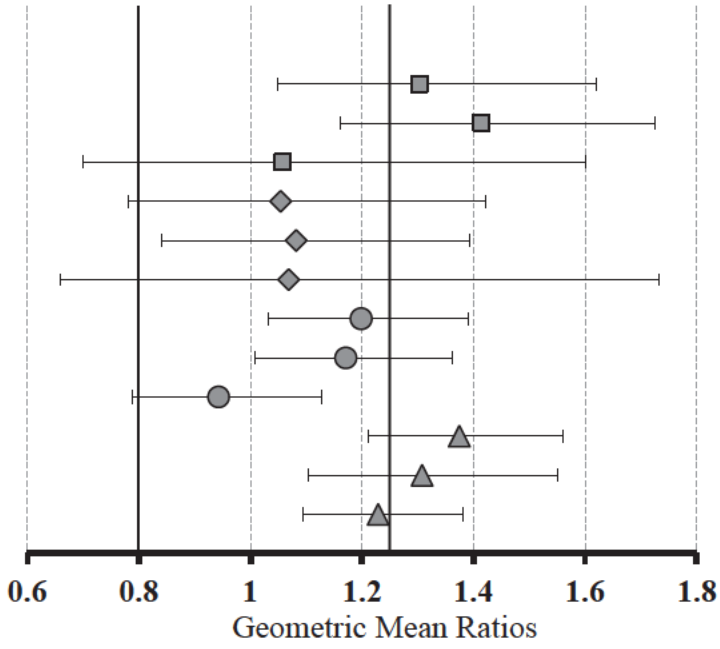
Stribild® (STB) is a fixed-dose combination tablet of elvitegravir (EVG, 150 mg), cobicistat (COBI, 150 mg), emtricitabine (FTC, 200 mg), and tenofovir disproxil fumarate (TDF, 300 mg). Stribild® was approved for the treatment of HIV-1 infection in antiretroviral (ART) treatment-naive adults in 2012.

This application consisted of an open-label study to evaluate the pharmacokinetics, safety, and antiviral activity of STB in HIV-1 infected ARV treatment-naive adolescents 12 to < 18 years of age, and weighing at least 35 Kg (Study GS-US-236-0112). The study consisted of two parts:

1. Part A: An initial group of subjects (n=14) were enrolled to evaluate the steady-state pharmacokinetics and confirm the dose of STB.
2. Part B: Following the confirmation of EVG exposure in Part A and a review of preliminary safety data, subjects were enrolled in Part B (n=36) to evaluate the safety, tolerability, and antiviral activity of STB.

The primary efficacy endpoint was the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm. At the interim Week 24 analysis, the virologic success rate was 85.7% (18 of 21 subjects).

Intensive pharmacokinetic (PK) evaluation was performed on Day 10 of part A of the study. A request to inspect the bioanalytical aspects of the study was submitted to the Office of Study Integrity and Surveillance (OSIS) on 09/14/2016. Overall, the primary FTC and COBI PK parameters AUCtau, Cmax, and Ctrough, were comparable in adolescents versus combined data from HIV-1 infected adult subjects, and exposure parameters of EVG and TFV in adolescents were higher than in adults. The relatively higher observed PK parameters are not considered clinically significant and are not expected to affect the safety of STB as evident by the similar safety profile in adolescents when compared to adults.



EVG (▬)	AUCtau
	Cmax
	Ctrough
COBI (◆)	AUCtau
	Cmax
	Ctrough
FTC (●)	AUCtau
	Cmax
	Ctrough
TFV (▲)	AUCtau
	Cmax
	Ctrough

Figure 1 Statistical Comparisons of EVG (▬), COBI (◆), FTC (●), and TFV (▲) Plasma Pharmacokinetic Parameter Estimates Following Administration of STB to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies.

2.1 Recommendations

The Office of Clinical Pharmacology review team finds this application acceptable and recommends approval. This recommendation is contingent upon acceptable findings of OSIS inspection of the bioanalytical aspects of Study GS-US-236-0112.

2.2 Labeling Recommendations

Labeling negotiations are currently ongoing. We agreed with the below paragraph proposed by the applicant to be added to section 12.3 of the labeling:

"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)*]."

3 Individual Study Review

3.1 Comparison of Stribild® Exposure between Adult and Adolescent HIV-Infected Patients

A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF [Stribild®, STB]) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents.
Study Period: 06 December 2012 – 24 July 2014 (for part A of the study).

Link: \\cdsesub1\evsprod\nda203100\0176\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-236-0112\24wk\report-body.pdf

Study GS-US-236-0112 Design

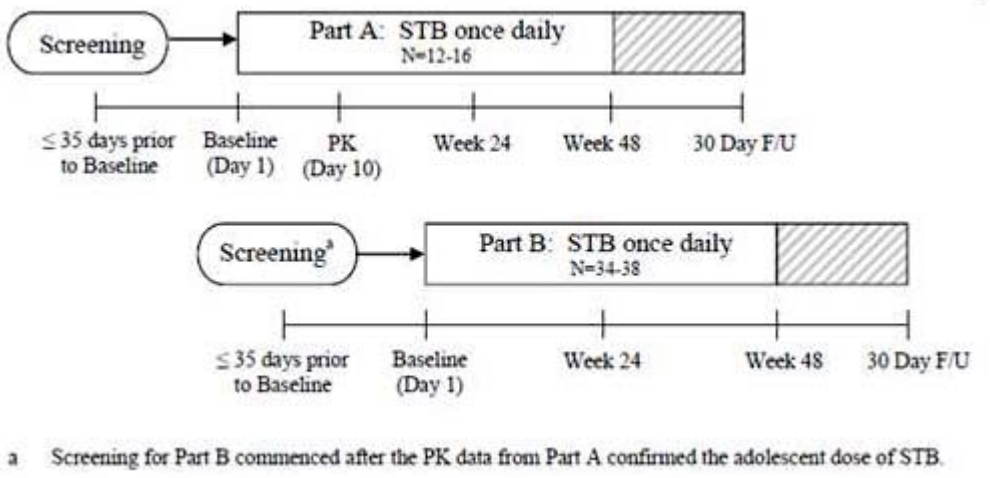


Figure 2 Open-label, Multicenter, Single-Group Study in HIV-1 Infected ART-Naive Adolescents.

Part A: An initial group of subjects to evaluate the steady-state pharmacokinetics and confirm the dose of STB. Planned number of subjects: 12 to 16, with at least 4 subjects aged 12 to < 15 years and at least 4 subjects aged 15 to < 18 years.
- 14 subjects were recruited and their data utilized for PK sub-study analysis sets.
- Intensive pharmacokinetic (PK) evaluation on Day 10 after one STB tablet daily given orally with food (breakfast), at approximately the same time each day.

Part B: Following the confirmation of EVG exposure in Part A, and review of preliminary safety and efficacy data, subjects were enrolled in Part B to evaluate the safety, tolerability, and antiviral activity of STB.

Study GS-US-236-0112 Characteristics

Table 1 Summary of Study Characteristics

Population	Adolescent subjects 12 to < 18 years of age, of either sex, that weigh at least 35 Kg.
Study Rationale	Extending the indication to adolescents 12 to < 18 years of age.
Dose Selection	The approved dose of STB; 150 EVG/ 150 COBI/ 200 FTC/ 300 TDF.

Rationale	
Formulation	Batch-lot numbers: BK1106B1, BK1201B1, BK1201B1-A.
Adherence	Subjects brought the original containers at each clinic visit for drug accountability.
Concomitant medications	Medications listed in the study exclusion criteria on page 34 of the CSR were prohibited in addition to individual agents from prescribing information for STB or its individual components.
PK sampling	Samples were collected on Day 10 at the following time-points: pre-dose (0), 2, 4, 4.5, 5, 8, and 12 hours post-dose.
PK Parameters	Primary: AUCtau for EVG. Secondary endpoints: AUCtau, Ctrough, and Cmax for COBI, FTC, and TFV, and Ctrough and Cmax for EVG.
PK Analysis	Non-compartmental.
Statistical Analysis	1-way analysis of variance (ANOVA) models were fitted to the natural log-transformed values of AUCtau, Cmax, and Ctrough with treatment group as a fixed effect for EVG, COBi, FTC, and TFV. 90% CIs were calculated for the ratios of the geometric least-squares means (GLSMs) for between test (adolescents) and reference (adults in historical studies) treatments.
Bioanalytical methods	Analytes: TFV, FTC, EVG (9137), and COBI (9350). Matrix: K_2EDTA human plasma. Method: LC-MS/MS.

Study GS-US-236-0112 Results

Fourteen subjects were enrolled in part A. Mean age was 16 years and mean weight was 56 Kg with all subjects being non-obese (BMI <30 kg/m2). The population was 64% male, 64% Black, 28% Asian, and 7% White, and had normal kidney function (estimated glomerular filtration rate by Schwartz formula between 102 and 198 mL/min/1.73 m^2).

Eight important protocol deviations were reported in seven subjects throughout the study. Of importance, three of 8 important protocol deviations occurred in 2 subjects who had dosing non-adherence issues (refer to Appendix 16.2, Study GS-US-236-0112 Important Protocol Deviation Log). None of these important protocol deviations affected the overall quality or interpretation of the study data.

Nonadherence was reported with two subjects; subject ID 2880-1004 with dosing non-compliance at week 32, and subject ID 2880-1011 with dosing noncompliance at weeks 4 and 12.

Table 2 Summary of Dosing Non-Compliance.

Subject ID	Week and Date of Non-Compliance	Description
2880-1004	Week 32 10 October 2013)	Subject 2880-1004/JCW was 60% compliant with dosing and returned 27 pills with 22 missed doses. According to site documentation, the subject was counseled regarding compliance at the Week 32 visit by the research staff.
2880-1011	Week 4 (7 June 2013)	Subject 2880-1011/ALC returned 9 tabs from the bottle dispensed on 7 May 2013. The bottle was returned on 7 June 2013 during week 4 visit. The compliance was 67%. According to site documentation, the subject

		was counseled regarding compliance at the week 4 visit. Subject compliance at Week 8 was 100%.
2880-1011	Week 12 (29 July 2013)	The subject reported 12 missed doses and was 57% compliant with dosing at Week 12.

With regard to concomitant medications, most subjects (84.8%, 28 of 33 subjects) used concomitant non-antiretroviral medications. The most frequently used concomitant medications were in the following drug classes: anti-bacterial agents for systemic use (57.6%, 19 of 33 subjects), analgesics and vitamins (each 36.4%, 12 subjects), and antihistamines for systemic use (33.3%, 11 subjects).
All bioanalytical methods were reported to be fully validated, with calibration ranges for all components reported as:
FTC and TFV: 5 - 3000 ng/mL
EVG: 20 - 10000 ng/mL
COBI: 5 - 2500 ng/mL

Pharmacokinetic Results

- Elvitegravir (EVG) AUCtau and Cmax were increased by 30.29%, and 41.5%, respectively, in adolescents in this study compared to parameters observed in adults in Phase II and Phase III studies (GS-US-236-0103 and GS-US-236-0104, and STB-treated subjects who participated in the PK sub-study in Study GS-US-236-0102). The adult subjects were HIV-infected, anti-retroviral treatment naïve in Phase III studies GS-US-236-0102 (STB vs. EFV/FTC/TDF), and study GS-US-236-0103 (STB vs. ATV/r + FTC/TDF), and the Phase II study GS-US-236-0104.
- Cobicistat (COBI) AUCtau and Cmax were similar and Ctrough was slightly higher compared to historical studies GS-US-236-0103 and GS-US-236-0104, STB-treated subjects who participated in the PK sub-study in Study GS-US-236-0102, and subjects who received COBI - ATV plus TVD in Studies GS-US-216-0105 and GS-US-216-0114.
- Emtricitabine (FTC) AUCtau, Cmax, and Ctrough 90% CI were contained within the equivalence boundaries. Historical studies used were GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104.
- Tenofovir (TFV) AUCtau and Cmax were increased by 37.46% and 30.78%, respectively, compared with adults in historical studies (GS-US-236-0103, GS-US-236-0104, and STB-treated subjects in the PK sub-study in Study GS-US-236-0102) while Ctrough was contained within the boundaries.

Pharmacokinetic Analysis

- Elvitegravir (EVG)

Exposure levels of EVG and TFV in adolescents in the current study (GS-US-236-112) are considered acceptable in comparison to plasma concentrations in adults from two pivotal Phase III studies in treatment naïve HIV-1 patients administered the commercial dosage form of STB as seen in the following analysis.

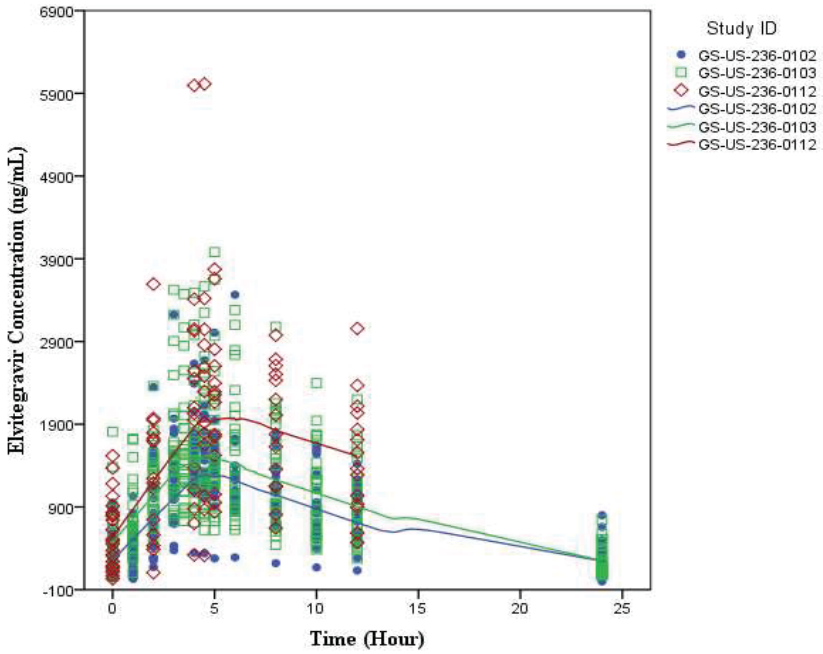


Figure 3 Elvitegravir (EVG) Plasma Concentration Values (ng/mL) from Adult and Adolescent Treatment Naïve HIV-1 Infected Patients vs Time (Hour).
Source: prepared by the reviewer. Study GS-US-236-0112 (red diamonds/line) represents the current study in adolescents; studies GS-US-236-0102 (blue circles/line) and GS-US-236-0103 (green squares/line) represent pivotal phase 3 studies in adult treatment naïve HIV-1 infected patients.

The higher EVG AUC0-tau and Cmax parameters in adolescents are not expected to cause safety concerns based on comparable mean AUC0-tau and Cmax values of 28,995.0 and 2526.3 ng/mL when STB was administered to adults in Part 1 of study GS-US-236-135 (Phase I multiple dose study evaluating the drug interaction potential between telaprevir and STB single tablet regimen.

Pharmacokinetic-pharmacodynamic analyses of the EVG exposure-safety relationship were performed by the Sponsor in treatment-naive HIV-1 infected subjects in the E/C/F/T STR Phase 2 (GS-US-236-0104) and Phase 3 (GS-US-236-0102 and GS-US-236-0103) studies using EVG exposures derived from population PK modeling (n=419). The relationship between EVG exposure parameters (AUCtau or Cmax) and incidence of the most common adverse events (present/absent) of headache, diarrhea, and nausea were studied. EVG exposures were comparable in subjects who experienced a key adverse event and those who did not. Logistic regression models confirmed that Cmax, Ctrough, and AUCtau were not statistically significant explanatory variables of the occurrence of side effects.

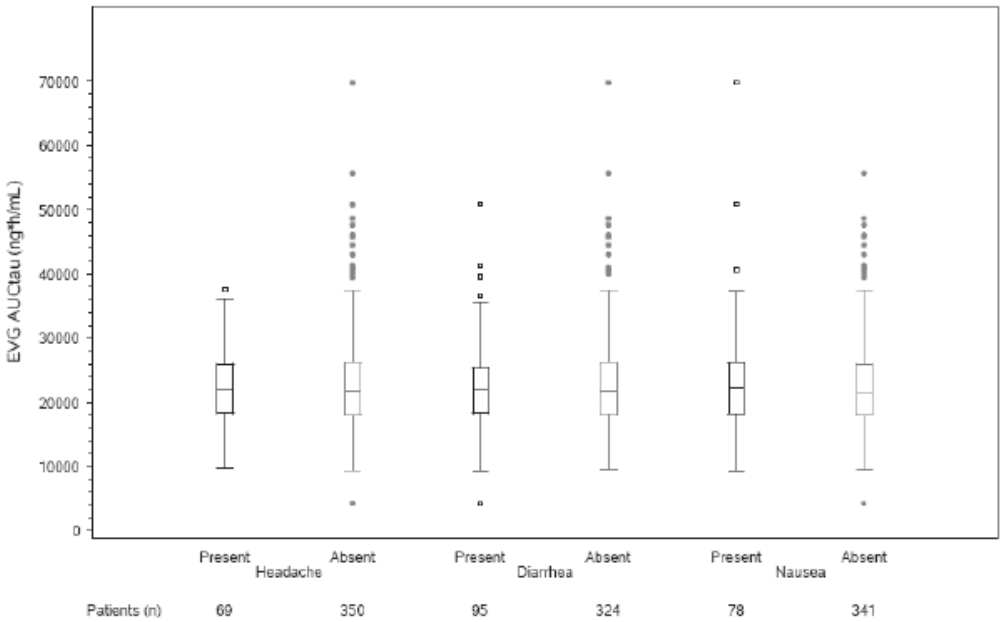


Figure 4 Boxplot of EVG AUCtau (ng•h/mL) Versus Incidence of Selected Adverse Events.
Source: Summary of Clinical Pharmacology Studies (22 October 2011) m5.3.4.2, QUAD PK/PD Figure 2.1- page 219.

- **Tenofovir (TFV)**

TFV exposure in adolescents (12 to 18 years of age) receiving oral once-daily doses of Viread® 300 mg tablets are comparable to those from the current STB adolescent study. TFV mean Cmax values were 380 (0.13) ng/mL and 409.41 ng/mL for Viread® and STB respectively. Likewise, TFV mean AUCinf values were 3390 ng.hr/mL and 4281.03 ng.hr/mL.

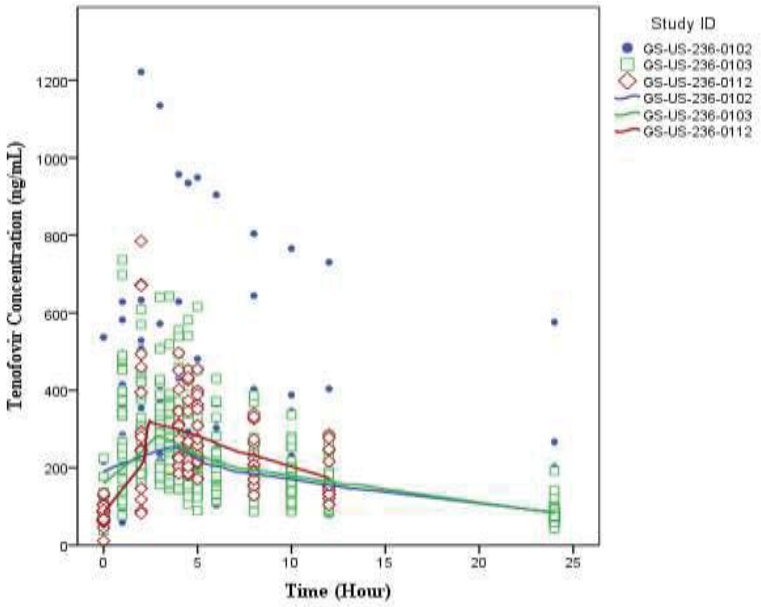


Figure 5 Tenofovir (TFV) Plasma Concentration Values (ng/mL) in Adult and Adolescent Treatment Naïve HIV-1 Infected Patients vs Time (Hour).

Source: prepared by the reviewer. Study GS-US-236-0112 (red diamonds/line) represents the current study in adolescents; studies GS-US-236-0102 (blue circles/line) and GS-US-236-0103 (green squares/line) represent pivotal phase 3 studies in adult treatment naïve HIV-1 infected patients.

TFV exposure levels in specific patients that experienced renal related safety signals were analyzed to determine if they were related to TFV exposure. TFV concentration values from sparse sampling for patients with ID numbers GS-US-236-0112-7521-1013, 1022, 1007, 1019, 1040, and 1003 at week 48 were comparable to the concentrations in the patients who did not show renal safety signals. Furthermore, these patients had consistent TFV concentration values across time (from the start of the study throughout week 48) and the renal events did not coincide with TFV exposure peaks as shown below.

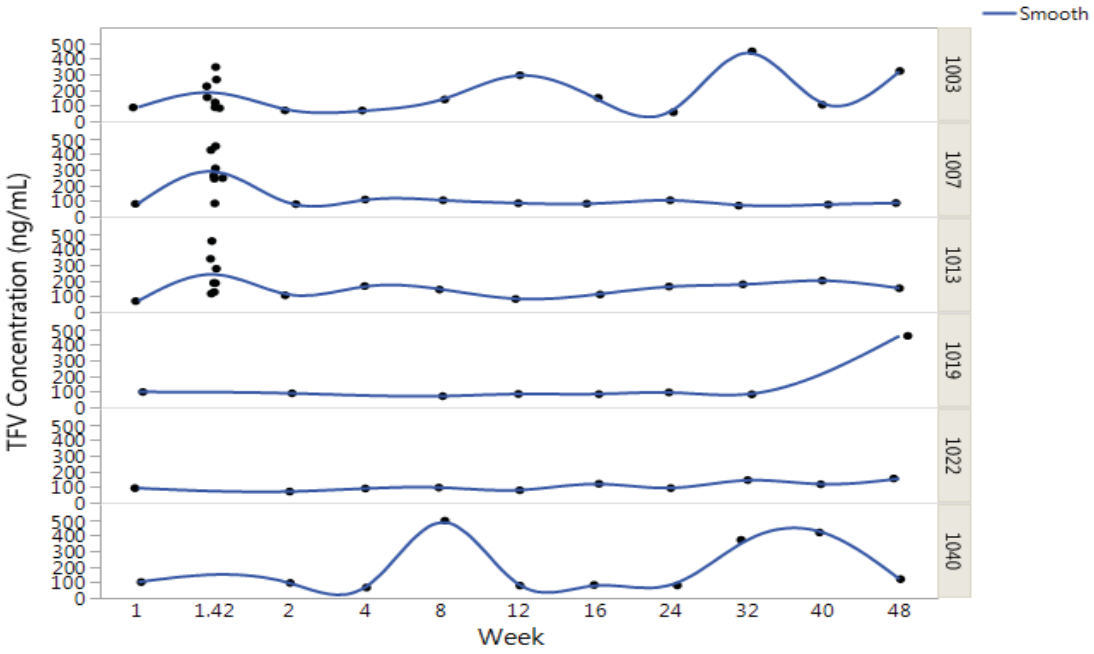


Figure 6 TFV Concentration Values (ng/mL) from for Patient ID numbers 1013, 1022, 1007, 1019, 1040, and 1003 vs Time (Week) Throughout the Study Period.
Source: prepared by the reviewer.

Reviewer Comments and Conclusions

We agree with the applicant's expansion in Stribild® indication and usage to include HIV-1 infection pediatric patients 12 years of age and older with body weight at least 35 kg (at Least 77 lbs).

4 Appendix

4.1 Criteria for Evaluation of Bioanalytical Methods and Study Sample Analyses.

	Characteristic
Validation	▪ Calibration and quality control samples range and number ▪ Accuracy and precision of the calibration curve and quality control samples ▪ Chromatograms provided ▪ Analyte (especially LLOQ) can be detected with adequate signal to noise ▪ Analyte can be detected without interference due to internal standard, carryover, sample extraction, concomitant medications, etc ▪ Overall performance ▪ Method fully validated
Study Samples Analysis	▪ Fully validated method used ▪ Samples analyzed within the established stability period ▪ Accuracy and precision of the calibration curve and quality control samples ▪ Sufficient number of quality control samples ▪ Incurred samples analysis ▪ Chromatograms provided ▪ Analyte (especially LLOQ) can be detected with adequate signal to noise ▪ Analyte can be detected without interference due to internal standard, carryover, sample extraction, concomitant medications, etc ▪ Incurred samples analysis ▪ Overall performance

The reviewer finds the bioanalytical method acceptable based on the above-mentioned criteria

4.2 Statistical Summary of EVG, COBI, FTC, and TFV Plasma Pharmacokinetic Parameter Estimates Following Administration of Stribild to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies.

PK Parameter	Test GLSM (Study GS-US-236-0112)	Reference GLSM (Historical Reference)	% GLSM Ratio Test/Reference (90% CI)
EVG	N=14	N=419	
AUCtau (ng•h/mL)	28,529.11	21,896.87	130.29 (104.79, 162.00)
Cmax (ng/mL)	2390.01	1689.04	141.50 (116.06, 172.52)
Ctrough (ng/mL)	410.08	387.42	105.85 (69.99, 160.09)
COBI	N=14	N=483	
AUCtau (ng•h/mL)	9200.48	8728.69	105.41 (78.12, 142.22)
Cmax (ng/mL)	1275.17	1178.59	108.20 (84.00, 139.36)
Ctrough (ng/mL)	18.93	17.72	106.86 (65.92, 173.21)
FTC	N=14	N=61	
AUCtau (ng•h/mL)	14,508.95	12,106.32	119.85 (103.27, 139.08)
Cmax (ng/mL)	2124.40	1813.97	117.11 (100.69, 136.21)
Ctrough (ng/mL)	98.48	104.44	94.29 (78.77, 112.88)

TFV	N=14	N=419	
AUCtau (ng•h/mL)	4281.03	3114.36	137.46 (121.01, 156.14)
Cmax (ng/mL)	409.41	313.05	130.78 (110.31, 155.05)
Ctrough (ng/mL)	83.83	68.21	122.89 (109.33, 138.14)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMAL AYYOUB
01/04/2017

ISLAM R YOUNIS
01/04/2017