CLINICAL PHARMACOLOGY REVIEW

NDA/SDN	NDA 207561/306 (S-14) NDA 208215/171 (S-5)
Submission Type	Efficacy supplement
Applicant Name	Gilead
Submission Dates	04/03/2017 04/11/2017
Generic Name	Elvitegravir (EVG), Cobicistat (COBI), Emtricitabine (FTC), and Tenofovir Alafenamide (TAF) (E/C/F/TAF) FTC and TAF
Dosage Form (Strength)	Tablet (150/150/200/10 mg) Tablet (200/25 mg)
Indication	Treatment of HIV-1 infection in adults and pediatric patients 6 to <12 years of age and older weighing at least 25 kg
Review Team	Mario Sampson, PharmD, Islam R. Younis, PhD

1 Contents

2 Background

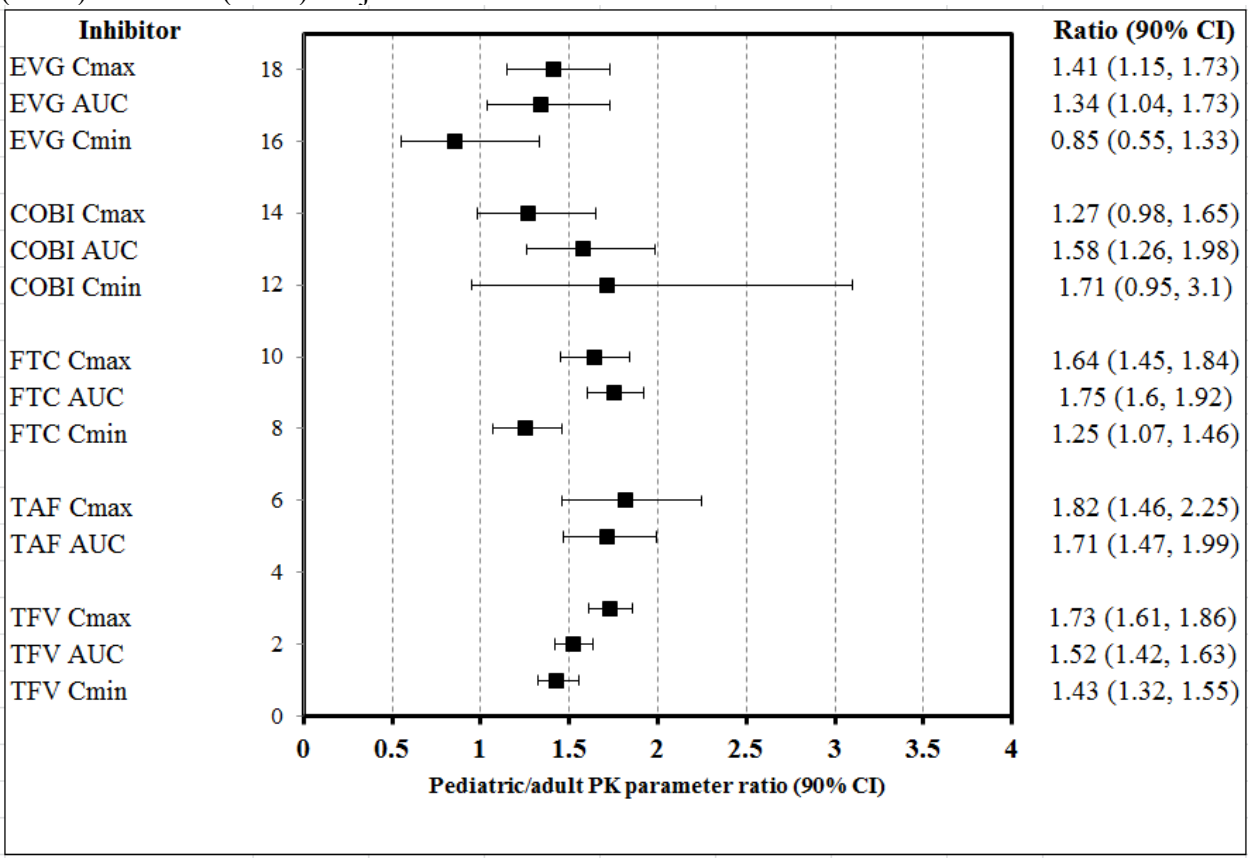
This efficacy supplement contains data from Cohort 2 Part A of pediatric PK, safety, and antiviral activity (week 24) study 292-0106, in which subjects aged 6 - <12 years and weighing ≥25 kg were administered E/C/F/TAF. Based on this study, the applicant is seeking an E/C/F/TAF indication for patients weighing ≥25 kg. The proposed F/TAF indication is patients weighing ≥35 kg in combination with other antiretrovirals (ARV) and for patients weighing ≥25 - <35 kg in combination with ARVs other than protease inhibitors that require a CYP3A inhibitor. In addition, the applicant proposes to use this study to partially fulfill PMR 3041-1, which requested a PK, safety, and antiviral activity study of F/TAF in subjects aged 6 - <12 years.

3 Summary of clinical pharmacology findings

The Office of Study Integrity and Surveillance recommended accepting the PK data without on-site inspection (NDA 208215 memorandum dated 7/13/2017). We found study conduct and bioanalytical methods to be acceptable. Compared to historical adult data, exposures of the

components of E/C/F/TAF were generally higher in pediatric subjects relative to adults, with mean ratios and upper 90% CIs generally less than two (Figure 1Figure 2). Exceptions where exposures were similar between pediatric and adult subjects included EVG and COBI Cmin (CI includes one). Exceptions where the upper 90% CI was between two and three included COBI Cmin and TAF Cmax. Increased exposures of EVG, COBI, FTC, and TAF in ages 6-<12 versus adults were acceptable as there are no exposure-related safety concerns associated with these components. While TFV has exposure-related safety concerns, exposures in ages 6-<12 years administered E/C/F/TAF are much lower compared to adults administered TDF.

Figure 1. Comparison of exposures of the components of E/C/F/TAF in HIV-infected pediatric (n=23) and adult (n=19) subjects.



Source: plotted by reviewer from data in CSR section 10.

4 Recommendations

The application is recommended for approval from a clinical pharmacology perspective.

5 Labeling recommendations

Table 1. Summary of clinical-pharmacology related labeling changes.

Labeling	Section	Issue	Description
F/TAF	7.1	TAF as a substrate of OATP	As previously communicated to the applicant under NDA 208351 S-2 S-3, we believe the results of in vitro study 120-2022 suggests that OATP contributes to the disposition of TAF. We edited labeling to state that TAF is a substrate of OATP1B1 and OATP1B3. The applicant accepted our edits.
F/TAF and E/C/F/TAF	12.3	Pediatric PK parameters	We requested the applicant add pediatric PK parameters for ages 6-<12 and 12-<18 years. The applicant added the PK parameter tables.

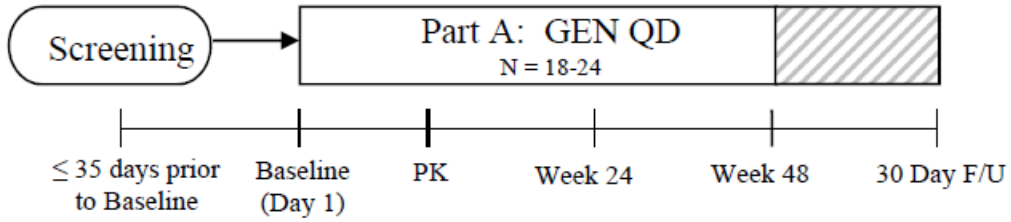
6 Review of E/C/F/TAF pediatric study GS-US-292-0106

Note: this interim study report contains the week 4 PK and week 24 safety data. The study is ongoing with the last visit being week 48.

Study #	GS-US-292-0106	**Study Period**	5/6/13 – 4/20/16
Title	A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children		
Link to study report	\\cdsesub1\evsprod\nda207561\0113\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5352-stud-rep-uncontr\gs-us-292-0106\report-body.pdf		

STUDY SUMMARY (As Reported by the Applicant)
OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS
Objectives: -Primary: PK of EVG and TAF, safety (week 24) -Secondary: PK of COBI, FTC, and TFV, antiviral activity, safety (week 48) A no effect boundary of 70-143% was used for comparison of adult and pediatric PK parameters.
Rationale: This study was done to determine if administration of the adult dose of E/C/F/TAF to children aged 6 - <12 years and weighing ≥25 kg results in sufficiently comparable exposures as compared to adults
Study design: Ongoing, open-label, multicenter, multicohort, single-group study

Cohort 2:



Population:
Cohort 2:
-HIV-infected and virologically suppressed (HIV RNA <50 copies/mL)
-receiving stable ARV treatment for ≥180 days
-age 6 - <12 years and weight ≥25 kg
-eGFR ≥90 mL/min/1.73 m^2 (Schwartz formula)
-AST and ALT ≤ 5 x ULN and total bilirubin ≤1.5 mg/dL

Dose Selection:
The E/C/F/TAF dose used in the study is the approved dose for patients ≥12 years of age

Administration: ☐ Fasted ☑ Fed

Formulation:
Tablets containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF

Excluded concomitant medications:
Alfuzosin, modafinil, telithromycin, phenobarbital, phenytoin, carbamazepine, oxcarbazepine, voriconazole, astemizole, terfenadine, rifampin, rifapentine, rifabutin, any ARV other than E/C/F/TAF, bepridil, bosentan, ergot derivatives, cisapride, SJW, echinacea, simvastatin, lovastatin, cerivastatin, pimozide, midazolam, triazolam (except one time use), all systemic glucocorticoids.

PK sampling:
Week 4 intensive PK: predose, 5 minutes, and 0.25, 0.5, 1, 1.5, 2, 4, 5, 8, and 24 hours postdose
Single PK sample: weeks 8 and 16
Trough PK sample: weeks 1, 24, and 48
Timed PK sample: one sample collected between 15 minutes and 4 hours postdose on week 12

RESULTS

Demographics
Twenty-three subjects were enrolled and all completed the week 24 visit. Fourteen subjects (61%) were enrolled at one site in Uganda, six subjects (26%) were enrolled across three sites in the US, and three subjects (13%) were enrolled at one site in Thailand (Table 2).

Table 2. Demographics.

Characteristic	Median (min, max) or N (%)
Age (years)	10 (8, 11)
Female	14 (61%)
Black race	18 (78%)
Hispanic ethnicity	0 (0%)
Baseline weight (kg)	30.5 (25.5, 58.2)
eGFR using Schwartz equation (mL/min/1.73 m^2)	150 (99, 182)

Source: CSR

Protocol Deviations
Three important protocol deviations were reported; baseline DEXA scan not performed entirely, baseline DEXA scan performed after initial dose of study drug, and baseline labs received at the lab beyond the duration of stability.

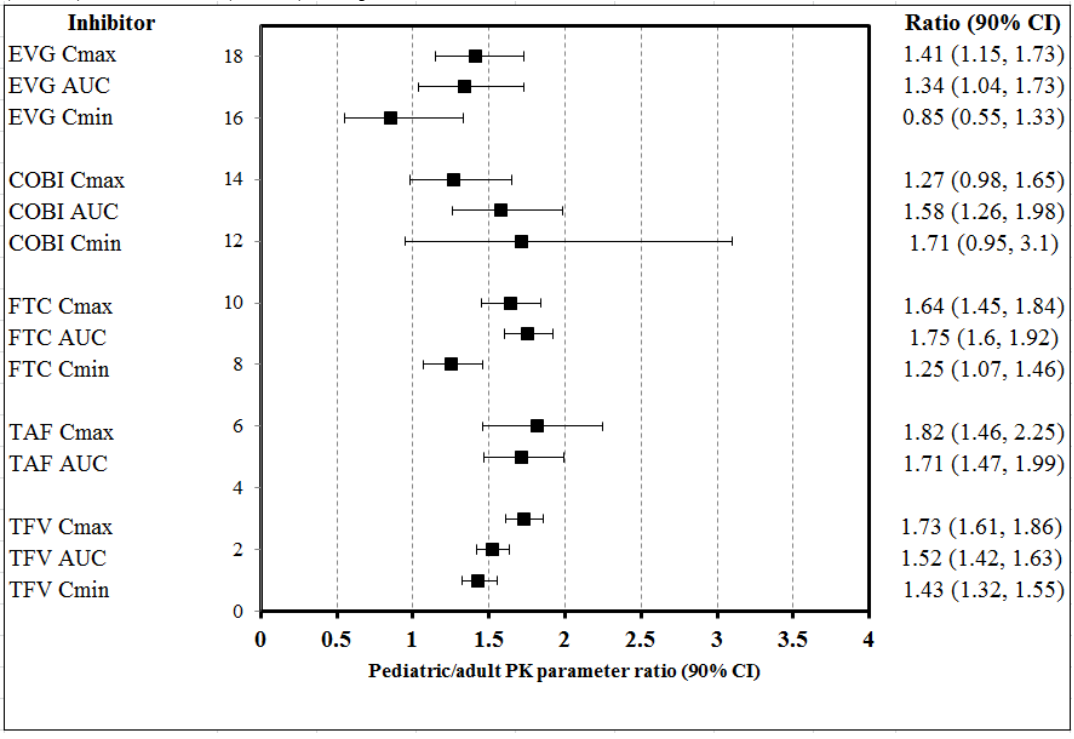
Concomitant medications
There was no reported use of prohibited concomitant medications during the study.

Bioanalytical Methods
Study drug concentrations in plasma (EVG, TAF, TFV, COBI, and FTC) and PBMCs (TFV-DP) were reported to have been determined using validated bioanalytical methods (see section 7.1).

Results
Pharmacokinetics

Pediatric exposures of the components of E/C/F/TAF were compared to historical adult data. Historical adult PK data for EVG, COBI, and FTC were from the intensive PK substudy of phase 2 E/C/F/TAF study 292-0102 (n=19). Historical adult PK data for TAF and TFV were from the population PK analysis of phase 3 E/C/F/TAF studies 292-0104 and 292-0111 (n=539 for TAF and n=841 for TFV). The no effect boundary selected by the applicant for the ratio of pediatric to adult PK parameters was 70-143%. Exposures of the components of E/C/F/TAF were generally higher in pediatric subjects relative to adults, with mean ratios and upper 90% CIs generally less than two (Figure 2). Exceptions where exposures were similar between pediatric and adult subjects included EVG and COBI Cmin (CI includes one). Exceptions where the upper 90% CI was between two and three included COBI Cmin and TAF Cmax.

Figure 2. Comparison of exposures of the components of E/C/F/TAF in HIV-infected pediatric (n=23) and adult (n=19) subjects.



Source: plotted by reviewer from data in CSR section 10.

CD4 counts

CD4 counts were found to decrease from baseline during the study in subjects aged 6 - <12 years (Table 3). We did not find the change from baseline in CD4 count to be associated with EVG, COBI, FTC, TAF, or TFV AUC. See the Clinical review for the complete discussion of this issue.

Table 3. Mean change in CD4+ count and percentage from baseline to week 24 in virologically suppressed pediatric patients from 6 to <12 years who switched to E/C/F/TAF.

	Week 2	Week 4	Week 12	Week 24
Mean Change in CD4+ Cell Count (cells/mm^3)	-162	-125	-162	-150
Mean Change in CD4%	+0.5%	-0.1%	-0.8%	-1.5%

Source: NDA 207561 FDA labeling edits dated 8/18/2017.

Efficacy

Twenty three subjects (100%) had HIV RNA <50 copies/mL at week 24.

Safety

Among the 23 subjects in the safety population (week 24 visit), there were no discontinuations due to AEs, SAEs, or deaths.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No ☐ N/A
- Use of prohibited concomitant medications did not affect the integrity of the study ☑ Yes ☐ No ☐ N/A
- Bioanalytical method performance in acceptable ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion

In the bioanalysis of study samples, analyte peaks were observed in chromatogram blanks for EVG and COBI, and several samples were reassayed due to carryover. We requested the applicant provide information on how carryover was assessed. In the response, the applicant stated that carryover was assessed in each run by placing an extracted matrix blank after each of the two ULOQ standards. If the blank had a peak area >20% of the LLOQ peak area, a carryover factor was calculated. This factor was then applied to all samples in the run. If the calculated carryover value for the preceding sample to the subsequent sample was >5%, the affected sample would be re-run (NDA 207561 SDN 344). We consider carryover to have been sufficiently addressed.

Increased exposures of EVG, COBI, FTC, and TAF in ages 6-<12 versus adults were acceptable as there are no exposure-related safety concerns associated with these components. While TFV has exposure-related safety concerns, exposures in ages 6-12 years administered E/C/F/TAF are much lower compared to adults administered TDF.

7 Appendix

7.1 Bioanalytical methods

We previously reviewed the method validation reports (NDA 207561) for assays used in this study and found the methods to be acceptable. Study sample analyses were also acceptable.

Table 4. Links to method validation and sample analysis reports.

Analyte	Report type	Link
TAF	Method validation	(b) (4)
	Sample analysis	
TFV	Method validation	
	Sample analysis	
FTC	Method validation	
	Sample analysis	
EVG and COBI	Method validation	
	Sample analysis	
TFV-DP	Method validation	
	Sample analysis	

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/s/

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09/08/2017

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09/11/2017