NDA	207561
Submission Dates	SDN 577 (3/29/2021) and SDN 598 (9/15/2021)
Generic Name	Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide
Brand Name	GENVOYA
Clinical Pharmacology Reviewer	Kunyi Wu, Pharm.D.
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OCP Division	DIDP
OND Division	DAV
Applicant	Gilead Sciences, Inc
Submission Type	sNDA

Background

GENVOYA is a four-drug combination tablet of elvitegravir [EVG, an HIV-1 integrase strand transfer inhibitor (INSTI)], cobicistat (COBI, a CYP3A inhibitor), and emtricitabine (FTC, an HIV-1 nucleoside analog reverse transcriptase inhibitor) and tenofovir alafenamide (TAF, an HIV-1 nucleoside analog reverse transcriptase inhibitor). The GENVOYA tablet, EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (E/C/F/TAF 150/150/200/10 mg), has been approved by the FDA for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 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 per 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 GENVOYA.

(b) (4)

the Applicant submitted the clinical study report, entitled "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 (Cohort 3, report date: 2/3/2021)" along with a population pharmacokinetic analysis report. Cohort 3 in Study 106 is an open-label, multicenter, multicohort, single-group study of the PK, safety, tolerability, and antiviral activity of E/C/F/TAF, 90/90/120/6 mg in HIV-1 infected, virologically suppressed children ≥ 2 years of age and weighing ≥ 14 to ≤ 25 kg at screening. The dose selection in pediatric patients is based on exposure-matching (i.e., extrapolation of efficacy from adults to pediatrics when exposures are comparable).

Recommendation

(b) (4)

Summary of Important Clinical Pharmacology Findings

All pharmacokinetic parameter estimates (i.e., AUCtau, Cmax, and Ctau) in pediatric patients in Cohort 3 are considered comparable (similar or no clinically meaningful differences) to those observed in adults or older pediatric patients except the Ctau of EVG based on the intensive PK (Table 3). Ctau of EVG in pediatric subjects in Cohort 3 were approximately 22% lower as compared to those observed in adults. Moreover, approximately 25% of observed Ctau at steady state were lower than 45 ng/mL, the protein-binding adjusted IC95 of wild-type HIV-1 virus[1]. Similarly, nearly 50% of subjects had observed EVG Ctau that were lower than model-driven in vivo EC90 (126 ng/mL)[1]. Please refer to Table 21 and Figure 24 in Appendix 3 of the Pharmacometics Review for detailed information. Therefore, the EVG Ctau is unacceptably low in a substantial number of study subjects (b) (4) .

Labeling Comments/Recommedations

The labeling language is still under discussion at the time this review was finalized.

[1] Ramanathan S et al. Clinical Pharmacokinetic and Pharmacodynamic Profile of the HIV Integrase Inhibitor Elvitegravir. Clin Pharmacokinet 2011: 50 (4): 229-244

Appendix 1.

Table 1. Method Validation and Performance for Study GS-US-292-0106 Cohort 3

Bioanalytical method review summary	The method validation was adequate to support Study GS-US-292-0106 including *1)* (b) (4) 60-1115 Amendment 7: An LC-MS/MS assay for the determination of GS-7340 (TAF) in K2EDTA human plasma was validated. The same method was used in the original approval. The amended parts, mainly for longer bench top/process stability and long-term storage stability, are summarized in the table below. *The reviewer did not review the validation report.* 2) (b) (4) 60-1343 Amendment 2: Partial Validation of a Method for the Determination of GS-9137 (EVG) and GS-9350 (COBI) in Human Plasma by LC-MS/MS. An LC-MS/MS assay for the simultaneous determination of GS-9137 and GS-9350 in K2EDTA human plasma was partially validated from (b) (4) 60-0949, the method used in the original NDA submission, using a different extraction procedure and LC conditions. 3) (b) (4) 60-1368 Amendment 3: Partial Validation of a Method for the Determination of Tenofovir (TFV) in Human Plasma by LC-MS/MS. This LC-MS/MS assay for the determination of tenofovir in K2EDTA human plasma was partially validated from (b) (4) 60-1116, the method used in original submission using a smaller sample volume and different LC conditions. *4)* (b) (4) 42-0831 Amendment 7: Validation of a Method for the Determination of Emtricitabine (FTC) and Tenofovir (TFV) in Human Plasma by LC-MS/MS. The same method was used in the original approval. The long-term storage stability was updated as shown in the table below. *The reviewer did not review the validation report.*	
Calibration curve concentration	EVG (20, 40, 100, 300, 1000, 3000, 9000, and 10000 ng/mL) COBI (5, 10, 25, 75, 250, 750, 2250, and 2500 ng/mL) FTC (5, 10, 60, 100, 300, 1500, 2700, and 3000 ng/mL) TAF (1, 2, 20, 50, 200, 500, 900, and 1000 ng/mL) TFV: (0.3, 0.6, 6, 20, 60, 150, 270, and 300 ng/mL)	
QC concentration	TAF (1, 3, 50, and 800 ng/mL) EVG (20, 60, 400, 4000, and 8000 ng/mL) COBI (5, 15, 100, 1000, and 2000 ng/mL) TFV (0.3, 0.9, 15, 160, and 240 ng/mL) FTC (5, 15, 150, 600, and 2400 ng/mL)	
Regression model & weighting	Linear regression analysis calculations were performed with $1/x^2$ weighting	
Validation parameters	**Method validation summary**	**Acceptability**
Standard calibration curve performance during accuracy & precision	EVG (GS-9137) and COBI (GS-9350)	Yes
	TFV	Yes
QCs performance during accuracy &	EVG (GS-9137) and COBI (GS-9350)	Yes

precision	TFV	Yes
Selectivity & matrix effect	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS for all	Yes
Bench-top/process stability in Plasma	TAF: 6.5 Hours in an Ice Bath/ 94 Hours at 4°C EVG: 20 Hours at Ambient Temperature (refer to 60-0949) COBI: 20 Hours at Ambient Temperature (refer to 60-0949) TFV: 16 Hours in an Ice Bath/190 hours at 4°C (refer to 60-1116) FTC: 16 Hours at Room Temperature/ 314 hours at 4°C	
Freeze-Thaw stability	TAF: Demonstrated stability through 5 Cycles at -20°C and -70°C EVG: 6 Cycles at -70°C (refer to 60-0949) COBI: 6 Cycles at -70°C (refer to 60-0949) TFV: 6 Cycles at -20°C and -70°C (refer to 60-1116) FTC: 6 Cycles at -20°C; 5 Cycles at -70°C	
Long-term storage*	EVG: 1099 days at –20°C and –70°C COBI: 1099 days at –20°C and –70°C FTC: 190 days at -20° C; 340 days at -70° C; 1426 days at -80° C TAF: 988 days at -70° C TFV: 366 days at -20°C; 1092 days at -70°C;	
Carry over	< 20%	Yes
Method Performance in GS-US-292-0106 Cohort 3		
Bioanalytical report review summary	1. (b) (4) 60-1314A Amendment 2: Determination of GS-7340 (TAF) in Human Plasma by LC-MS/MS Supporting GS-US-292-0106 2. (b) (4) 60-1314B: Determination of Tenofovir in Human Plasma by LC-MS/MS Supporting GS-US-292-0106 3. (b) (4) 60-1314C: Determination of Emtricitabine in Human Plasma by LC-MS/MS Supporting GS-US-292-0106 4. (b) (4) 60-1314D: Determination of GS-9137 and GS-9350 in Human Plasma by 5. LC-MS/MS Supporting GS-US-292-0106	
Bioassay Performance	**Acceptable**	

Reviewer's Comment: A bioanalytical site inspection was requested. OSIS concluded that an inspection is not warranted as OSIS inspected the site in (b) (4) *, which falls within the surveillance interval (refer to OSIS memo dated 5/21/2021 under NDA207561).*

Appendix 2. Individual Study Review

Title of study: 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 (Cohort 3, report date: 2/3/2021)

Study design of Cohort 3: This is an open-label, multicenter, multicohort, single-group study of the PK, safety, tolerability, and antiviral activity of E/C/F/TAF, 90/90/120/6 mg in HIV-1 infected, virologically suppressed children ≥ 2 years of age and weighing ≥ 14 to ≤ 25 kg at

screening. A total of 27 subjects received at least 1 E/C/F/TAF, 90/90/120/6 mg tablet daily, orally with food, at approximately the same time each day for 48 weeks (median [Q1, Q3] exposure 48.3 [48.0, 60.1] weeks). On completion of 48 weeks of study treatment, subjects were given the option to continue to receive the E/C/F/TAF, 90/90/120/6 mg tablet in an open-label extension phase. Three out of the 27 subjects received the adult GENVOYA (E/C/F/TAF 150/150/200/10 mg) tablet after attaining a weight ≥ 25kg, one at Week 12 and two at Week 32. The primary and secondary endpoints were as follows:

Primary Objectives	Primary Endpoints
• To evaluate the PK of EVG and TAF and confirm the dose of the STR in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg administered E/C/F/TAF low-dose (LD) (90/90/120/6 mg) STR	• The PK parameter AUC_{tau} for EVG and TAF
• To evaluate the safety and tolerability of E/C/F/TAF LD STR through Week 24 in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg	• The incidence of treatment-emergent serious adverse events (SAEs) and all treatment-emergent adverse events (AEs) through Week 24
Secondary Objectives	**Secondary Endpoints**
• To evaluate the antiviral activity of switching to E/C/F/TAF LD STR through Week 48 in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg	• The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm • The change from baseline in CD4 cell count (cells/µL) and percentage at Weeks 24 and 48 • The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 (missing = failure [M = F] and missing = excluded [M = E] analyses)
• To evaluate the safety and tolerability of E/C/F/TAF LD STR through Week 48 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg	• The incidence of treatment-emergent SAEs and all treatment-emergent AEs through Week 48 • The PK parameters C_{tau}, C_{max}, apparent CL/F, and apparent V_z/F for EVG; C_{max}, apparent CL/F, and apparent V_z/F for TAF; and AUC_{tau}, C_{max}, and C_{tau} for FTC, tenofovir (TFV), and COBI

<u>PK sampling schedule (Cohort 3 only)</u>:
Intensive PK sampling schedule: Intensive PK sampling were performed at Week 2. Samples were collected at 0 (predose, ≤ 30 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, and 8 hours post-dose.

Single PK sampling: A timed PK sample were collected between 0.25 and 4 hours post-dose at Weeks 8, 12, and 16.

Trough PK sampling: Ctau samples were collected at Weeks 4 and 24.

Results:
Based on the summary in Table 2 below, most subjects in Cohort 3 were black (N=24). No white subjects were enrolled. The minimal age was 3 years. No subjects age ≥ 2 years and < 3 years were enrolled.

Reviewer's comment: Because weight but not age is the significant covariate in the final population PK model for the four components in GENVOYA and the maturation level of liver and kidney is similar between pediatric subjects 2 years and 3 years of age, (b) (4) .

The statistical comparison of PK parameter estimates is shown in Table 3 below.

Reviewer's comment: The dose selection of E/C/F/TAF, 90/90/120/6 mg in children ≥ 2 years and weighing between 14 to 25 kg was based on exposure similarity at steady state between the study population in study GS-US-292-0106 Cohort 3 and adult patients administered adult GENVOYA:

- *EVG: The Ctau of EVG in pediatric subjects were lower than those observed in adults. Ctau is the PK parameter considered critical to match to ensure antiviral activity and avoid the potential for the development of resistance. About 25% of the observed Ctau in Cohort 3 were below 45 ng/mL (Table 21 and Figure 24 in Appendix 3), the protein-adjusted EC90 in vitro. Nearly 50% of subjects had observed EVG Ctau that were lower than model-driven in vivo EC90 (126 ng/mL)[1]. In the Stribild program, E-R analyses of EVG for efficacy were conducted in treatment naïve HIV-1 infected patients based on intensive and sparse pharmacokinetic data available from 373 subjects who received the fixed dose combination in GS-US-236-0102 and GS-US-236-0103. A relatively flat exposure-response relationship was identified across the EVG exposures, specifically EVG AUC (min-max) from 4358 to 69754 ng·hr/mL and EVG Ctau (min-max) from 58 to 2341 ng/mL.*
- *TAF: The Cmax of TAF in pediatric patients were lower as compared to those observed in adults (T/R ratio (90% CI): 71.19 (55.55, 91.23)). The Applicant justified the lower Cmax based on the FDA BE Guidance 2003 and General Clinical Pharmacology Considerations for Pediatric Studies[2]. Specifically, on page 52 in the Study Report, the Applicant stated "Equivalency in PK could be concluded if the 90% CIs of the GLSM ratios were contained within the equivalence boundaries of 70% and 143%."and "The sample size for the study was considered adequate if the 95% CIs of the CL/F and Vz/F estimates for each parameter were between 60% and 140% of the point estimate." The reviewer does not find any equivalent limits except 80-125% in the FDA BE guidance 2003. The 95% CI of 60-140% is discussed for the samples size calculation and should not be used as a bioequivalence limit. However, the population Cmax value observed in Cohort 3 is similar to the one in adolescence in the original approval. According to the submission for original approval in 2015, TAF has flat exposure response relationships for efficacy, thus 30% reduced exposures are acceptable. However, the reference the Applicant provided does not support this argument.*

[2] https://www.fda.gov/media/90358/download

- *FTC: The Ctau in pediatric subjects in Cohort 3 were up to 28% lower as compared to those observed in adults. According to the Clinical Pharmacology review for the original NDA approval, the relationship between FTC dose and antiviral activity was relatively flat at doses of 50-400 mg per day. Therefore, the 28% decrease in Ctau is acceptable.*

Table 2. Demographics and Baseline Characteristics (Adapted from Table 5.1 in the Study Report)

	E/C/F/TAF Cohort 3: Age >= 2 Years and Weight 14 to < 25 kg (N=27)
Age (years)	
N	27
Mean (SD)	6 (1.9)
Median	6
Q1, Q3	4, 8
Min, Max	3, 9
Age Group	
2-5 Years Old	11 (40.7%)
6-12 Years Old	16 (59.3%)
Sex at Birth	
Male	10 (37.0%)
Female	17 (63.0%)
Race	
American Indian or Alaska Native	0
Asian	3 (11.1%)
Black	24 (88.9%)
Native Hawaiian or Pacific Islander	0
White	0
Other	0
Not Permitted	0
Ethnicity	
Hispanic or Latino	0
Not Hispanic or Latino	27 (100.0%)
Not Permitted	0
Baseline Weight (kg)	
N	27
Mean (SD)	19.0 (2.55)
Median	19.3
Q1, Q3	17.0, 20.5
Min, Max	14.6, 23.5

Table 3. Statistical Comparisons of Pharmacokinetic Parameter Estimates Between Test and Historical Reference Treatments for TAF, TFV, EVG, COBI, and FTC

	Pediatric Patients in Cohort 3 in Study 106 (Test)				Adult Patients (Reference)			
	Based on simulation results		Based on the intensive PK				Based on simulation results	Based on the intensive PK dataset
TAF PK	n	GLSM	n	GLSM	n	GS-US-292-0104 and 0111*	Test/Reference (90% CI)	Test / Reference (90% CI)
AUCtau (h*ng/mL)	27	206.18	17	343.54	539	178.3	115.64 (110.11, 121.45)	192.68 (165.97,223.67)
Cmax (ng/mL)	27	103.14	27	217.75	539	144.88	71.19 (55.55, 91.23)	150.29 (115.68,195.27)
TFV						GS-US-292-0104 and 0111*		
AUCtau (h*ng/mL)	27	333.8	27	326.7	841	283.86	117.59 (110.15, 125.54)	115.09 (106.96,123.84)
Cmax (ng/mL)	27	18.61	27	19.07	841	14.79	125.88 (114.72, 138.13)	128.95 (119.46,139.20)
Ctau (ng/mL)	27	11.27	27	11.14	841	10.3	109.40 (102.43, 116.83)	108.12 (100.11,116.78)
EVG						GS-US-292-0102**		
AUCtau (h*ng/mL)	27	27168.82	24	29864.03	19	21553.74	126.05 (104.85, 151.54)	138.56 (111.93,171.52)
Cmax (ng/mL)	27	2172.4	27	2850.88	19	1997.55	108.75 (90.79, 130.27)	142.72 (112.94,180.35)
Ctau (ng/mL)	27	266.85	22	195.43	19	247.71	107.73 (78.77, 147.33)	78.90 (53.13,117.17)
COBI						GS-US-292-0102**		
AUCtau (h*ng/mL)	27	11036.81	21	12262.48	19	8975.72	122.96 (101.78, 148.56)	136.62 (103.01,181.20)
Cmax (ng/mL)	27	1371.01	27	1274.56	19	1400.19	97.92 (83.13, 115.34)	91.03 (71.04,116.64)
Ctau (ng/mL)	27	16.99	18	16.61	19	17.01	99.87 (71.00, 140.49)	97.64 (64.57,147.66)
FTC						GS-US-292-102**		
AUCtau (h*ng/mL)			27	18620.48	19	11576.55		160.85 (143.01, 180.90)
Cmax (ng/mL)			27	2808.24	19	2014.35		139.41 (120.28, 161.59)
Ctau (ng/mL)			27	77.4	19	89.11		86.86 (72.30, 104.34)

** PK parameters for the reference group were estimated from PopPK modeling using data from Genvoya-treated, HIV-1 infected adult subjects in Studies GS-US-292-0104 and GS-US-292-0111 who received the E/C/F/TAF 150/150/200/10 mg adult tablet.*

*** Intensive PK parameters for the reference group were derived from Genvoya-treated, HIV-1 infected adult subjects in Study GS-US-292-0102 who received the E/C/F/TAF 150/150/200/10 mg adult tablet.*

GLSM: geometric least square mean

PK estimates of TAF, TFV, EVG, COBI, FTC are from Table 44.1, 44.3, 44.2, 44.4, and 44.5 in the Study Report, respectively.

Appendix 3 Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

The Applicant presented PopPK analyses on elvitegravir (**EVG**), cobicistat (**COBI**), and tenofovir alafenamide (**TAF**, prodrug of tenofovir or **TFV**) as components (no PopPK analysis performed on emtricitabine) of fixed-dose combination tablet Genvoya® for HIV-1 infected and virologically suppressed pediatric subjects who are at least 2 years of age and weigh ≥14 to <25 kg.

The PopPK models for **TAF** (as well as the sequential model for **TFV**) and **COBI** are generally adequate in: 1) describing the pooled pharmacokinetic (PK) data, 2) supporting simulations to predict exposure ranges, and 3) supporting PK exposure matching from historic adult data to target pediatric subjects.

For **EVG** (EVG is boosted by COBI unless specified otherwise in this review), while the overall performance of the PopPK model was adequate for the pooled PK data, discordance was identified regarding low EVG Ctau, which is the PK/PD driver correlated with efficacy, being observed in the target pediatric cohort. As EVG Ctau was lower than observed adult population, efficacy results cannot be extrapolated from adult to pediatric population who are at least 2 years of age and weighing at least 14 kg to <25 kg. This observation is further elaborated below with reviewer's independent analyses.

1.2 Introduction

The Applicant's primary objectives of the PopPK analyses on **TAF** and **TFV** were to:

- Develop a joint, sequential model of TAF and TFV
- Evaluate the PopPK model in pooled adolescents and children (target population) PK samples and estimate the inter-individual variability (IIV) of PK parameters
- Evaluate covariate impact on PK parameters (i.e., drug exposure)
- Estimate individual exposures for comparison against reference data
- Support weight-band based dosing recommendation for fixed-dose combination tablet Genvoya® in HIV-1 infected pediatric subjects

Similarly, the primary objectives of Applicant's PopPK analyses on **EVG** and **COBI** were to:

- Evaluate the PopPK model in pooled adolescents and children (target population) PK samples and estimate the inter-individual variability (IIV) of PK parameters
- Evaluate covariate impact on PK parameters (i.e., drug exposure)
- Estimate individual exposures for comparison against reference data
- Support weight-band based dosing recommendation for fixed-dose combination tablet Genvoya® in HIV-1 infected pediatric subjects

1.3 Model development

PK data from a total of 4 Phase 2/3 studies were included to conduct PopPK analysis: GS-US-292-0106, GS-US-292-1515, GS-US-311-1269, and GS-US-380-1474. Of note, Cohort 3 study GS-US-292-106 is the target pediatric population for current submission. **Table 1** lists the relevant study, dosage, and PK sampling type for all subjects.

Table 1. Studies PK and Dosing Summary

Study	Study Design/Population	Treatment	Sampling (Intensive/Sparse)
GS-US-292-0106	A Phase 2/3, Open-Label Study of the Pharmacokinetics (PK), Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1–Infected, Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children	Cohorts 1 and 2 (adolescents and children [6 to < 18 years of age, weighing ≥ 25 kg]): E/C/F/TAF 150/150/200/10 mg fixed-dose combination (FDC) Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): E/C/F/TAF 90/90/120/6 mg FDC	Intensive + Sparse
GS-US-292-1515	A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1–Infected, Virologically Suppressed Adolescents	E/C/F/TAF 150/150/200/10 mg FDC	Sparse
GS-US-311-1269	A Phase 2/3, Open-Label, Multicohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1–Infected Children and Virologically Suppressed Adolescents on a 2-Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Containing Regimen	Cohort 1 (adolescents 12 to < 18 years of age, weighing ≥ 35 kg): F/TAF 200/25 mg or 200/10 mg FDC Cohort 2 Group 1 (children 6 to < 12 years of age, weighing ≥ 25 kg): F/TAF 200/25 mg Cohort 2 Group 2 (children 2 to < 12 years of age, weighing ≥ 17 to < 25 kg): F/TAF 120/15 mg	Intensive + Sparse
GS-US-380-1474	A Phase 2/3, Open-Label Study of the PK, Safety, and Antiviral Activity of the GS-9883/F/TAF) FDC in HIV-1–Infected, Virologically Suppressed Adolescents and Children	Cohorts 1 and 2 (adolescents [12 to < 18 years of age] and children [6 to < 12 years of age]): B/F/TAF 50/200/25 mg FDC Cohort 3 (children ≥ 2 years of age weighing ≥ 14 to < 25 kg): B/F/TAF 30/120/15 mg FDC	Intensive + Sparse

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetic(s).

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Table 1, page 23

Data for TAF/TFV

Table 2, **Table 3**, and **Table 4** describe the baseline characteristics of subjects in the TAF and sequential TAF-TFV PopPK analyses by study and number of PK samples retained for PopPK model development. **Figure 1** depicts the TAF concentration-time profiles by study using time since last dose. Overall, a total of 337 subjects contributed

1709 and 3176 PK samples for TAF and TFV, respectively, for PopPK analysis. M3 method was used to handle BLQ data for TAF.

Table 2. TAF PK Data

Description	Total Number of Samples	Number of BLQ Samples	Number of Subjects
PopPK dataset	3141	1709	337
Excluded samples with time after last dose > 5.5 h	1432	1364	0
Total excluded from PopPK analysis	1432	1364	0
Total included in PopPK analysis	1709	345	337

BLQ = below the limit of quantitation; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Table 6, page 35

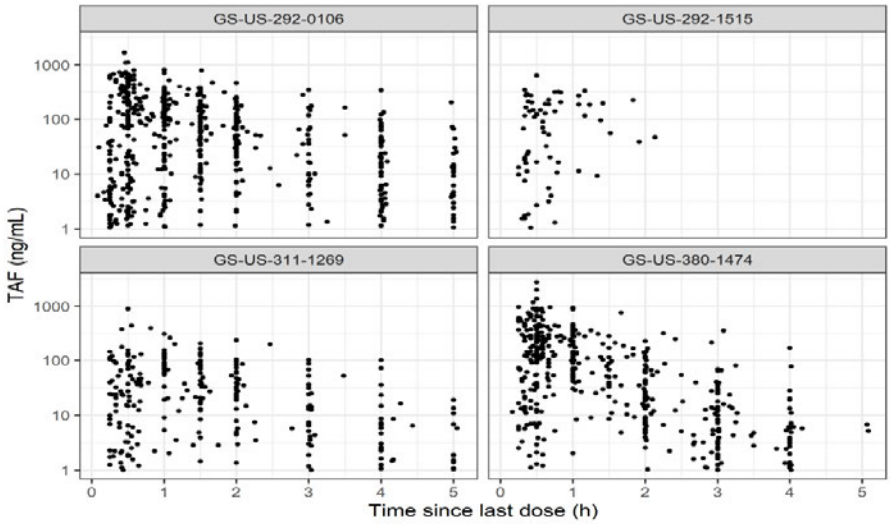
Table 3. TFV PK Data

Description	Number of Samples	Number of Subjects
PopPK dataset	3190	337
Excluded BLQ samples	10	0
Excluded samples with |CWRES| > 6	4	0
Total excluded from PopPK analysis	14	0
Total included in PopPK analysis	3176	337

BLQ = below the limit of quantitation; CWRES = conditional weighted residuals; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Table 31, page 61

Figure 1. TAF Concentration-time Profile by Study



Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 3, page 38

Table 4. Baseline Characteristics of Study Subjects by Study (TAF/TFV)

Covariate	Statistics	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 50)	GS-US-311-1269 (N = 36)	GS-US-380-1474 (N = 122)	Total (N = 337)
Age (years)	Mean (SD)	10.9 (3.72)	14.8 (1.62)	13.1 (2.35)	10.8 (3.76)	11.7 (3.68)
	Median [Min, Max]	11.0 [3.00, 17.0]	15.0 [12.0, 17.0]	13.0 [8.00, 17.0]	11.0 [3.00, 17.0]	12.0 [3.00, 17.0]
WT (kg)	Mean (SD)	36.9 (15.8)	54.1 (13.9)	43.1 (9.19)	37.6 (18.0)	40.4 (16.9)
	Median [Min, Max]	33.1 [14.6, 88.8]	52.2 [35.1, 101]	43.4 [22.0, 62.4]	34.0 [14.1, 123]	38.0 [14.1, 123]
BMI (kg/m^2)	Mean (SD)	17.9 (3.44)	21.3 (4.92)	19.1 (2.33)	18.6 (5.04)	18.8 (4.36)
	Median [Min, Max]	17.4 [12.4, 31.8]	19.8 [15.5, 38.6]	18.7 [14.0, 25.1]	17.7 [12.6, 45.7]	17.9 [12.4, 45.7]
BSA (m^2)	Mean (SD)	1.19 (0.326)	1.54 (0.211)	1.33 (0.194)	1.19 (0.333)	1.25 (0.327)
	Median [Min, Max]	1.12 [0.640, 2.03]	1.52 [1.19, 2.13]	1.35 [0.880, 1.71]	1.14 [0.590, 2.37]	1.23 [0.590, 2.37]
BCL_{CRSW} (mL/min/ 1.73 m^2)	Mean (SD)	154 (28.4)	160 (26.2)	162 (31.4)	156 (29.0)	156 (28.7)
	Median [Min, Max]	150 [98.6, 284]	158 [102, 223]	157 [108, 236]	151 [89.0, 259]	153 [89.0, 284]

BMI = body mass index; BSA = body surface area; BCL_{CRSW} = baseline creatinine clearance derived by Schwartz equation; N = number of subjects; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight

Sex	Male	54 (41.9%)	18 (36.0%)	19 (52.8%)	52 (42.6%)	143 (42.4%)
	Female	75 (58.1%)	32 (64.0%)	17 (47.2%)	70 (57.4%)	194 (57.6%)
Race	White	2 (1.6%)	1 (2.0%)	3 (8.3%)	3 (2.5%)	9 (2.7%)
	Black	105 (81.4%)	49 (98.0%)	15 (41.7%)	84 (68.9%)	253 (75.1%)
	Asian	22 (17.1%)	0 (0%)	1 (2.8%)	29 (23.8%)	52 (15.4%)
	Other	0 (0%)	0 (0%)	17 (47.2%)	6 (4.9%)	23 (6.8%)
P-gp inhibitors	No	97 (75.2%)	50 (100%)	34 (94.4%)	109 (89.3%)	290 (86.1%)
	Yes	32 (24.8%)	0 (0%)	2 (5.6%)	13 (10.7%)	47 (13.9%)
Booster groups	Unboosted	0 (0%)	0 (0%)	14 (38.9%)	122 (100%)	136 (40.4%)
	COBI	129 (100%)	50 (100%)	0 (0%)	0 (0%)	179 (53.1%)
	LPV/RTV	0 (0%)	0 (0%)	22 (61.1%)	0 (0%)	22 (6.5%)
PPIs	No	126 (97.7%)	50 (100%)	35 (97.2%)	120 (98.4%)	331 (98.2%)
	Yes	3 (2.3%)	0 (0%)	1 (2.8%)	2 (1.6%)	6 (1.8%)
H2RAs	No	128 (99.2%)	49 (98.0%)	35 (97.2%)	121 (99.2%)	333 (98.8%)

COBI = cobicistat; H2RA = histamine 2 receptor antagonist; LPV = lopinavir; N = number of subjects; P-gp = P-glycoprotein; PopPK = population pharmacokinetic; PPI = proton-pump inhibitor; RTV = ritonavir; TAF = tenofovir alafenamide

Note: the inclusion of LPV/RTV treatment is not relevant for the purpose of this review
Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Table 31, page 61

Data for EVG

Table 5 and **Table 6** describe the number of PK samples retained and the baseline characteristics of subjects in EVG PopPK analyses by study. Overall, a total of 229 subjects contributed 2147 PK samples for EVG PopPK modeling. **Figure 2** depicts the EVG concentration-time profiles using time since last dose.

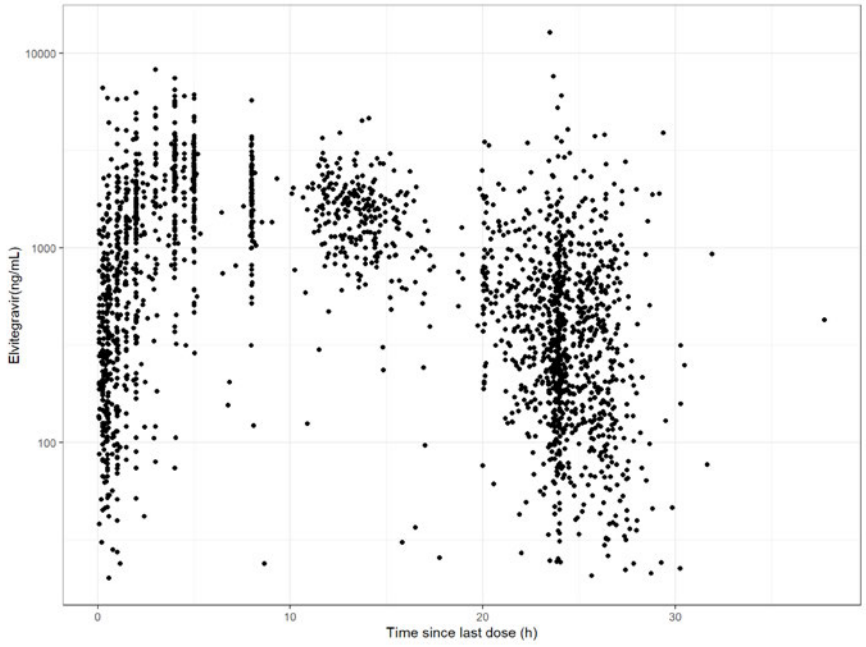
Table 5. EVG PK Data

Description	Number of Samples	Number of Subjects
Population PK dataset	2512	252
Excluded BLQ samples	139	0
Excluded samples with missing DV	0	0
Excluded samples from Study GS-US-183-0152	226	23
Total included in population PK analysis	2147	229
Total included in exposure-prediction dataset	2373	252

BLQ = below the limit of quantitation; DV = observed concentration; EVG = elvitegravir; PK = pharmacokinetic

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Table 4, page 30

Figure 2. EVG Concentration-time Profiles



Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 1, page 32

Table 6. Baseline Characteristics of Study Subjects by Study (EVG)

Subject Characteristic	Statistics	GS-US-236-0112 (N = 50)	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 50)	Total (N = 229)
Age (years)	Mean (SD)	15.5 (1.49)	10.9 (3.72)	14.8 (1.62)	12.7 (3.66)
	Median (min, max)	16.0 (12.0, 17.0)	11.0 (3.0, 17.0)	15.0 (12.0, 17.0)	13.0 (3.0, 17.0)
Weight (kg)	Mean (SD)	56.4 (13.3)	36.9 (15.8)	54.1 (13.9)	44.9 (17.4)
	Median (min, max)	56.4 (35.1, 91.2)	33.1 (14.6, 88.8)	52.2 (35.1, 101.0)	44.2 (14.6, 101)
BMI (kg/m^2)[a]	Mean (SD)	21.1 (3.22)	17.9 (3.44)	21.3 (4.92)	19.3 (4.09)
	Median (min, max)	20.9 (15.9, 28.5)	17.4 (12.4, 31.8)	19.8 (15.5, 38.6)	18.3 (12.4, 38.6)
BSA (m^2)[a]	Mean (SD)	1.59 (0.234)	1.19 (0.326)	1.54 (0.211)	1.35 (0.342)
	Median (min, max)	1.62 (1.09, 2.14)	1.12 (0.640, 2.03)	1.52 (1.19, 2.13)	1.34 (0.640, 2.14)
BCLCRSW ($mL/min/1.73m^2$)	Mean (SD)	146 (24.6)	154 (28.4)	160 (26.2)	153 (27.4)
	Median (min, max)	140 (102, 198)	150 (98.6, 284)	158 (102, 223)	150 (98.6, 284)

BCLCRSW = baseline creatinine clearance derived by Schwartz equation; BMI = body mass index; BSA = body surface area; EVG = elvitegravir; Max = maximum; Min = minimum; N = number of subjects; PopPK = population pharmacokinetic; SD = standard deviation; WT = baseline body weight.

Subject Characteristic	Statistics	GS-US-236-0112 (N = 50)	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 50)	Total (N = 229)
Sex	Male	35 (70.0%)	54 (41.9%)	18 (36.0%)	107 (46.7%)
	Female	15 (30.0%)	75 (58.1%)	32 (64.0%)	122 (53.3%)
Race	White	1 (2.0%)	2 (1.6%)	1 (2.0%)	4 (1.7%)
	Black	34 (68.0%)	105 (81.4%)	49 (98.0%)	188 (82.1%)
	Asian	14 (28.0%)	22 (17.1%)	0 (0%)	36 (15.7%)
	Other	1 (2.0%)	0 (0%)	0 (0%)	1 (0.4%)
Patient status	HIV treatment naive	50 (100%)	129 (100%)	0 (0%)	179 (78.2%)
	HIV treatment experienced	0 (0%)	0 (0%)	50 (100%)	50 (21.8%)
Coadministration of P-gp inhibitors	No	40 (80.0%)	97 (75.2%)	50 (100%)	187 (81.7%)
	Yes	10 (20.0%)	32 (24.8%)	0 (0%)	42 (18.3%)
Food	Fasted	48 (96.0%)	128 (99.2%)	50 (100%)	226 (98.7%)
	Fed	1 (2.0%)	1 (0.8%)	0 (0%)	2 (0.9%)
	Missing	1 (2.0%)	0 (0%)	0 (0%)	1 (0.4%)

EVG = elvitegravir; N = number of subjects; P-gp = P-glycoprotein

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Tables 5 and 6, page 31

Data for COBI

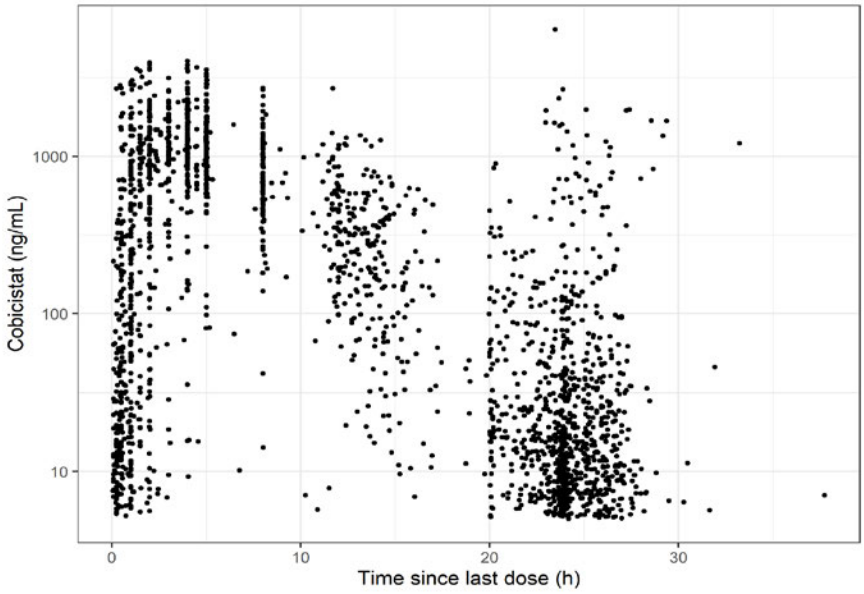
Table 7 and **Table 8** describe the number of PK samples retained and the baseline characteristics of subjects in COBI PopPK analyses by study. Overall, a total of 247 subjects contributed 2142 PK samples for COBI PopPK modeling. **Figure 3** depicts the COBI concentration-time profiles using time since last dose.

Table 7. COBI PK Data

Description	Number of Samples	Number of Subjects
Population PK dataset	2490	248
Excluded BLQ samples	348	1
Excluded samples with missing DV	0	0
Total excluded from population PK analysis	348	1
Total included in population PK analysis	2142	247
Total included in the exposure-prediction dataset	2490	248

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Tables 22, page 49

Figure 3. COBI Concentration-time Profile



Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 7, page 51

Table 8. Baseline Characteristics of Study Subjects by Study (COBI)

Subject Characteristic	Statistics	GS-US-216-0128 (N = 22)	GS-US-236-0112 (N = 50)	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 47)	Total (N = 248)
Age (years)	Mean (SD)	14.2 (1.77)	15.5 (1.49)	10.9 (3.72)	14.9 (1.59)	12.9 (3.57)
	Median (min, max)	14.0 (12.0, 17.0)	16.0 (12.0, 17.0)	11.0 (3.00, 17.0)	15.0 (12.0, 17.0)	13.5 (3.00, 17.0)
Weight (kg)	Mean (SD)	54.8 (13.0)	56.4 (13.3)	36.9 (15.8)	54.4 (14.1)	45.8 (17.3)
	Median (min, max)	52.7 (32.3, 81.4)	56.4 (35.1, 91.2)	33.1 (14.6, 88.8)	52.4 (35.1, 101)	46.0 (14.6, 101)
BMI (kg/m^2)	Mean (SD)	21.9 (3.87)	21.1 (3.22)	17.9 (3.44)	21.5 (5.01)	19.6 (4.15)
	Median (min, max)	21.2 (16.7, 29.5)	20.9 (15.9, 28.5)	17.4 (12.4, 31.8)	20.0 (15.5, 38.6)	18.7 (12.4, 38.6)
BSA (m^2)	Mean (SD)	1.54 (0.217)	1.59 (0.234)	1.19 (0.326)	1.54 (0.211)	1.37 (0.338)
	Median (min, max)	1.53 (1.12, 1.96)	1.62 (1.09, 2.14)	1.12 (0.640, 2.03)	1.53 (1.19, 2.13)	1.42 (0.640, 2.14)
BCLCRSW ($mL/min/1.73m^2$)	Mean (SD)	161 (28.5)	146 (24.6)	154 (28.4)	160 (26.8)	154 (27.7)
	Median (min, max)	160 (108, 211)	140 (102, 198)	150 (98.6, 284)	158 (102, 223)	152 (98.6, 284)

BCLCRSW = baseline creatinine clearance derived from Schwartz equation; BMI = body mass index; BSA = body surface area; COBI = cobicistat; Max = maximum; Min = minimum; N = number of subjects; PopPK = population pharmacokinetic; SD = standard deviation

Subject Characteristic	Statistics	GS-US-216-0128 (N = 22)	GS-US-236-0112 (N = 50)	GS-US-292-0106 (N = 129)	GS-US-292-1515 (N = 47)	Total (N = 248)
Sex	Male	14 (63.6%)	35 (70.0%)	54 (41.9%)	16 (34.0%)	119 (48.0%)
	Female	8 (36.4%)	15 (30.0%)	75 (58.1%)	31 (66.0%)	129 (52.0%)
Race	White	7 (31.8%)	1 (2.0%)	2 (1.6%)	0 (0%)	10 (4.0%)
	Black	5 (22.7%)	34 (68.0%)	105 (81.4%)	47 (100%)	191 (77.0%)
	Asian	8 (36.4%)	14 (28.0%)	22 (17.1%)	0 (0%)	44 (17.7%)
	Other	2 (9.1%)	1 (2.0%)	0 (0%)	0 (0%)	3 (1.2%)
Patient status	HIV treatment naive	0 (0%)	50 (100%)	129 (100%)	0 (0%)	179 (72.2%)
	HIV treatment experienced	22 (100%)	0 (0%)	0 (0%)	47 (100%)	69 (27.8%)
Coadministration of P-gp inhibitors	No	21 (95.5%)	40 (80.0%)	97 (75.2%)	47 (100%)	205 (82.7%)
	Yes	1 (4.5%)	10 (20.0%)	32 (24.8%)	0 (0%)	43 (17.3%)
Food[a]	Fasted	236 (97.9%)	564 (95.6%)	1532 (98.0%)	94 (97.9%)	2426 (97.4%)
	Fed	0 (0%)	13 (2.2%)	29 (1.9%)	1 (1.0%)	43 (1.7%)
	Missing	5 (2.1%)	13 (2.2%)	2 (0.1%)	1 (1.0%)	21 (0.8%)

COBI = cobicistat; N = number of subjects; P-gp = P-glycoprotein

a Food was a time varying variable, and the total number of samples was used for the summary instead of the total number of subjects.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Tables 23 and 24, pages 49-50

Base model for TAF and sequential TAF-TFV

The base model for TAF was 1-compartment model parameterized with first-order absorption (Ka into depot) and first-order elimination (CL) from the central compartment (V). Fixed allometric scalers of 0.75 and 1 were incorporated as exponents on body weight (centered to 70 kg) on CL and V, respectively. Effect of COBI was modeled on bioavailability. IIV was included on CL, V, Ka and proportional error term; however, random effects were fixed to zero for CL and V for model reproducibility and stability. A combined error model (proportional and additive) was used to describe residual variability. Of note, the additive error term was fixed to half of LLOQ of PK samples (0.5 ng/mL). Table 9 lists the parameter estimates of the base model for TAF.

A joint TAF-TFV model was developed using the final PK parameters from TAF PopPK model. A 2-compartment model was used to characterize TFV PK profile, assuming a 98.3% metabolic conversion rate of 98.3% from TAF central compartment. Additionally, parallel absorption compartments (depot) were utilized to improve the base model performance (presence of LPV/RTV booster subgroup). The base model also included body weight effects on TFV clearance, central volume of distribution, intercompartmental flow, and peripheral volume of distribution with fixed allometric scalers (0.75 for clearance related terms and 1 for volume of distribution related terms). IIV was included on the same structural parameters as body weight effects, and a combined error model was used for residual variability. A schematic of the base sequential structural model is shown in **Figure 4** and the base model parameters are listed in **Table 10**.

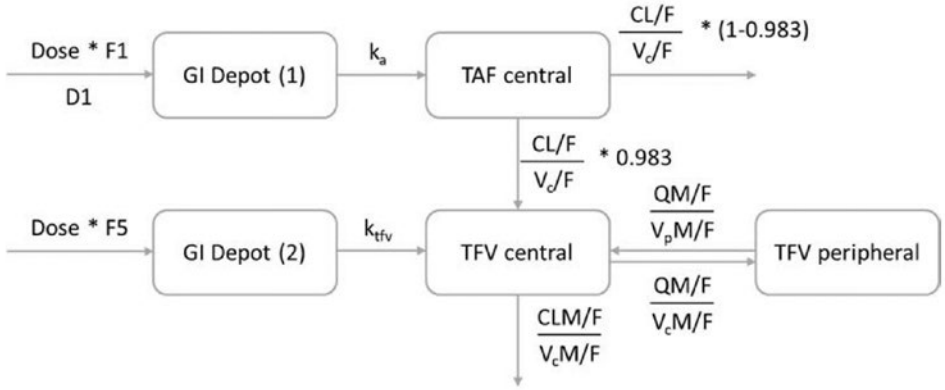
Table 9. Summary of Base TAF PopPK Model

	Parameter Estimates		IIV	
Parameter	**Typical Value**	**%RSE**	**Magnitude (%CV)**	**%RSE**
exp(θ_1): Apparent oral clearance (L/h)	121	8.3%	--	--
exp(θ_2): Apparent central volume of distribution (L)	60.7	13.4%	--	--
exp(θ_3): First order absorption rate constant (1/h)	0.992	0.1%	139%	11.2%
θ_6: COBI effect on F1	1.69	17.8%	--	--
. $\overline{\theta_4}$: Residual proportional variability (%)	118	0.7%	55%	26.3%
θ_5: Residual additive	0.5 [FIXED]	--	--	--

θ = parameter estimate; %CV = percentage coefficient of variation; %RSE = percentage relative standard error;
COBI = cobicistat; F1 = relative bioavailability of TAF; IIV = interindividual variability; OFV = objective function value;
TAF = tenofovir alafenamide
Minimum OFV = 15,662.334.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Table 9, page 43

Figure 4. Schematic for Sequential TAF-TFV PopPK Analysis



CLM/F = apparent oral clearance of TFV; k_{tfv} = first order absorption rate constant from second depot compartment; F1 = relative bioavailability of TAF; F5 = relative bioavailability for TFV; GI = gastrointestinal; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; TAF = tenofovir alafenamide; TFV = tenofovir; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 12, page 62

Table 10. Summary of Base TAF-TFV Sequential PopPK Model

	Parameter Estimates		IIV	
Parameter	Typical Value	%RSE	Magnitude (%CV)	%RSE
exp(θ_1): Apparent oral clearance (L/h)	124	2%	26%	11%
exp(θ_2): Apparent central volume of distribution (L)	1750	16%	116%	21%
exp(θ_4): Intercompartmental clearance (L/h)	2280	16%	54%	36%
exp(θ_3): Apparent peripheral volume of distribution (L)	5510	6%	24%	65%
exp(θ_8): TFV first order absorption rate constant from second depot compartment (1/h)	0.155	61%	--	--
θ_7: LPV/RTV effect on TFV relative bioavailability	2.01	9%	--	--
Residual proportional variability (%)	45	1%	--	--
Residual additive variability (ng/mL)	1.17	21%	--	--

θ = parameter estimate; %CV = percentage coefficient of variation; %RSE = percentage relative standard error; IIV = interindividual variability; LPV/RTV = lopinavir/ritonavir; OFV = objective function value; PopPK = population pharmacokinetic; TFV = tenofovir
Minimum OFV = 11,443.482.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Table 32, page 63

Base model for EVG

The final base model was a 2-compartment model with zero- and first-order (sequential) absorption and linear elimination. Body weight effects on CL and V related parameters were modeled as power function with fixed allometric scalers of 0.75 and 1, respectively. IIV was modeled on CL, Vp (peripheral volume of distribution), Q (intercompartmental flow), and D (duration of zero-order absorption). A combined error model was used to describe residual variability. The base model was retained as final model. See base/final EVG PopPK model parameter estimates in **Table 17**.

Base model for COBI

The base COBI PopPK model was a 1-compartment structural model with a zero- and first-order (sequential) absorption and first-order elimination. IIV was modeled on CL and D, and proportional error model was used to describe residual variability. **Table 11** lists the parameter estimates from the base PopPK model.

Table 11. Summary of Base COBI PopPK Model

		Final Parameter Estimate		Between-Subject Variability/Residual Variability	
Parameter	Parameter Description	Typical Value	%RSE	Magnitude	%RSE
$\exp(\theta_1)$	Apparent oral clearance (L/h)	16.6	5	94%	4
$\exp(\theta_2)$	Apparent central volume (L)	42.5	9	40%	23
$\exp(\theta_3)$	Absorption duration (h)	0.802	9	109%	12
$\exp(\theta_4)$	Absorption rate constant (1/h)	0.263	4	—	—
$\sqrt{\theta_5}$	Residual proportional error (%)	94	4	43%	17

θ = parameter estimate; COBI = cobicistat; RSE = relative standard error
Note: Minimum value of the objective function = 2779.5

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Table 25, page 52

Covariate analysis

Covariate tested for base PopPK models of TAF, TAF-TFV, EVG, and COBI are listed in **Table 12**. Covariate analysis results for EVG and COBI are listed in **Table 13** and **Table 14**, respectively. Of note, the base EVG model with age as a covariate on CL encountered model stability and model misfits. As such, age on Cl was ultimately not retained in the final model.

Table 12. Covariates Tested in Structural Models

Base Structural Models	Covariates Tested
TAF and TAF-TFV	AGE, SEX, RACE, BCLCRSW, P-gp inhibitors co-medication
EVG	AGE, RACE, WT
COBI	AGE, SEX, RACE, BCLCRSW, P-gp inhibitors co-medication, WT

**BCLCRSW, baseline creatinine clearance using Schwartz equation; WT, baseline body weight*

Table created by reviewer; adapted from relevant PopPK reports

Table 13. EVG Covariate Analysis

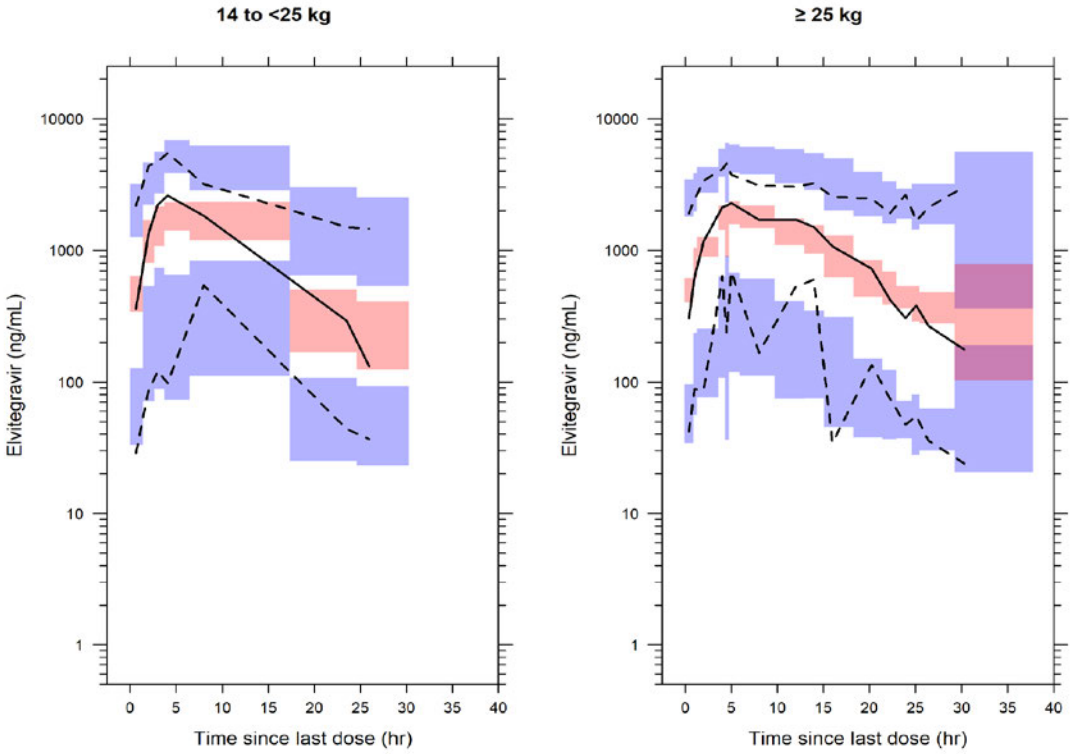
Reference Model	Covariate Relation	OFV	P-Value
Base model	None	28629.21	Reference
	CL/F-AGE	28609.27	0.000008
CL/F-AGE	CL/F-AGE CL/F- BCL_{CRSW}	28598.87	0.001256
CL/F-AGE CL/F- BCL_{CRSW}	CL/F-AGE	28609.27	0.001256

AGE = baseline age; BCL_{CRSW} = baseline creatinine clearance derived by Schwartz equation; EVG = elvitegravir; OFV = objective function value; p = p-value between the new model and the reference model.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Table 7, page 33

Reviewer's comments: the reviewer encountered significant challenges in reproducibility of EVG base/final model parameter estimates and OFV values, whether the model files were unmodified or modified. The reviewer was able to reproduce the base and variants of the base model as independent sensitivity analyses with the exact NONMEM version that the Applicant used (based on their .lst file) and without parallel retries nor different initial parameter estimates. Overall, the model captured the general trends of the observed data; however, the EVG Ctau values would be over-projected from model predictions, as well as for the purpose of simulation. Refer to the reviewer's independent analysis section for details.

Figure 5. VPC of EVG PopPK Model (Age on CL)



CI = confidence interval; EVG = elvitegravir; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic
Note: The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median and the blue area is the 95% CI of the simulated 5th and 95th percentiles.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 2, page 35

Table 14. COBI Covariate Analysis

	P-Value		
Covariates	**ETA CL/F**	**ETA D_1**	**ETA Proportional Error**
AGE	0.004473	0.005897	0.1133
BCL_{CRSW}	0.5683	0.5621	0.7104
CMPGP	0.00007816	0.01728	0.4128
RACE	0.006638	0.05092	0.01986
SEX	0.1980	0.04137	0.1736
WT	0.002225	0.001365	0.1697

AGE = baseline age; ANOVA = analysis of variance; CMPGP = concomitant administration of P-gp inhibitors; COBI = cobicistat; ETA = random effect; WT = baseline body weight
Note: P-values show the significance of slope for continuous covariates and ANOVA of categorical covariates.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Table 26, page 54

1.4 Final Model

TAF

TAF PK data were best describe by a 1-compartment model with sequential zero- and first-order absorption and first-order elimination. Body weight effects were modeled on CL and V with fixed exponent of 0.75 and 1, respectively. In addition to COBI effect on F, a separate V was modeled for Asian subjects. IIV was modeled in the same structural fashion as the base model but was modeled additionally on D in the final model. A combined error model described the residual variability (with IIV on proportional error term). Final PopPK parameter estimates are listed in **Table 15**. Diagnostics are described in **Figure 6** and **Figure 7**.

Table 15. Final PopPK Parameter Estimates for TAF

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles][b]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	130 [5.4%]	121 [115;139]	129 [121;141]
$\exp(\theta_2)$	Apparent central volume of distribution, V_c/F (L)	24.6 [3.5%]	30.2 [29.1;46.8]	25.4 [23.7;27.3]
$\exp(\theta_3)$	First order absorption rate constant, k_a (1/h)	1.7 [0.9%]	1.76 [1.69;1.86]	1.72 [1.68;1.75]
θ_6	COBI effect on F1	1.64 [1.1%]	1.36 [0.989;1.85]	1.64 [1.6;1.68]
$\exp(\theta_7)$	Duration of zero-order absorption, D1 (h)	1.5 [0.4%]	0.947 [0.933;1.11]	1.49 [1.48;1.5]
θ_8	Asian effect on V_c/F	-0.788 [0.7%]	-0.732 [-0.811;-0.624]	-0.797 [-0.81;-0.784]
$\sqrt{\theta_4}$	Residual proportional error (%)	126 [0.1%]	123 [118;125]	126 [126;126]
θ_5	Residual additive	0.5 [fixed]	0.5 [fixed]	0.5 [fixed]
$\omega 55$	IIV of D1 (%)	108 [0.3%]	116 [114;132]	108 [107;108]
$\omega 44$	IIV of proportional error (%)	60 [0.1%]	61 [55.7;65.1]	59.8 [59.7;59.9]

θ = parameter estimate; ω = standard deviation of between-subject variability; COBI = cobicistat; IIV = interindividual variability; PopPK = population pharmacokinetic; RSE = relative standard error; TAF = tenofovir alafenamide

a RSE is defined as the SE divided by the $\theta \times 100\%$ for nontransformed parameters and as SE × 100% for log-transformed parameters.

b Runs with terminated minimization due to rounding errors were included in the calculation of the bootstrap estimates of parameter uncertainty.

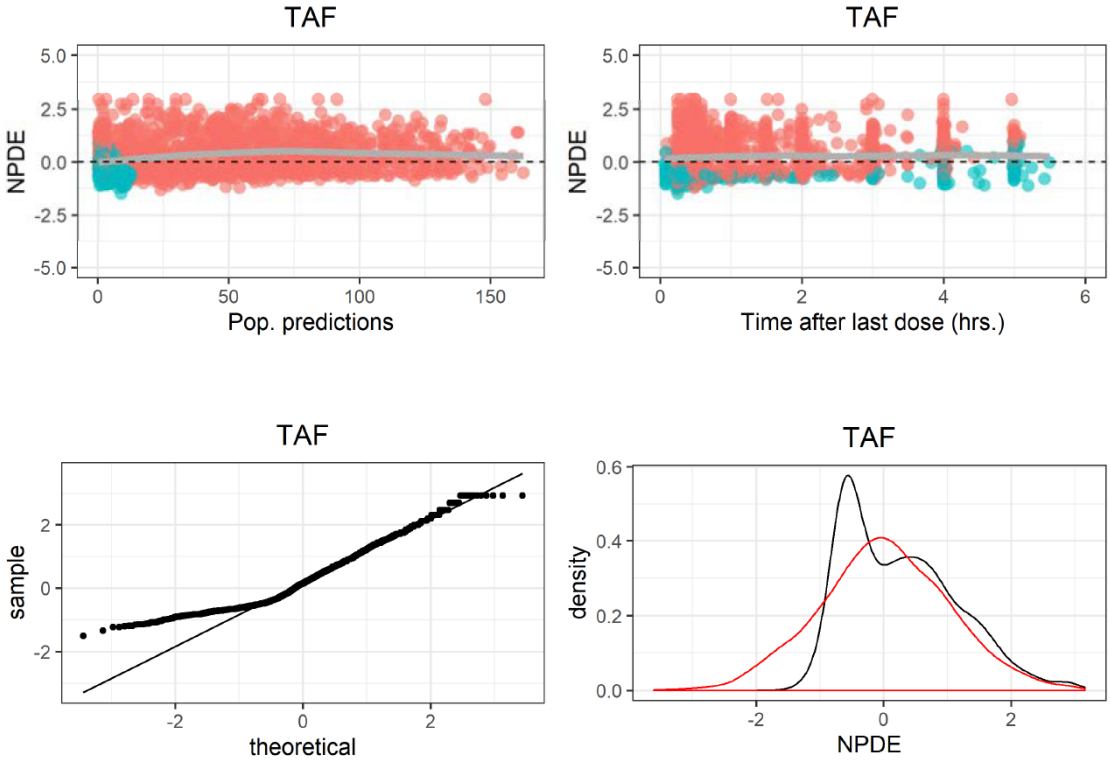
Parameter	Parameter Description	Shrinkage (%)
$\sqrt{\theta_4}$	Residual proportional error (%)	2.8
$\omega 44$	IIV of proportional error	23.2
$\omega 55$	IIV of D1	0.2

θ = parameter estimate; ω = standard deviation of between-subject variability; IIV = interindividual variability; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Tables 11 and 13, pages 45 and 51

Reviewer's comments: the reviewer encountered TAF model run problems with rounding errors, termination problems, or failed covariance step despite conducting independent runs across NONMEM versions and with or without tweaked initial parameter estimates. Based on the Applicant's PopPK report, the final model parameters were precise with <5.4% for RSEs. Shrinkages were low to modest (0.2-23.2%). The standard GoF plots are less reliable due to the M3 method implemented for BLOQ observed data. No obvious trends were seen in the NPDE plots. The pcVPC plots demonstrated that the final PopPK model generally described the PK data well for TAF in the target pediatric population of 14 to <25 kg, although a slight under-prediction in the absorption phase is noted around the median. However, the upper and lower bounds generally capture the observed data. Overall, the TAF PopPK model describes the data adequately to support simulation of exposure metrics for comparison against adult reference data.

Figure 6. Diagnostic Plots for Final TAF PopPK Model

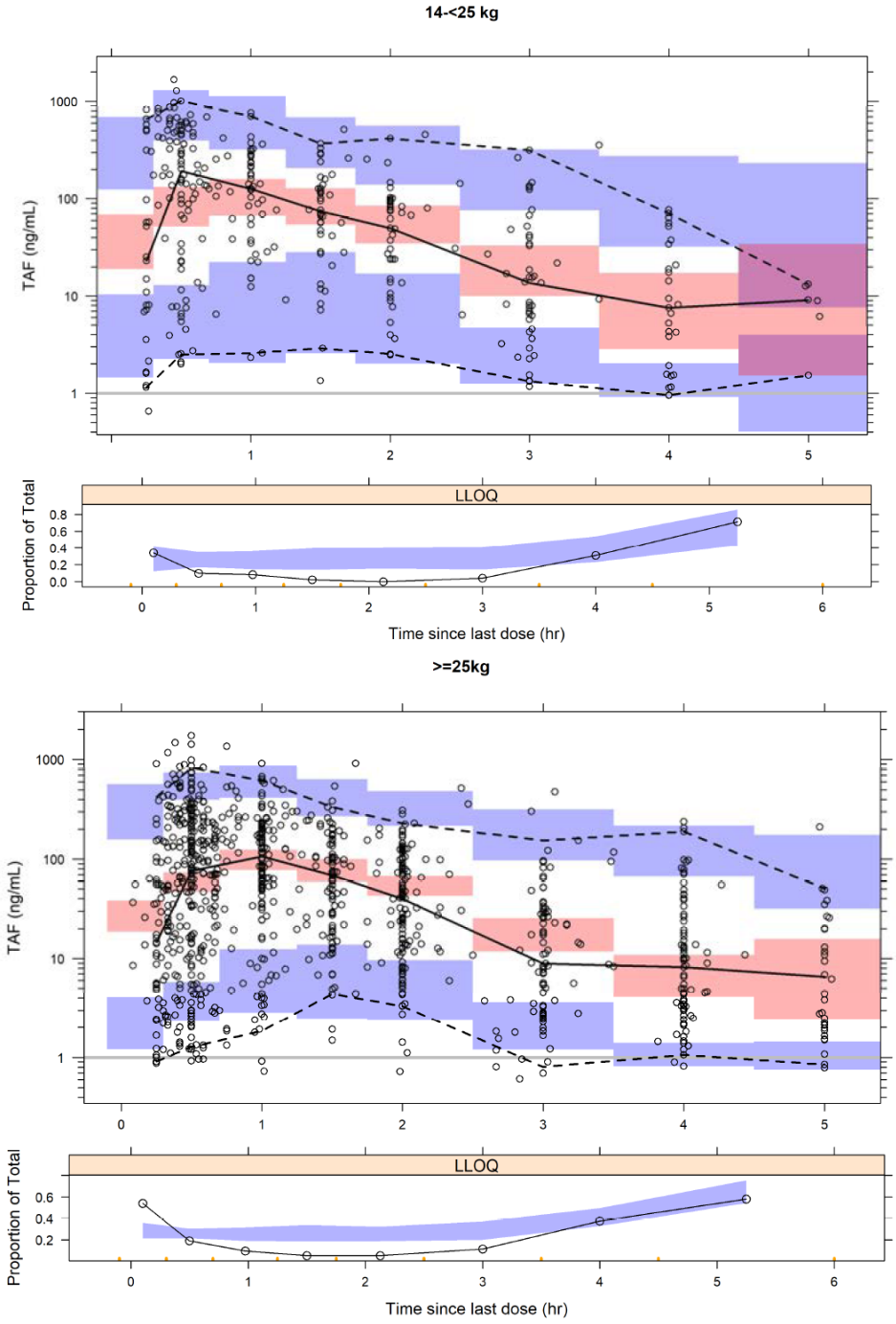


NPDE = normalized prediction distribution errors; Pop. = population; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide

The circles represent individual data points. Red and light blue circles represent measurable and BLQ samples, respectively; the gray lines represent loess smooth curves. The black and red lines in the density plot represent density of the NPDE distribution and density of the standard normal distribution, respectively.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 7, pages 46

Figure 7. pcVPC of Final TAF PopPK Model by Weight Bands



CI = confidence interval; DV = observed concentrations; LLOQ = lower limit of quantitation; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 8, pages 48

TAF-TFV

The structural model as shown in Figure 4 is retained for the final, joint PopPK model for TAF-TFV. Body weight effects on TFV clearance, central volume of distribution, intercompartmental flow, and peripheral volume of distribution with fixed allometric scalers (0.75 for clearance related terms and 1 for volume of distribution related terms). BCLCRSW (baseline CRCL based on Schwartz equation) was included on CL in the TFV structural model. IIV was included on the same structural parameters as body weight effects, and a combined error model was used for residual variability. The final PopPK parameter estimates (for TFV) are listed in **Table 16**. Diagnostic plots are listed in **Figure 8** and **Figure 9**. **Figure 10** describes the observed data.

Table 16. Final PopPK Parameter Estimates for TFV

Parameter	Parameter Description	Final Model Estimate [RSE][a]	Bootstrap Estimate Median [2.5th; 97.5th Percentiles]	SIR Estimate Median [2.5th; 97.5th Percentiles]
$\exp(\theta_1)$	Apparent oral clearance, CLM/F (L/h)	124 [1%]	123 [120;127]	124 [120;127]
$\exp(\theta_2)$	Apparent central volume of distribution, V_cM/F (L)	1750 [15%]	1720 [1270;2260]	1730 [1320;2240]
$\exp(\theta_4)$	Apparent intercompartmental clearance, QM/F (L/h)	2300 [15%]	2310 [1730;3090]	2340 [1820;2990]
$\exp(\theta_3)$	Apparent peripheral volume of distribution, V_pM/F (L)	5520 [6%]	5520 [4880;6210]	5480 [4910;6080]
$\exp(\theta_8)$	TFV first order absorption rate constant from second depot compartment, k_{TFV} (1/h)	0.151 [58%]	0.146 [0.0539;0.51]	0.141 [0.0504;0.415]
θ_7	LPV/RTV effect on relative bioavailability	2.1 [8%]	2.09 [1.75;2.42]	2.09 [1.74;2.43]
θ_9	BCL_{CRSW} effect on CLM/F	0.583 [17%]	0.58 [0.385;0.775]	0.575 [0.398;0.778]
$\sqrt{\theta_5}$	Residual proportional error (%)	45 [1%]	45.3 [42.4;47.5]	45.3 [43.8;46.8]
θ_6	Residual additive error	1.15 [21%]	1.16 [0.664;1.55]	1.15 [0.842;1.41]
ω11	IIV of CLM/F (%)	23 [12%]	23.3 [20.5;26.1]	23.5 [21;25.8]
ω22	IIV of V_cM/F (%)	116 [21%]	115 [86.2;137]	116 [95.6;137]
ω33	IIV of V_pM/F (%)	24 [65%]	23.4 [5.82;38.2]	24.4 [9.69;35.4]
ω44	IIV of QM/F (%)	55 [35%]	53.4 [27.6;71]	56.2 [41.3;69]

θ = parameter estimate; ω = standard deviation of between-subject variability; CLM/F = apparent clearance of TFV; IIV = interindividual variability; k_{tfv} = first order absorption rate constant from second depot compartment; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; SIR = sampling importance resampling; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

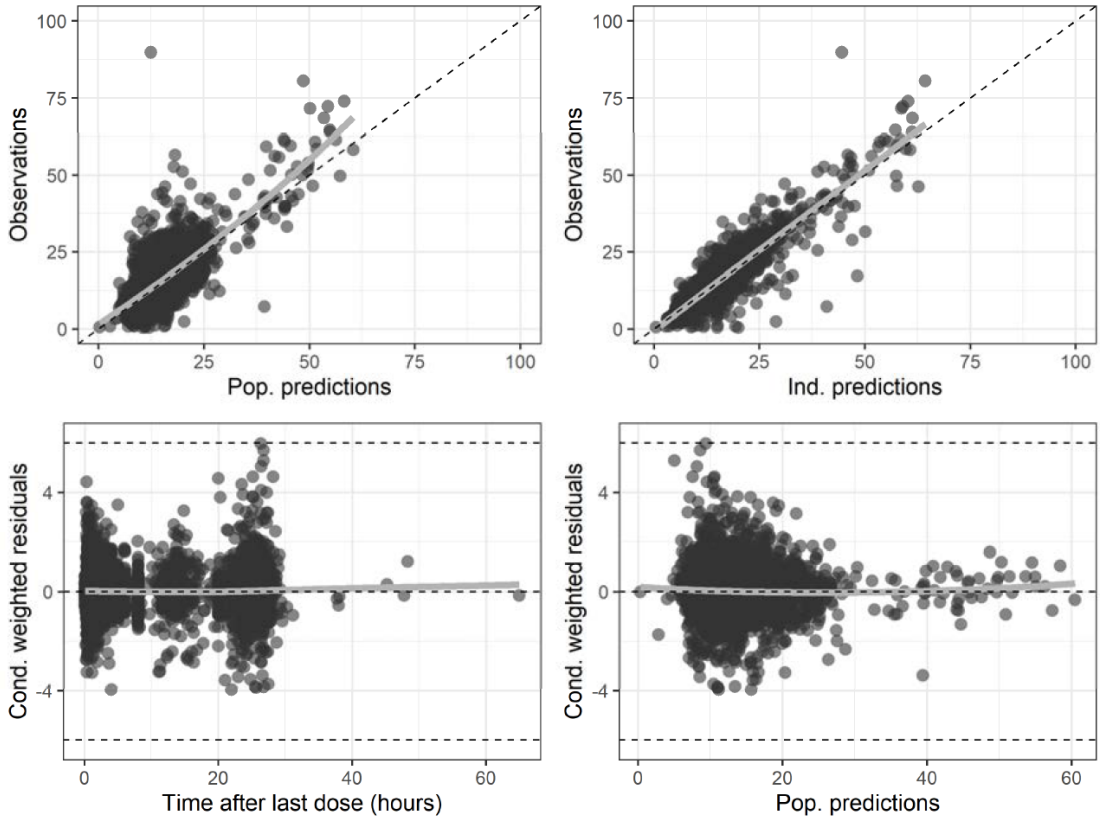
a RSE is defined as the SE divided by the θ × 100% for nontransformed parameters and as SE × 100% for log-transformed parameters.

Parameter	Parameter Description	Shrinkage (%)
$\sqrt{\theta_4}$	Residual proportional error (%)	7.9
θ_6	Residual additive	7.9
ω11	IIV of CLM/F	7.3
ω22	IIV of V_cM/F	33.7
ω33	IIV of V_pM/F	74.3
ω44	IIV of QM/F	60.7

ω = standard deviation of between-subject variability; CLM/F = apparent clearance of TFV; IIV = interindividual variability; PopPK = population pharmacokinetic; QM/F = apparent intercompartmental clearance of TFV; TFV = tenofovir; V_cM/F = apparent central volume of distribution of TFV; V_pM/F = apparent peripheral volume of distribution of TFV

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Tables 34 and 46, pages 67 and 70

Figure 8. GoF Plots for Final TFV PopPK Model

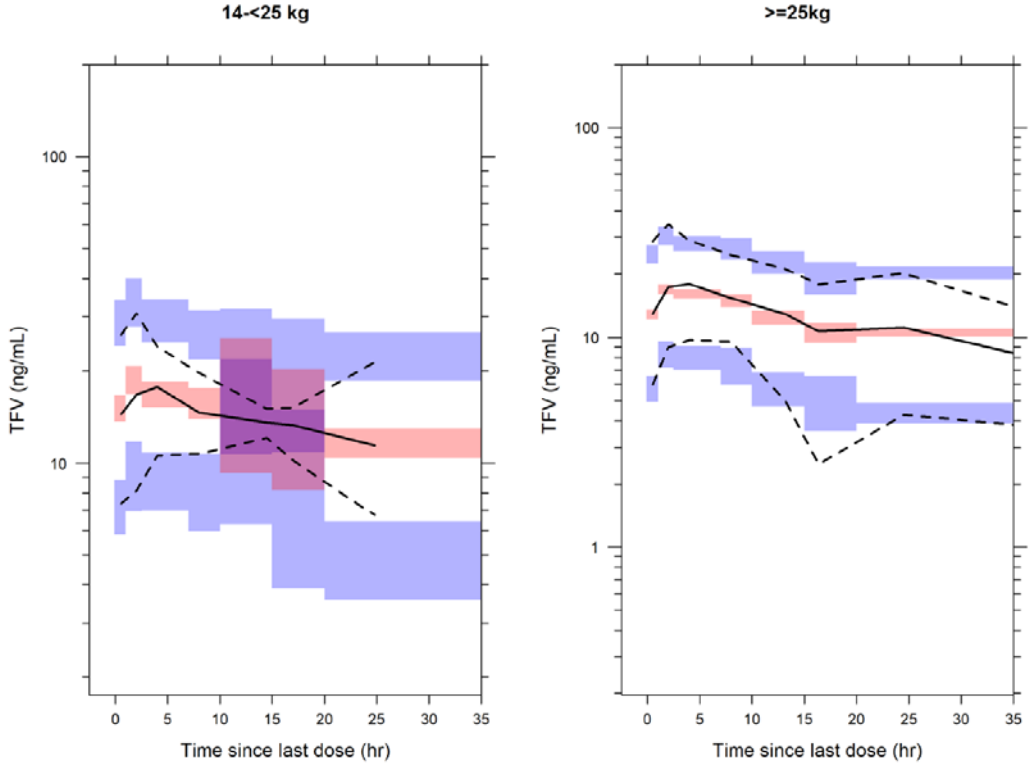


Cond. = conditional; CWRES = conditional weighted residuals; Ind. = individual; Pop. = population; PopPK = population pharmacokinetic; TFV = tenofovir

The circles represent individual data points; the gray lines represent loess smooth curves; and the dashed lines represent either the line of equality (y = x), or a CWRES of 6.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 15, page 67

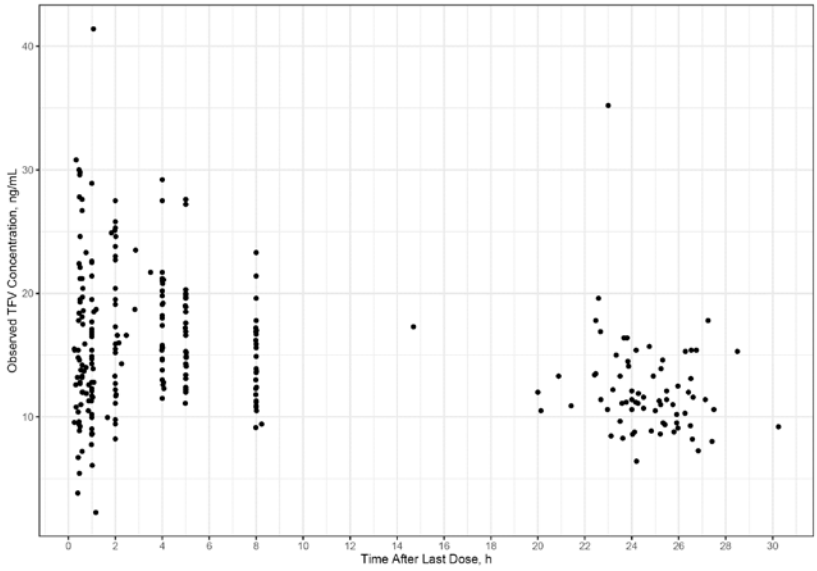
Figure 9. pcVPC of Final TFV PopPK Model by Weight Bands



CI = confidence interval; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; TFV = tenofovir; WT = baseline body weight
The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figures 15, page 68

Figure 10. Reviewer's Analysis: TFV Concentration-time Profiles for Target Population



Reviewer's independent analysis based on PK data from Study GS-US-292-0106, Cohort 3, n=27

Reviewer's comments: The final sequential model for TAF-TFV captures the PK data reasonably. The PK parameters were modestly precise with RSE% under 21% except that the second depot compartment (from parallel absorption compartments) had a moderate RSE% at 58%; however, this is for the LPV/RTV booster effect. RSE% on IIV were moderate (12% to 65%). High shrinkages were observed (up to 60.7%) while others were acceptable (lowest 7.3%). The GoF plots did not show any obvious model bias or misspecification. For the target population of 14 to <25 kg, the pcVPC showed less than ideal predictions between 10 to 20 hours (time since last dose). When the observed concentration-time data were visualized, the reviewer noted the sparse samples during a window of 8 to 20 hours (time since last dose), and this is the most probable explanation for such prediction. Overall, the model adequately described the PK data and is acceptable for simulating exposure metrics to compare against adult reference data.

EVG

The final PopPK model for EVG was unchanged from the base model. The final PK parameter estimates are listed in **Table 17**.

Table 17. Final PopPK Parameter Estimates for EVG

Parameter	Parameter Description	Final PopPK Model Estimates (RSE%)[a]	Bootstrap Final Model Median (2.5th, 97.5th Percentiles)[b]	SIR Final Model Median (2.5th, 97.5th Percentiles)
θ_1	Apparent oral central clearance, CL/F (L/h)	7.05 (0.2)	6.74 (5.87, 7.26)	7.14 (6.45, 7.86)
θ_2	Apparent central volume of distribution, V_c/F (L)	37.2 (7.2)	37.1 (31.2, 42.5)	37.3 (32.1, 42.9)
θ_3	Apparent peripheral volume of distribution, V_p/F (L)	15.1 (1.3)	13.1 (2.69, 17.7)	19.7 (15, 24.8)
θ_4	Apparent intercompartmental clearance, Q/F (L/h)	6.26 (8.4)	6.25 (3.68, 13.4)	5.85 (5.05, 6.65)
θ_5	First-order absorption rate constant for E/C/F/TAF study drug, k_{a1} (1/h)	0.203 (1.5)	0.197 (0.176, 0.223)	0.203 (0.202, 0.203)

Parameter	Parameter Description	Final PopPK Model Estimates (RSE%)[a]	Bootstrap Final Model Median (2.5th, 97.5th Percentiles)[b]	SIR Final Model Median (2.5th, 97.5th Percentiles)
θ_6	First-order absorption rate constant for E/C/F/TDF study drug, k_{a2} (1/h)	0.163 (2.1)	0.168 (0.131, 0.202)	0.163 (0.163, 0.164)
θ_7	Duration of zero-order infusion, D_1 (h)	2.3 (5.5)	1.82 (1.82, 2.93)	2.2 (2.2, 2.42)
sqrt (θ_8)	Residual proportional error (%)	74 (0.4)	74.6 (71.2, 78.1)	74.1 (73.7, 74.5)
θ_9	Residual additive error (ng/mL)	33.5 (0.1)	23.4 (5.49, 41)	14.3 (1.2, 34.3)
ω_{11}	IIV on CL/F (%)	36 (38)	36 (28, 45)	35.7 (35.6, 35.9)
ω_{22}	IIV on V_p/F (%)	350 (16.7)	376 (309, 463)	350 (350, 351)
ω_{33}	IIV on Q/F (%)	75 (17.5)	79 (31.8, 159)	75.1 (74.9, 75.2)
ω_{44}	IIV on D_1 (%)	112 (2.4)	111 (91.1, 138)	112 (112, 112)

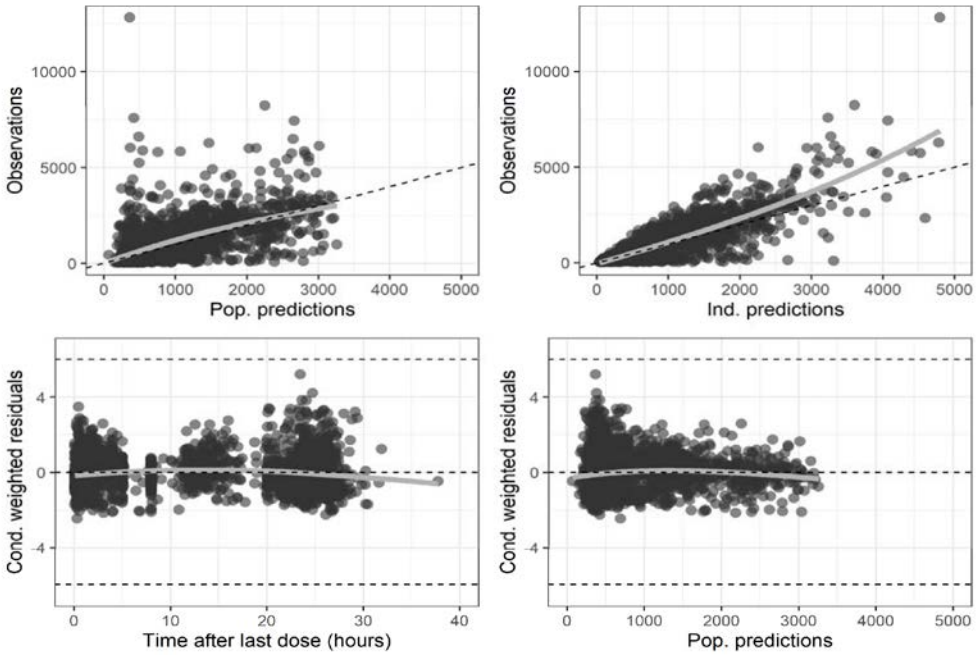
θ = parameter estimate; ω = standard deviation of between-subject variability; EVG = elvitegravir; IIV = interindividual variability; k_a = first-order absorption rate constant; PopPK = population pharmacokinetic; QRSE = relative standard error; SE = standard error;

a RSE is defined as the SE divided by the $\theta \times 100\%$ for nontransformed parameters and as SE $\times$ 100% for log-transformed parameters.

b Runs with terminated minimization due to rounding errors were included in the calculation of the bootstrap estimates of parameter uncertainty.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Table 12, page 42

Figure 11. GoF Plots for EVG Final PopPK Model

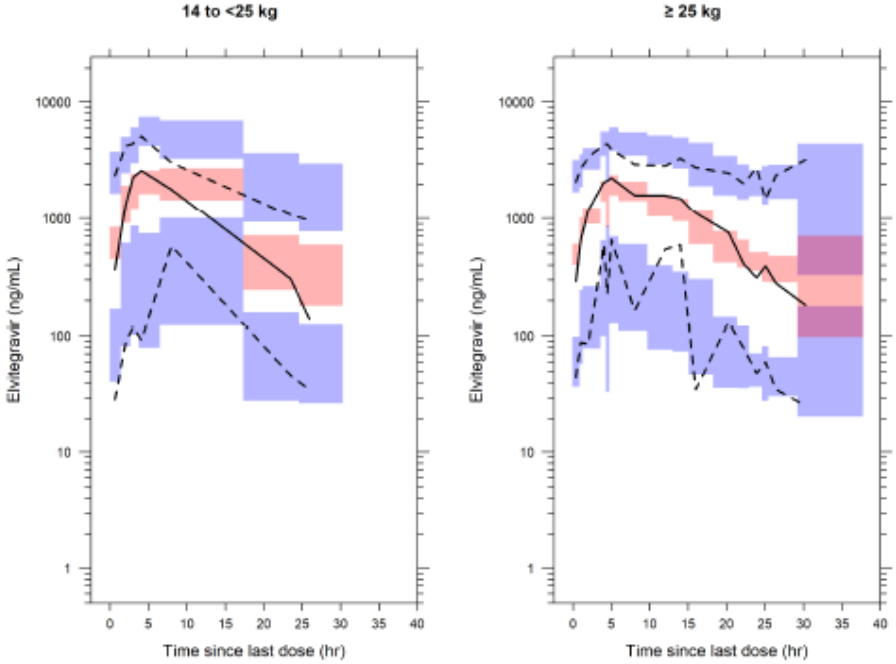


Cond. = conditional; EVG = elvitegravir; Ind. = individual; PK = pharmacokinetic; Pop. = population; PopPK = population pharmacokinetic

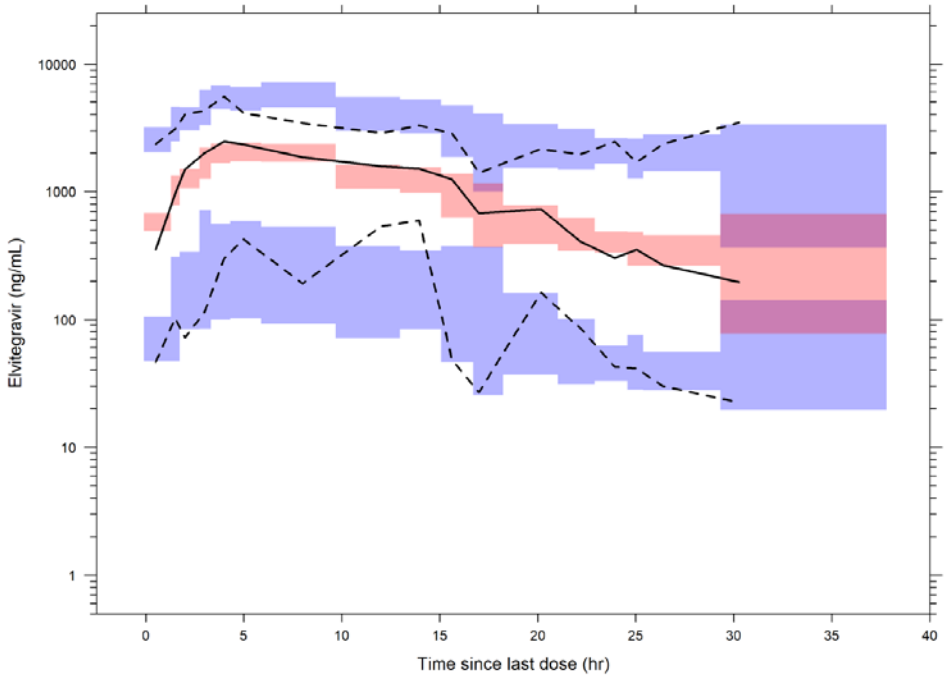
Note: The gray line is the locally estimated scatterplot smoothing (loess) smooth curve.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 3, page 38

Figure 12. pcVPC for Final EVG PopPK Model



CI = confidence interval; DV = observed concentrations; EVG = elvitegravir; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic
Note: The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median and the blue area is the 95% CI of the simulated 5th and 95th percentiles.



CI = confidence interval; DV = observed concentrations; EVG = elvitegravir; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic
Note: The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median and the blue area is the 95% CI of the simulated 5th and 95th percentiles.

Source: Applicant's PopPK Report, (b) (4)-2020-1049, Figure 4s and 5, pages 39-40

Reviewer's comments: the reviewer was able to reproduce the exact Applicant's EVG model run results despite encountering numerous run problems, including failed covariance steps or early termination. Of note, the model converged without errors under NONMEM 7.4.3 only (the other version tested was 7.5.0). The final model estimated the final PK parameters with reasonable precision (under 8.4%) while RSE% for IIV were low to modest (2.4%-38%). The standard GoF plots did not show aberrant trends. The final pcVPC plot for the target population of 14 to <25 kg (left panel) demonstrated that the final model did improve on peak concentration predictions when compared to **Figure 5** *(age effect on CL); however, the trend for overpredicting median Ctau worsened during the dosing interval.*

While the generality of model performance is adequate in describing the data (particularly Cmax and AUC during dosing intervals at steady state), considerations and additional analyses regarding steady-state Ctau were further described in reviewer's independent analysis section below. Of note, Ctau is considered the PK/PD driver for antiviral efficacy for EVG.

COBI

The final COBI PopPK model was a 1-compartment structural model parameterized with zero- and first-order absorption, ALAG, and first-order elimination. Body weight was modeled on CL and V with fixed allometric scalers of 0.75 and 1, respectively. IIV was modeled on CL, D, and ALAG. Proportional error model was used to describe residual error. The final parameter estimates are listed in **Table 18**.

Table 18. Final PopPK Parameter Estimates for COBI

Parameter	Parameter Description	Final PopPK Model Estimate (RSE)[a]	Bootstrap Final Model Median Estimate (2.5th; 97.5th Percentiles)[b]
$\exp(\theta_1)$	CL/F (L/h)	14.5 (6)	14.6 (13.5; 16.1)
$\exp(\theta_2)$	V_c/F (L)	33.8 (10)	34.2 (30.2; 41.9)
$\exp(\theta_3)$	D_1 (h)	1 (FIXED)	1 (1; 1)
$\exp(\theta_4)$	k_a (1/h)	0.251 (5)	0.251 (0.239; 0.268)
$\exp(\theta_6)$	Absorption lag time (h)	0.316 (4)	0.321 (0.273; 0.435)
$\text{sqrt}(\theta_5)$	Residual proportional error (%)	88 (3)	87.8 (84; 92.2)
ω_{11}	IIV on CL/F (%)	39 (109)	38.6 (30.3; 47.7)
ω_{21}	Correlation CL/F-D_1	0.2 (91)	0.2 (0.0361; 0.397)
ω_{22}	IIV of D_1 (%)	108 (2)	109 (97.4; 140)
ω_{55}	IIV on ALAG	134 (9)	133 (108; 143)
ω_{44}	IIV of proportional error (%)	50 (71)	50.2 (42.2; 56.3)

θ = parameter estimate; ω = standard deviation of between-subject variability; ALAG1 = absorption lag time; COBI = cobicistat; IIV = interindividual variability; PopPK = population pharmacokinetic; RSE = relative standard error; SE = standard error

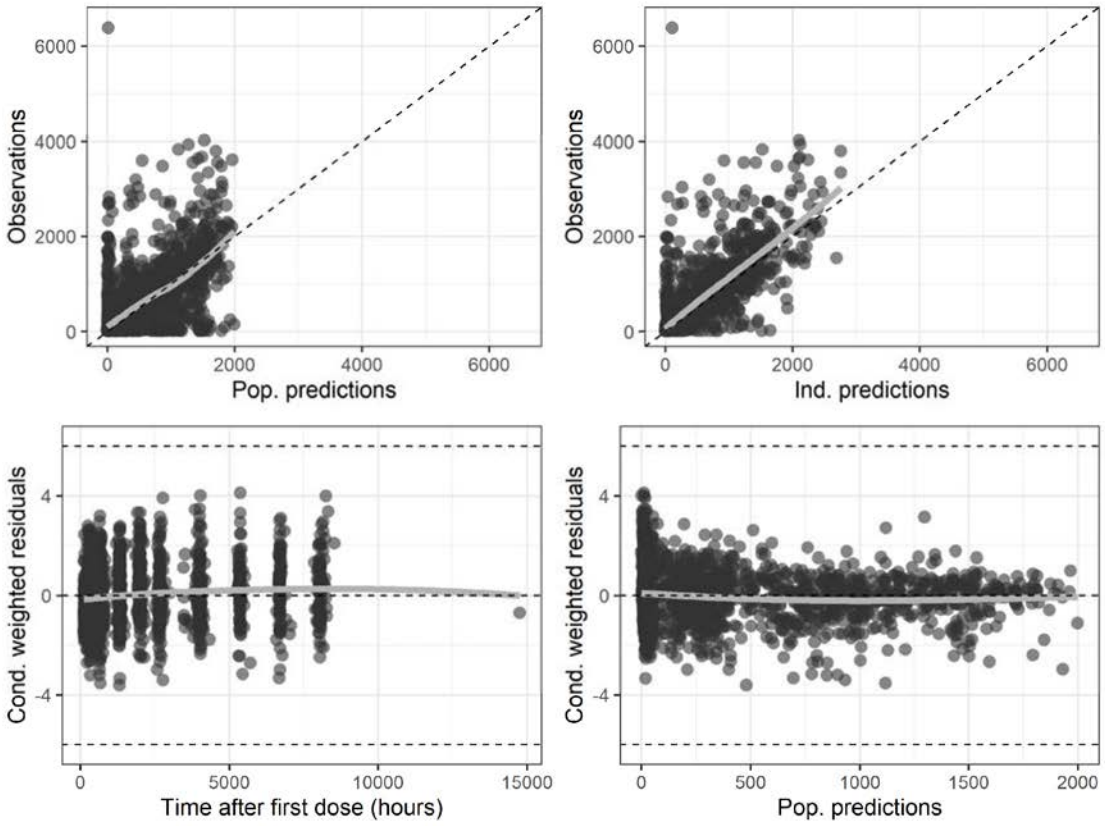
a RSE is defined as the SE divided by the $\theta \times 100\%$ for nontransformed parameters and as SE × 100% for log-transformed parameters.

b Runs with terminated minimization because rounding errors were not included in the calculation of the bootstrap estimates of parameter uncertainty.

Parameter	Parameter Description	Shrinkage (%)
ω_{11}	IIV on CL/F (%)	9.8
ω_{22}	IIV on D1 (%)	41.5
ω_{44}	IIV on proportional error (%)	1.9

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Table 39, page 60

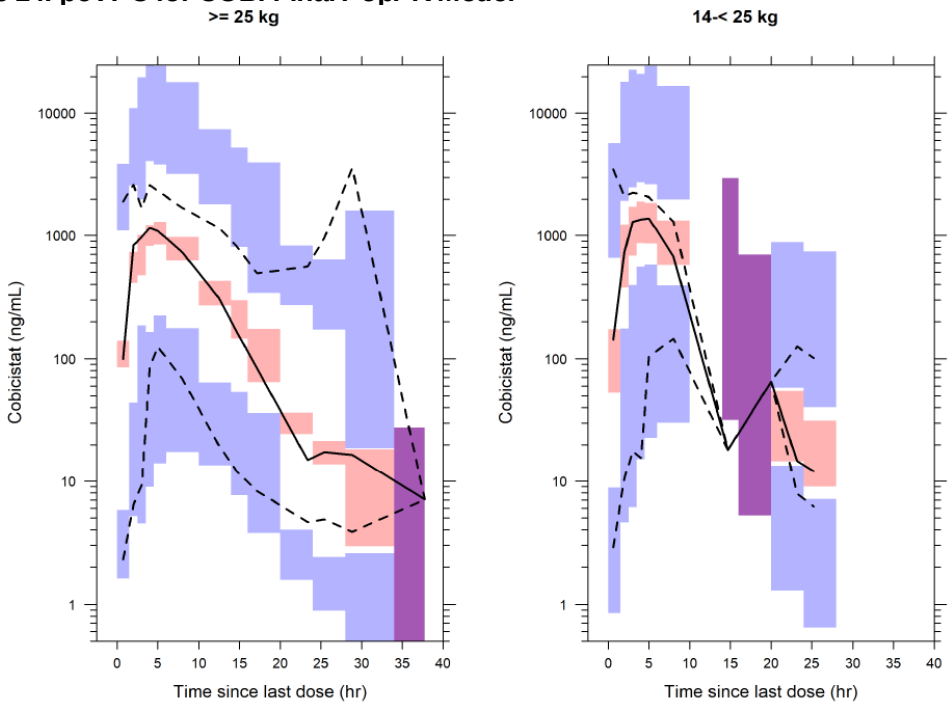
Figure 13. GoF Plots for COBI Final PopPK Model



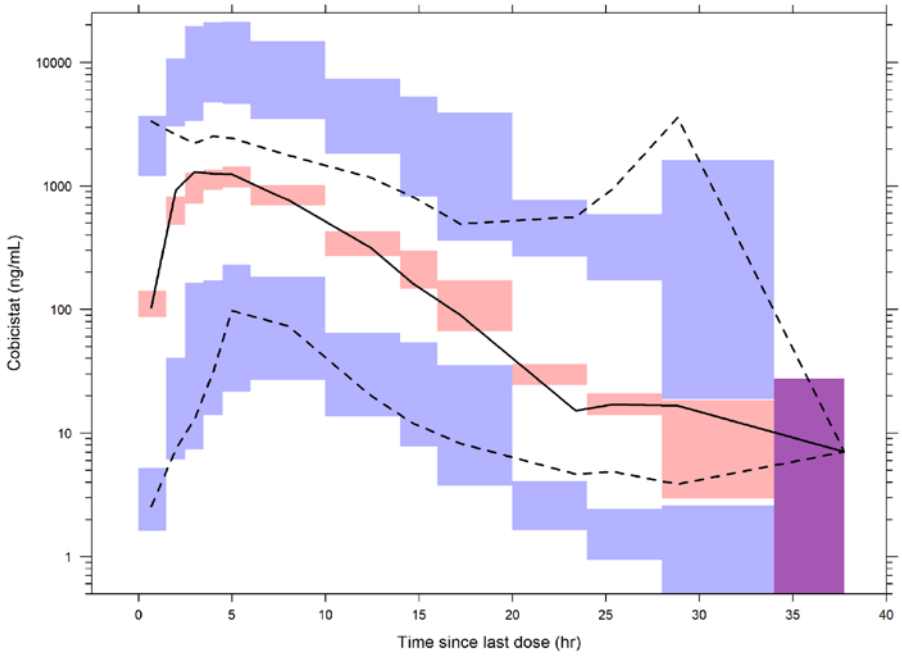
Cond. = conditional; COBI = cobicistat; CWRES = conditional weighted residuals; Ind. = individual; Pop. = population; PopPK = population pharmacokinetic
Note: The circles represent individual data points, the gray lines represent loess smooth curves, and the dashed lines represent either the line of equality (y = x) or a |CWRES| of 6.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 9, page 57

Figure 14. pcVPC for COBI Final PopPK Model



CI = confidence interval; COBI = cobicistat; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic
Note: The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.



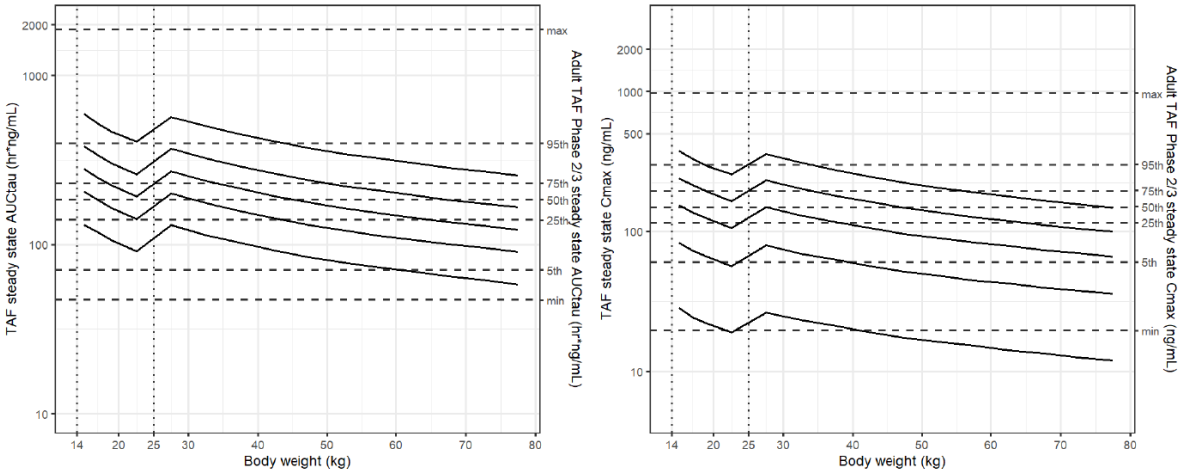
CI = confidence interval; COBI = cobicistat; DV = observed concentrations; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic
Note: The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentile, dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 Figures 10 and 11, pages 58-59

*Reviewer's comments: The reviewer was able to reproduce the final model. Overall, the final PopPK model described the COBI data with good precision (under 10% RSE for PK parameters) except that the precision for IIV of CL was low (RSE% at 109%). One explanation could be the highly variable observed concentrations beyond 20 hours of the dosing interval **(Figure 3**). Shrinkages for CL and IIV of proportional error term were low (9.8% and 1.9%, respectively), but moderately high for IIV on D at 41.5%. The GoF plots did not show any aberrant trends, though a slight under-prediction was noted. The underprediction was also demonstrated by the pcVPC towards end of the dosing interval. In addition, an overprediction was noted around peak concentration and the subsequent elimination, this overprediction likely contributed to the slightly higher simulated Cmax (95th percentile at steady state) in pediatric patients compared to that of maximum value of adult reference data. See simulation results below. Overall, the COBI PopPK model reasonably describes the PK data for target population and is acceptable for simulating exposure estimates to compare to adult reference.*

Simulations of Target Pediatric Exposures and Adult Reference

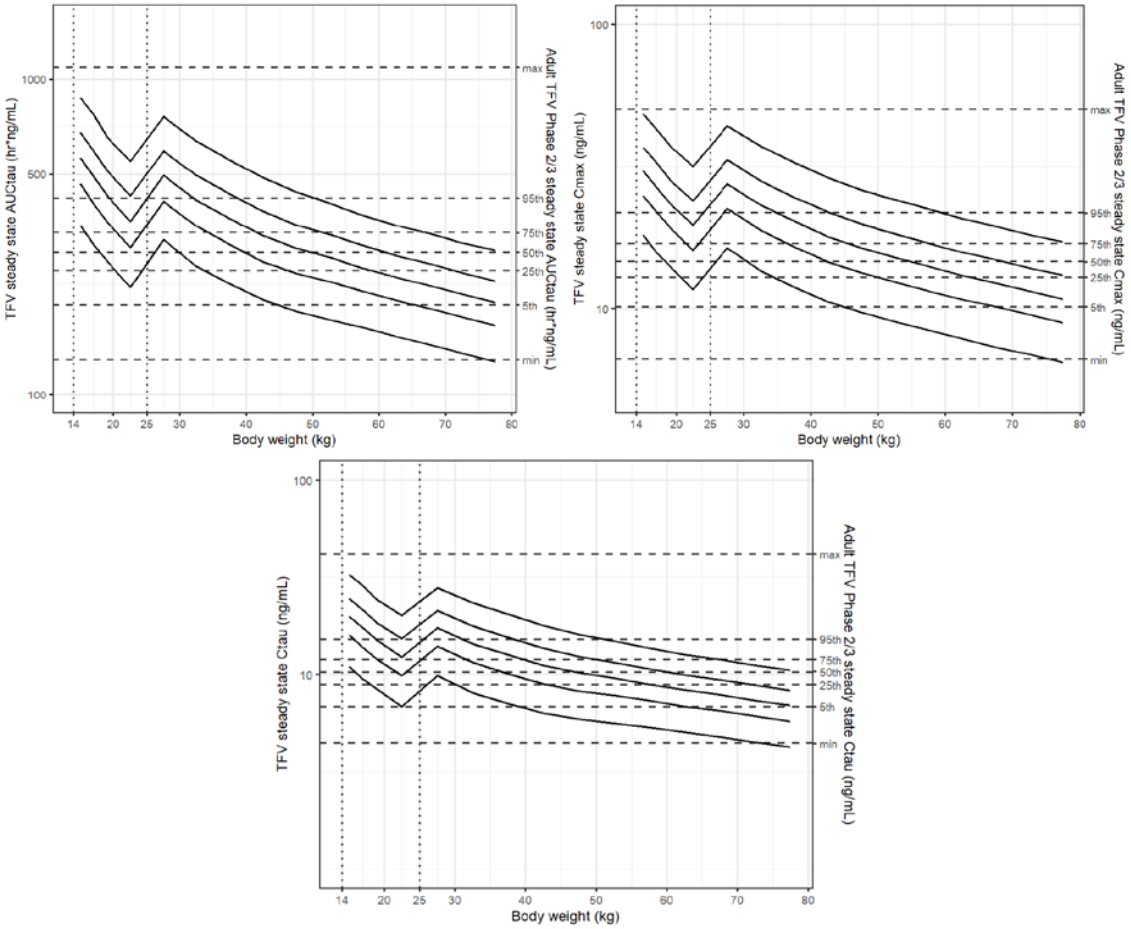
Figure 15 . Simulated SS TAF Exposure Metrics



COBI = cobicistat; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; WT = baseline body weight
Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 14-, and 25-kg cutoffs. Adult exposures are the PopPK-predicted exposures from TAF Phase 2/3 studies {TAF and TFV Population PK Report from Adult E/C/F/TAF NDA 207561; N = 539 adult patients with both determinable TAF and TFV exposure}; minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Left and right panels show AUC_{tau} and C_{max}, respectively.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 20, page 85

Figure 16. Simulated SS TFV Exposure Metrics

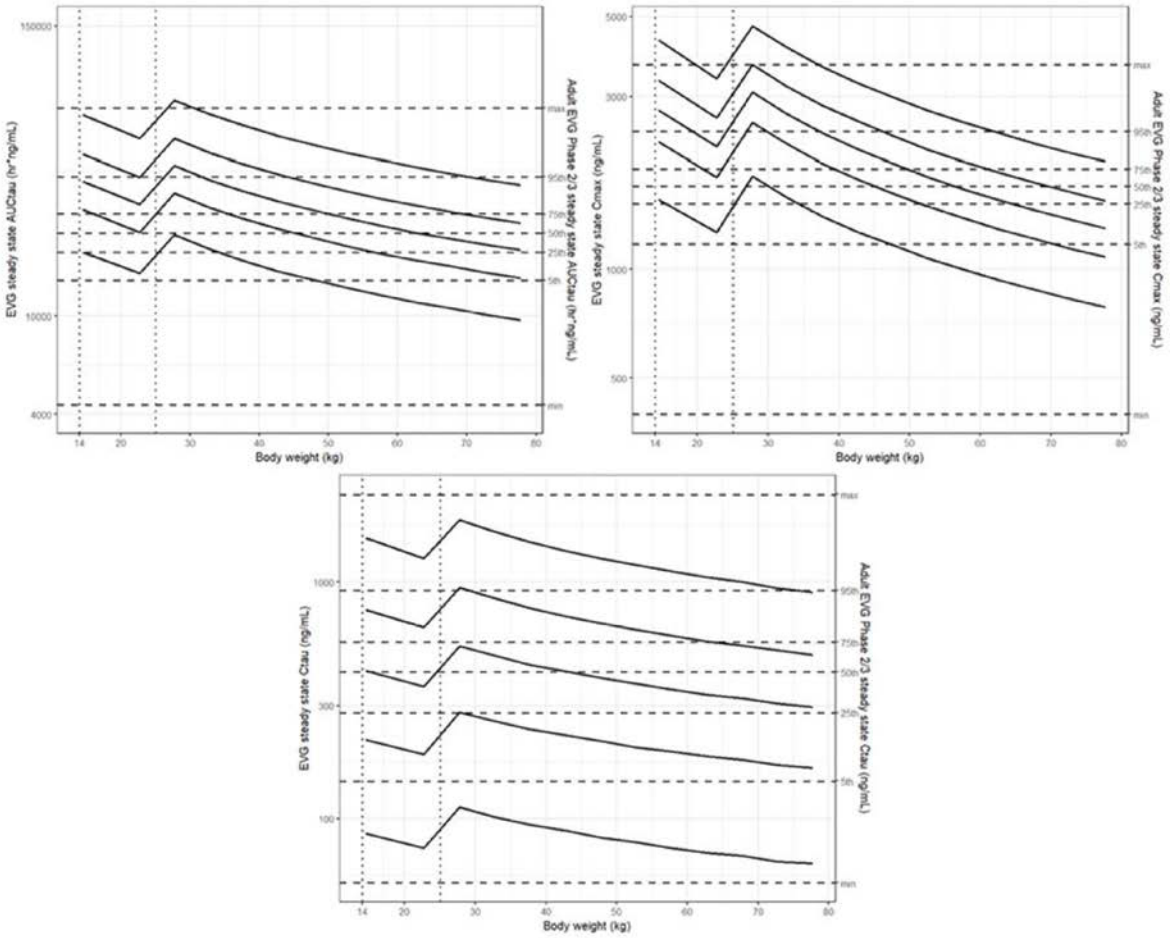


COBI = cobicistat; PopPK = population pharmacokinetic; TAF = tenofovir alafenamide; TFV = tenofovir; WT = baseline body weight

Solid lines represent 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 14-, and 25-kg cutoffs. Adult exposures are the PopPK-predicted exposures from TAF Phase 2/3 studies {TAF and TFV Population PK Report from Adult E/C/F/TAF NDA 207561; N = 539 adult patients with both determinable TAF and TFV exposure}; minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Left and right top panels show AUC_{tau} and C_{max}, whereas the bottom panel shows C_{tau}.

Source: Applicant's PopPK Report, (b) (4)-2020-1048 TAF-TFV Peds Pop PK, Figure 21, page 86

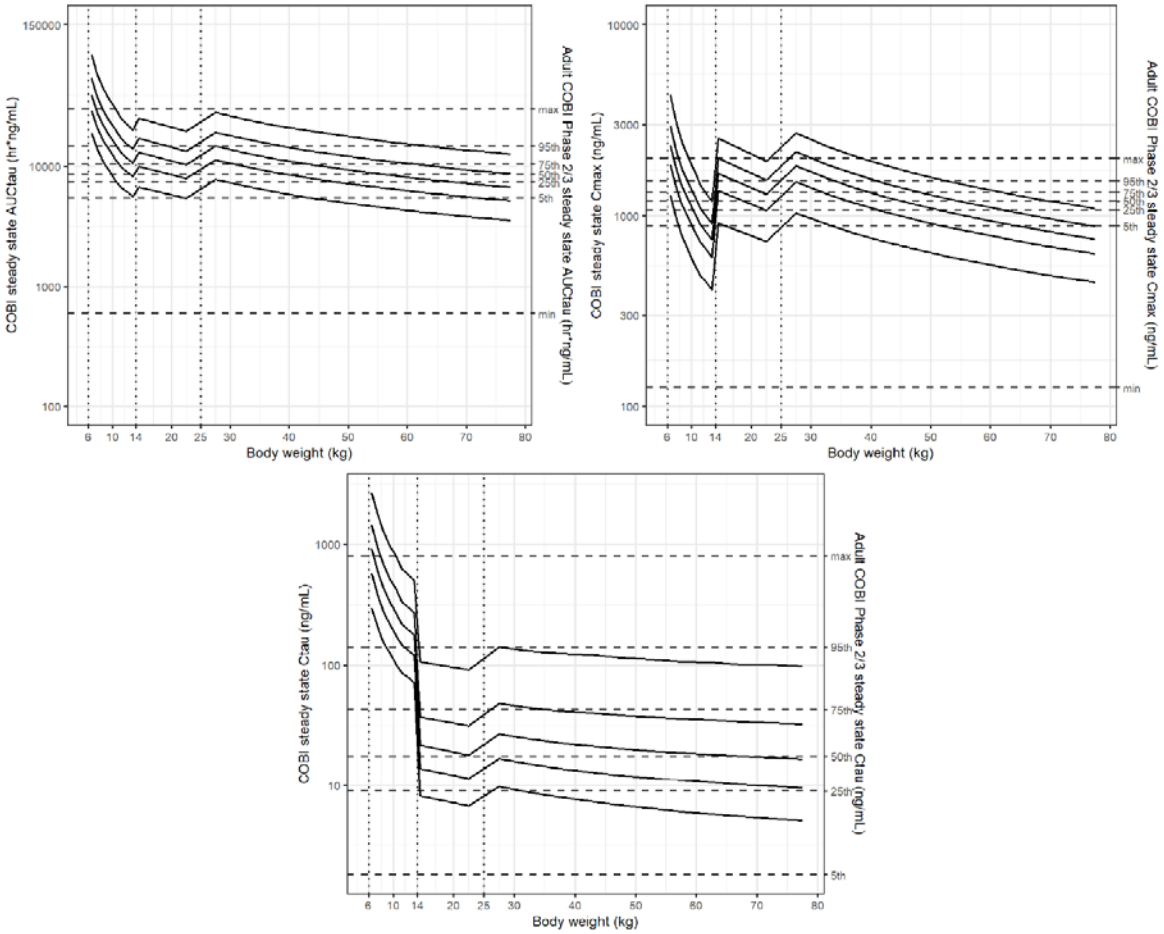
Figure 17. Simulated SS EVG Exposure Metrics



EVG = elvitegravir; PopPK = population pharmacokinetic
Note: Solid lines represent the 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 14- and 25-kg cutoffs. Adult exposures are the PopPK-predicted exposures from EVG Phase 2/3 studies with Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; coformulated) (Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104) (Population Pharmacokinetics of Cobicistat (COBI)-boosted Elvitegravir (EVG) dated 20 October 2011); the minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Left and right panels show AUC_{tau} and C_{max}, respectively and lower panel shows C_{tau}.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 13, page 67

Figure 18. Simulated SS COBI Exposure Metrics



COBI = cobicistat; PopPK = population pharmacokinetic

Note: Solid lines represent the 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; vertical dashed lines indicate 6-, 14-, and 25-kg cutoffs. Adult exposures are the PopPK-predicted exposures from COBI Phase 2/3 studies Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; coformulated) or cobicistat-boosted atazanavir + Truvada® (emtricitabine/tenofovir disoproxil fumarate; coformulated) (Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0104, GS-US-216-0105, and GS-US-216-0114) (Population Pharmacokinetics of Cobicistat (COBI) dated 12 April 2012); the minimum, 5th, 25th, 50th, 75th, and 95th percentiles, and maximum are shown. Left and right panels show AUC_{tau} and C_{max}, respectively and lower panel shows C_{tau}.

Source: Applicant's PopPK Report, (b) (4)-2020-1049 COBI-EVG Peds Pop PK, Figure 14, page 68

1.5 Reviewer's Independent Analysis

1.5.1 Introduction

The reviewer conducted additional analysis to evaluate two observations:

1) observed low EVG Ctau as this is the PK/PD driver for efficacy, and

(b) (4)

1.5.2 Objectives

Analysis objectives are:

- Assess model-predicted EVG data vs observed values in target pediatric population (n=27)

(b) (4)

1.5.3 Methods

All data was extracted and manipulated in R 3.6.3 and relevant packages. All plots were generated using *ggplot2* package for R (Wickham H (2016). ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York. ISBN 978-3-319-24277-4, https://ggplot2.tidyverse.org.). Exposure metrics were derived using NONMEM 7.4.3 and 7.5.0. Databases utilized for independent analyses are listed in **Table 19**.

For #1, the final EVG PopPK model (for this submission) outputs were generated by reviewer and evaluated against those submitted by the Applicant. In this review, only the latter is shown to avoid duplication of identical results (run32). The reviewer first assessed the model fitting towards lower end of EVG concentrations, and then, the reviewer performed sensitivity model runs to assess the predictive performance towards lower end of observed concentrations. Lastly, observed data were used in the target pediatric population to compare to historic data in Stribild® program and Genvoya® adult PK data.

(b) (4)

Table 19. Reviewer's Independent Analyses

Item	Files/Description	Link to EDR
NONMEM Final EVG PopPK Model output by the Applicant	run32.tab	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225(b) (4)-2020-1049-cobi-evg-peds-pop-pk(b) (4)-2020-1049-cobi-evg-peds-pop-pk\runs\evg_sponsorRun
NONMEM Final EVG PopPK Model output by the reviewer	run32_JL.tab	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225(b) (4)-2020-1049-cobi-evg-peds-pop-pk(b) (4)-2020-1049-cobi-evg-peds-pop-pk\runs\evg_run1_noRetries
NONMEM Final EVG PopPK Model with estimated allometric scalers output by the reviewer (NM 7.4.3)	run32_est_exp.mod	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225(b) (4)-2020-1049-cobi-evg-peds-pop-pk(b) (4)-2020-1049-cobi-evg-peds-pop-pk\runs\evg_final_est_expo
Genvoya EVG Exposure for Adult Subjects	ADPP.xlsx	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\GEN_adult
NONMEM Final PopPK Model for Stribild EVG Exposure for Adult Subjects	Finalpoppk150mg.csv run41.mod sdtab41	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Stribild
(b) (4)		

1.5.4 Results

Analysis #1: Low EVG Ctau in pediatric cohort (n=27)

A review of published literature (*Ramanathan et al. Clin Pharmacokinet. 2011 Apr;50(4):229-44.*) suggested that EVG Ctau is the PK/PD driver for efficacy:

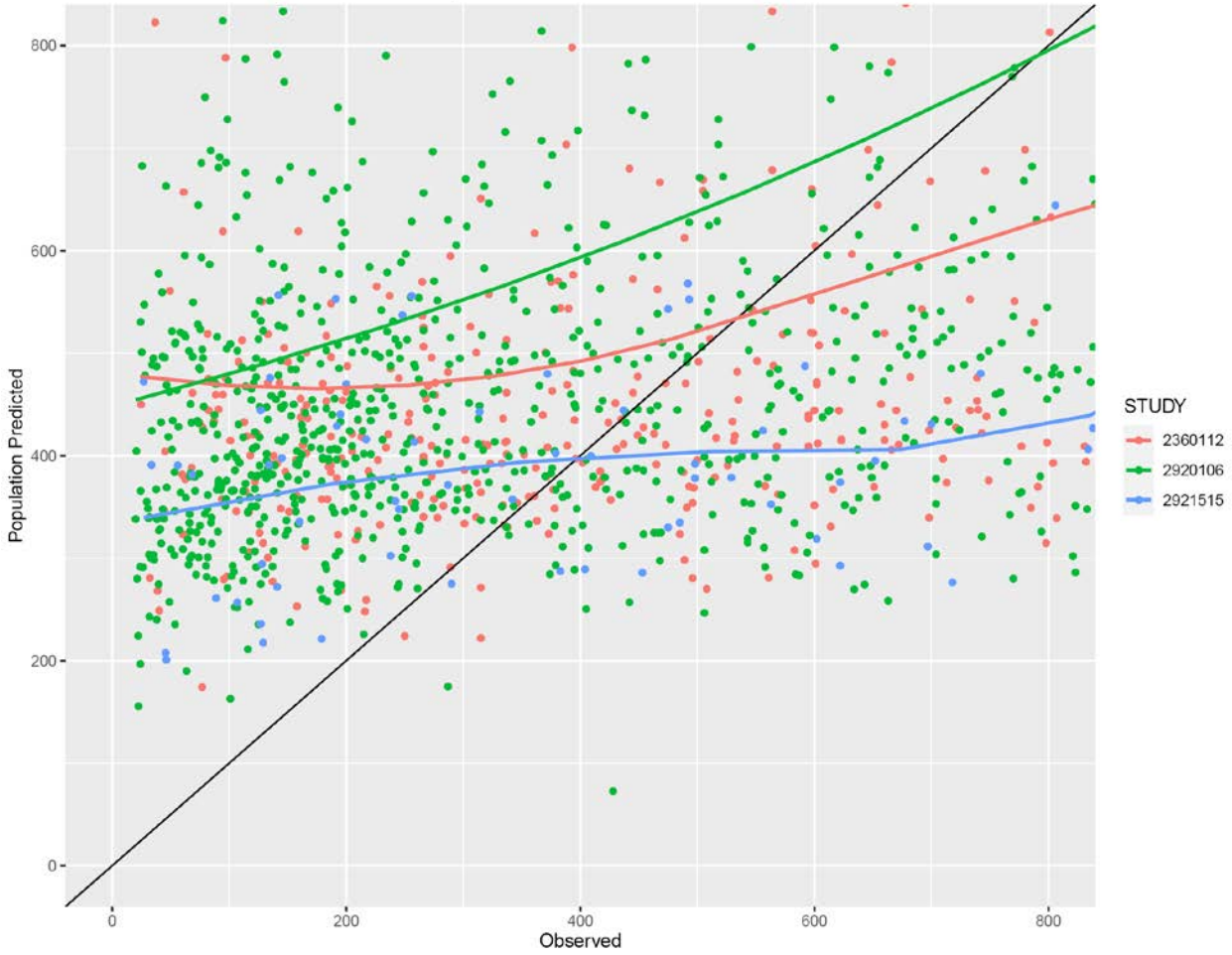
- IC95 = 45 ng/mL for wild type HIV-1 virus (*in vitro* with protein-binding adjusted)
- EC90 = 126 ng/mL (Emax model estimates based on phase 2 study)

Despite that most subjects maintained virologic suppression after switching to Genvoya (n=26/27) in Cohort 3 of the GS-US-292-0106 study, a higher proportion of pediatric subjects demonstrated low EVG Ctau within the study period (**Table 21**). As demonstrated in **Figure 19**, **Figure 20**, and **Figure 21** below, the reviewer noted that over-predictions take place towards lower end of observed data for EVG, when stratifying by included studies, stratifying by cohorts within the GS-US-292-0106 Study, or examining the n=27 target subjects. Of note, no trend was identified in ETA CL vs body weight in the subgroup GS-US-292-0106 study data (**Figure 22**).

The reviewer also conducted sensitivity model run with estimated allometric scalers for CL and V (OFV, 28608.081; AIC, 28638.081) and saw an improvement vs. Applicant developed final PopPK model (OFV, 28629.209; AIC, 28655.209); however, similar

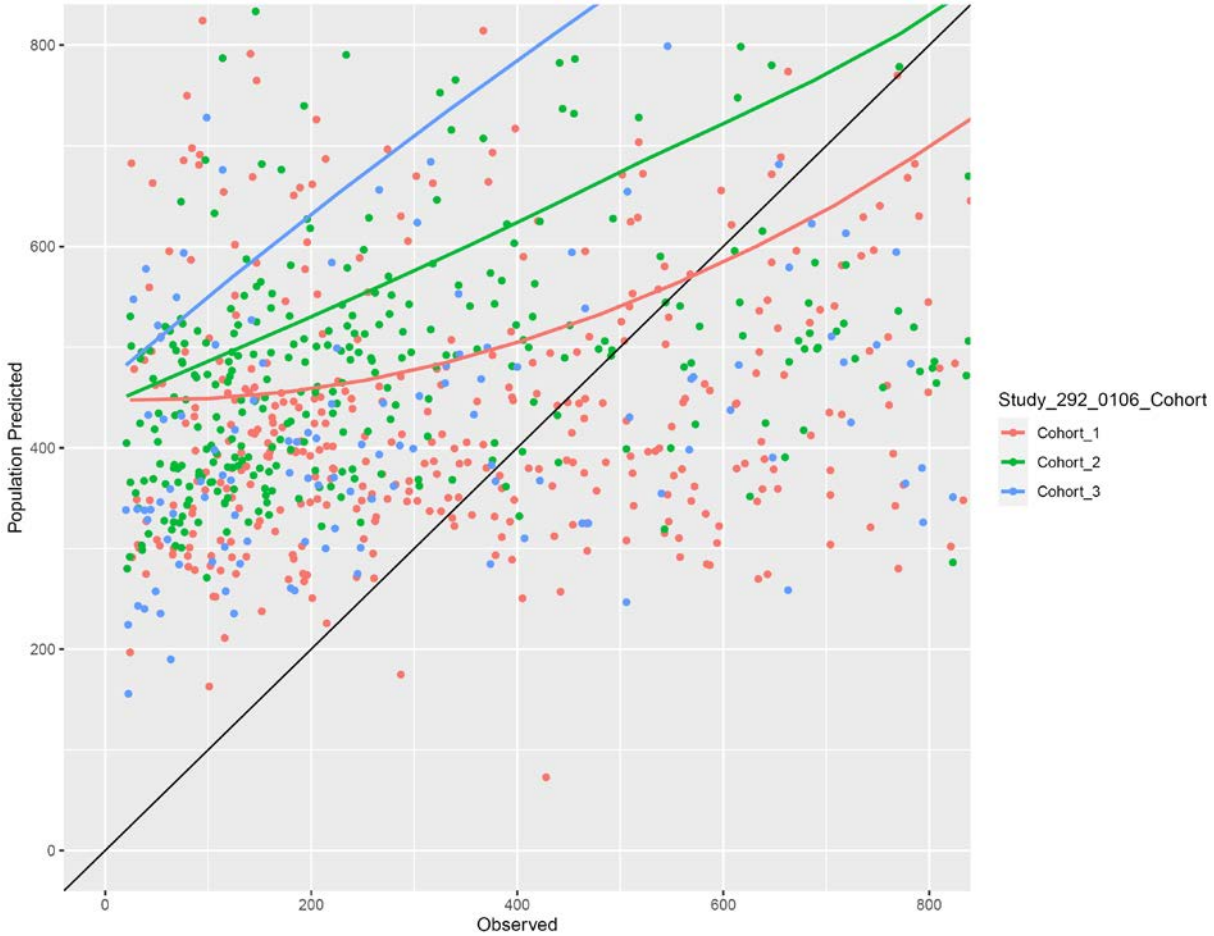
trends were observed with regard to over-predictions across studies and cohorts of GS-US-292-0106 while no abnormal trends were noted on ETA CL vs body weight (**Figure 23**). Parameter estimates are listed in **Table 20**.

Figure 19. Reviewer's Analysis: Observed vs. Predicted EVG Concentration in Final PopPK Model



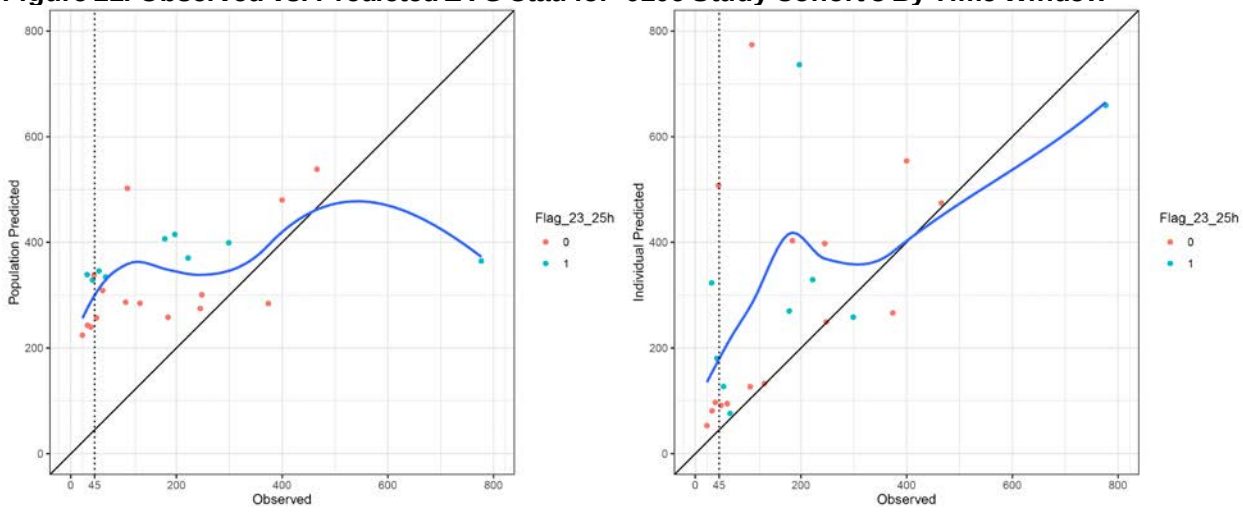
Note: x and y range were restricted to 800 ng/mL for illustration purposes; colored regression lines: LOESS fit; n=229

Figure 20. Reviewer's Analysis: Observed vs. Predicted EVG Concentration in Final PopPK Model



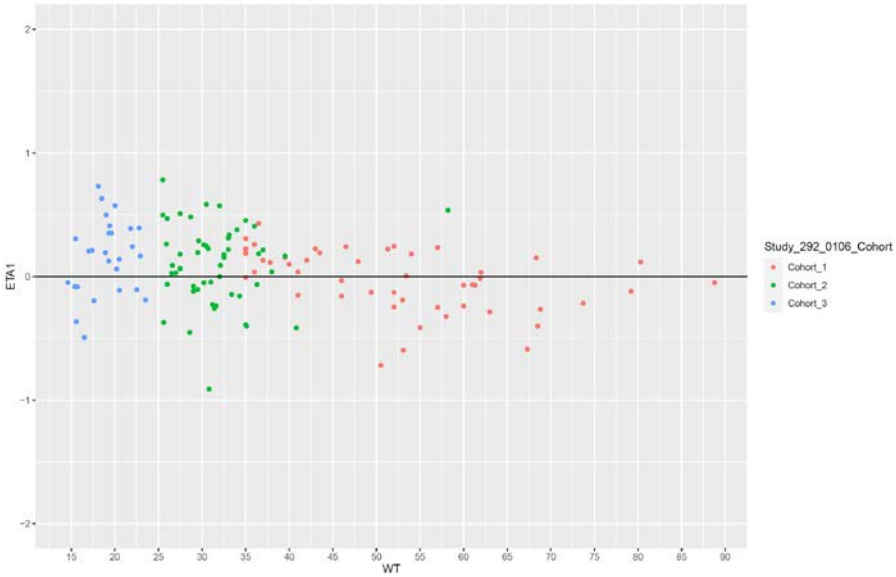
Note: GS-US-292-0106 study data only; x and y range were restricted to 800 ng/mL for illustration purposes; colored regression lines: LOESS fit; n=129

Figure 21. Observed vs. Predicted EVG Ctau for -0106 Study Cohort 3 By Time Window



Color-coded stratifying variable was arbitrarily set from 23-25 hours; data were extracted based on PK samples beyond 20 hours from last dose; 1 (or green) indicates data points within the bounds of 23 to 25 hours, inclusively; 0 (or orange) indicates data points being outside of 23 to 25 hours

Figure 22. Reviewer's Analysis: ETA CL vs Body Weight (kg) in Final PopPK Model (0106 Study)



Note: GS-US-292-0106 study data only; n=129

Figure 23. Reviewer's Analysis: Observed vs. Predicted Sensitivity Analysis of EVG PopPK Model with Estimated Allometry

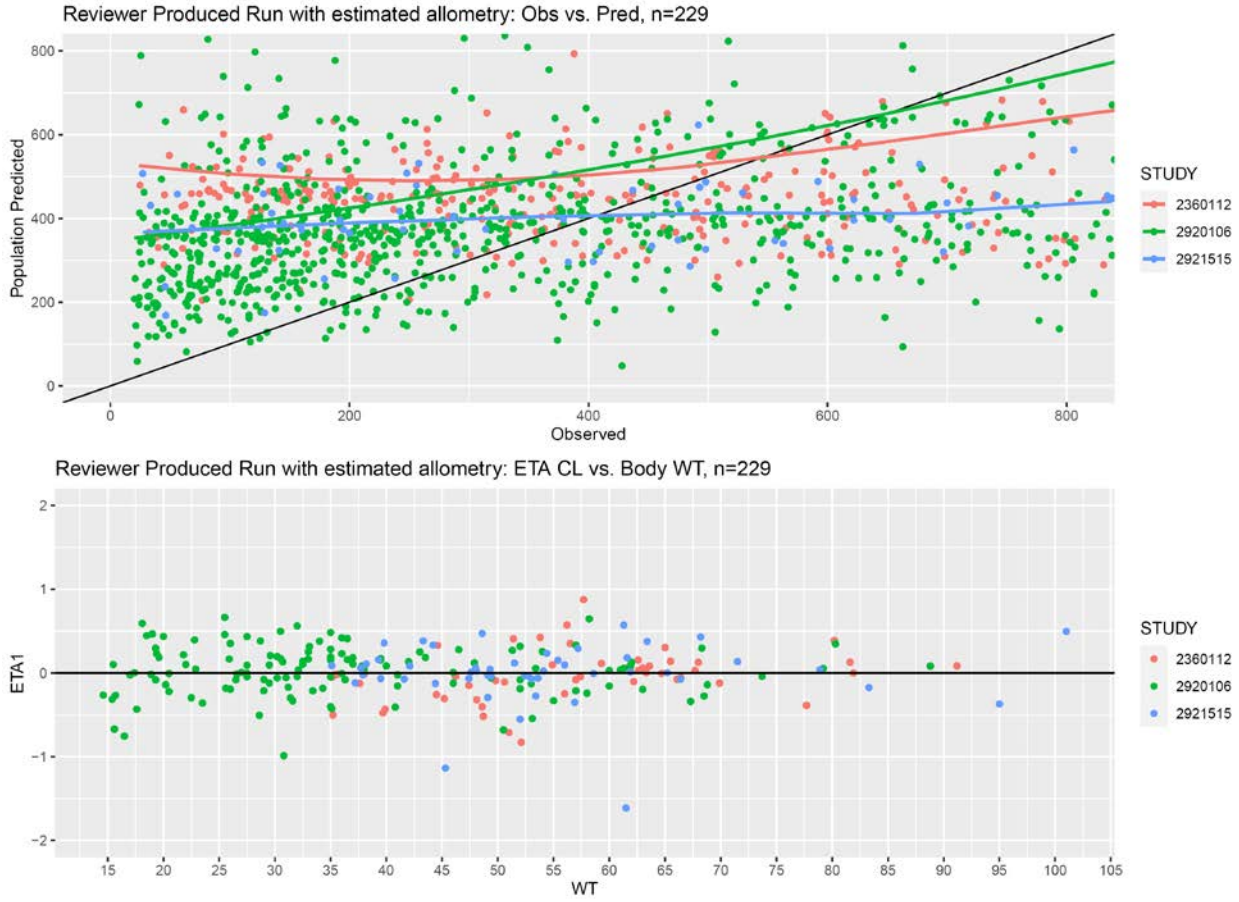


Table 20. Reviewer's Analysis: Sensitivity Analysis of EVG PopPK Model with Estimated Allometry

Parameter estimates

Theta	Description	Estimate	FIX	SE	RSE	95%CI	[lower,	init,	upper]
1	CL	6.11	-	0.004	0.1%	6.102-6.118	0	6.9	+Inf
2	V2	40.9	-	0.0339	0.1%	40.834-40.966	0	39.4	+Inf
3	V3	6.85	-	0.0687	1%	6.715-6.985	0	17	+Inf
4	Q	6.46	-	0.0023	0%	6.455-6.465	0	5.74	+Inf
5	KA1 STUDYTX=1	0.19	-	0.0001	0%	0.19-0.19	0	0.195	+Inf
6	KA2 STUDYTX=5	0.165	-	0.0001	0%	0.165-0.165	0	0.214	+Inf
7	D1	2.27	-	0.0008	0%	2.268-2.272	0	2.12	+Inf
8	proportional error	0.54	-	0.0005	0.1%	0.539-0.541	0	0.952	+Inf
9	additive error	15.6	-	0.0301	0.2%	15.541-15.659	0	45	+Inf
10	WTCL	0.464	-	0.0005	0.1%	0.463-0.465	0	0.75	+Inf
11	WTV	1.1	-	0.0004	0%	1.099-1.101	0	1	+Inf

Omega	Description	Estimate	SE	RSE	Etabar	p val	Shrinkage
1,1	1. CL	0.126	0.0186	14.8%	0.008 (0.021)	0.7151	11.5%
3,3	3. Vp	23.7	1.81	7.6%	0.627 (0.169)	0.0002	47.3%
4,4	4. Q	0.53	0.0076	1.4%	0.034 (0.013)	0.0071	74%
5,5	5. D1	1.67	0.0226	1.4%	-0.005 (0.051)	0.9189	40%

Sigma	Description	Estimate	SE	RSE	Shrinkage
1,1	residual variability	1	.	.	2.1%

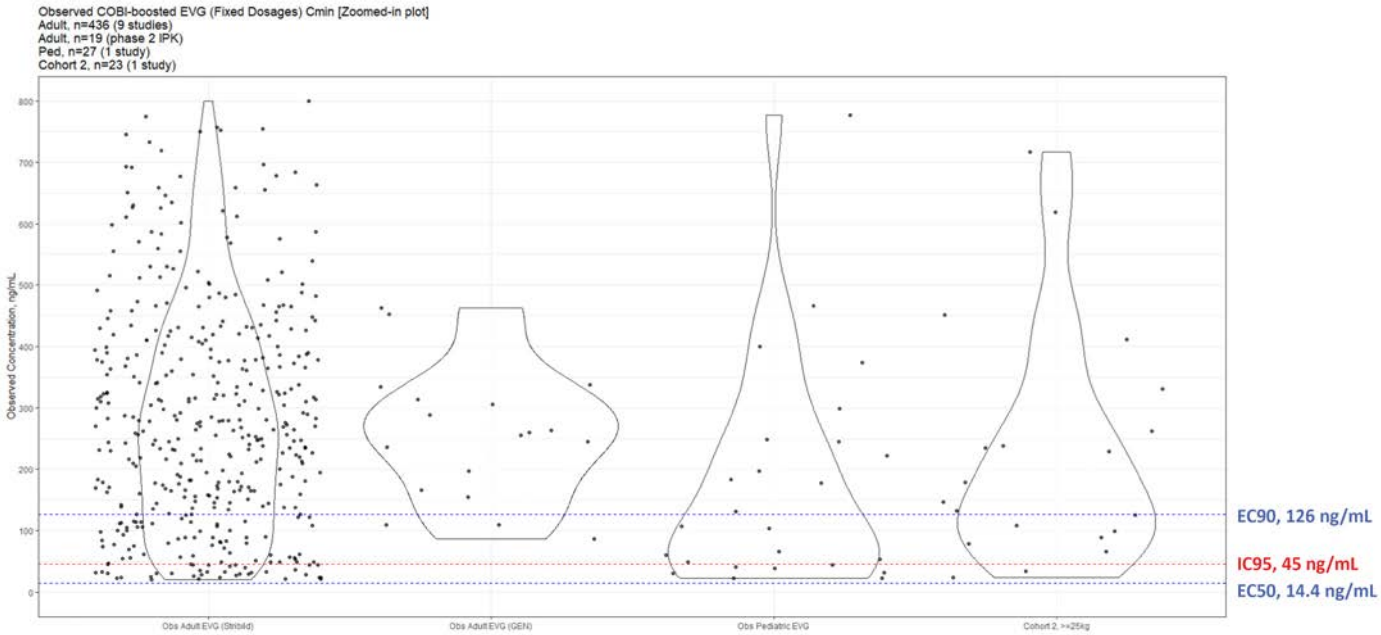
Table 21. Reviewer's Analysis on Observed EVG Ctau by Study Programs and Subgroups

Study Programs	Groups	N	Observed EVG Data					
			Min	1st quartile	Median	3rd quartile	Max	% below 45 ng/mL
Stribild	Adult, Phase 1, 2, 3	436	20.2	144.1	276.1	428.7	2694.7	7.8%
	Adult, Phase 2, 3	275	22.0	121.7	233.6	397.0	2694.7	6.2%
Genvoya	Adult, Phase 2	19	86.8	181.7	259.3	324.0	880.5	0
	Pediatric subjects 14-25kg Cohort 3	27	22.2	46.5	131.0	273.5	1030.0*	25.9%
	Adolescent Cohort 2*	23	24.3	103.6	229.3	431.0	1810.0	8.7%

** Includes outliers*

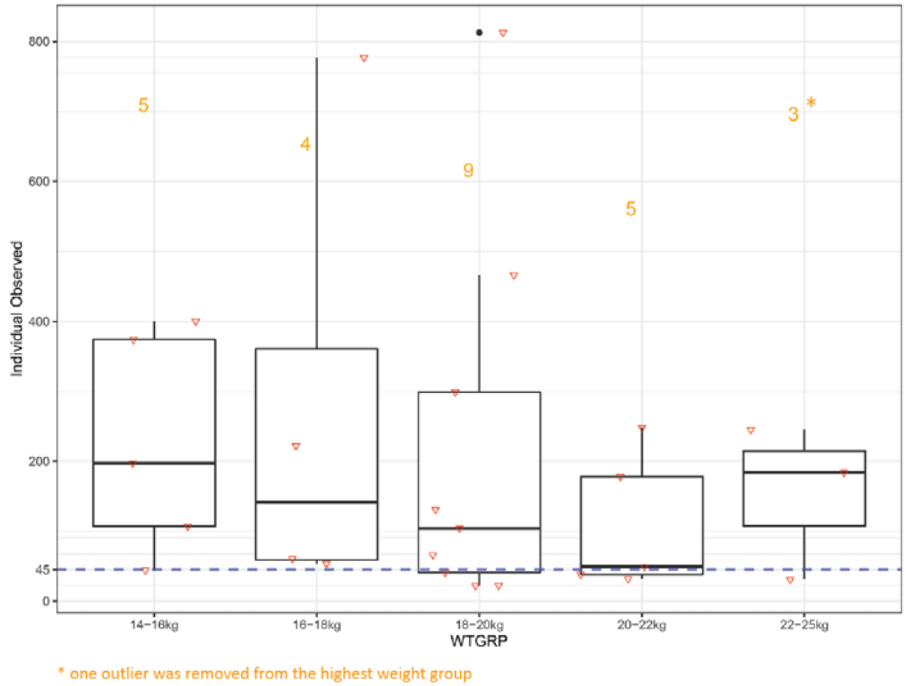
*** GS-US-292-0106 Study*

Figure 24. Reviewer's Analysis: Comparison of Observed EVG Ctau (COBI Boosted) by Studies and Subgroups



Cmin refers to Ctau; all adult data in Stribild program is based on six Phase 1 (healthy), one Phase 2 (HIV-1 infected), and two phase 3 (HIV-1 infected) studies; Genvoya adult data was extracted from one Phase 2 study (HIV-1 infected) with intensive PK sampling for n=19 subjects; observed pediatric EVG (3rd data cluster) represents target pediatric population of cohort 3 in GS-US-292-0106 study excluding outliers; cohort 2 in the figure represents cohort 2 subjects who weighed ≥25 kg in the GS-US-292-0106 study

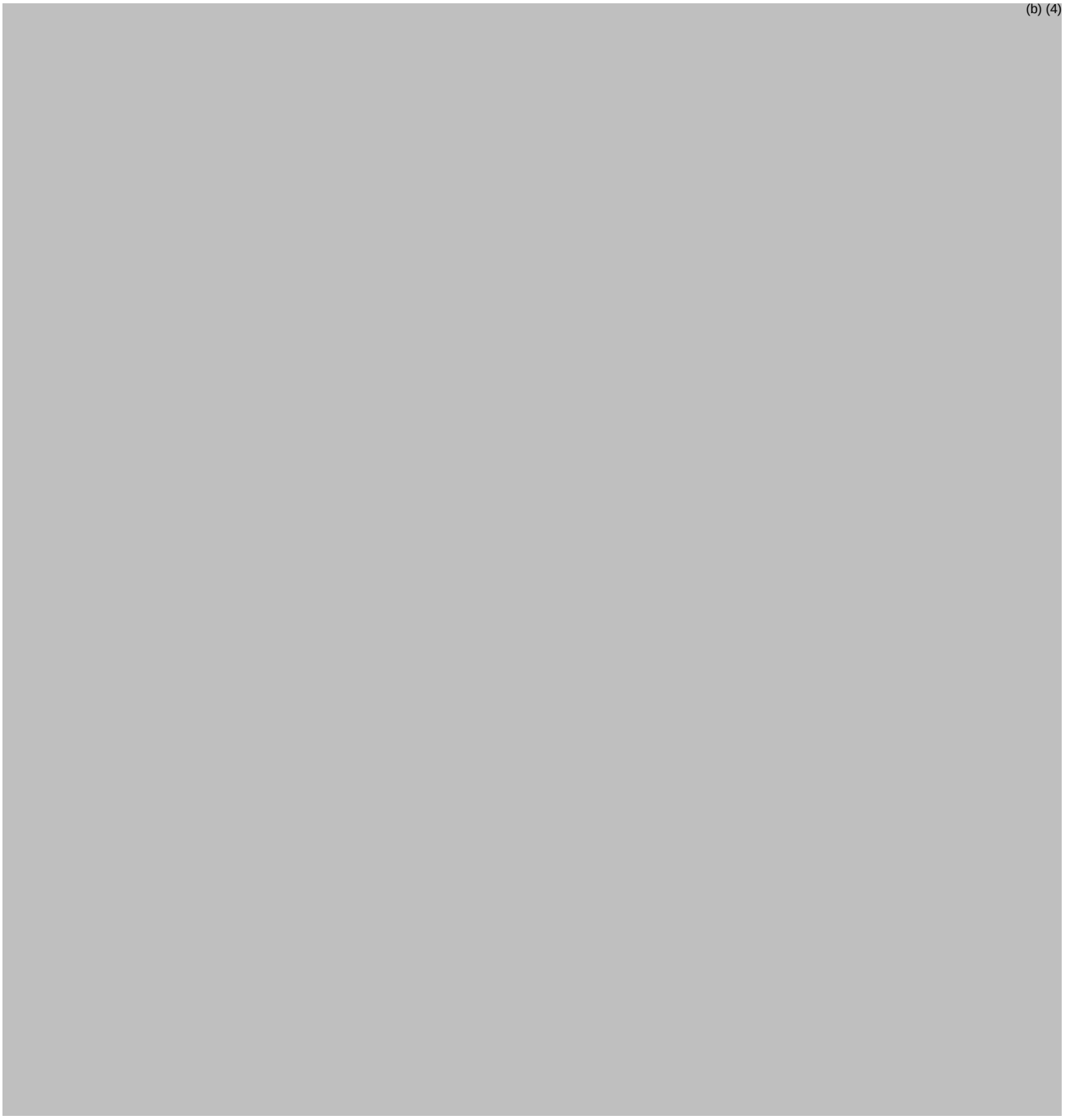
Figure 25. Reviewer's Analysis: Observed EVG Ctau by Weight Groups



* one outlier was removed from the highest weight group

Because of the suboptimal predictive performance (i.e., over-predictions) at the lower range of observed EVG PK data, alternative approach was taken to examine the observed data. A violin and jitter plot in **Figure 24** illustrates the relatively high proportion of target pediatric subjects weighing 14 to <25 kg (third data cluster) experiencing lower EVG Ctau (b) (4). In **Figure 25**, observed EVG Ctau was binned by weight groups. A down-trending was noted for EVG Ctau as the body weight approach upper bound of the (b) (4) weight band. Overall, despite the acceptable generality of model performance in characterizing peak and AUC of EVG, the predicted Ctau could not accurately capture the observed data and the low EVG Ctau may raise efficacy concerns given the limited sample size.

(b) (4)



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1.5.5 Listing of analyses codes and output files

Item	Files/Description	Location in \\cdsnas\pharmacometrics\
NONMEM Base Model TAF	run071.mod	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\Runs\run1_taf_base
NONMEM Final Model TAF	run078_tv.mod	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\Runs\run1_taf
NONMEM Final Model TAF by reviewer with tweaked initial estimates and parallel/minimal retries	run078_tv.mod	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\Runs\run1_taf_nm75_twked
NONMEM Final Model TFV	run028.mod	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\Runs\run2_tfv
TAF/TFV R script	(b) (4)-2020-1049-cobi-evg-peds-pop-pk.R	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1048-taf-tfv-peds-pop-pk\(b) (4)-2020-1048-taf-tfv-peds-pop-pk
NONMEM Final Model EVG	run32_JL.mod evg.csv	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1049-cobi-evg-peds-pop-pk\(b) (4)-2020-1049-cobi-evg-peds-pop-pk\runs\evg_run1_noRetries
NONMEM Final EVG PopPK Model with estimated allometric scalers output by the reviewer (NM 7.4.3)	run32_est_exp.mod	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1049-cobi-evg-peds-pop-pk\(b) (4)-2020-1049-cobi-evg-peds-pop-pk\runs\evg_final_est_expo
EVG/COBI R script	(b) (4)-2020-1049-cobi-evg-peds-pop-pk.R	…\NDA207591_(b) (4)_Genvoya_JIAJUNLIU\PPK_Analysis\NONMEM\Genvoya\0225\(b) (4)-2020-1049-cobi-evg-peds-pop-pk\(b) (4)-2020-1049-cobi-evg-peds-pop-pk

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