OFFICE OF CLINICAL PHARMACOLOGY REVIEW	
NDA Number (SDN)	210251 (234)
Link to EDR	\\CDSESUB1\evsprod\NDA210251\0050
Submission Date	12/20/2018
Submission Type	Efficacy supplement - pediatric
Brand Name	BIKTARVY®
Generic Name	Bictegravir (B or BIC), emtricitabine (F or FTC), and tenofovir alafenamide (TAF)
Dosage Regimen	One tablet (B/F/TAF; 50/200/25 mg) taken once daily with or without food in patients with body weight at least 25 Kg
Route of Administration	Oral
Proposed Indication	Treatment of human immunodeficiency virus type 1 (HIV-1) infection
Applicant	Gilead Sciences, Inc.
OCP Review Team	Hazem E. Hassan, PhD, MS, RPh, RCDS Ruojing Li, PhD Chao Liu, PhD Qin Sun, PhD

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1. Executive summary

BIKTARVY® is a fixed-dose combination (FDC) of B, an HIV-1 integrase strand transfer inhibitor (INSTI), F and TAF, both are HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs). BIKTARVY® is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY®. The recommended dosage for adults is one tablet (B/F/TAF at 50/200/25 mg) taken once daily with or without food.

The Applicant submitted this Prior Approval Efficacy Supplement in support of expanding the indication of BIKTARVY® to pediatric patients weighing at least 25 kg. The proposed pediatric dosage using the adult-strength once daily without regard to food was supported by pharmacokinetic (PK), safety and efficacy data from a Phase 2/3 trial GS-US-380-1474 in HIV-1 infected, virologically suppressed pediatric patients (Cohort 1: 12 to < 18 years of age, weighing ≥ 35 kg; Cohort 2: 6 to < 12 years of age, weighing ≥ 25 kg). Although some PK parameters of B, F and TAF in adolescent or children were outside the pre-defined no effect boundaries (70-143%) compared to the results in adults, those are not considered clinically significant based on the exposure-response relationship analyses. The current submission partially fulfills the postmarketing requirement (PMR) 3322-1 which required conducting a study in pediatric patients 2 to <18 years old (data for pediatrics 2 to <6 years old are pending).

This submission also includes a summary of further drug-drug interaction analyses to support the Applicant proposed labeling revisions pertaining to the coadministration of BIKTARVY® with polyvalent cation-containing antacids/supplements. These analyses were performed using previously submitted data from trials GS-US-380-3909, GS-US-380-1489 and GS-US-380-1490.

2. Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that this pediatric efficacy supplement is *approvable* from a clinical pharmacology perspective. The key review issues, specific recommendations, and comments are summarized below.

3. Labeling Updates

Clinical pharmacology related labeling updates and comments are summarized below:

Section/heading	Updates (Bold) and Comments
1. INDICATIONS AND USAGE	BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (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 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.
2.2 Recommended Dosage	BIKTARVY is a three-drug fixed dose combination product containing 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food **in adults and pediatric patients with body weight at least 25 kg** [*see Clinical Pharmacology (12.3)*].
7.5 Established and Potentially Significant Drug Interactions Table 3, Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Calcium or iron supplements, Cation-containing antacids or laxatives, Sucralfate, Buffered medications	***Current Language*** <u>Antacids containing Al/Mg or Calcium:</u> BIKTARVY can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium. Routine administration of BIKTARVY simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended. <u>Supplements containing Calcium or Iron:</u> BIKTARVY and supplements containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended. ***Applicant Proposed Language # 1*** (b) (4) ***<u>Review team's comment to the Applicant on 04/23/2019</u>***

	The proposed labeling about polyvalent cations is not acceptable. (b) (4) [redacted] ***Applicant's Response on 05/09/2019*** The applicant acknowledged the FDA response and proposed a modified language to clarify recommendations for the use of BIKTARVY with antacids/supplements (outlined below). ***Applicant Proposed Language # 2*** Antacids containing Al/Mg: BIKTARVY can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIKTARVY together with, or 2 hours after, antacids containing Al/Mg is not recommended. Supplements or antacids containing Calcium or Iron: BIKTARVY and supplements or antacids containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions together with, or 2 hours after, supplements or antacids containing calcium or iron is not recommended. ***Review team's comments*** The proposed language is acceptable and considered final.

4. Key Clinical Pharmacology Review Question(s)

Is the proposed dosing regimen appropriate for pediatric patients with body weight at least 25 kg for which the indication is being sought?

Yes, we agree that the proposed dosing regimen, 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF, is appropriate for pediatric patients with body weight ≥ 25 kg for which the indication is being sought.

Population PK (PPK) models were developed for BIC and TAF, respectively, based on the data from HIV-1 infected pediatric patients. The systemic exposures of BIC and TAF in adolescents weighing ≥ 35 kg and children weighing ≥ 25 kg that were predicted by the PPK model were compared with those from

BIC/FTC/TAF treated, HIV-1 infected adult subjects in the Phase 3 Studies. The predefined PK equivalence boundary for geometric least squares mean (GLSM) ratios and associated 90% confidence intervals (CIs) is 70% to 143%. For BIC, the comparisons of plasma PK parameters between pediatrics and adults are shown in **Table. 1**.

Table 1 Comparisons of BIC plasma PK parameter estimates between pediatrics and adults (PPK analysis set)

BIC PK Parameter	%GLSM Ratio (90% CI) Test/Reference	
	Adolescents vs. Adults	**Children vs. Adults**
AUC_{tau} (h*ng/mL)	86 (80, 93)	125 (117, 134)
C_{max} (ng/mL)	100 (94, 107)	153 (143, 163)
C_{tau} (ng/mL)	65 (58, 73)	89 (81, 98)

GLSM = geometric least-square mean

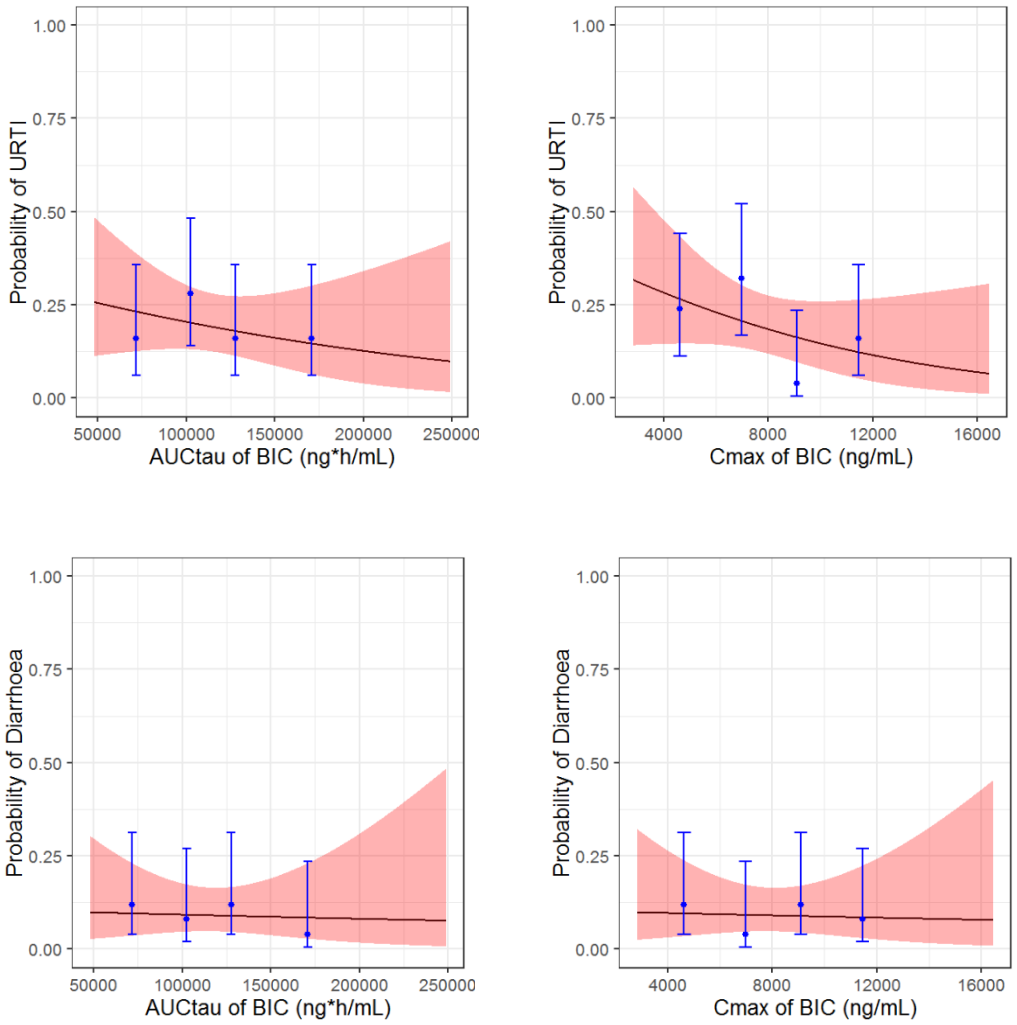
Population PK parameters for the test group were from BIC/FTC/TAF-treated pediatrics in Study GS-US-380-1474; N = 50 for adolescents and children, respectively.
Population PK parameters for the reference group were from B/F/TAF-treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878; N = 1193.
Source: Adapted from Applicant's Summary of Clinical Pharmacology Table 2 and Table 3.

BIC C_{tau} in adolescents was 35% lower than that in adults. This decrease was considered acceptable because: (1) Applicant's analysis indicated that no exposure-efficacy relationship was observed for BIC C_{tau} range across 604.9 to 7397 ng/mL, which covered the majority of the exposure range in Study GS-US-380-1474; (2) In the pediatric clinical study, 100% of the subjects achieved HIV-1 RNA < 50 copies/mL at Week 24; and (3) In the pediatric clinical study, 98.7% (74/75) subjects achieved HIV-1 RNA < 50 copies/mL at Week 48, indicating the high rates of maintained virologic suppression under the proposed dosing regimen.

BIC C_{max} in children was 53% higher compared to adults. Reviewer conducted independent exposure-response analysis for the most two common treatment-emergent adverse events (upper respiratory tract infection (19.0%) and diarrhea (9.0%)) in pediatric subjects (Study GS-US-380-1474). As shown in **Figure**

1, there was no positive E-R relationship for either upper respiratory tract infection (URTI) or diarrhea. In addition, adverse events considered related to study drug were reported for 10.0% (10/100) of subjects. Among study drug-related AEs, only abdominal discomfort (2.0%, 2 subjects) was reported with greater than single subject incidence. In each case, the abdominal discomfort was Grade 1 in severity and transient. Therefore, given the flat exposure-safety relationship and minor safety signals observed in the pediatric clinical study, the higher exposures of BIC in pediatrics compared to those in adults were considered acceptable (details refer Pharmacometrics Review).

Figure 1 BIC exposure-response relationships for treatment-emergent adverse events



Source: Reviewer independent analysis

For TAF, the comparisons of plasma PK parameters between pediatrics and adults are shown in **Table 2.**

Table 2 Comparisons of TAF plasma PK parameter estimates between pediatrics and adults (PPK analysis set)

TAF PK Parameter	%GLSM Ratio (90% CI) Test/Reference	
	Adolescents vs. Adults	Children vs. Adults
AUC_{tau} (h*ng/mL)	128 (116, 141)	183 (165, 202)
C_{max} (ng/mL)	89 (75, 106)	153 (136, 173)

GLSM = geometric least-square mean

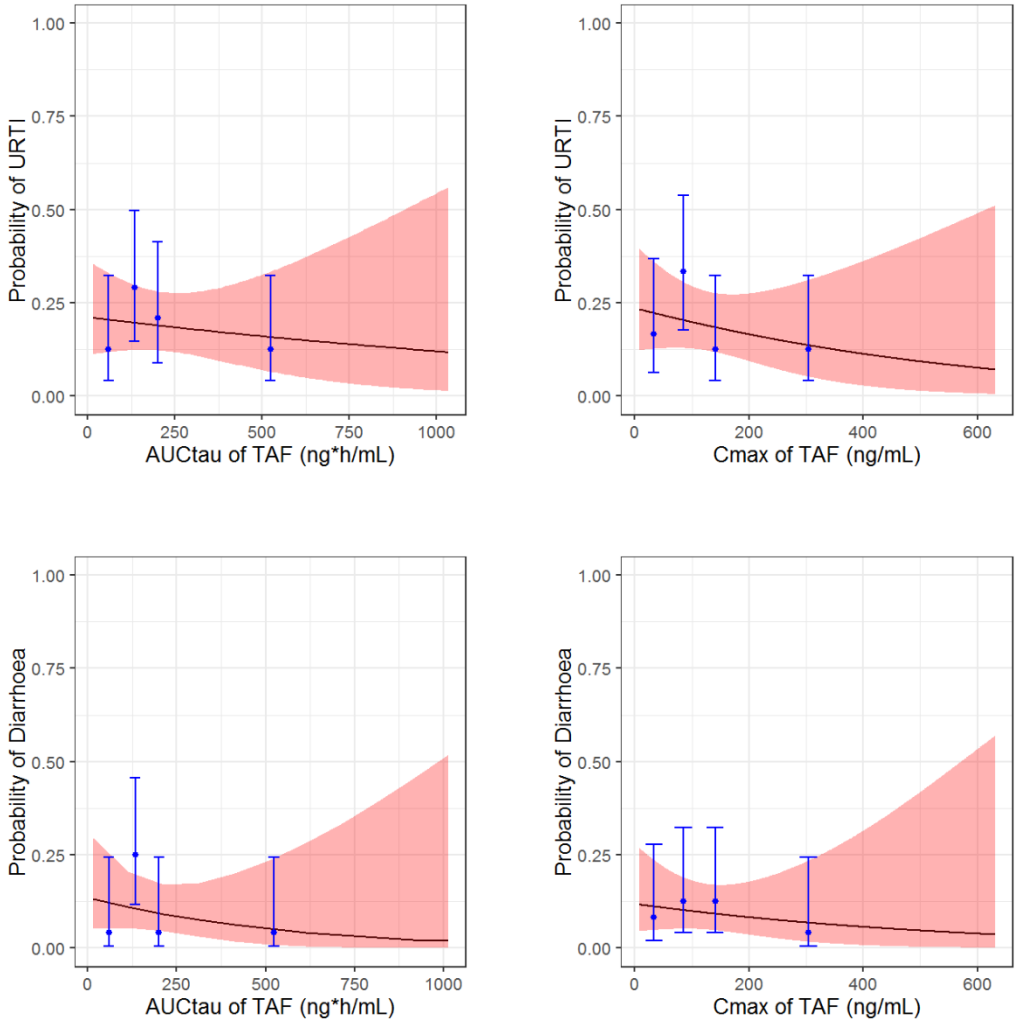
Population PK parameters for the test group were from B/F/TAF-treated pediatrics in Study GS-US-380-1474; N = 49 for adolescents; N = 47 for children.

Population PK parameters for the reference group were from B/F/TAF-treated adults in Studies GS-US-380-1489 and GS-US-380-1490; N = 486.

Source: adapted from Applicant's Summary of Clinical Pharmacology Table 4 and Table 5

The %GLSM ratios show that AUC_{tau} and C_{max} were 83% and 53% higher than those in adults, respectively, which were beyond the predefined PK equivalent boundary (70% to 143%). Thus, Reviewer conducted independent E-R analysis for URTI and diarrhea based on the TAF exposures from Study GS-US-380-1474. As shown in **Figure 2**, flat E-R relationships were observed for both URTI and diarrhea. In addition, given the minor safety signals observed among study drug-related AEs as discussed for BIC, the higher TAF exposures in children were considered acceptable (details refer Pharmacometrics Review).

Figure 2 TAF exposure-response relationships for treatment-emergent adverse events



Source: Reviewer independent analysis

For FTC, no PPK model was developed. The systemic exposures in adolescents weighing ≥ 35 kg and children weighing ≥ 25 kg receiving adult-strength B/F/TAF were estimated based on the intensive PK data. The comparison of the exposures between pediatrics and adults were shown in **Table 3.**

Table 3 Comparisons of FTC plasma PK parameter estimates between pediatrics and adults (intensive PK analysis set)

FTC PK Parameter	%GLSM Ratio (90% CI) Test/Reference	
	Adolescents vs. Adults	Children vs. Adults
AUC_{tau} (h*ng/mL)	112 (102, 124)	142 (127, 159)
C_{max} (ng/mL)	127 (111, 145)	185 (162, 210)
C_{tau} (ng/mL)	69 (61, 78)	95 (70, 129)

GLSM = geometric least-square mean

Intensive PK parameters for the test group were from B/F/TAF-treated pediatrics in Study GS-US-380-1474; N = 24 for adolescents; N = 25 for children.

Intensive PK parameters for the reference group were from B/F/TAF-treated adults in Studies GS-US-380-1489 and GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878; N = 77.

Source: adapted from Applicant's Summary of Clinical Pharmacology Table 7 and Table 8

In adolescents ≥ 35 kg, the 90% CI of the GLSM ratio of FTC exposures were generally within the predefined 70% to 143% boundary, while C_{tau} was slightly lower than 70%. Given the high proportion of subjects achieved RNA < 50 copies/mL at Week 24 and Week 48 in the pediatric clinical study, the slightly lower C_{tau} was considered acceptable. In Children ≥ 25 kg, FTC C_{max} was 85% higher than that in adults. Considered the favorable safety profile of B/F/TAF as discussed before, the higher exposures in children were not deemed clinically important.

5. Individual Study Review

GS-US-380-1474 (EDR Link)*

**This review focuses only on the clinical pharmacology aspects of this trial (Please refer to clinical review regarding efficacy and safety).*

Title:

A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883 (Bictegravir)/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination (FDC) in HIV-1 Infected Virologically Suppressed Adolescents and Children.

Study Period*:* 09/21/2016 – 08/01/2018

Objectives:

Cohorts 1 and 2

Primary:

Part A: To evaluate the steady-state PK of B, F and TAF 50/200/25 mg FDC in HIV-1 infected, virologically suppressed adolescents (12 to < 18 years of age) and children (6 to < 12 years of age).

Parts A and B: To evaluate the safety and tolerability of the adult-strength B/F/TAF FDC through Week 24 in HIV-1 infected, virologically suppressed adolescents (12 to < 18 years of age) and children (6 to < 12 years of age).

Secondary:

- To evaluate the safety and tolerability of the adult-strength B/F/TAF FDC through Week 48 in HIV-1 infected, virologically suppressed adolescents (12 to < 18 years of age) and children (6 to < 12 years of age).
- To evaluate the antiviral activity of the adult-strength B/F/TAF FDC through Weeks 24 and 48 in HIV-1 infected, virologically suppressed adolescents (12 to < 18 years of age) and children (6 to < 12 years of age).

Cohort 3

Primary:

Part A: To evaluate the steady-state PK of B and confirm the dose of B/F/TAF 30/120/15 mg FDC in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg

Parts A and B: To evaluate the safety and tolerability of the low-dose B/F/TAF FDC tablet through Week 24 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg

Secondary:

- To evaluate the safety and tolerability of the low-dose B/F/TAF FDC tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.
- To evaluate the antiviral activity of the low-dose B/F/TAF FDC tablet through Weeks 24 and 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg

This review only pertains to the submitted interim analysis of the study which includes data from 1) all subjects in Cohort 1 Parts A and B and Cohort 2 Part A who had completed their Week 48 visit and 2) all subjects in Cohort 2 Part B had completed their Week 24 visit, or prematurely discontinued study drug.

Main Inclusion Criteria:

- HIV-1 infected adolescents (12 to < 18 years of age, weight ≥ 35 kg) and children (6 to < 12 years of age, weight ≥ 25 kg) virologically suppressed (HIV-1 RNA < 50 copies/mL or undetectable HIV-1 RNA if the limit of detection of the local assay used was ≥ 50 copies/mL) for ≥ 6 months prior to screening on a stable antiretroviral regimen.
- Estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula; eGFR Schwartz) at screening.
- No documented or suspected resistance to F, tenofovir (TFV), or INSTIs.

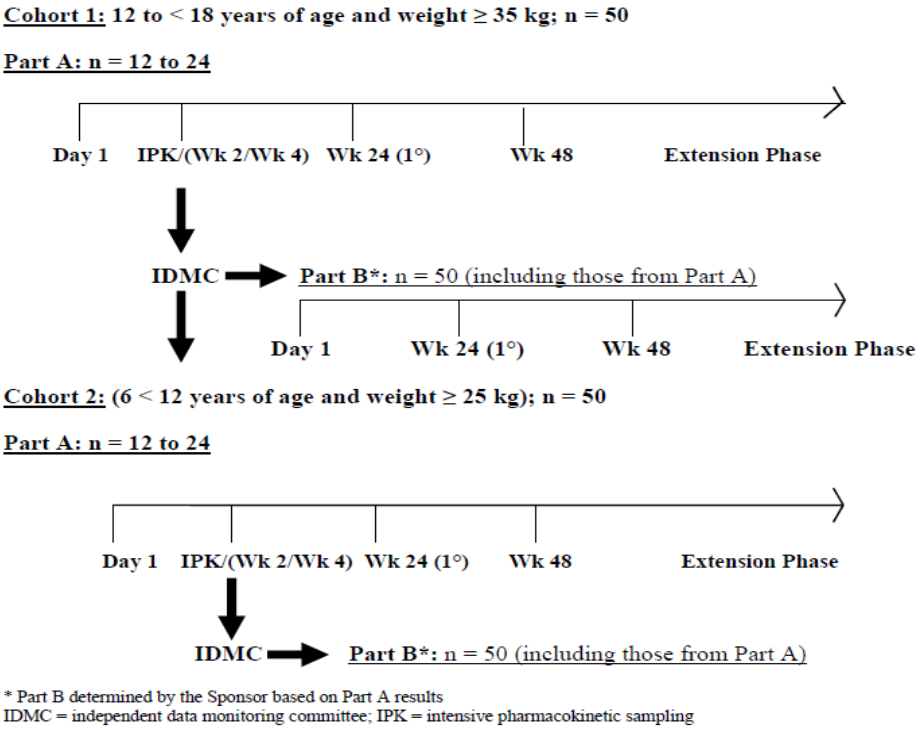
Test Product, Dose and Mode of Administration:

FDC tablet of B/F/TAF (50/200/25 mg) administered orally, once daily, without regard to food.

Trial Design:

This is an open-label, multicenter, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of the B/F/TAF FDC in HIV-1 infected, virologically suppressed adolescents and children. Approximately 100 subjects were planned to be enrolled in the study for Cohorts 1 and 2. Duration of treatment was at least 48 weeks.

Study Scheme



* Part B determined by the Sponsor based on Part A results
IDMC = independent data monitoring committee; IPK = intensive pharmacokinetic sampling

Source: Clinical Study Report, P. 29

Bioanalytical method:

The precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration.

Results:

Main Subject Demographics and Baseline Disease Characteristics

- Number of Subjects: Enrolled: 102, Plasma PK Analysis Set: 100, intensive PK set: 49
- Most subjects (overall 59.0%) in Cohorts 1 and 2 were female (64.0% and 54.0%, respectively).
- Median ages (range) were: Cohort 1, 15 (12 to 17) years; Cohort 2, 10 (6 to 11) years.
- Race and ethnicity were similar in the 2 cohorts (overall, 68.7% of subjects were black and 24.2% of subjects were Asian, and 98.0% were not Hispanic or Latino).
- All subjects had baseline plasma HIV-1 RNA < 50 copies/mL.
- Median (Q1, Q3) baseline eGFR Schwartz was similar in each cohort (overall, 150.5 [136.5, 172.5] mL/min/1.73 m^2).

Pharmacokinetics

The PK parameters for B, F, and TAF in adolescent or children patients are summarized in **Table 4** and **Table 5**. Compared to the results in adults, the 90% confidence interval (CI) of the geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in children and adolescent patients were outside the pre-defined no effect boundaries (70-143%) (**Table 6** and **Table 7**). However, this is deemed clinically insignificant (*please refer to Key Clinical Pharmacology Review Question, subsection 4*).

Table 4: Multiple Dose PK Parameters of B, F, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 12 to less than 18 years.

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	6.24 (27.1)	2.69 (34.0)	0.133 (70.2)
AUC_{tau} (microgram•h per mL)	89.1 (31.0)	13.6 (21.7)	0.196 (50.3)
C_{trough} (microgram per mL)	1.78 (44.4)	0.064 (25.0)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 1 of Trial 1474 (n=50 for BIC; n=49 for TAF).

b. From Intensive PK analysis of cohort 1 of Trial 1474 (n=24).

Mean B C_{max}, and exposures of F and T (AUC_{tau} and Cmax) achieved in 50 pediatric patients between the ages of 6 to less than 12 years and weighing at least 25 kg who received BIKTARVY in Trial 1474 were higher than exposures in adults; however, the increase was not considered clinically significant as the safety profiles were similar in adult and pediatric patients (see Clinical review).

Table 5: Multiple Dose PK Parameters of B, F, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 6 to less than 12 years

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	9.46 (24.3)	3.89 (31.0)	0.205 (44.6)
AUC_{tau} (microgram•h per mL)	128 (27.8)	17.6 (36.9)	0.278 (40.3)
C_{trough} (microgram per mL)	2.36 (39.0)	0.227 (323)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 2 of Trial 1474 (n=50 for BIC; n=47 for TAF).

b. From Intensive PK analysis of cohort 2 of Trial 1474 (n=25 except n=24 for C_{trough}).

Table 6: Geometric least squares mean (GLSM) ratios of some PK parameters of B and F in adolescents relative to adults. PK parameters were estimated by population PK modeling using all available intensive and sparse plasma concentration data (Parts A and B of Cohorts 1 and 2; N=50/Cohort or a total N = 100).

PK Parameter	Adolescents Geometric mean (% CV)	Adults[a] Geometric mean (% CV)	% GLSM (90% CI) Adolescents/Adults
B C_{tau} (ng/mL)	1784.3 (44.4)	2609.9 (35.2)	65.38 (58.32, 73.28)
F C_{max} (ng/mL)	2689.2 (34.0)	2127.0 (34.7)	127.15 (111.45, 145.06)
F C_{tau} (ng/mL)	64.4 (25.0)	96.0 (37.4)	69.25 (61.55, 77.92)

[a] Historic data; Trials GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878

Sources: Summary of Clinical Pharmacology, Tables 2 and 7

Table 7: Geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in children relative to adults. PK parameters were estimated by population PK modeling using all available intensive and sparse plasma concentration data (Parts A and B of Cohorts 1 and 2; N=50/Cohort or a total N = 100).

PK Parameter	Children Geometric mean (% CV)	Adults[a] Geometric mean (% CV)	% GLSM (90% CI) Children/Adults
B C_{max} (ng/mL)	9462.8 (24.3)	6145.8 (22.9)	152.70 (142.82, 163.25)
F AUC_{tau} (h·ng/mL)	17565.1 (36.9)	12293.6 (29.2)	142.27 (127.33, 158.96)
F C_{max} (ng/mL)	3888.4 (31.0)	2127.0 (34.7)	184.72 (162.45, 210.05)
TAF AUC_{tau} (h·ng/mL)	277.5 (40.3)	142.0 (17.3)	182.83 (165.20, 202.34)
TAF C_{max} (ng/mL)	204.8 (44.6)	121.3 (15.4)	153.35 (135.64,173.39)

[a] Historic data; Trials GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878

Sources: Summary of Clinical Pharmacology, Tables 3, 5 and 8

Note: The PK parameter estimates in the summary of clinical pharmacology are different from those in Trail 1474 body report because in the body report, B, F and TAF exposures were estimated by non-compartmental analyses using intensive PK data collected at Week 2 or Week 4 visit (Part A only: N=24 for Cohort 1, N=25 for Cohort 2), while in the summary of clinical pharmacology the parameters were estimated by population PK modeling using all available intensive and sparse plasma concentration data (Parts A and B of Cohorts 1 and 2; N=50/Cohort or a total N = 100).

Data Integrity-Related Consults (OSIS Inspections)

Analytical site inspection for Study GS-US-380-1474 was not conducted by the Office of Study Integrity and Surveillance (OSIS) because the site was previously inspected in (b) (4) which falls within the surveillance interval. The final classification for the inspections was No Action Indicated (NAI). (Refer to Dr. Angel Johnson's memorandum for details)

Conclusions

- No clinically relevant differences in B/F/TAF exposure parameters were observed in adolescents or children compared with adults.
- The B/F/TAF exposure data submitted in this interim analysis support the use of B/F/TAF 50/200/25 mg for the treatment of HIV-1 infection in adolescents and children 6 to < 18 years of age weighing ≥ 25 kg.

Reviewer's Overall Assessment

- The study design, results and conclusions are acceptable.

6. Pharmacometrics Review

Population PK (PPK) models were developed by Applicant to describe the PK of bictegravir (BIC), tenofovir alafenamide (TAF) and tenofovir (TFV) in HIV-1 infected adolescents and children. The individual exposures of BIC and TAF were estimated and used for comparison with the exposures in adult patients, respectively. In this review, FDA Pharmacometrics Reviewer validated Applicant's population PK model for BIC, TAF and TFV, as well as conducted independent exposure-response analysis for safety based on the data collected from the pediatric clinical study.

1. BIC

The purpose of the population PK analysis of BIC is to characterize the BIC PK based on the data from a single pediatric study (**Table 1**) and to estimate the steady-state exposures of BIC in pediatric participants who received 50mg BIC in the FDC. In total, 100 participants were included in this PPK

analysis. Participants were defined as evaluable for PPK analysis if they have at least one adequately documented BIC administration and a corresponding PK sample collection after the dose.

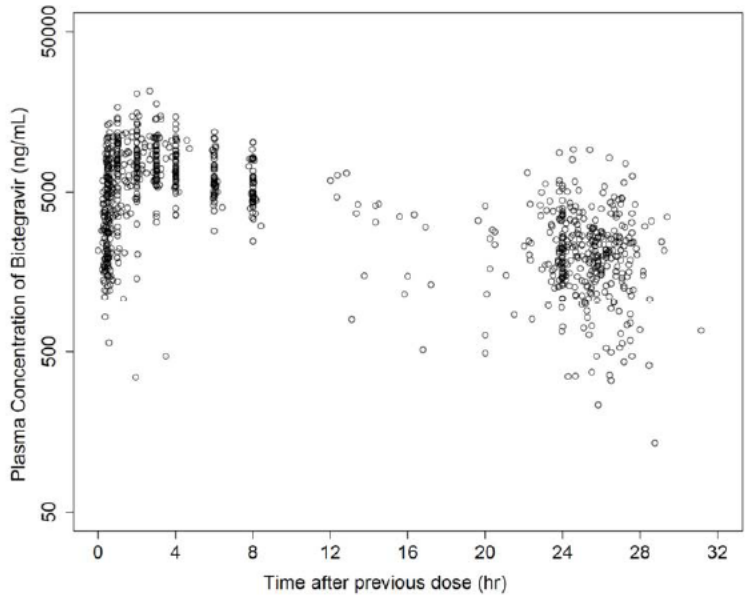
Table 1 Summary of participants included in the PPK analysis for BIC

Study	Population	Phase	Treatment	Sampling (Intensive/Sparse)
GS-US-380-1474	HIV-1 infected	2/3	BIC/FTC/TAF 50/200/25mg FDC	Intensive + Sparse

Source: Applicant's QP-2018-1028 BIC HIV Pediatric PopPK Report page 12 Table 1.

The model development dataset included a total of 898 data points with at least one measurable concentration from 100 participants. **Figure 3** Shows the BIC plasma concentrations versus time profile for observations from all participants.

Figure 3 BIC concentration versus time after previous dose



Source: Applicant's QP-2018-1028 BIC HIV Pediatric PopPK Report page 18 Figure 1.

The final model to describe BIC PK in HIV-1 infected pediatric participants was a 1-compartment model with first order absorption, first order elimination from the central compartment and a lag time (T_{lag}), interindividual variability (IIV) on CL/F, Vc/F, and first-order absorption rate constant (ka), covariance on CL/F and Vc/F, ka and lag time (T_{lag}), an additive error model (for log-transformed data), and IOV on CL/F and Vc/F.

Parameter estimates for the final PPK model for BIC are presented in **Table 2**.

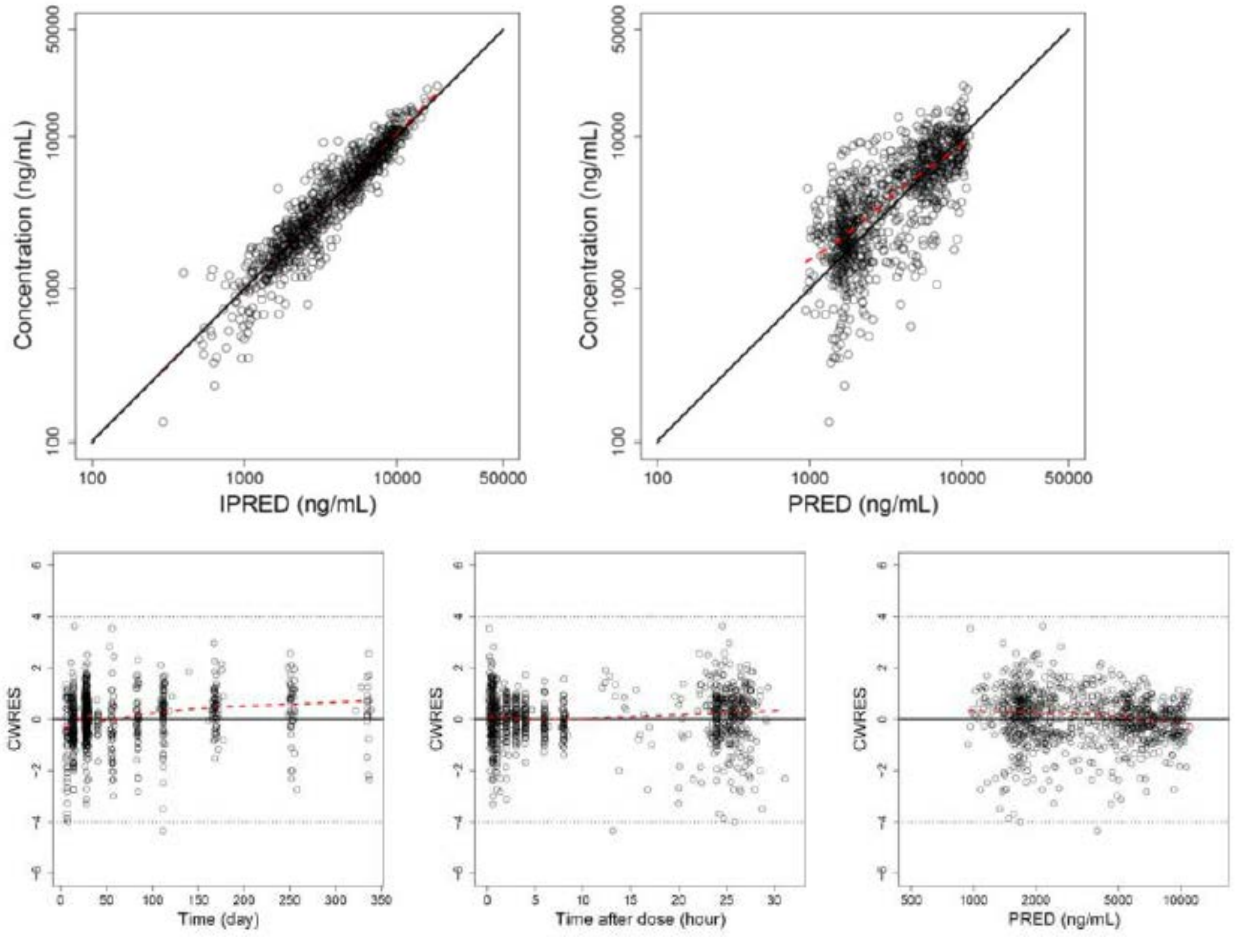
Table 2 Summary of final BIC population PK parameters

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	Interindividual Variability(%)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)	WT 41 kg	0.506	—	34.5
$exp\left(\theta_1 + 0.75 \times \frac{WT}{41}\right)$		Fifth percentile of WT (26 kg)	0.360	-28.9	
		95th percentile WT (69 kg)	0.748	47.8	
$exp(\theta_2)$	Apparent central volume, V_c/F (L)	WT 41 kg	8.21	—	17.9
$exp\left(\theta_2 + 1 \times \frac{WT}{41}\right)$		Fifth percentile of WT (26 kg)	5.21	-36.5	
		95th percentile WT (69 kg)	13.8	68.1	
$exp(\theta_3)$	Absorption rate constant, Ka (hours^{-1})	Without PPI usage	2.44	—	122
$exp(\theta_3 + \theta_7)$		With PPI usage	1.07	-56.1	
$exp(\theta_4)$	Lag time T_{lag} (h)		0.323	—	—
$\omega_{(CL,Vc)}$	Covariance between CL/F and V_c/F		0.053		—
σ	Residual error		31.1		—

Source: Applicant's QP-2018-1028 BIC HIV Pediatric PopPK Report page 21 Table 3.

The general goodness-of-fit plots of the final BIC PPK model are shown in **Figure 4**

Figure 4 Goodness-of-fit plots for the final BIC PPK model



Source: Applicant's QP-2018-1028 BIC HIV Pediatric PopPK Report page 23 Figure 3 & 4.

Shrinkage of the final model parameters is presented in **Table 3**.

Table 3 Shrinkage of the final BIC model parameters

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	9.59
$\omega_{Vc/F}$	IIV of V_c/F	24.6
ω_{IOVCL}	IOV on CL/F	32.0
ω_{IOVVc}	IOV on V_c/F	53.4
ω_{Ka}	IIV of K_a/F	25.9
σ	EPS (residual error)	14.0

Source: Applicant's QP-2018-1028 BIC HIV Pediatric PopPK Report page 28 Table 6.

PPK model predicted systemic exposures of BIC in adolescents 12 to < 18 years of age weighing ≥ 35 kg (Cohort 1) and children 6 to < 12 years of age weighing ≥ 25 kg (Cohort 2) receiving adult-strength B/F/TAF were compared with those from B/F/TAF treated, HIV-1 infected adult subjects in the Phase 3 Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878 (N = 1193). The predefined PK equivalence boundary for geometric least squares mean (GLSM) ratios and associated 90% confidence intervals (CIs) is 70% to 143%. The results for comparison are shown in **Table 4** and **Table 5**.

Table 4 Statistical comparisons of BIC plasma PK parameter estimates between adolescents and adults (PPK analysis set; Cohort 1)

BIC PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	GS-US-380-1474 (Test) (N = 50)	GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 (Reference) (N = 1193)	
AUC_{tau} (h•ng/mL)	89094.5 (31)	102001.0 (26.9)	86.25 (80.01, 92.97)
C_{max} (ng/mL)	6236.4 (27.1)	6145.8 (22.9)	100.31 (93.81, 107.26)
C_{tau} (ng/mL)	1784.3 (44.4)	2609.9 (35.2)	65.38 (58.32, 73.28)

%CV = percentage coefficient of variation; GLSM = geometric least-squares mean
Population PK parameters for the reference group were from B/F/TAF-treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878

Source: Applicant's summary of clinical pharmacology page 18 Table 2.

Table 5 Statistical comparisons of BIC plasma PK parameter estimates between children and adults (PPK analysis set; Cohort 2)

BIC PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	GS-US-380-1474 (Test) (N = 50)	GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 (Reference) (N = 1193)	
AUC_{tau} (h•ng/mL)	128126.4 (27.8)	102001.0 (26.9)	125.07 (116.66, 134.10)
C_{max} (ng/mL)	9462.8 (24.3)	6145.8 (22.9)	152.70 (142.82, 163.25)
C_{tau} (ng/mL)	2358.1 (39.0)	2609.9 (35.2)	88.88 (80.59, 98.02)

%CV = percentage coefficient of variation; GLSM = geometric least-squares mean
Population PK parameters for the reference group were from B/F/TAF-treated adults in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878

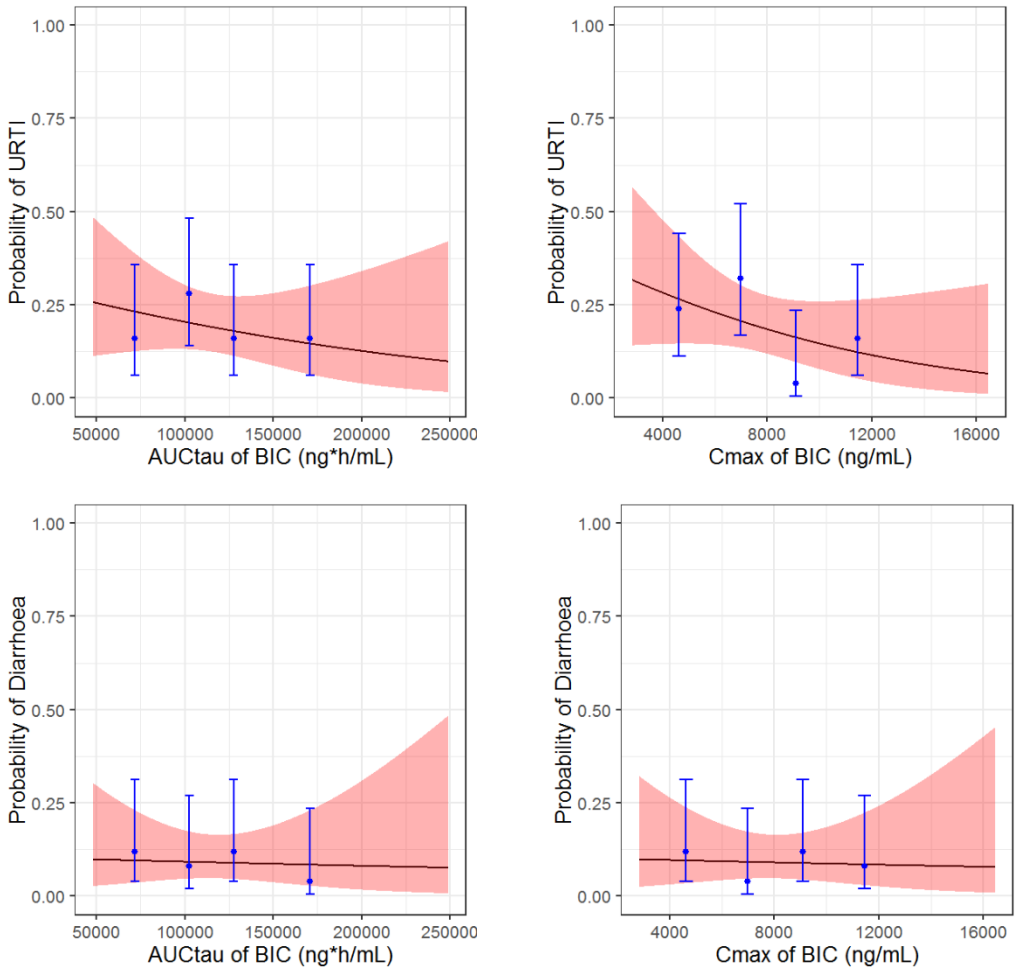
Source: Applicant's summary of clinical pharmacology page 19 Table 3.

Reviewer's comment: The final population PK model of BIC is acceptable. The goodness-of-fit plots show a good agreement between the predicted concentrations and observed concentrations in the pediatric clinical study. To validate the applicant's PPK final model, Reviewer re-ran the model, and the parameter estimates were similar with Applicant's results in ***Table 2*** *with acceptable diagnostic plots. The magnitude of shrinkage of the final PPK model was small for CL/F, Vc/F and ka. Thus, the final PPK model was considered robust to estimate the exposures at steady-state in the pediatric patients for the comparison with adult exposures.*

The co-administration of PPI was binary covariate in the PPK model without detailed information regarding to when PPI was used (at the same time with BIC or 2 hours before/after BIC). Therefore, BIC exposures estimated based on the PPK model under different usage of PPI could be questionable.
BIC C_{tau} in adolescents was 35% lower than that in adults. This decrease was not considered clinically significant because: (1) Applicant's analysis indicated that no exposure-efficacy relationship was observed for BIC C_{tau} range across 604.9 to 7397 ng/mL, which covered the majority of the exposure range in Study GS-US-380-1474; (2) In the pediatric clinical study, 100% of the subjects achieved HIV-1 RNA < 50 copies/mL at Week 24; and (3) In the pediatric clinical study, 98.7% (74/75) subjects achieved HIV-1 RNA < 50 copies/mL at Week 48, indicating the high rates of maintained virologic suppression under the proposed dosing regimen.

BIC C_{max} in children was 53% higher compared to that in adults. Reviewer conducted independent exposure-response analysis for the most two common treatment-emergent adverse events (upper respiratory tract infection (URTI) (19.0%) and diarrhea (9.0%)) in pediatric subjects (Study GS-US-380-1474). As shown in ***Figure 5****, there was no positive E-R relationship for either URTI or diarrhea. In addition, adverse events considered related to study drug were reported for 10.0% (10/100) of subjects. Among study drug-related AEs, only abdominal discomfort (2.0%, 2 subjects) was reported with greater than single subject incidence. In each case, the abdominal discomfort was Grade 1 in severity and transient. Therefore, given the flat exposure-safety relationship and minor safety signals observed in the pediatric clinical study, the higher exposures of BIC in pediatrics compared to those in adults were not considered clinically impactful.*

Figure 5 BIC exposure-response relationships for treatment-emergent adverse events



Source: Reviewer independent analysis

2. TAF and TFV

TAF is the prodrug of TFV in the BIC/FTC/TAF FDC (BIKTARVY). The purpose of the PPK analysis was to characterize TAF and TFV PK and estimate the steady-state exposures in treatment-naïve and treatment-experience HIV-infected children and adolescents ≥ 25 kg, receiving a regimen containing TAF at a dose of 25 mg with unboosted third agents, or 10 mg with boosted third agents.

The PPK analysis dataset included 4 ongoing phase 2/3 studies in HIV-1 infected participants as shown in ***Table 6***.

Table 6 Summary of clinical studies included in the PPK analyses for TAF and TFV

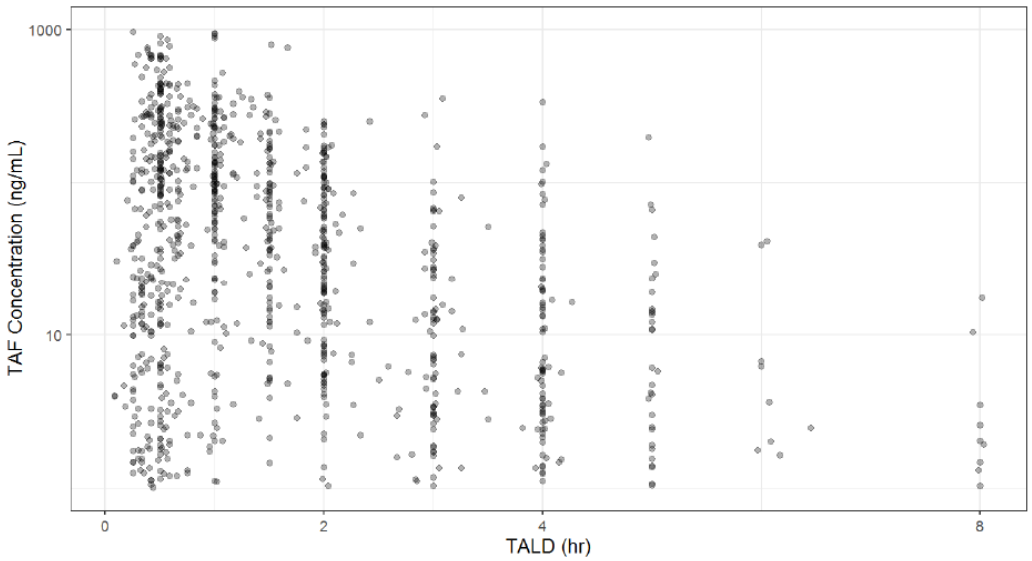
Study	Population	Phase	Treatment	Sampling (Intensive/Sparse)
GS-US-380-1474	HIV-1 infected	2/3	BIC/FTC/TAF 50/200/25 mg FDC	Intensive + Sparse
GS-US-292-0106	HIV-1 infected	2/3	EVG/COBI/FTC/TAF 150/150/200/10 mg FDC	Intensive + Sparse
GS-US-292-1515	HIV-1 infected	2/3	EVG/COBI/FTC/TAF 150/150/200/10 mg FDC	Sparse
GS-US-311-1269	HIV-1 infected	2/3	FTC/TAF 200/25 mg or 200/10 mg FDC	Intensive + Sparse

Source: Applicant's QP-2018-1027 TAF TFV HIV Pediatric Population PK Report page 8

2.1 TAF

A total of 979 data points with at least one measurable concentration from 252 participants were used for the PPK analysis. ***Figure 6*** shows the TAF plasma concentrations versus time profile for observations from all participants.

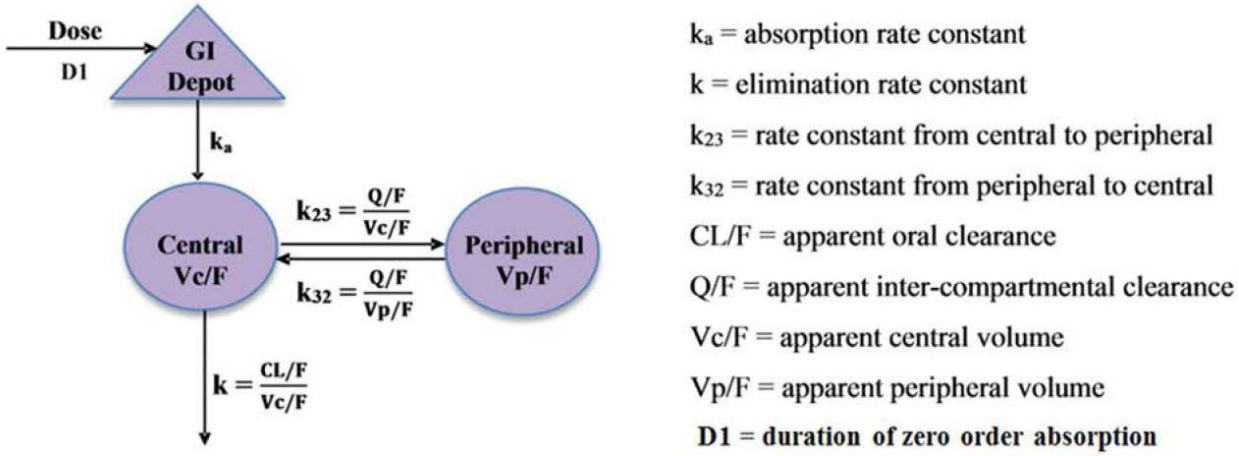
Figure 6 TAF concentration versus time after dose profiles



Source: Applicant's TAF TFV HIV Pediatric Population PK Report page 24 Figure 1

TAF plasma concentrations were best described by a 2-compartment model with the M3 method, zero-order input with first-order absorption, linear elimination, IIV on CL/F, Vc/F, ka and D1, covariance on CL/F & Vc/F, and ka & D1 a proportional error model (for log-transformed data) (**Figure 7**).

Figure 7 TAF PPK model diagram



Source: Applicant's TAF TFV HIV Pediatric Population PK Report page 25 Figure 2

Parameter estimates for the final PPK model are provided in **Table 7**.

Table 7 Summary of final TAF model PK parameters

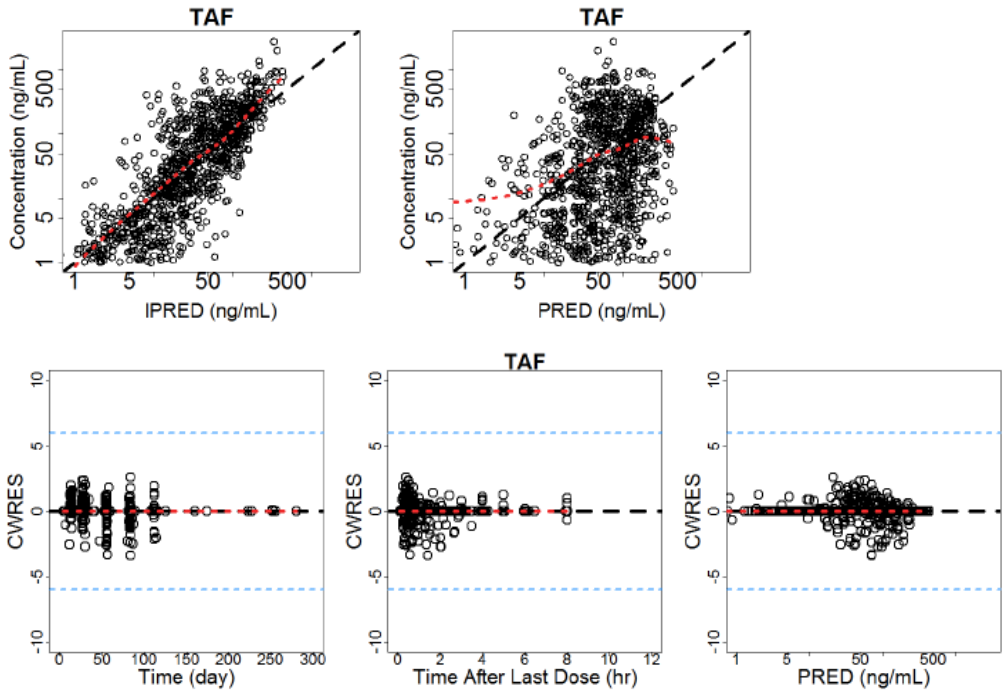
Parameter	Parameter Description		Population Estimate	Change from Typical (%)	Interindividual Variability (%)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)		90.0	--	51.5
$exp\left(\theta_1 + \theta_{11} \times \log\frac{WT}{41}\right)$	Influence of WT on CL/F (L/h)	fifth percentile of WT (26 kg)	64.0	-28.9	
		95th percentile of WT (69 kg)	133	47.8	
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		54.6	--	91.4
$exp\left(\theta_2 + \theta_{12} \times \log\frac{WT}{41}\right)$	Influence of WT on V_c/F (L)	fifth percentile of WT (26 kg)	34.6	-36.6	
		95th percentile of WT (69 kg)	91.9	68.3	
$exp(\theta_3)$*	Apparent inter-compartmental clearance, Q/F (L/h)		5.53	--	--
$exp(\theta_4)$*	Apparent oral peripheral volume V_p/F, (L)		18.4	--	--
$exp(\theta_5)$	Absorption rate constant, k_a (h^{-1})		1.65	--	68.1
$exp(\theta_6)$	Duration of zero-order input, D_1 (h)		1.05	--	74.7
	Influence of boosting agent on fraction absorbed (F1)	Unboosted TAF (BFTAF)	1	--	--
$exp(\theta_8)$		LPV/r boosted TAF	1.25	25	
$exp(\theta_9)$		COBI boosted TAF	3.32	232	
$exp(\theta_{10})$		Unboosted TAF (DVY)	2.95	195	
θ_{11}**	Influence of WT on CL/F (L/h)		0.75	--	--
θ_{12}**	Influence of WT on V_c/F (L)		1	--	--
$\sqrt{\theta_7}$	Residual error (%)		100		

* Parameters were estimated during model development and then fixed to improve model stability
** Parameters were fixed using standard allometry

Source: Applicant's TAF TFV HIV Pediatric Population PK Report page 28 Table 4

The general goodness-of-fit plots of the final TAF PPK model are shown in **Figure 8**

Figure 8 Goodness-of-fit plots for the final TAF PPK model



Source: Applicant's TAF TFV HIV Pediatric Population PK Report page 30 Figure 3 & 4.

Shrinkage of the final model parameters is presented in **Table 8**

Table 8 Shrinkage estimates of inter-individual and intra-individual variability in the final TAF PPK model

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	3.53
$\omega_{Vc/F}$	IIV of V_c/F	21.6
ω_{ka}	IIV of k_a /F	27.7
ω_{D1}	IIV of D_1	20.4

Source: Applicant's TAF TFV HIV Pediatric Population PK Report page 34 Table 7.

The final TAF PPK model was used to predict systemic exposures of TAF in adolescents weighing ≥ 35 kg and children weighing ≥ 25 kg receiving adult-strength BIC/FTC/TAF. The exposures were compared with those from BIC/FTC/TAF-treated HIV-1 infected adult subjects in the Phase 3 Studies GS-US-380-1489 and GS-US-380-1490 (N=486). The predefined PK equivalence boundary of GLSM ratios and associated 90% CIs for exposures was 70% to 143%.

Table 9 Statistical comparisons of TAF plasma PK parameter estimates between adolescents and adults (Cohort 1)

TAF PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	GS-US-380-1474 (Test) (N = 49)	GS-US-380-1489, GS-US-380-1490 (Reference) (N = 486)	
AUC_{tau} (h•ng/mL)	195.9 (50.3)	142.0 (17.3)	128.25 (116.43,141.28)
C_{max} (ng/mL)	132.9 (70.2)	121.3 (15.4)	88.56 (74.99,105.59)

%CV = percentage coefficient of variation; GLSM = geometric least-squares mean

Source: Applicant's Summary of Clinical Pharmacology page 20 Table 4

Table 10 Statistical comparisons of TAF plasma PK parameter estimates between children and adults (Cohort 2)

TAF PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	GS-US-380-1474 (Test) (N = 47)	GS-US-380-1489, GS-US-380-1490 (Reference) (N = 486)	
AUC_{tau} (h•ng/mL)	277.5 (40.3)	142.0 (17.3)	182.83 (165.20, 202.34)
C_{max} (ng/mL)	204.8 (44.6)	121.3 (15.4)	153.35 (135.64,173.39)

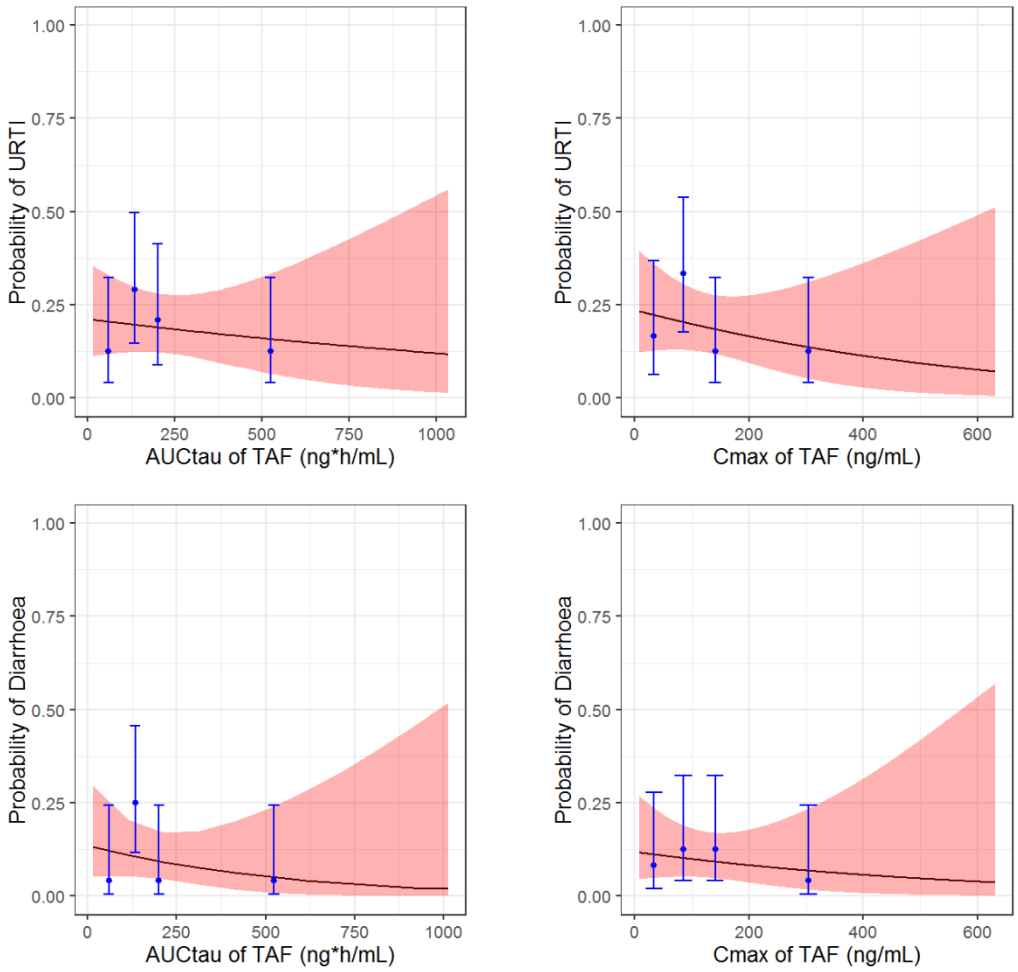
%CV = percentage coefficient of variation; GLSM = geometric least-squares mean

Source: Applicant's Summary of Clinical Pharmacology page 20 Table 5

Reviewer's comment: Applicant's final population PK model of TAF is acceptable. In the goodness-of-fit plots, a good agreement between the predicted concentrations and the observed concentrations was obtained. The shrinkage for CL/F, Vc/F and D1 was considered small. Thus, the estimates of systemic exposures based on the final PPK model were reliable.

*The %GLSM ratios show that AUC_{tau} and C_{max} in children were 83% and 53% higher than those in adults, respectively, which were beyond the predefined PK equivalent boundary (70% to 143%). Thus, Reviewer conducted independent E-R analysis for URTI and diarrhea based on the TAF exposures from Study GS-US-380-1474. As shown in **Figure 9**, flat E-R relationships were observed for both URTI and diarrhea. In addition, given the minor safety signals observed among study drug-related AEs as discussed for BIC, the higher TAF exposure in children was not considered clinically concerning.*

Figure 9 TAF exposure-response relationships for treatment-emergent adverse events

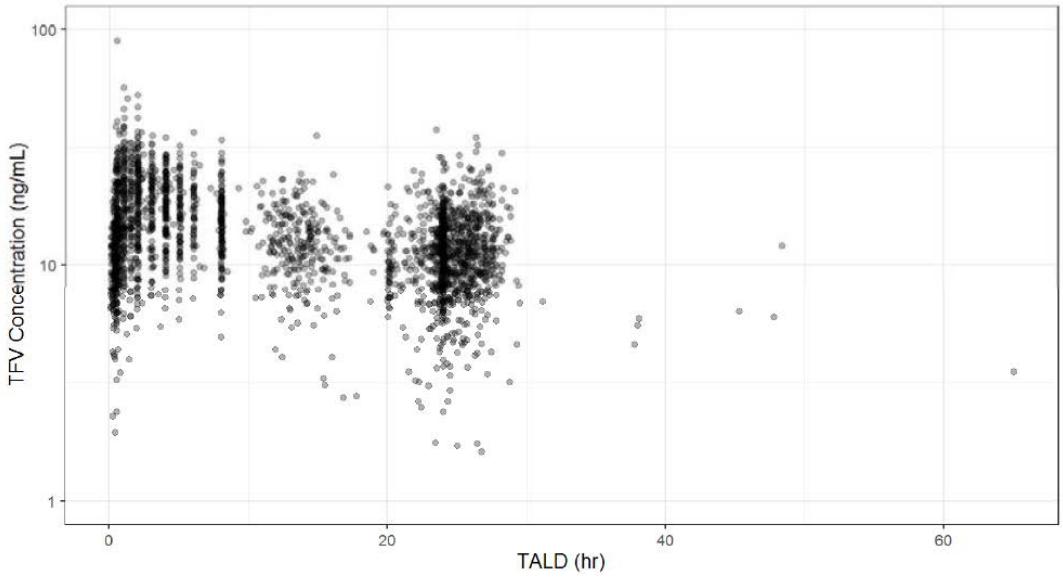


Source: Reviewer independent analysis

2.2 TFV

The TFV final PPK analysis dataset included a total of 2500 data points with at least one measurable concentration from 274 participants. **Figure 10** shows the TFV plasma concentrations versus time profile for observations from all participants.

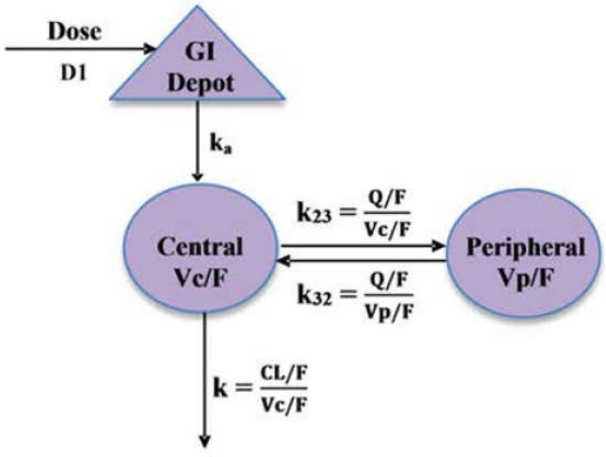
Figure 10 TFV concentration versus time after dose profiles



Source: Applicant's TAF TVF HIV Pediatric Population PK Report Page 37 Figure 10

TFV plasma concentrations were best described by a 2-compartment model, zero-order input with first-order absorption, linear elimination, IIV on CL/F, Vc/F and D1, covariance on CL/F & Vc/F, and a proportional error model (for log-transformed data) **(Figure 11)**.

Figure 11 TFV PPK model diagram



k_a = absorption rate constant

k = elimination rate constant

k_{23} = rate constant from central to peripheral

k_{32} = rate constant from peripheral to central

CL/F = apparent oral clearance

Q/F = apparent inter-compartmental clearance

Vc/F = apparent central volume

Vp/F = apparent peripheral volume

D1 = duration of zero order absorption

Source: Applicant's TAF TVF HIV Pediatric Population PK Report Page 38 Figure 11

Parameter estimates for the final TFV PPK model are provided in **Table 11**

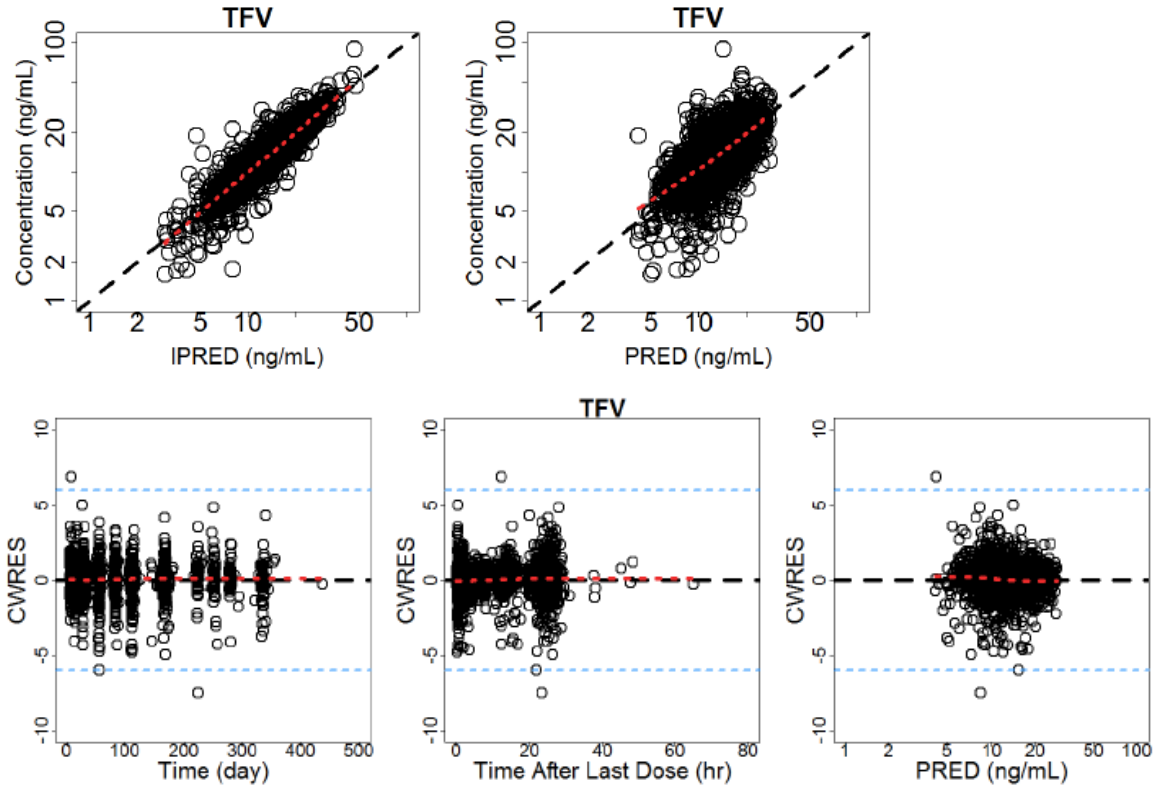
Table 11 Summary of final TFV model PK parameters

Parameter	Parameter Description		Population Estimate	Change from Typical (%)	Interindividual Variability (%)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/h)		75.2	--	20.2
$exp\left(\theta_1 + \theta_7 \times \log\frac{WT}{41}\right)$	Influence of WT on CL/F (L/h)	fifth percentile of WT (26 kg)	53.4	-28.9	
		95th percentile of WT (69 kg)	111	47.8	
$exp\left(\theta_1 + \theta_9 \times \log\frac{BCLCRSW}{154}\right)$	Influence of BCL_{CRSW} on CL/F (L/h)	fifth percentile of BCL_{CRSW} (113 mL/min)	64.1	-14.8	
		95th percentile of BCL_{CRSW} (213 mL/min)	88.9	18.2	
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		2980	--	24.9
$exp\left(\theta_2 + \theta_8 \times \log\frac{WT}{41}\right)$	Influence of WT Vc/F (L)	fifth percentile of WT (26 kg)	1890	-36.6	
		95th percentile of WT (69 kg)	5020	68.3	
$exp(\theta_3)$*	Apparent Inter-compartment clearance, Q/F (L/h)		247	--	--
$exp(\theta_4)$*	Apparent peripheral volume, V_p/F (L)		1530	--	--
$exp(\theta_5)$	Absorption rate constant, k_a (h^{-1})		3.94	--	--
$exp(\theta_6)$	Duration of zero-order input, D_1 (h)		0.761	--	90.4
$exp(\theta_6 + \theta_{13} \times BAS1 + \theta_{14} \times BAS2 + \theta_{15} \times BAS4)$	Influence of boosting agent on D_1	BAS1=0, BAS2=0, BAS4=0 (BIC + F/TAF-FDC)	0.761	--	
		BAS1=1 (Boosted, COBI + F/TAF-FDC)	2.09	175	
		BAS2=1 (Boosted, LPV/r + F/TAF -FDC)	1.43	88.5	
		BAS4=1 (Unboosted, F/TAF - FDC)	1.70	124	
$exp(\theta_{10} + \times BAS1 + \theta_{11} \times BAS2 + \theta_{12} \times BAS4)$	Influence of boosting agent on F1	BAS1=0, BAS2=0, BAS4=0 (BIC + F/TAF-FDC)	1	--	--
		BAS1=1 (Boosted, COBI + F/TAF-FDC)	2.46	146	
		BAS2=1 (Boosted, LPV/r + F/TAF -FDC)	2.95	195	
		BAS4=1 (Unboosted, F/TAF - FDC)	0.579	-42.1	

Source: Applicant's TAF TVF HIV Pediatric Population PK Report Page 41 Table 12

The goodness-of-fit plots of the final TFV PPK model are shown in **Figure 12**

Figure 12 Goodness-of-fit plots for the final TFV PPK model



Source: Applicant's TAF TVF HIV Pediatric Population PK Report Page 44 Figure 12 & 13

Shrinkage of the final model parameters is presented in **Table 12**

Table 12 Shrinkage estimates of inter-individual and intra-individual variability in the final model

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	18.6
$\omega_{Vc/F}$	IIV of V_c/F	18.6
ω_{D1}	IIV of D_1	43.3
ω_{IOVCL}	IOV of CL/F (%)	46.4
ω_{IOVVc}	IOV of V_c/F (%)	52.6
σ	EPS (residual error)	12.6

Source: Applicant's TAF TFV HIV Pediatric Population PK Report Page 49 Table 15

Reviewer's comment: The structure of population PK model could be further improved from a biological perspective. Based on the mechanism, TAF is going through selective intracellular cleavage to TFV, and then to the pharmacologically active metabolite TFV diphosphate. The applicant's PPK model described

*the absorption of TFV in HIV-1 infected pediatric participants by zero-order input with first-order absorption from dose depot directly, as shown in **Figure 11**. This structure is not biologically robust. Instead of using separate PK models to describe TAF and TFV as if the two drugs were orally administrated separately, a joint parent-metabolite PPK model that can characterize the exposures of TAF and TFV simultaneously would be more mechanistically appropriate. However, for PK description purpose, applicant's final TFV PPK model appeared to be acceptable based on the goodness-of-fit plots.*

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