CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213983Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Clinical Pharmacology Review

<table>
<tr><td>NDA/SDN</td><td>204790/744 (S-25) (tablets)
213983/1 (tablets for oral suspension)</td></tr>
<tr><td>Submission Date</td><td>12/12/2019</td></tr>
<tr><td>Submission Type</td><td>Efficacy supplement - pediatric</td></tr>
<tr><td>Drug</td><td>Tivicay® (dolutegravir [DTG])</td></tr>
<tr><td>Applicant</td><td>VIIV Healthcare Co</td></tr>
<tr><td>Indication</td><td>Treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with:
• other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 30 kg.
• rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen (ARVs) in those who are virologically suppressed on a stable ARVs for at least 6 months with no history of treatment failure or known resistance.</td></tr>
<tr><td>Formulation</td><td>Film Coated Tablets: 10, 25, and 50 mg, Dispersible Tablet: 5 mg</td></tr>
<tr><td>Dosage and Administration</td><td>May be taken orally without regard to food.
<table>
<tr><th>Adult Population</th><th>Recommended Dose</th></tr>
<tr><td>Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine[a]</td><td>50 mg once daily</td></tr>
<tr><td>Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers</td><td>50 mg twice daily</td></tr>
<tr><td>INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b]</td><td>50 mg twice daily</td></tr>
</table>
[a] Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
[b] Alternative combinations that do not include metabolic inducers should be considered where possible</td></tr>
<tr><td>OCP division</td><td>DIDP</td></tr>
<tr><td>OND division</td><td>DAV</td></tr>
<tr><td>OCP review team</td><td>Qin Sun, Ph.D, Ruojing Li, Ph.D, Justin Earp, Ph.D, Su-Young Choi, Pharm.D, Ph.D</td></tr>
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1. Executive Summary

Tivicay® (DTG) is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in combination with other ARVs for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 30 kg, or in combination with rilpivirine as a complete regimen in adults to replace the current ARVs in those who are virologically suppressed on a stable ARVs for at least 6 months with no history of treatment failure.

For adults, the recommended dosage is 50 mg once daily for INSTI-naïve or virologically suppressed adults switching to dolutegravir plus rilpivirine. The recommended dosage is 50 mg twice daily for patients with certain INSTI-associated resistance, or when DTG is co-administered with certain UGT1A or CYP3A inducers. The dosage may be taken without regard to food. For pediatric patients (INSTI-naïve patients weighing at least 30 kg), the recommended dosage is 50 mg once daily for ≥40 kg, and 35 mg once daily for 30 to <40 kg.

The applicant submitted a supplemental New Drug Application (sNDA) for Tivicay Film-coated Tablets (FCTs) (sNDA 204790) and an original NDA for Tivicay Dispersible Tablets (DTs) for Oral Suspension (NDA 213983) to support the use of Tivicay in pediatric patients aged ≥4 weeks and weighing ≥3 kg. The sNDA and original NDA fulfills post-marketing requirements (PMRs) 3091-1 ([(b) (4)] 15 kg) and 3091-2 (15 to 30 kg).

This submission contains three supportive studies (IMPAACT P1093, Odyssey PK sub-study [PENTA 20], and a relative bioavailability [rBA] Study 205893) and a population pharmacokinetic (PopPK) analysis report based on combined data from P1093 and the Odyssey PK sub-study. The pediatric dose of DTG was determined by an exposure-matching approach, with supportive antiviral activity from P1093 and safety data from P1093 and the Odyssey PK sub-study. The use of four 10 mg FCTs for the 14 to <20 kg weight band was supported by rBA Study 205893 and modeling and simulation.

In this submission, the applicant proposed the following dosing regimens for pediatrics aged ≥4 weeks and weighing ≥3 kg (**Table 1**). Upon review of the data, the review team concluded the following:

- The DTG C_{24h} and $AUC_{0\text{-}24h}$ values in P1093 and the Odyssey PK sub-study following the applicant proposed dose regimen were comparable to those observed in adults receiving 50 mg once daily or twice daily, based on both intensive PK and PopPK analyses. The higher C_{max} (<2-fold), compared to levels in adults, is not considered to be clinically relevant, based on overall safety profiles of DTG in pediatrics as well as in adults, the lack of no new or worse safety signals observed in pediatrics, and no apparent exposure-response relationship for adverse events in pediatric patients. Although the exposure following the applicant's proposed dose regimen meets PK targets, the review team recommends simplifying the dosing stratification for the 6 to <10 kg weight band [(b) (4)].

- The safety data in P1093 and the Odyssey PK sub-study were comparable to those observed in adults.

- The overall effectiveness of DTG observed in in P1093 was comparable to that of treatment-experienced adult patients. About 62% and 69% of pediatric subjects had HIV RNA <50 copies/mL at Week 24 and Week 48, respectively (the efficacy evaluation in the Odyssey study is still ongoing and not submitted in the current efficacy supplement). While the lower weight bands had lower success rates at Week 24, it is difficult to draw conclusions about the relationship between younger age/weight band and outcome due to small sample sizes. Also, younger pediatric patients may take longer to reach viral suppression (similar results observed in other HIV pediatric studies), which may be why the lower weight bands did slightly better at Week 48 (refer to the clinical review).

Table 1. Recommended dosage by the applicant for pediatrics aged at least 4 weeks and weighing at least 3 kg

Body Weight	TIVICAY Tablets for Oral Suspension		TIVICAY Tablets	
	Daily Dose[a]	Number of 5-mg Tablets[b]	Daily Dose[a]	Number of Tablets[b]
3 kg to less than 6 kg	5 mg once daily	1	NA	NA
6 kg to less than 10 kg (b) (4)	(b) (4) 15 mg once daily	(b) (4) 3	NA	NA
10 kg to less than 14 kg	20 mg once daily	4	NA	NA
14 kg to less than 20 kg	25 mg once daily	5	40 mg once daily	4 x 10-mg
20 kg and greater	30 mg once daily	6	50 mg once daily#	1 x 50-mg

* (b) (4) *The recommended dose regimen for 6 to 10 kg is 15 mg once daily (see details in Section 2).*
 # Currently, 50 mg FTC is approved for pediatric patients weighing 40 kg and above and 35 mg FTC is approved for pediatric patients weighing 30 to <40 kg.

2. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the submitted studies and the applicant's proposed labeling. The proposed pediatric dosing regimen for pediatric patients aged ≥4 weeks and weighing ≥3 kg is acceptable. In addition, the review team recommends

simplifying the dosing stratification for the 6 to <10 kg weight band to be based on BW (b) (4) .

Based on the following rationale, the review team recommends 15 mg DT once daily for patients weighing 6 to <10 kg:

- For the 6 to <10 kg weight band, the applicant proposed (b) (4) once daily. While the proposed dosing regimen is supported by PK data from the two pediatric trials, our main concern is potential dosing error by prescribers and caregivers especially given that all other ARVs in this weight band are administered solely based on weight (b) (4). Therefore, the review team evaluated whether (b) (4) (b) (4) 15 mg DT can be approved (b) (4).
- (b) (4)
- For a 15 mg DT dose, no PK data are available in patients aged <6 months. This dose would likely provide sufficient C_{24} but produce higher C_{max} for the subjects in this weight band as compared to C_{max} at 10 mg DT. However, the simulated C_{max} values at 15 mg DT are similar with the simulated C_{max} under 25 mg DT dose for 14 to <20 kg or 50 mg FTC dose for 20 to <25 kg ***(Table 14)***. Thus, higher C_{max} at 15 mg DT in this weight band not considered clinically relevant.

3. Labeling Updates

The clinical pharmacology-related labeling recommendations are listed below. The labeling language is still under discussion at the time that this review was finalized.

1. Across labeling sections, add DTG DT or FTC application for pediatrics aged at least 4 weeks and weighing at least 3 kg.
2. In Section 12.3, add rBA results for DT compared to FCT and update the pediatric intensive PK data based on new results from Studies P1093 and Odyssey.

4. Key Clinical Pharmacology Findings

Study P1093 is a Phase I/II, multi-center, open-label PK, safety and tolerability and antiviral activity of DTG, in combination regimens in HIV-1 infected infants, children and adolescents. Odyssey is an open-label, multi-centre, randomised, non-inferiority, Phase II/III, 96-week, 2-arm clinical trial to compare the efficacy and toxicity of DTG plus 2 nucleoside reverse transcriptase

inhibitors (NRTIs) vs. standard of care (SOC) in HIV-infected children aged <18 years who are starting first-line antiretroviral therapy (ART) (Odyssey A) or switching to second-line ART (Odyssey B). The available PK and safety data from relevant sub-studies nested within Odyssey were submitted to support the proposed dose regimen of DTs or FCTs in pediatric subjects, while the efficacy from Odyssey is still ongoing. Study 205893 is a 2-part, Phase I, single dose, crossover relative bioavailability (rBA) study of both Tivicay 10 mg FCTs and 5 mg DTs compared to conventional Tivicay FCTs in healthy adult subjects.

The applicant's target geometric mean [GM] [range] values were 995 [697 to 2260] ng/mL for C_{24h} (primary PK endpoint), and 46 [37 to 134] µg*h/mL for $AUC_{0\text{-}24h}$ (secondary PK endpoint), based on exposure in adults after 50 mg once daily or twice daily; no PK target was set for C_{max}. The applicant's proposed dose regimen is BW based, except for 6 to 10 kg (based on both BW and age [6 months]) (see **Table 1**).

The intensive PK results based on combined data from P1093 and Odyssey PK sub-study for the applicant's proposed dosing regimen are summarized in **Table 2**. Both C_{24h} and $AUC_{0\text{-}24h}$ values were within the targeted PK ranges. For the 6 to <10 kg weight band, (b) (4) compared to pediatrics aged ≥6 months who received 15 mg DT. This may be due to not fully matured UGT1A1 (major metabolism enzyme for DTG) activity in pediatrics <6 months. The C_{max} was up to 70% higher compared to values observed in adults.

The PopPK predicted C_{24h} values for the applicant's proposed dosing regimen are summarized in **Figure 1**. The predicted C_{24h} values were within the targeted PK range, and similar across different BW ranges. In addition, PopPK predicted C_{24h}, $AUC_{0\text{-}24h}$, and C_{max} GM (95% prediction interval [PI]) are summarized in **Table 3**. Similar as intensive PK results, PopPK predicted C_{24h} and $AUC_{0\text{-}24h}$ were within targeted PK ranges, while C_{max} was up to 80% higher than values in adults across all body weight bands. However, the higher C_{max} (<2-fold) is not considered clinically relevant based on overall safety profiles of DTG in pediatrics as well as in adults, the lack of no new or worse safety signals observed in pediatrics, and no apparent exposure-response relationship for adverse events in pediatric patients (refer to the clinical review). (b) (4) , an information request (IR) was sent to the applicant to request new PopPK analysis for the 6 to <10 kg weight band (b) (4) (b) (4) 15 mg DT. (b) (4) . For 15 mg DT, the predicted C_{24h} met PK target (b) (4) (**Table 3**, highlighted in blue box). Thus, 15 mg DT can help minimize the underdose and prevent potential drug resistance in pediatrics. Although the predicted C_{max} for 15 mg DT will be ~ 70% higher than those in adults, it is not considered clinically relevant as discussed above.

The rBA study (205893) suggests that the exposure is similar for DTs administered as a dispersion, compared to DTs administered directly by mouth. Thus, DTs may be swallowed

whole or dispersed in drinking water. Furthermore, Study 205893 suggests that five 10 mg FCTs are bioequivalent to one 50 mg FCT and the rBA between 5 mg DTs and 10 or 50 mg FCTs is ~ 160%. The rBA data between 10 mg FCTs and 5 mg DTs supports the use of four 10 mg FCTs in pediatrics weighing 14 to <20 kg, since the exposure is predicted to be similar as that from the proposed single 25 mg DT (**Table 3**).

Table 2. Intensive PK parameters: Combined data from P1093 and Odyssey PK sub-study

Weight Band (kg)	DTG Dosage Form (Strength [mg])[a]	Dose (mg)	N (Total N=119)	PK Parameter GM (%CVb)		
				Cmax (µg/mL)	AUC0-24h (µg*h/mL)	C24h (ng/mL)
3 to <6	DT (5)	5	8	3.80 (34)	49.37 (49)	962 (98)
(b) (4)						
10 to <14	DT (5)	20	13	5.99 (33)	68.75 (48)	977 (100)
14 to <20	DT (5)	25	19	5.97 (42)	58.97 (44)	725 (75)
≥20	DT (5)	30[b]	9	7.16 (26)	71.53 (26)	759 (73)
	FCT (10, 25, 50)	50	49	4.92 (40)	54.98 (43)	778 (62)
					Target AUC0-24h[c] 46 (37-134)	**Target C24h[c] 995 (697-2260)**

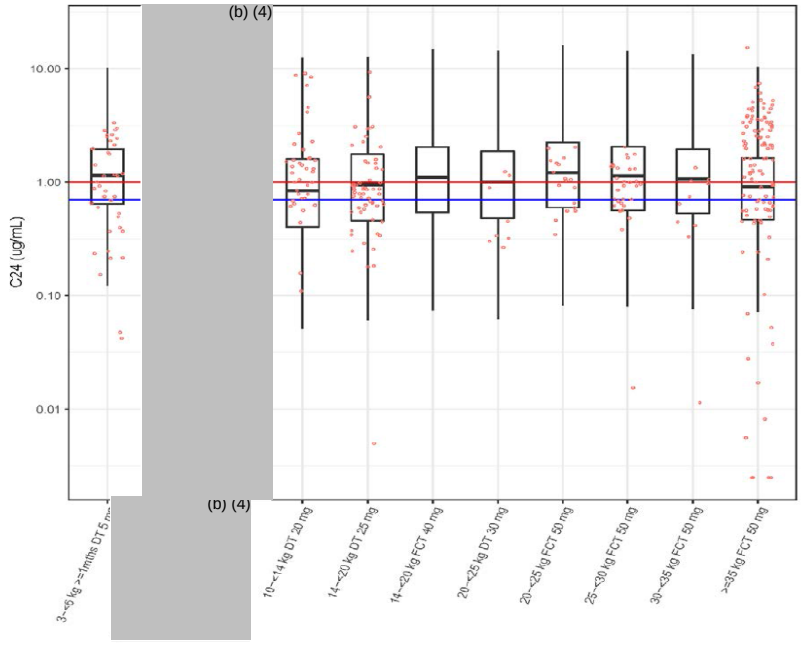
[a.] *The bioavailability of DTG DT is ~1.6-fold DTG FCT.*
[b] *30mg DT once daily was evaluated in participants 20 to <25 kg.*
Source: 2019N422597_combined PK report, P8

Table 3. PopPK predicted C_{max}, C_{24h}, and AUC_{0-24h} (GM [95% PI]) in pediatrics aged ≥4 weeks and weighing ≥3 kg

Weight Band	Dose (mg)	Formulation	C_{max} (µg/mL)	C_{24} (µg/mL)	AUC_{0-24} (µg·hr/mL)
3-<6 kg ≥1mths	5	DT	4.02 (3.81-4.24)	1.07 (0.941-1.21)	49.4 (46.1-53.2)
(b) (4)					
10-<14 kg	20	DT	6.61 (6.26-6.90)	0.719 (0.623-0.847)	63.1 (59.7-67.6)
14-<20 kg	25	DT	7.17 (6.89-7.49)	0.824 (0.713-0.950)	69.5 (65.1-73.5)
14-<20 kg	40	FCT	6.96 (6.64-7.28)	0.972 (0.822-1.14)	72.6 (68.2-77.5)
20-<25 kg	30	DT	7.37 (7.06-7.77)	0.881 (0.736-1.01)	72.0 (67.0-77.1)
20-<25 kg	50	FCT	7.43 (7.11-7.80)	1.08 (0.919-1.24)	78.6 (73.7-83.6)
25-<30 kg	50	FCT	6.74 (6.44-7.06)	0.997 (0.885-1.14)	71.4 (67.6-76.5)
30-<35 kg	50	FCT	6.20 (5.92-6.51)	0.944 (0.810-1.06)	66.6 (62.4-70.3)
≥35 kg	50	FCT	4.93 (4.70-5.19)	0.814 (0.710-0.931)	54.0 (50.6-58.3)
(b) (4)					
6-<10 kg	15	DT	7.19 (6.88-7.54)	1.15 (1.01-1.33)	76.0 (71.1-81.0)

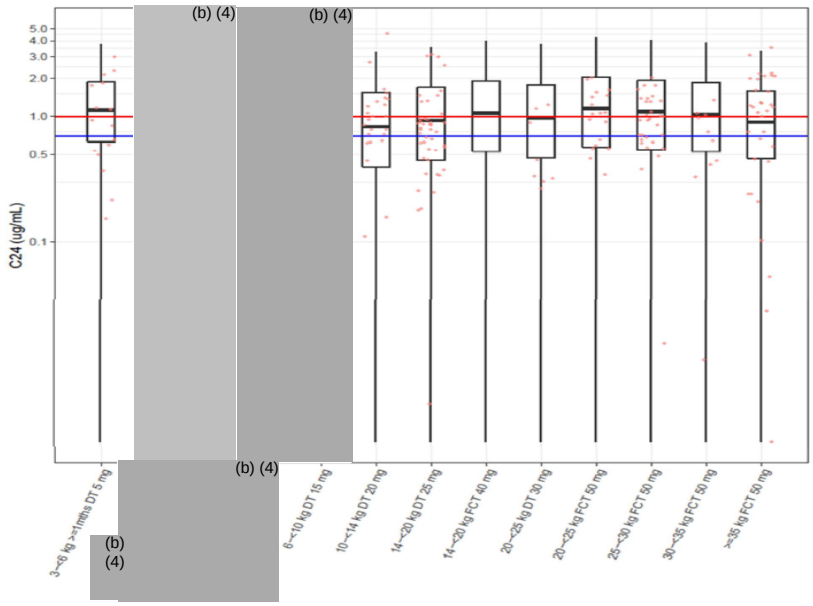
Source: 2019n424147-PopPK report, P113;applicant's response to IR, SDN:765, date:3/10/2020.
C_{max} observed in adults: 3.67 and 4.15 µg/mL for 50 mg once daily and twice daily, respectively.

Figure 1: PopPK predicted C_{24h} following applicant's proposed dose regimen



*The black center line represents median and the top and base of the box represent first and third quartiles [inter-quartile range (IQR)]. Whiskers represent 1.5*IQR. Red circles represent observed concentrations. Red solid line represents target geometric mean C_{24h} of 0.995 µg/mL. Blue solid line represents lower bound targeted GM C_{24h} of 0.697 µg/mL.Source: 2019n424147-PopPK report, P24*

Figure 2. PopPK predicted C_{24h} for 6 to <10 kg (b) (4)



*The black center line represents median and the top and base of the box represent first and third quartiles [inter-quartile range (IQR)]. Whiskers represent 1.5*IQR. Red circles represent observed concentrations. Red solid line represents target geometric mean C_{24h} of 0.995 µg/mL. Blue solid line represents lower bound targeted GM $_{C24h}$ of 0.697 µg/mL. Source: Applicant's response to IR, SDN:765, date:3/10/2020.*

5. Individual Study Review

5.1 Study P1093 (**EDR Link**)**:** Phase I/II, Multi-Center, Open-Label PK, Safety, Tolerability and Antiviral Activity of DTG, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents: Cohorts I-V, Interim Report

Clinical Trial Site and Duration of the Trial

This is a multicenter study conducted at 34 Clinical Research Sites in 9 countries. The study duration is April 20, 2011 to April 30, 2019 (PK and safety cut-off date; Week 24 efficacy cut-off date: February 14, 2019).

Objectives

Primary objective:
- To evaluate the safety and tolerability, the steady-state PK, and the appropriate dose of DTG in combination with an optimized background regimen (OBR) in HIV-1 infected pediatrics aged ≥4 weeks and weighing ≥3 kg

Secondary objectives:
- To assess the antiviral activity, immunologic changes, drug resistance, PopPK and covariates, and E-R relationship for antiviral activity and safety

Trial Design

P1093 is a Phase I/II multi-center, open-label, non-comparative study of PK parameters, safety, tolerability, and efficacy of DTG in ARV-experienced or naïve pediatric populations. Participants initially began sequential enrollment in age-specific cohorts to assess different formulations as shown below:

Cohort I: Adolescents ≥12 to <18 years of age (FCT);
Cohort IIA: Children ≥6 to <12 years of age (FCT);
Cohort IIB: Children ≥6 to <12 years of age (granules for suspension);
Cohorts III: Children ≥2 to <6 years of age (granules for suspension);
Cohort III-DT: Children ≥2 to <6 years of age (DT);
Cohort IV: Children ≥6 months to <2 years (granules for suspension);
Cohort IV-DT: Children ≥6 months to <2 years of age (DT);
Cohort V-DT: Infants ≥4 weeks to <6 months (DT).

Reviewer's comments:
(b) (4)
. The data from Cohort I and IIa have been previously reviewed by the Agency. Thus, the review of P1093 will focus on Cohort III-DT, Cohort IV-DT, and Cohort V-DT as underlined. Enrollment of sufficient participants to analyze by weight band (3 to <6 kg, 6 to <10 kg,10 to <14 kg, and14 to <20 kg) to was also incorporated into the protocol (v5.0).

Patients were enrolled in 2 sequential stages: Stage I and II. In Stage I, once 10 participants with evaluable data were enrolled to Cohorts III-DT, IV-DT, and V-DT, additional enrollment was only permitted if a participant was contributing to the minimum weight-band group enrollment of 8 evaluable participants. Stage II enrollment opened once a dose had been accepted based on analysis of data from Stage I enrollments, and each cohort progressed independently until the target of 22 per cohort was met. For DT, instructions were to disperse using 2 to 5 mL of water per tablet in dosing cups and dispense.

The applicant proposed PK geometric mean [GM] [range] targets are 995 [697 to 2260] ng/mL for C_{24h} (primary PK endpoint), and 46 [37 to 134] µg*h/mL for AUC_{0-24h} (secondary PK endpoint), respectively, based on exposure in adults after 50 mg once daily or twice daily; no PK target was set for C_{max}. A dose of DTG was considered acceptable if the dose was tolerated and if C_{24h} and AUC_{0-24h} met the PK targets. The dose of the DT formulation was selected at 0.8 to 1.25 mg/kg based on the approved adult and adolescent doses and the rBA of DTs compared to FTCs.

Inclusion/Exclusion/Concomitant Medications:

Subjects with history or presence of any illness or conditions and the use of concomitant medications that might confound the results of the study or poses an additional risk to the subject were excluded.

Sample Collection and Bioanalysis

Sample Collection
Intensive PK samples were collected between Day 5 and Day 10 at pre-dose and up to 24 h post-dose under fasting conditions in Stage I, and the sparse PK samples were collected at Weeks 4, 12, and 24 without regard to food in both Stage I and Stage II.

Bioanalytical site and method
The bioanalytical site is (b) (4) . The bioanalytical methods were fully validated, and the precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration of 60 months for DTG at -80°C.

Request for bioanalytical inspection: The Office of Study Integrity and Surveillance (OSIS) recommended accepting the study data after an on-site inspection (Refer to OSIS's review by Dr. Yiyue Zhang dated 4/3/2020 for details under NDA 204790).

Pharmacokinetic Results

No major protocol deviations were reported.

The intensive PK parameters at the final recommended doses by BW band for the DT formulation are summarized in **Table 4**. Both C_{24h} and AUC_{0-24h} met PK targets for most BW ranges, except for 14 to 20 kg. For 14 to 20 kg, following the recommended DT dose at 25 mg,

$AUC_{0\text{-}24h}$ was lower than the targeted GM, but still higher than the lower bound; C_{24h} was lower than the lower bound. This may be caused by the large exposure variability in pediatrics and the limited subject number; Both C_{24h} and $AUC_{0\text{-}24h}$ met PK targets based on combined data from P1093 and Odyssey PK sub-study for 14 to <20 kg (see Section 4, **Table 2**).

(b) (4)

Table 4. Intensive PK parameters by BW band for theDT formulation in P1093

Weight Band (kg)	DTG Dosage Form[a]	Once Daily Dose (mg)	N	PK Parameter GM (%CVb)		
				Cmax (μg/mL)	AUC0-24h (μg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	8	3.80 (34)	49.37 (49)	962 (98)
(b) (4)						
10 to <14	DT	20	8	5.67 (43)	68.47 (64)	1066 (135)
14 to <20	DT	25	6	4.05 (51)	41.24 (50)	512 (80)
					Target AUC0-24h[b,c] 46 (37-134)	**Target C24h[b,c] 995 (697-2260)**

Source: Protocol, P113-114

(b) (4)

Conclusions

The intensive PK results in P1093 demonstrated that DTG (b) (4) met the PK targets for both C_{24h} and $AUC_{0\text{-}24h}$.

5.2 Study Odyssey PK sub-study (EDR Link**):** A Randomized Trial of DTG-based ARV vs. Standard of Care in Children with HIV-1 Infection Starting First-line or Switching to Second-line ARV: Interim Results from PK Sub-study

Clinical Trial Site and Duration of the Trial

Odyssey is a multicenter study conducted in 8 countries, and the PK sub-study enrolled a sub-population at 5 clinical sites in 3 countries including Uganda, South Africa, and Zimbabwe. The study duration is July 3, 2018 to February 28, 2019 (PK and safety cut-off date)

Objectives

Primary objective:

- To evaluate the efficacy and safety of once daily DTG-based ARVs compared with standard of care in pediatrics aged ≥4 weeks and weighing 3 to 40 kg, who start first- or second-line ARV in resource-limited and well-resourced settings
- To assess steady-state PK and safety of DTs and FCTs at the proposed pediatric dosing in PK sub-study

Trial Design

Odyssey is an ongoing, open-label, multicenter, randomized (1:1), non-inferiority, Phase II/III, 96-week, 2-arm clinical trial to compare the efficacy and toxicity of DTG plus 2 NRTIs vs. standard of care in HIV-infected children aged ≤18 years who are starting first-line ARV (Odyssey stratum A) or switching to second-line ARV (Odyssey stratum B). Within each stratum, participants were randomized 1:1 to either DTG-based ARV or standard of care. PK sub-study was embedded in the ongoing Odyssey study, and BW ranges (b) (4)

3 to <6 kg, 5 mg DT (PK not available at the time of cut-off);
6 to <10 kg (≥6 months), 15 mg DT (no pediatrics <6 months);
10 to <14 kg, 20 mg DT;
14 to <20 kg, 25 mg DT;
20 to <40 kg, 30 mg DT or 50 mg FCT.

For DTs, all tablets were dispersed in water (10 and 15 mL for <14 and ≥14 kg, respectively) in a measuring cup and swallowed, and then rinsed with 10 mL of water. For FCTs, the tablets were taken with 100 mL of water.

Reviewer Comments
Initially, 25 and 35 mg FCTs were evaluated for patients weighing 25 to <40 kg. However, due to lower exposures observed, doses were changed later as described above.

Inclusion/Exclusion/Concomitant Medications:

Subjects with history or presence of any illness or conditions and the use of concomitant medications that might confound the results of the study or poses an additional risk to the subject were excluded.

Sample Collection and Bioanalysis

Sample Collection
Intensive PK samples were collected following at least 7 days of DTG dosing at pre-dose and up to 24 h post-dose. Sparse samples were also collected during the trial for PopPK analysis.

Bioanalytical site and method
The bioanalytical site is (b) (4) The bioanalytical methods were fully validated, and the precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration of 31 months for DTG at -40°C.

Request for bioanalytical inspection: The Office of Study Integrity and Surveillance (OSIS) recommended accepting the study data after reviewing the Odyssey method validation and bioanalytical reports plus the information request responses (Refer to OSIS's review by Dr. Stanley Au dated 4/22/2020 for details under NDA 204790; OSIS was unable to conduct the onsite inspection due to the COVID-19 pandemic).

In addition, OSIS recommends that the review team evaluate whether correcting the values for Subject (b) (6) at 0 h from 0.0097 µg/mL to <LLOQ would affect PK analysis. The review team confirms that the change had no effect on PK analysis.

Results

Pharmacokinetic Analysis
No major protocol deviations were reported.

The intensive PK parameters (b) (4) by BW band for DT and FCT formulation are summarized in **Table 6**. Both C_{24h} and AUC_{0-24h} met PK targets for most BW ranges, except for 6 to 10 kg (≥6 months). For 6 to 10 kg (≥6 months), following the recommended DT dose at 15 mg, C_{24h} was lower than the lower bound. This may be caused by the large exposure variability in pediatrics and the limited subject number; C_{24h} met PK target based on combined data from P1093 and Odyssey PK sub-study for 6 to 10 kg (≥6 months) at 15 mg (b) (4) (see Section 4, **Table 2**).

Table 6. Intensive PK parameters by BW band for DT and FCT formulations in Odyssey PK sub-study

Weight Band (kg)	DTG Dosage Form[a]	Once Daily Dose (mg)	N	PK Parameter GM (%CVb)		
				Cmax (μg/mL)	AUC0-24h (μg*h/mL)	C24h (ng/mL)
6 to <10 & ≥6 months	DT	15	5	5.25 (77)	44.85 (130)	387 (396)
10 to <14	DT	20	5	6.54 (7)	69.21 (14)	849 (51)
14 to <20	DT	25	13	7.14 (21)	69.56 (30)	852 (67)
20 to <25	DT	30	9	7.16 (26)	71.53 (26)	759 (73)
	FCT	50	7	6.07 (29)	62.82 (30)	770 (51)
25 to <30	FCT	50	15	5.36 (26)	57.16 (30)	706 (46)
30 to <40	FCT	50	13	5.10 (23)	54.30 (28)	692 (47)
					Target AUC0-24h[b,c] 46 (37-134)	**Target C24h[b,c] 995 (697-2260)**

Source: Protocol, P74

Conclusions

The intensive PK results in Odyssey the PK sub-study demonstrated that DTG (b) (4) for both DTs and FCTs met the PK targets for both C_{24h} and $AUC_{0\text{-}24h}$.

5.3 Study 205893 (rBA) (EDR Link**):** A 2-Part, Phase I, Single Dose, Crossover rBA Study of Both DTG 10 mg FCTs and 5 mg DTs Compared to Conventional DTG FCTs in Healthy Adult Subjects

Clinical Trial Site and Duration of the Trial

The clinical site is PPD Phase I Clinic, Austin, TX. The study duration is May 3, 2017 to June 23, 2017.

Objectives

Primary objectives:
Part 1: to evaluate rBA of 10 mg FCTs (5 tablets) administered direct to mouth as compared to a 50 mg FCTs (reference) administered direct to mouth
Part 2: to evaluate rBA of 5 mg DTs (5 tablets) administered as "disperse and immediately take" and of 5 mg DTs (5 tablets) administered direct to mouth as compared to a 25 mg FCTs (reference) administered direct to mouth

Secondary objectives:
Part 1: to evaluate the single dose PK and safety/tolerability of 10 mg FCTs (5 tablets) administered direct to mouth as compared to a 50 mg FCTs (reference) administered direct to mouth
Part 2: to evaluate the single dose PK and safety/tolerability of 5 mg DTs (5 tablets) administered as "disperse and immediately take" and of 5 mg DTs (5 tablets) administered direct to mouth as compared to a 25 mg FCTs (reference) administered direct to mouth

Trial Design

The study was an open label, balanced, randomized single-dose, three-treatment, six-sequence, three-period, crossover relative bioavailability study in healthy adults under fasting conditions.

This study was conducted as a 2-part, open-label, randomized, crossover design with 1 group of subjects in Part 1 of the study randomized to receive each of 2 study treatments (A and B) over 2 dosing periods, and another group of subjects in Part 2 of the study randomized to receive each of 3 study treatments (C, D, and E) over 3 dosing periods. There was a washout of at least 7 days between doses of study medication. The drugs were administered under fasting conditions.

Part 1:
Treatment A = 10 mg FCTs (5 tablets, test) administered direct to mouth
Treatment B = 50 mg FCTs (reference) administered direct to mouth

Part 2:
Treatment C = 5 mg DTs (5 tablets, test 1) administered as a dispersion and immediately taken
Treatment D = 5 mg DTs (5 tablets, test 2) administered as direct to mouth

Treatment E = 25 mg FCTs administered as direct to mouth (reference)

Inclusion/Exclusion/Concomitant Medications:

Subjects with history or presence of any illness or conditions and the use of concomitant medications that might confound the results of the study or poses an additional risk to the subject were excluded.

Dose Selection:
For FCTs, adult recommended dose at 50 mg was used. For DTs, 25 mg was used considering the pill burden (Two 25 mg FCTs are bioequivalent to a 50 mg FCT).

Sample Collection and Bioanalysis
Sample Collection
Plasma samples for PK analyses were collected at pre-dose and up to 72 hours post-post in each period.

Reviewer's comments:
The overall study design including washout periods and PK sample collection is reasonable based on the PK characteristics of DTG.

Bioanalytical site and method
The bioanalytical site is (b) (4). The bioanalytical methods were fully validated, and the precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration of 558 days for DTG at -20°C.

Request for bioanalytical inspection: The Office of Study Integrity and Surveillance (OSIS) recommended accepting the study data and an inspection is not warranted since the analytical site has been inspected recently with no issue identified (Refer to OSIS's review by Dr. Ting Wang dated 2/11/2020 for details under NDA 213983).

Results

Pharmacokinetic Analysis
No major protocol deviations were reported. A total of 38 subjects were enrolled in the study: 14 subjects in Part 1 and 24 subjects in Part 2, and all subjects completed the study.

The PK parameters and statistical analyses are summarized in **Table 7** and **Table 8**. The five 10 mg FCTs were bioequivalent to a 50 mg FCT. The five 5 mg DTs were not bioequivalent to a 25 mg FCT, and the rBA of DT was ~160% of FCT. In addition, there was no exposure difference for DTs administered as a dispersion or as direct to mouth.

Table 7. DTG PK parameters by study part and treatment

	Part 1		Part 2		
Parameter Summary Statistics	**Treatment A (N = 14)**	**Treatment B (N = 14)**	**Treatment C (N = 24)**	**Treatment D (N = 24)**	**Treatment E (N = 24)**
AUC(0-t) (h•ng/mL)					
Arithmetic Mean (SD)	58800 (17900)	56900 (14200)	49700 (8580)	48100 (11900)	31700 (11000)
95% CI	(48500, 69200)	(48800, 65100)	(46100, 53400)	(43100, 53200)	(27100, 36400)
Min, Max	26200, 87200	30700, 81000	34200, 65700	23700, 70600	19800, 59500
AUC(0-∞) (h•ng/mL)					
Arithmetic Mean (SD)	62200 (19400)	60600 (16100)	52100 (9770)	50400 (13200)	33400 (11800)
95% CI	(51000, 73400)	(51300, 69900)	(48000, 56300)	(44900, 56000)	(28400, 38300)
Min, Max	28800, 92800	31500, 86800	34800, 75200	25200, 78700	20500, 63400
Cmax (ng/mL)					
Arithmetic Mean (SD)	2980 (1010)	2780 (690)	2770 (686)	2810 (751)	1590 (574)
95% CI	(2390, 3560)	(2380, 3170)	(2480, 3060)	(2490, 3130)	(1350, 1830)
Min, Max	1030, 4700	1690, 4000	1670, 4170	994, 4350	953, 2830
Tmax (h)					
Median (Min, Max)	2.01 (1.00, 6.00)	2.00 (0.50, 5.03)	1.00 (0.50, 6.00)	1.00 (0.50, 5.00)	1.75 (0.50, 4.00)
Tlag (h)					
Median (Min, Max)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
t½ (h)					
Arithmetic Mean (SD)	16.20 (3.88)	16.56 (3.56)	15.85 (2.62)	15.63 (2.37)	15.95 (2.50)
95% CI	(13.96, 18.44)	(14.51, 18.62)	(14.74, 16.95)	(14.63, 16.64)	(14.89, 17.00)
Min, Max	12.08, 24.32	12.38, 23.68	12.22, 24.54	11.79, 23.17	12.93, 23.60
CL/F (L/h)					
Arithmetic Mean (SD)	0.906 (0.370)	0.891 (0.278)	0.496 (0.0924)	0.530 (0.148)	0.833 (0.260)
95% CI	(0.692, 1.12)	(0.730, 1.05)	(0.457, 0.535)	(0.468, 0.593)	(0.723, 0.943)
Min, Max	0.539, 1.73	0.576, 1.59	0.332, 0.718	0.318, 0.992	0.394, 1.22
Vz/F (L)					
Arithmetic Mean (SD)	20.9 (9.85)	20.5 (4.80)	11.1 (1.68)	11.8 (3.40)	18.9 (5.85)
95% CI	(15.2, 26.6)	(17.8, 23.3)	(10.4, 11.9)	(10.4, 13.2)	(16.5, 21.4)
Min, Max	11.8, 50.8	14.7, 31.2	8.25, 14.0	7.50, 25.1	9.97, 31.4

Treatment A = 10 mg FCTs (5 tablets, test) administered direct to mouth
Treatment B = 50 mg FCTs (reference) administered direct to mouth
Treatment C = 5 mg DTs (5 tablets, test 1) administered as a dispersion and immediately taken
Treatment D = 5 mg DTs (5 tablets, test 2) administered as direct to mouth
Treatment E = 25 mg FCTs administered as direct to mouth (reference)
Source: study report, P43

Table 8. Statistical analysis of DTG PK parameters by study part and treatment

Part 1:

Parameter Treatment	N	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
AUC(0-t) (h•ng/mL)						
A	14	14	55800	A/B	1.0121	(0.8648, 1.1845)
B	14	14	55200			
AUC(0-∞) (h•ng/mL)						
A	14	14	58900	A/B	1.0084	(0.8626, 1.1789)
B	14	14	58400			
Cmax (ng/mL)						
A	14	14	2780	A/B	1.0329	(0.8623, 1.2373)
B	14	14	2700			

Part 2:

Parameter Treatment	N	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
AUC(0-t) (h•ng/mL)						
C	24	24	49000	C/E	1.6292	(1.5030, 1.7661)
D	24	24	46700	D/E	1.5519	(1.4317, 1.6822)
E	24	24	30100			
AUC(0-∞) (h•ng/mL)						
C	24	24	51300	C/E	1.6242	(1.4986, 1.7604)
D	24	24	48800	D/E	1.5448	(1.4253, 1.6743)
E	24	24	31600			
Cmax (ng/mL)						
C	24	24	2690	C/E	1.7933	(1.6226, 1.9819)
D	24	24	2700	D/E	1.7974	(1.6263, 1.9865)
E	24	24	1500			

Treatment A = 10 mg FCTs (5 tablets, test) administered direct to mouth
Treatment B = 50 mg FCTs (reference) administered direct to mouth
Treatment C = 5 mg DTs (5 tablets, test 1) administered as a dispersion and immediately taken
Treatment D = 5 mg DTs (5 tablets, test 2) administered as direct to mouth
Treatment E = 25 mg FCTs administered as direct to mouth (reference)
Source: study report, P46

Conclusions

The FCT formulations (10, 25, or 50 mg FCT) are bioequivalent when dose at 50 mg. The DT formulation is not bioequivalent to the FCT formulation and the rBA of the DT formulation is ~ 160% of FCT. In addition, DT formulation can be taken as a dispersion or directly by mouth.

<u>Reviewer's comments</u>:
*Based on the rBA between DT and FCT formulations, five 5 mg DTs are equivalent to four 10 mg FCTs (the proposed dosing regimen for the 14 to 20 kg weight band), and 6*5 mg DTs are equivalent to a 50 mg FCT (the prosed dosing regimen for patients weighing 20 kg and greater).*

The applicant did not determine the food effects for the new formulation (DT). However, the food effect was assessed as part of the population pharmacokinetics (Table 12). Approximately 10% increase in exposure was observed when Tivicay DTs was administered without regard to food as compared to fasted conditions.

6. Pharmacometrics Review

A population pharmacokinetic (PPK) model was developed by the applicant to describe the PK of dolutegravir (DTG, TIVICAY™) in HIV infected pediatric subjects in Studies ING112578 (P1093) and 201296 (ODYSSEY). With additional data available from P1093 and ODYSSEY (WB-PK1 and WB-PK2), the existing PPK model was updated. The DTG exposures (AUC_{0-24}, C_{max} and C_{24}) for all pediatric subjects from P1093 and ODYSSEY were estimated from empirical Bayesian estimates (EBE), and were compared with the DTG exposures in adults. The exposure-response relationships were also assessed for efficacy and safety. From the pharmacometrics perspective, dolutegravir for pediatric subjects is approvable. In this review, the FDA pharmacometrics reviewer validated the applicant's PPK model for DTG, as well as evaluated the applicant's exposure-response analysis for efficacy and safety.

Two clinical studies were included in the analysis as summarized in **Table 9**, **Table 10** and **Table 11**.

Table 9. Summary of P1093 study information included in the population PK analysis

Cohort (Status)	Cohort Description/No. Subjects	DTG Dose/Treatment Duration	DTG Formulation
I (Completed)	Age cohort: Adolescents ≥12 to <18 years of age N=23 (10 on Stage I and 13 on Stage II)	· Stage I: Weight band-based fixed doses (Table 6-2) with continuation of the current failing ARV or as monotherapy for those not taking ARV, then in combination with OBR for a minimum of 24 weeks · Stage II: Dose based on Stage I data with OBT simultaneously for a minimum of 24 weeks	FCT
IIA (Completed)	Age cohort: Children ≥6 to < 12 years of age N=23 (11 on Stage I and 12 on Stage II)		FCT
IIB (Completed)	Age cohort: Children ≥6 to < 12 years of age N=~15 (all on Stage I; 4 on Mini-1 cohort and 11 on full cohort*)		GS
III (Completed)	Age cohort: Children ≥2 to < 6 years of age ~N=10		GS
III-DT* (Ongoing)	Age cohort: Children ≥2 to < 6 years of age ~N=22		DT
IV (Completed)	Age cohort: Children ≥6 months to < 2 years of age N=~10		GS
IV-DT (Ongoing)	Age cohort: Children ≥6 months to < 2 years of age ~N=22		DT
V-DT (complete)	Age cohort: Children ≥4 weeks to < 6 months of age N=22		DT

GS=Granules, FCT=Film coated tablet, DT=Dispersible tablet

Source: Applicant's population PK report.

Table 10. DTG weight-band based DTG dosing evaluated in P1093

Weight band (kg)	Film coated Tablet (mg)	Granule-1* (mg)	Granule-2* (mg)	Dispersible Tablet (DT)** (mg)
Interim population PK analysis				
8 to <15	NS	(b) (4)		NS
15 to <20	20			NS
20 to <30	25			NS
30 to <40	35			NS
≥40	50	NS	NS	NS
CURRENT ANALYSIS (WHO based)†				
3 to <6	NS	NS	NS	5 (one 5 mg DT)
6 to <10	NS	NS	NS	10 (Two 5 mg DT); 15 (Three 5 mg DT)
10 to <14	NS	NS	NS	15 (Three 5 mg DT); 20 (Four 5 mg DT)
14 to <20***	NS	NS	NS	15 (Three 5 mg DT); 25 (Five 5 mg DT)

*Granule dose was increased (from Granule-1 to Granule-2 dose) based on Cohort IIB Mini-1 PK results.
**Bioavailability of Dispersible tablet is similar to Granules. Dispersible Tablet in 2-5mL water. Intense PK was collected under protocol defined fasted conditions; Sparse PK was collected without regard to food.
*** 15 - <20kg for Film coated tablet (FCT), NS: Not studied
† Current analysis includes data from interim population PK analysis
Source: Applicant's population PK report.

Table 11. WHO weight-band based DTG dosing in evaluated in Odyssey

WHO weight bands (kg)	Administered DTG QD (formulation and daily dose, mg)	
6-<10*	15 mg (Three 5 mg DT)	NA
10-<14	20 mg (Four 5 mg DT)	NA
14-<20	25 mg (Five 5 mg DT)	25 mg (one 25 mg FCT)
20-<25	30 mg (Six 5 mg DT)	25 mg (One 25 mg FCT) **or** 50 mg (one 50 mg FCT)
25-<30		25 mg (one 25 mg FCT) **or** 50 mg (one 50 mg FCT)
30-<40		35 mg (one 25 mg + one 10 mg FCT) **or** 50 mg (one 50 mg

* > 6 months of age, Source: ODYSSEY, Protocol Version 4.0 [2]

Source: Applicant's population PK report.

1. Population PK Analysis

The current population PK analysis included a total of 2650 observations (1711 from P1093 and 939 from ODYSSEY) from 239 subjects. The applicant previously developed interim pediatric DTG PPK model based on available data from Study P1093. The model was able to predict the overall observed DTG data from P1093 and ODDESSEY reasonably. With additional data available, the applicant updated the PPK model by adding a maturation function (Hill model) on CL/F since body weight alone is insufficient to predict CL/F in neonates and infants from adult estimates for most drugs and there is approximately 13% of subjects aged <1 year in the analysis dataset:

$$Fmat_i = \frac{PMA_i^{Hill}}{TM_{50}^{Hill} + PMA_i^{Hill}}$$

The final PPK model for DTG in a pediatric population was a one-compartment model with first-order absorption and elimination. The selected final model incorporated the effect of age on CL/F, body weight on CL/F and V/F parameters. The absorption rate constant was formulation-specific, and bioavailability was both formulation and diet-specific. The model estimates are shown in **Table 12**.

Table 12. Parameter estimates of fixed and random effects for the final population PK model

Parameter [Units]	NONMEM Estimates				
	Point Estimate	95% CI	%RSE		
CL/F [L/hr]	1.03	0.980-1.07	2.31		
V/F [L]	13.6	13.0-14.3	2.42		
KA, FCT [hr^{-1}]	0.854	0.686-1.06	11.2		
KA~DT and Granules [hr^{-1}]	2.04	1.41-2.67	15.7		
F, Fasted FCT	1.00	-	-		
F, without regard to food, FCT	1.10	1.03-1.17	3.03		
F, Fasted DT/Granules	1.53	1.43-1.63	3.26		
CL/F~WT	0.455	0.418-0.492	4.15		
V/F~WT	0.556	0.514-0.598	3.87		
TM_{50} [week][a]	52.2 FIX	-	-		
Hill[a]	3.43 FIX	-	-		
Inter-individual variability		**Etabar (SE)**	**p val**	**CV%**	**Shr%**
ω^2_{CL}	0.0863	0.00139	0.925	29.4	21.5
Covar η_{CL}, η_V	0.0499	-	-	R=0.643	-
ω^2_V	0.0698	0.000651	0.961	26.4	22.2
Covar η_{CL}, η_{KA}	0.0953	-	-	R=0.372	-
Covar η_V, η_{KA}	0.138	-	-	R=0.598	-
ω^2_{KA}	0.762	-0.00170	0.964	107	33.2
$\omega^2_{IOV,CL}$	0.115	0.0220	0.171	33.9	26.6
$\omega^2_{IOV,CL}$	0.115	0.0314	0.0409	-	29.8
$\omega^2_{IOV,CL}$	0.115	-0.0213	0.0835	-	43.8
$\omega^2_{IOV,CL}$	0.115	-0.0306	0.0183	-	40.7
$\omega^2_{IOV,KA}$	0.610	0.0868	0.00415	91.7	39.9
$\omega^2_{IOV,KA}$	0.610	0.000116	0.993	-	73.6
Residual variability		**95% CI**	**%RSE**		
Proportional Error, P1093	0.0818	0.0695-0.0941	7.67	28.6	16.7
Additive Error (ug/mL), P1093	0.00164	-0.00142-0.00470	95.1	SD=0.0405	-
Proportional Error, ODYSSEY	0.0123	0.00787-0.0167	18.4	11.1	16.3
Additive Error (ug/mL), ODYSSEY	0.0900	0.0677-0.112	12.7	SD=0.300	-

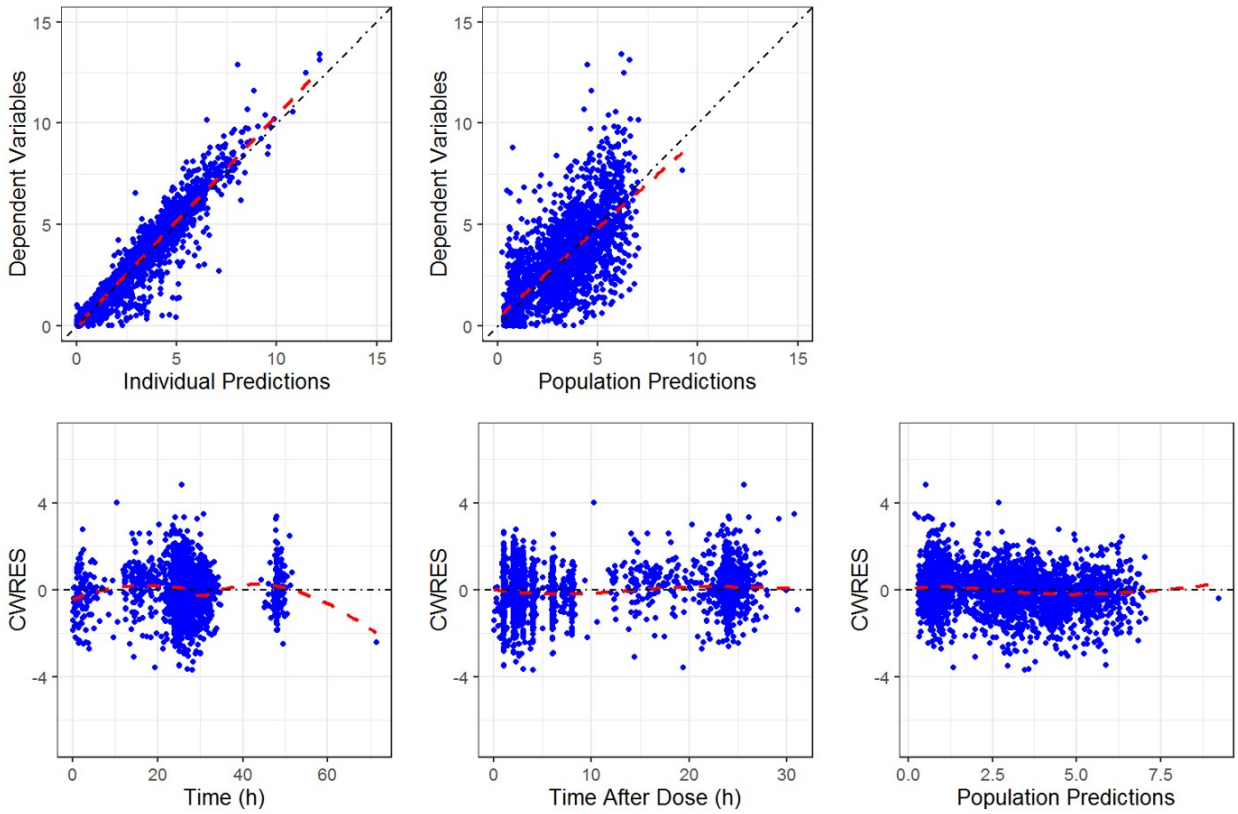
Abbreviations: %RSE: percent relative standard error of the estimate = SE*100; CL/F = apparent clearance, V/F = apparent volume, KA= absorption rate constant, Q/F = apparent inter-compartmental clearance, ω^2_{CL}, ω^2_V, ω^2_{KA} = variance of random effect of CL/F, V/F and KA and Q/F, respectively, DT=Dispersible tablet, FCT=Film coated tablet, F=Relative bioavailability, TM_{50} [week] =maturation half-time and Hill=Hill coefficient related to the slope of this maturation process.
Etabar is the arithmetic mean of the η estimates and the p-value for the null hypothesis that the true mean is 0, Shr=shrinkage. [a] SD
For IIV, if $\omega^2 > 0.15$, CV% = $100 * \sqrt{e^{\omega^2} - 1}$.
The reference population is a 70 kg subject.

[a]Parameters were taken from Anderson [14] and were used in the model with maturation function.
Covariate relationships:
CL/F =1.03* [(Weight /70)$^{0.455}$
V/F =13.6*(Weight /70)$^{0.556}$
KA (DT and granules)=1.74 (95% CI: 1.20-2.28), calculated as 0.854*2.04 (95% CI: 0.854*1.41-0.854*2.67)
F, without regard to food, DT/Granules =1.68 (1.47-.91), calculated as 1.10*1.53 (95% CI: 1.03*1.43-1.17*1.63)

Source: Applicant's population PK report.

*Reviewer comment: FDA reviewer validated the applicant's PPK model, and the goodness-of-fit plots from all data are shown in **Figure 3**.*

Figure 3. Final DTG population PK model Goodness-of-Fit plots from all data

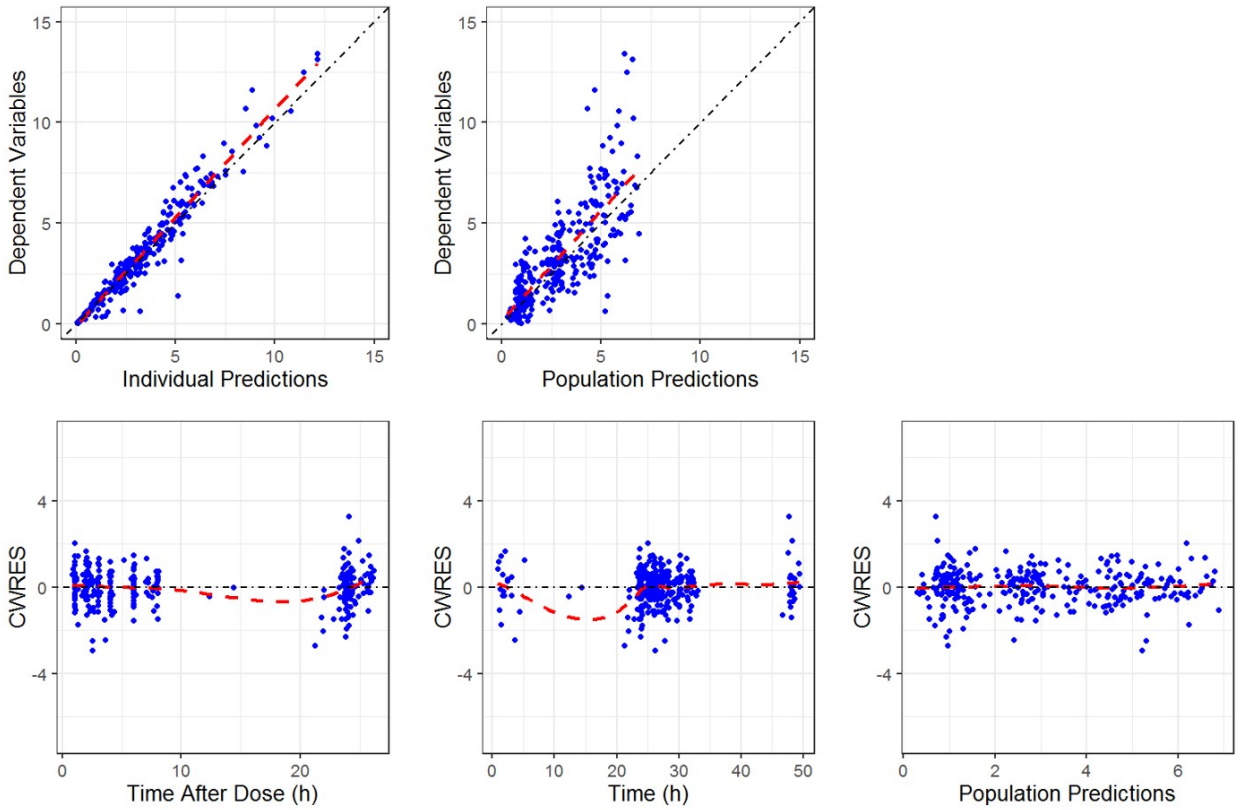


Source: Reviewer's analysis

The goodness-of-fit (GOF) plots show a good agreement between the predicted concentrations and the observed concentrations for DTG. A slight underprediction was observed in high concentrations. Overall, no apparent bias was observed in the residual plots versus time, time after last dose (TAD) and population predicted concentrations (PRED). The shrinkage for CL/F and V/F was considered acceptable. Therefore, the final PPK model was reliable for prediction of PK parameters and the exposures at steady-state that would be used to compare between pediatrics and adults (discussed in the following sections).

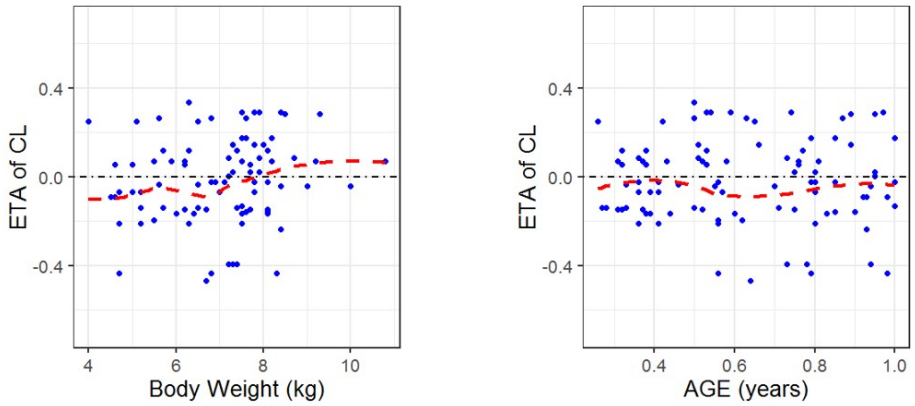
To assess whether the maturation function performed well to predict the DTG concentrations for neonates and infants, GOF plots for subjects aged <1 years old were generated as shown in ***Figure 4****. Overall, the predicted DTG concentrations adequately captured the observations. A slight underprediction was observed in high concentrations. The residual plots versus time, TAD and PRED are consistent with those generated from all data. In addition, the ETA versus covariate plots for the subjects <1 year old are shown in* ***Figure 5****. The ETA of CL versus body weight and age plots suggested that there were no CL-body weight or CL-age relationships remaining for subjects <1 year old.*

Figure 4. Final DTG population PK model Goodness-of-Fit plots from subjects < 1 year old



Source: Reviewer's analysis

Figure 5. Plots of ETA of CL Versus body weight and age



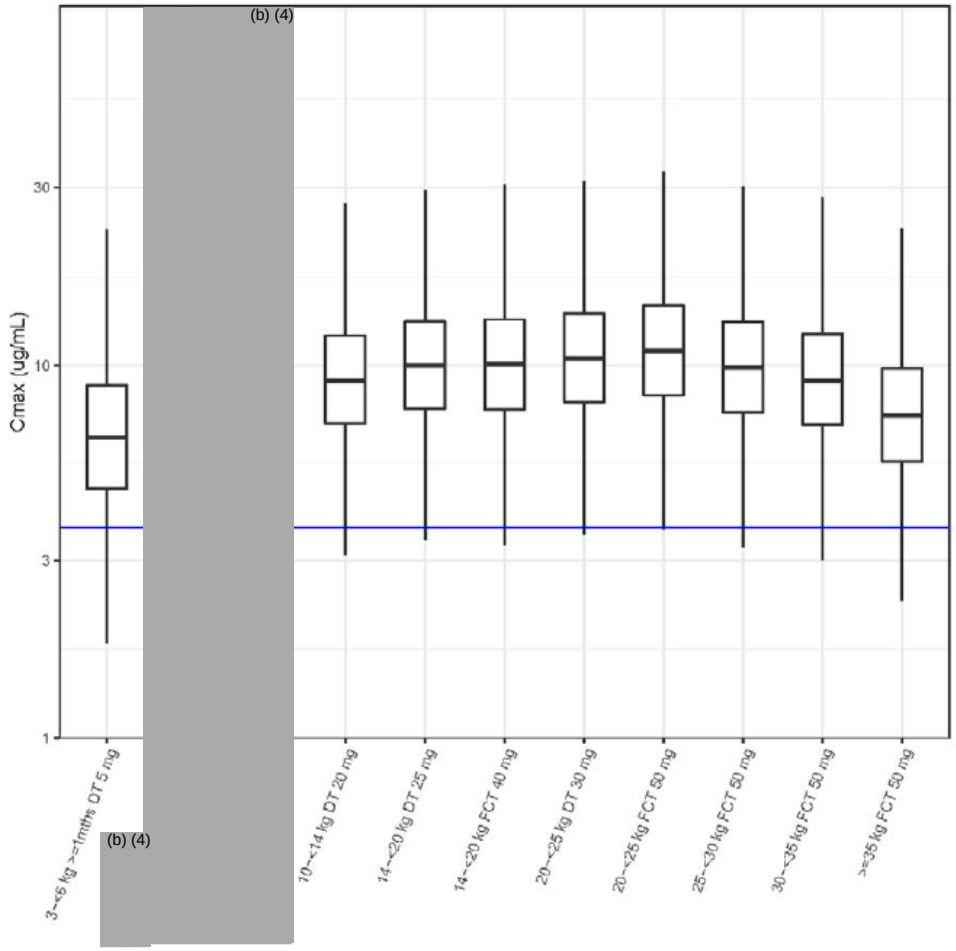
Source: Reviewer's analysis

2. Simulations

The applicant conducted a series of simulations to evaluate the appropriateness of DTG dosing regimens based on WHO weight bands and formulations.

2.1 QD dosing simulation

This simulation with QD dosing evaluated 11 weight band and dose combinations and included 2,200 subjects (200 subjects per weight band/dose combination), with equal distribution of males and females. The box plots of steady-state C_{24} for each cohort overlaid by the observed C_{24} are shown in **Figure 1**.



Reviewer's comment: The applicant performed simulation to evaluate the appropriateness for QD dosing regimens. The FDA reviewer agrees with the applicant that the QD dosing regimens are appropriate. Based on the simulation results for QD dosing regimens and Table 5.10-1 in the applicant's population PK report, not shown in this review), the C_{24} were comparable across the different weight bands for the FCT and DT formulations. The geometric means of C_{max}, C_{24} and AUC_{0-24} were comparable between the pediatric population and the respective adult exposure at 50 mg daily dose.

(b) (4)

Reference is made to your study report titled "Population pharmacokinetic and exposure-response analysis for dolutegravir in HIV-1 infected pediatric subjects in studies ING112578 (IMPAACT P1093) and 201296 (ODYSSEY, PENTA 20)". We are requesting additional simulated dolutegravir exposures in pediatric patients weighing 6 to < 10 kg. Please submit the simulated exposures for dolutegravir dosing regimens as follows, and a comparison with the adult exposures. Submit the results in graph and table formats. Also submit the virtual pediatric population that was constructed based on United States CDC growth charts and used for the simulation.

- *6 kg to less than 10 kg, 10 mg once daily regardless of age.*
- *6 kg to less than 10 kg, 15 mg once daily regardless of age.*

The applicant provided simulations results as shown in **Table 13** and **Figure 2**.

Table 13. Steady-state simulated C_{max}, C_{24} and AUC_{0-24} for 6 to <10 kg pediatric subjects following 10 mg and 15 mg DTG dispersible tablet dose

Weight Band	Dose (mg)	Formulation	Statistic	C_{max} (µg/mL)	C_{24} (µg/mL)	AUC_{0-24} (µg·hr/mL)
6-<10 kg	10	DT	10th percentile of the median of the geometric means (95% PI)	(b) (4)		
			Median of the geometric means (95% PI)			
			90th percentile of the median of the geometric means (95% PI)			
			%<10th percentile of adult value[1]			
			%>90th of percentile of adult value[1]			
			%<Min Target[2]			
			%>Max Target[2]			
6-<10 kg	15	DT	10th percentile of the median of the geometric means (95% PI)	4.43 (4.13-4.80)	0.307 (0.231-0.425)	39.4 (36.2-44.9)
			Median of the geometric means (95% PI)	7.19 (6.88-7.54)	1.15 (1.01-1.33)	76.0 (71.1-81.0)
			90th percentile of the median of the geometric means (95% PI)	11.7 (10.6-12.9)	3.88 (3.27-4.55)	148 (133-167)
			%<10th percentile of adult value[1]	0 (0-1.00)	11.0 (6.50-15.0)	2.00 (0.500-4.01)
			%>90th of percentile of adult value[1]	90.0 (86.0-94.0)	30.5 (24.5-36.0)	50.5 (44.0-57.0)
			%<Min Target[2]	NA	19.0 (13.0-24.0)	1.50 (0-3.50)
			%>Max Target[2]	NA	NA	14.0 (9.99-17.5)

[1]PK parameters at 10th and 90th percentiles of adults at 50 mg daily dose were post-hoc estimates derived from the Pop PK model based on HIV-1 infected treatment-experienced adults. 10th and 90th percentiles were 2.33 and 4.42 µg/mL for C_{max}, 0.323 and 2.07µg/mL for C_{24}, and 26.7 and 75.1 µg·hr/mL for AUC_{0-24}.

[2]The minimum exposures were defined as 0.5 µg/mL for C_{24} and 25 µg·hr/mL for AUC_{0-24}; the maximum exposure was defined as 134 µg·hr/mL for AUC_{0-24}. NA: Not available.

Source: Applicant's response to Clinical Pharmacology IR

Reviewer's comment: The applicant's original proposed dosing regimen for (b) (4) *15 mg DT for 6 to <10 kg* (b) (4) *was well supported by available PK data without concerns of too low C_{24} or too high C_{max}.* (b) (4) *a simplified dosing regimen for this body weight band group was sought.*

Based on the applicant's simulation in response to our IR, compared with originally proposed dosing regimens, the dosing regimen of (b) (4) *the dosing regimen of 15 mg for 6 to <10 kg* (b) (4) *would likely provide sufficient high C_{24} but produce higher C_{max} for the subjects in this weight band, which may associate safety concerns given no data were available for patients* (b) (4) (b) (4) *in this body weight group. The FDA Reviewer compared the applicant's simulated exposures for the dosing regimen* (b) (4) *with the simulated exposures for other body weight bands (**Table 14**) in the applicant's population PK study report, the simulated C_{max} and AUC_{0-24}*

under dosing regimen (b) (4) *are similar with the simulated Cmax under 25 mg DT dose for 14 to<20 kg and the simulated* AUC_{0-24} *under 50 mg FCT dose for 20 to <25 kg, respectively;* (b) (4) *After evaluation of the benefit and risk profile, FDA reviewer recommends 15 mg for 6 to <10 kg pediatric subjects.*

Table 14. Simulated steady-state post-hoc DTG C_{max}, C_{24} ***and*** AUC_{0-24} ***for 10 to <14 kg, 14 to <20 kg and 20 to <25 kg pediatric subjects***

Weight Band	Dose (mg)	Formulation	Statistic	C_{max} (µg/mL)	C_{24} (µg/mL)	AUC_{0-24} (µg*h)/mL
10-<14 kg	20	DT	10th %tile of the median of the geometric means (95% PI)	4.30 (3.89-4.56)	0.184 (0.122-0.242)	34.3 (30.8-38.1)
			Median of the geometric means (95% PI)	6.61 (6.26-6.90)	0.719 (0.623-0.847)	63.1 (59.7-67.6)
			90th %tile of the median of the geometric means (95% PI)	10.2 (9.43-11.1)	2.56 (2.22-3.07)	115 (105-129)
14-<20 kg	25	DT	10th %tile of the median of the geometric means (95% PI)	4.63 (4.29-4.96)	0.212 (0.159-0.299)	37.8 (33.4-42.4)
			Median of the geometric means (95% PI)	7.17 (6.89-7.49)	0.824 (0.713-0.950)	69.5 (65.1-73.5)
			90th %tile of the median of the geometric means (95% PI)	11.2 (10.4-12.1)	2.87 (2.42-3.36)	127 (115-143)
20-<25 kg	50	FCT	10th %tile of the median of the geometric means (95% PI)	4.73 (4.31-5.11)	0.289 (0.191-0.380)	43.2 (38.5-47.9)
			Median of the geometric means (95% PI)	7.43 (7.11-7.80)	1.08 (0.919-1.24)	78.6 (73.7-83.6)
			90th %tile of the median of the geometric means (95% PI)	11.8 (10.8-12.8)	3.62 (3.03-4.37)	145 (128-157)

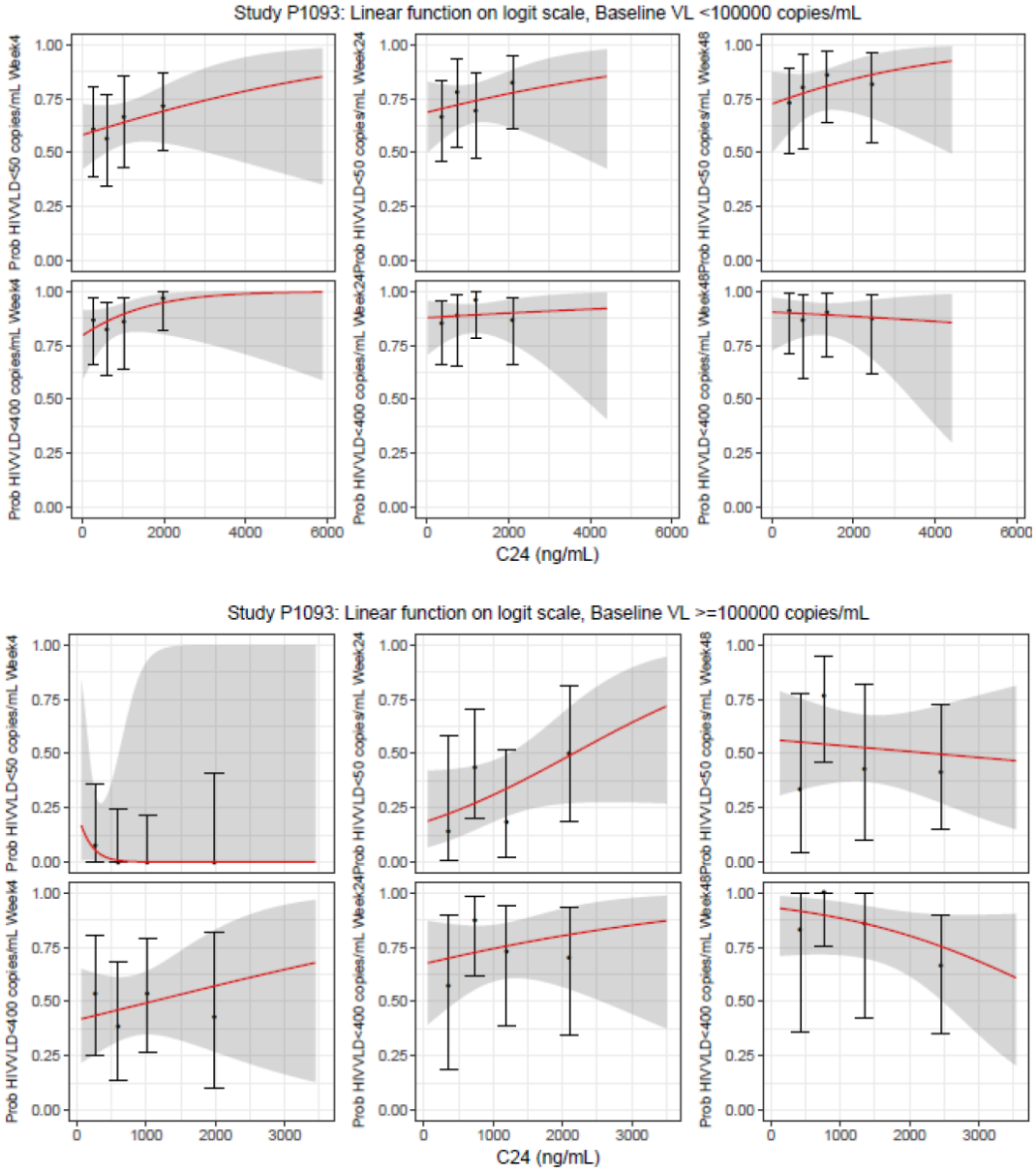
Source: adapted from Applicant's table 5.9-1 in popPK study report

3. Exposure-Response Analyses

3.1 Exposure-Response Analyses for efficacy

The applicant conducted exposure-response (E-R) analyses to evaluate the relationship between DTG exposure and long-term (HIV-1 RNA<50 or <400 copies/mL at Weeks 4, 24 and 48) viral response and to characterize the effects of covariates. A total of 143, 135 and 112 viral load (VL) response observations were available at Weeks 4, 24 and 48, respectively, from study P1093.**Figure 6** shows the ER relationship for long-term virologic response of HIV-1 RNA <50 and <400 copies/mL versus C_{24} by VL ≥100,000 copies/mL at enrollment. Similar results were observed for using AUC_{0-24} and C_{avg} as the PK metrics.

Figure 6. Viral load response rate versus C_{24}



Red line: linear logistic regression model fit; grey shaded area: 95% CI for linear logistic regression model fit; error bars: observed response rates (and 95% CI)
Source: Applicant's study report 2019n424148

The final parameter estimates for the final model evaluating the probability of achieving a virologic response of HIV-1 RNA <50 copies/mL at Week 4, Week 24 and Week 48 are presented in **Table 15**, **Table 16** and **Table 17**.

Table 15. Parameter estimates of the final logistic regression model for VL<50 copies/mL at Week 4

Parameter [Units]	NONMEM Estimates			
	Point Estimate	95% CI	%RSE	Implementation of Covariate Effect
θ_1: Intercept	0.584	0.165, 1.00	36.6	θ_1
θ_3: VL ≥100,000 copies/mL at enrolment effect (BASEHIVLDF)	-4.43	-6.45, -2.41	23.3	$\theta_1+\theta_3$*BASEHIVLDF

Data Source: 060.sum, Table 9.3-4
Abbreviations: %RSE, percent relative standard error of the estimate = SE/parameter estimate * 100; BASEHIVLDF=Baseline HIV Viral load flag > 100,000 copies/mL
No random effects or residual error were estimated since data consisted of one observation per participant.

Source: Applicant's study report 2019n424148

Table 16. Parameter estimates of the final logistic regression model for VL <50 copies/mL at Week 24

Parameter [Units]	NONMEM Estimates			
	Point Estimate	95% CI	%RSE	Implementation of Covariate Effect
θ_1: Intercept	1.03	0.564, 1.50	23.1	θ_1
θ_3: VL ≥100,000 copies/mL at enrolment effect (BASEHIVLDF)	-1.69	-2.47, -0.912	23.5	$\theta_1+\theta_3$*BASEHIVLDF

Data Source: 061.sum, Table 9.3-5
Abbreviations: %RSE, percent relative standard error of the estimate = SE/parameter estimate * 100; BASEHIVLDF=Baseline HIV Viral load flag > 100,000 copies/mL
No random effects or residual error were estimated since data consisted of one observation per participant.

Source: Applicant's study report 2019n424148

Table 17. Parameter estimates of the final logistic regression model for VL <50 copies/mL at Week 48

Parameter [Units]	NONMEM Estimates			
	Point Estimate	95% CI	%RSE	Implementation of Covariate Effect
θ_1: Intercept	1.07	0.613, 1.53	21.8	θ_1
θ_3: BVL effect (LBASEHIVVLD)	-0.929	-1.42, -0.435	27.1	$\theta_1+\theta_3$*(LBASEHIVVLD-4.6)

Data Source: 062.sum, Table 9.3-6
Abbreviations: %RSE, percent relative standard error of the estimate = SE/parameter estimate * 100; BVL=baseline viral load
No random effects or residual error were estimated since data consisted of one observation per participant.

Source: Applicant's study report 2019n424148

The only significant predictor of the probability of achieving a virologic response of HIV-1 RNA <50 copies/mL at Week 4 and Week 24 was VL ≥100,000 copies/mL at enrolment. Participants with VL ≥100,000 copies/mL at enrolment had a lower probability of achieving a virologic response of HIV-1 RNA <50 copies/mL at Week 4 or Week 24 compared to VL <100,000 copies/mL at enrolment. Similarly, the only significant predictor of the probability of achieving a virologic response of HIV-1 RNA <50 copies/mL at Week 48 was baseline viral load (BVL). The probability of achieving a virologic response of HIV-1 RNA <50 copies/mL at Week 48 decreased with increasing BVL.

Reviewer's comment: The applicant's E-R analyses for efficacy is acceptable for dose selection. None of the DTG exposure metrics (C_{24}, AUC_{0-24} and C_{avg}) were identified to be predictive of virologic response in the analyses, indicating that the exposure ranges were on the plateau level within the DTG-virologic response relationship.

3.2 Exposure-response analyses for safety

3.2.1 Relationship between DTG PK and safety end-points

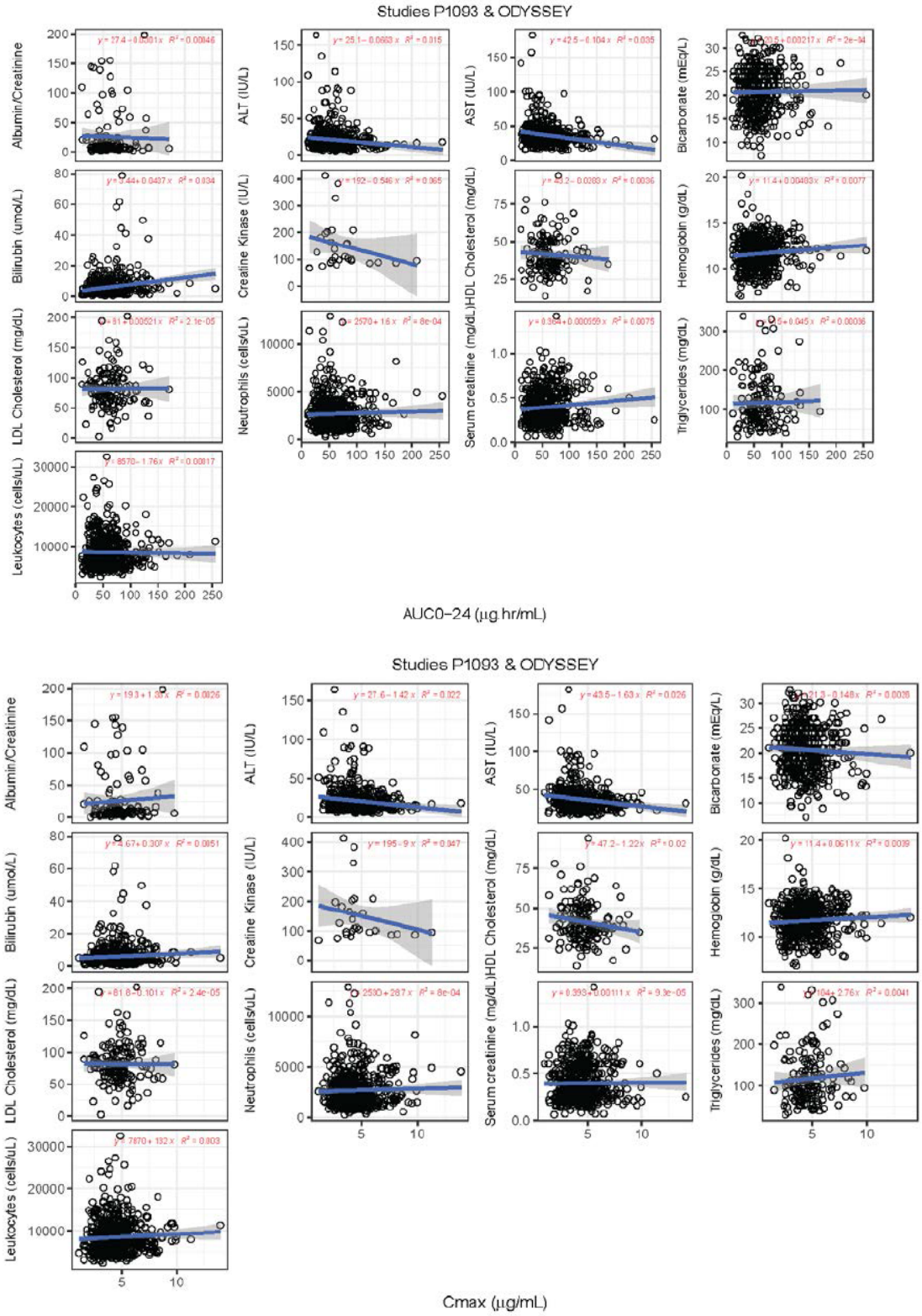
The applicant conducted E-R analyses for selected safety endpoints based on the lab data from Studies P1093 and ODYSSEY. The safety end-points included in the regression analysis using model-derived exposures were time-matched with exposure parameters (C_{max} and AUC_{0-24}). The following safety endpoints were explored:

- Liver: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin,
- Lipid: triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol,
- Kidney: serum creatinine, urine albumin/creatinine ratio,
- Other: Bicarbonate blood concentration, creatine kinase,
- Blood: neutrophils, leukocytes, and haemoglobin.

The model derived AUC_{0-24} and C_{max} values plotted against selected safety-endpoints for all data are presented in

Figure 7.

Figure 7. Plots of model derived AUC_{0-24} and C_{max} versus safety endpoints (linear regression model), all data

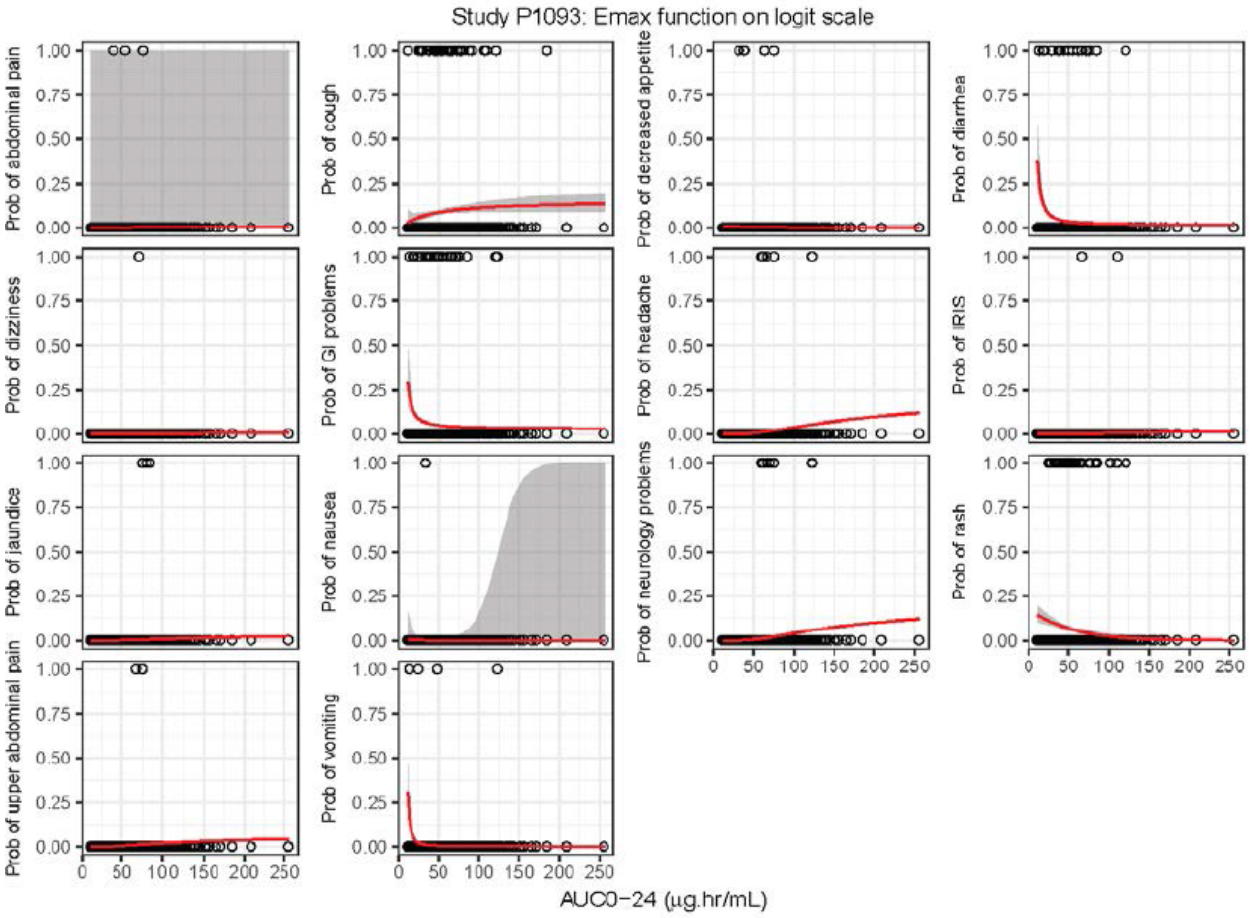


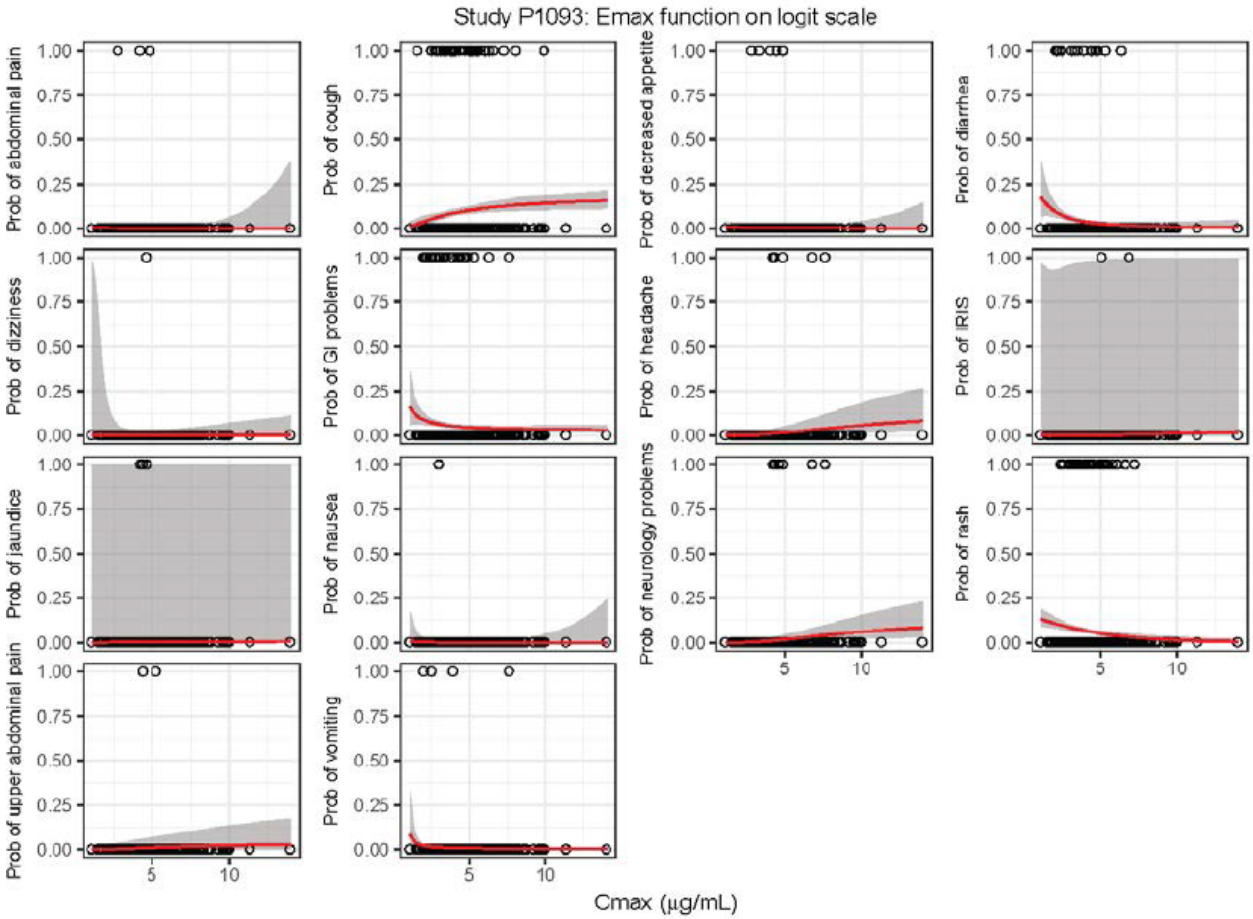
Source: Applicant's population PK report

3.2.1 Relationship between DTG PK and adverse events (AEs)

The applicant utilized an E_{max} function of DTG exposure on the logit scale. The observed and model derived DTG exposures plotted against the probability of occurrence of selected AEs for Study P1093 are shown in **Figure 8**. These plots indicate that no correlation between DTG exposure and incidence of AEs was apparent.

Figure 8. Plots of model derived AUC_{0-24} and C_{max} versus selected AEs (E_{max} function on the logit scale), Study P1093





Source: Applicant's population PK report

Reviewer's comment: The applicant's E-R analyses for safety are acceptable. No apparent positive E-R relationship for selected safety endpoints or AEs were identified.

In conclusion, the applicant developed population PK model with maturation function (Hill model) on CL/F that can adequately describe the PK of DTG. The FDA reviewer recommends a new dosing regimen of 15 mg for 6 to <10 kg pediatric subjects. The exposure-efficacy analyses showed that viral load ≥100,000 copies/mL at enrollment was a significant predictor of efficacy (HIV-1 RNA <50 copies/mL at Week 24 and virologic response HIV-1 RNA <400 copies/mL at Week 4) and BVL was a significant predictor at Week 48. The exposure-safety analyses showed that no positive E-R relationship was identified for safety. From the pharmacometrics perspective, DTG for pediatrics is approvable.

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