OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	204,790 S-8 (pediatric efficacy supplement)
Product name	TIVICAY® (dolutegravir)
Submission Date	December 9, 2015
Action Date	June 8, 2016
Clinical Pharmacology Reviewer	Su-Young Choi, Pharm.D., Ph.D
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D
Pharmacometrics Reviewer/Team Leader	Jeff Florian, Ph.D
OCP Division	Division of Clinical Pharmacology IV
OND Division	Division of Antiviral Products (DAVP)
Applicant	GSK/Viiv
Formulation/Strength	Oral tablet, 50 mg, 25 mg, 10 mg
Indication in Adults	Tivicay can be taken without regard to meals. • Treatment-naïve or treatment-experienced integrase strand transfer inhibitor (INSTI)-Naïve: 50 mg once daily • Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers: 50 mg twice daily • INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance: 50 mg twice daily

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EXECUTIVE SUMMARY

TIVICAY® (dolutegravir, DTG) is an integrase strand transfer inhibitor approved for the treatment of HIV-1 in adult and adolescent patients. The applicant submitted a pediatric efficacy supplement to support the use of TIVICAY in subjects weighing at least (b) (4).

Table 1. Proposed Dosing Regimens for Pediatric Patients by the Applicant

Weight	TIVICAY dose
(b) (4)	
30 to < 40 kg	35 mg
≥ 40 kg	50 mg

To support the proposed doses in pediatric patients, the applicant submitted the clinical study report, entitled "A Phase I/II, Multi-Center, Open-Label Study of the Pharmacokinetics, Safety, Tolerability, and Antiviral Activity of GSK1349572, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children, and Adolescents: Results of Cohort I Week 48/Cohort IIA Week 24 Analyses (IMPAACT P1093)" and a population pharmacokinetic analysis report. Consistent with most pediatric HIV trials, an exposure-matching approach (i.e., extrapolation of efficacy from adults to pediatrics when exposures are comparable) was used to support the approval of DTG in pediatric patients.

In addition, the submission contains chemistry, manufacturing and controls data to support the introduction of the two new lower strength tablets, 10 mg and 25 mg.

RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the submission and agrees that the submitted data support the use of dolutegravir in pediatric subjects weighing at least 30 kg. (b) (4)

SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

In this Phase I/II multi-center, open-label study in HIV-1-infected pediatric subjects (P1093), pediatric patients (aged 6 years and older) received approximately 1 mg/kg DTG. DTG exposures in pediatric patients weighing 30 kg and above were comparable to those observed in adults. However, in subjects providing intensive PK samples in the 20 to < 30 kg group, DTG exposures were significantly lower as compared to those observed in adults. Simulated PK parameters in this weight band were comparable to those in adults. No intensive PK data were collected in subjects weighing 15 to < 20 kg. (b) (4)

Table 2. DTG Pharmacokinetics in Pediatric Patients by Weight Band

Weight band	DTG daily dose (mg/kg dose)	Type of PK data	C_{max} (µg/mL)	AUC_{24h} (µg·hr/mL)	C_{24hr} (µg/mL)
≥ 40 kg	50 mg (≤ 1.25 mg/kg)	Intensive (n=14)	3.91 (42.2%)	50.1 (51.8%)	0.99 (64.7%)
		Population PK	3.80 (26.5%)	60.3 (31.1%)	1.30 (52.0%)
30 to < 40 kg	35 mg (0.88 to 1.67 mg/kg)	Intensive PK (n=3)	4.40 (53.8%)	64.5 (63.7%)	1.33 (92.3%)
		Population PK	4.01 (28.4%)	62.2 (20.2%)	1.32 (18.0%)
20 to < 30 kg	25 mg (0.83 to 1.25 mg/kg)	Intensive PK (n=4)	2.84 (50.7%)	34.1 (45.9%)	0.51 (43.7%)
		Population PK	3.67 (29.2%)	53.6 (25.2%)	0.94 (40.4%)
15 to < 20 kg	20 mg (1.00 to 1.33 mg/kg)	Intensive PK	None	None	None
		Population PK	4.09 (14.0%)	55.4 (25.0%)	0.90 (51.7%)
Adult	**50 mg**	**Population PK (label)**	**3.64 (20%)**	**53 (27%)**	**1.11 (46%)**

Data expressed as geometric mean (%CV)

LABELING RECOMMENDATION

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

INDIVIDUAL TRIAL REVIEW

Title: A Phase I/II, Multi-Center, Open-Label Study of the Pharmacokinetics, Safety, Tolerability, and Antiviral Activity of GSK1349572, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children, and Adolescents: Results of Cohort I Week 48/Cohort IIA Week 24 Analyses

Primary Objectives:

- To select a DTG dose for chronic dosing in infants, children, and adolescents that achieves similar exposure to the DTG adult dose
- To determine the safety and tolerability of DTG in HIV-1-infected infants, children, and adolescents at 24 and 48 weeks
- To evaluate the steady-state PK of DTG in combination with other antiretrovirals (optimized background therapy, [OBT]) in treatment-experienced, HIV-1-infected infants, children, and adolescents, and to determine the dose of DTG that achieves a targeted AUC_{24} (primary PK endpoint) and C_{24h} (secondary PK endpoint) in this population

Study Design

P1093 is a Phase I/II multi-center, open-label study in HIV-1-infected pediatric subjects ages ≥4 weeks to <18 years to evaluate the PK parameters, safety, tolerability, and antiviral activity of DTG when administered both prior to starting, and in combination with optimized background therapy (OBT).

There are five age-defined groups in P1093 (enrolled in six cohorts) as follows:

- Cohort I: Adolescents ≥ 12 to <18 years of age (tablet formulation)
- Cohort IIA: Children ≥ 6 to <12 years of age (tablet formulation)
- Cohort IIB: Children ≥ 6 to <12 years of age (pediatric formulation)
- Cohort III: Children ≥ 2 to <6 years of age (pediatric formulation)
- Cohort IV: Children ≥ 6 months to <2 years (pediatric formulation)
- Cohort V: Infants ≥ 4 weeks to <6 months (pediatric formulation)

The current submission contains Week 48 data of Cohort I and Week 24 data of Cohort IIA. Subjects were enrolled sequentially in age-defined cohorts. Each age cohort consists of two sequential stages: Stage I and II. The objectives of Stage I were to examine PK parameters after intense sampling and evaluate the short term tolerability and safety of DTG in approximately 10 subjects, allowing the selection of a dose for further study in additional subjects in Stage II. Longer-term safety and antiviral activity of DTG were assessed from data obtained from both Stage I and Stage II.

Reviewer comments:
Data from Cohort I through Week 24 were submitted at the time of the original NDA application and reviewed. While this review is primarily focused on the new data (Cohort IIA through Week 24), previous PK data from Cohort I will be used for combined analyses to compare PK across weight bands.

Treatment Assignment

For those subjects who enrolled in Stage I (intensive PK stage), DTG treatment was added to a stable, failing ARV regimen or started as monotherapy for those not taking ARVs. After intensive PK sampling was performed between Days 5 to 10, the background ARV regimen was immediately optimized. To minimize the impact of drug-drug interactions on PK, the use of atazanavir/ritonavir (ATV/ RTV), ATV, nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), FPV/RTV, tipranavir (TPV), or TPV/RTV was not allowed prior to the initial PK evaluation but could be added as part of optimized background therapy. All ARV regimens must have contained at least one fully active drug and one additional drug in the OBT, in addition to DTG. For subjects receiving concomitant rifampin, EFV, FPV/RTV, or TPV/RTV after the intensive PK was performed, it was recommended that the dose of DTG be increased to twice-daily administration.

Table 3. Doses for Subjects Enrolled in P1093 Cohort I and IIA

Weight Range (kg)	Dose (mg)	Tablets taken	Dose in mg/kg for lower weight subjects	Dose in mg/kg for upper weight subjects
15 - <20	20	Two 10 mg tablets	1.33	1.00
20 - <30	25	One 25 mg tablet	1.25	0.83
30 - <40	35	One 10 mg tablet AND one 25 mg tablet	1.17	0.88
≥40	50	One 50-mg tablet	1.25	≤1.25

Concomitant Medications

Data on prior and concomitant medications were collected throughout the study. Raltegravir or elvitegravir could not be co-administered with DTG. Dofetilide and medications for HCV therapy were also prohibited. Due to their enzyme induction potential, the following medications could not be administered concurrently with DTG; barbiturates, modanafil, oxcarbazepine, pioglitazone, troglitazone, rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine, or St. John's wort. DTG was to be administered 2 hours before or 6 hours after taking antacid products containing divalent cations (e.g. aluminum and magnesium) or iron supplements.

Key Inclusion Criteria

Key inclusion criteria include antiretroviral therapy (ART)-experienced, INI-naïve infants, children, and adolescents age ≥ 4 weeks to <18 years at study entry, with confirmed HIV-1 infection, and an optimized background regimen that contains at least one fully active drug.

Key Exclusion Criteria

Key exclusion criteria include known resistance to an integrase inhibitor, presence of any active AIDS-defining opportunistic infections, known Grade 3 and Grade 4 lab toxicities, evidence of pancreatitis, liver toxicity, or known exposure to an integrase inhibitor.

Description of Investigational Products

Table 4. Description of Investigational Products

Investigational Product	Strength and Packaging	Batch Numbers from Certficate of Analysis	Lot Number
Dolutegravir	**10 mg tablets** 30 tablets per bottle	101276423 121353478	111277992 121353478
	25 mg tablets 30 tablets per bottle	101271002 121353498	101275522 121353498
	50 mg tablets 30 tablets per bottle	101258083 111287795	101257683 111288487

Reviewer comments

According to the applicant, the clinical image tablets and the commercial image tablets are identical except that the clinical image tablets are plain film coated with (b) (4) *and the commercial image tablets are debossed and coated with* (b) (4) *yellow. The applicant submitted in vitro dissolution study results to support the approval of the commercial image tablets. Refer to Dr. Om Anand's review for detailed information.*

Pharmacokinetic Sample Collection

Pharmacokinetic samples were collected at time-points outlined in Table 5.

For intensive PK sampling, the PK evaluation was scheduled so that witnessed dosing of DTG was as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects were to be compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit was to be re-scheduled. Subjects were fasted for 6 hours prior to dosing. Liquids including milk and juice could be consumed up to 4 hours prior to dosing. Subjects could consume a light meal of their choice 4 hours after dosing on the intensive PK day.

Table 5. Sample Collection Times for Stages I (intensive PK) and Stages II (Sparse PK) in P1093

Stage I	Sample Times Relative to Dose
Between Days 5-10	Pre-dose, 1, 2, 3, 4, 6, 8, and 24 hours post dose
Week 4	Pre-dose, 2-4 hours post dose
Week 12	Any time post dose
Week 24	2 samples of 2 hours apart between 12 and 26 hours post dose
Stage II	
Week 4	Pre-dose, 2-4 hours post dose
Week 12	Any time post dose
Week 24	2 samples of 2 hours apart between 12 and 26 hours post dose

Bioanalysis

Human plasma samples were analyzed at (b) (4) using a validated LC/MS/MS method. The bioanalytical method and quality control (QC) results are summarized in Table 6.

Table 6. Summary of Bioanalysis

Analytes and matrix	Dolutegravir in plasma with EDTA
Extraction method	Protein precipitation using acetonitrile
Internal standard	[$^{15}N^2H_7$]-dolutegravir
Quantitation range (LLOQ-ULOQ)	5 ng/mL to 10,000 ng/mL
QC concentrations and results (Inter-day precision and accuracy)	15, 450, and 9000 ng/mL %CV: 8.5 to 10.2% % deviation: -3.0% to 1.4%
Regression	Linear regression with $1/x^2$ weighing
stability	Freeze/thaw: three cycles at – 80 ºC Short term: 2 hours at room temperature (in plasma) Long term: 36 months at – 80 ºC (ongoing) Injection matrix stability: 3 days in autosampler Stock solution: 13 months at 4 ºC (ongoing)
Max sample storage duration from collection to analysis	13 months
Incurred sample analysis	50/464 (10.8% of samples) % of incurred samples with % concentration difference more than 20% : 28%

The following key analysis acceptance criteria were applied.

- QC: Quality controls should fall within ± (b) (4)% of the nominal concentration to be accepted. (b) (4) of the controls must be in range, and no two at the same concentration can be out of range.

- Standard Curve: A minimum of six calibration standards must be used to define a curve.. Standard back-calculated values should be within ± (b) (4)% of the nominal concentration except at the LLOQ where it can be within ± (b) (4)% for acceptance. The standard curve coefficient of determination (r^2) should be a minimum of (b) (4).

Pharmacokinetic Analyses

Steady-state PK parameters were determined from plasma concentration-time profiles using non-compartmental methods (WinNonlin version 5.2.1). Per standard practice for samples collected at steady state, half the lower assay limit for below the limit of quantification (BLQ) result was used. Samples collected following first dose that were BLQ were zero.

Results

Subject Disposition, Demographics and Baseline Characteristics.

This report contains data from Cohort I through Week 48 and Cohort IIA through Week 24, both with a data cut-off date of 14 February 2015. A total of 23 subjects from Thailand (n = 3) and the US (n = 20) were enrolled in Cohort I (Stage I, n = 10; Stage II, n = 13). A total of 23 subjects from South Africa (n = 4), Thailand (n = 3), and the US (n = 16) were enrolled in Cohort IIA (Stage I, n = 11; Stage II, n = 12) and received DTG.

Table 7. Subject Accountability

Population	DTG Once Daily + OBT	
	Cohort I[a]	Cohort IIA[b]
Enrolled, N	**23**	**23**
Safety (treated with IP), N	23	23
Subjects completed Week 24, n	23	22
Subjects completed Week 48, n	21	16
Off Study Drug, n	13	4
Completed Treatment	1	0
Protocol Defined Clinical Event[c]	0	1
Pregnancy	1	0
Unable to attend clinic visits	5	1
Non-compliance	4	1
Lost to Follow-up	1	1
Other[d]	1	0

a. Cohort I = ages ≥12 to <18 years of age
b. Cohort IIA = ages ≥6 to <12 years of age
c. Protocol Defined Clinical Event in this case is a virologic failure
d. Family moved out of state; subject withdrew consent

Table 8. Baseline Demographics

Demographics	DTG Once Daily + OBT	
	Cohort I[a] N=23	Cohort IIA[b] N=23
Age in Years, median (range)	15 (12 – 17)	10 (6 – 11)
Sex, n (%)		
Male	5 (22)	16 (70)
Female	18 (78)	7 (30)
Weight, mean kg (range)	55 (33 – 91)	30 (18 – 54)
Ethnicity, n (%)		
Hispanic or Latino	6 (26)	6 (26)
Race, n (%)		
African American/African Heritage	12 (52)	12 (52)
American Indian or Alaskan Native	0	0
Asian	3 (13)	3 (13)
Native Hawaiian or other Pacific Islander	0	1 (4)
White – White/Caucasian/European Heritage	8 (35)	4 (17)
More than one race	0	1 (4)
Unknown	0	2 (9)

a. Cohort I = ages ≥12 to <18 years of age
b. Cohort IIA = ages ≥6 to <12 years of age

Table 9. Summary of Baseline Characteristics

Baseline Characteristics	DTG Once Daily+ OBT	
	Cohort I[a] N=23	Cohort IIA[b] N=23
Median (range) Baseline HIV-1 RNA (log_{10} c/mL)	4.3 (3.1 – 5.4)	5.0 (2.9-7.0)
Median (range) Baseline CD4+ (cells/mm^3)	466 (11 – 1025)	645 (9 – 1700)
Median (range) Baseline CD4+ Percent	22 (1 - 39)	24 (<1 – 44)
CDC Category C[c] or HIV Stage 3, n (%)	9 (39)	6 (26)

a. Cohort I = ages ≥12 to <18 years of age
b. Cohort IIA = ages ≥6 to <12 years of age
c. Only Category C was collected

Concomitant Medications

The list of concomitant ARVs used in subjects in Cohort IIA is summarized in Table 10.
In addition, the applicant provided the list of non-ARV concomitant medications used in Cohort I and IIA. Concomitant non-ARV medications include antibiotics, analgesics, ADHD treatments, vaccines and vitamins. None of the reported concomitant medications were prohibited medications per the protocol.

Table 10. Cohort IIA: Concomitant ARV from Day 1 to Optimization and Post-Optimization

Concomitant ART	Day 1 to Optimization Cohort IIA[a] Stage I N=11 n (%)	Post Optimization Cohort IIA[a] Stage I and II N=23 n (%)
Subjects with one or more concomitant ART	8 (73)	23 (100)
3TC (lamivudine)	4 (36)	10 (44)
ABC (abacavir)	2 (18)	3 (13)
ATV (atazanavir)	0	6 (26)
d4T (stavudine)	1 (9)	1 (4)
ddI (didanosine)	3 (27)	2 (9)
DRV (darunavir)	0	4 (17)
EFV (efavirenz)	0	2 (9)
FTC (emtricitabine)	1 (9)	9 (39)
IDV (indinavir)	1 (9)	0
LPV/RTV (lopinavir/ritonavir)	4 (36)	5 (22)
RTV (ritonavir)	1 (9)	9 (39)
TDF (tenofovir)	0	11 (48)
ZDV (zidovudine)	5 (46)	4 (17)

a: 6 to < 12 years old
In two subjects receiving concomitant efavirenz, one subject received twice daily DTG.

Pharmacokinetic Results

Pharmacokinetic Subject disposition

The number of subjects providing intensive PK samples or sparse samples for the population pharmacokinetic analyses is summarized in Table 11 (by age cohort) and Table 12 (by weight). Note that the accountability of subjects is not mutually exclusive for intensive and sparse PK.

Table 11. Subject Accountability for PK Sampling by Cohort

	All (safety and efficacy population)	Number of subjects with intensive sampling	Number of subjects with sparse sampling	Total daily doses
Cohort I (12 to < 18 years)	23	10	23	50 mg (n=19) 35 mg (n=4)
Cohort II (6 to < 12 years)	23	11	13	70 mg (35 mg BID, n=1) 50 mg (n=5) 35 mg (n=6) 25 mg (n=8) 20 mg (n=3)

Table 12. Subject Accountability for PK Sampling by Weight

	DTG daily dose	Total number of subjects (safety population)	Intensive PK	Sparse PK
≥ 40 kg	50 mg (≤ 1.25 mg/kg)	24	14	24
≥ 30 to 40 kg	35 mg (0.88-1.67 mg/kg)	11	3	6
≥ 20 to 30 kg	25 mg (0.83 – 1.25 mg/kg)	8	4	4
≥ 15 to 20 kg	20 mg (1.00 – 1.33 mg/kg)	3	0	2

Reviewer comments

1. Intensive PK data from Cohort I have been previously reviewed to support the approval of DTG in the adolescent population. The data were included in this review to compare exposures across weight bands.

2. In Cohort IIA, only 13 out of 23 subjects provided sparse samples. In a recent teleconference (4/27/2016), the applicant stated that they recently discovered that some sparse PK samples for approximately 10 subjects were collected but were not shipped to the bioanalytical site. The applicant stated that (b) (4) *Detailed information as to subject IDs and site IDs for these additional samples is not available at this time.*

3. No intensive PK samples were collected from subjects in the lowest weight band (15 to <20 kg).

Pharmacokinetic Results

DTG pharmacokinetics by age cohorts and weight bands are summarized in Table 13 and 14, respectively.

Table 13. DTG Pharmacokinetic Parameters by Age Cohort (Intensive PK)

	Cohort I (12 to < 18 years old, N=10)	Cohort II (6 to < 12 years old, N=11)	Adults (TIVICAY USPI)
AUC_{24}(µg*hr/mL)	46 (43.1%)	50 (63.9%)	53
C_{max}(µg/mL)	3.49 (38.4%)	3.96 (50.0%)	3.64
C_{24h} (µg/mL)	0.90 (58.6%)	0.93 (89.3%)	1.11
Half life (hr)	12.9 (42.7%)	11.2 (43.0%)	14

Data are expressed as geometric means (CV%). Adult data are from TIVICAY USPI ®

Table 14. DTG Pharmacokinetic Parameters by Weight Band (Intensive PK)

Weight band	DTG daily dose (mg/kg dose)	C_{max} (µg/mL)	AUC_{24h} (µg·hr/mL)	C_{24hr} (µg/mL)
≥ 40 kg	50 mg (≤ 1.25 mg/kg)	3.91 (42.2%)	50.1 (51.8%)	0.99 (64.7%)
30 to < 40 kg	35 mg (0.88 to 1.67 mg/kg)	4.40 (53.8%)	64.5 (63.7%)	1.33 (92.3%)
20 to < 30 kg	25 mg (0.83 to 1.25 mg/kg)	2.84 (50.7%)	34.1 (45.9)	0.51 (43.7%)
15 to < 20 kg	20 mg (1.00 to 1.33 mg/kg)	None	None	None
Adult	50 mg	3.64 (20%)	53 (27%)	1.11 (46%)

Data expressed as geometric mean (%CV) for intensive PK and geometric median (95% CI) for population PK results, respectively. PK parameters in adults are from TIVICAY USPI.

Reviewer Comments

The proposed dolutegravir doses for pediatric subjects weighing 30 kg and above achieve exposures comparable to those observed in adults. However, DTG exposures were lower in subjects weighing 20 to < 30 kg as compared to adults. No issues (e.g., using metabolic inducers) were identified that can potentially produce lower exposures in these subjects.

<Demographic characteristics and PK parameters of four pediatric subjects weighing 20 to < 30 kg in Cohort IIA, Stage I (Intensive PK)>

Subject ID	*450399*	*507090*	*362614*	*852592*
Age (years old)	*6.7*	*9.3*	*8.1*	*7.8*
Sex	*F*	*M*	*M*	*M*
Weight (kg)	*22.6*	*21.2*	*24.9*	*21.4*
Dose mg (mg/kg)	*25 mg (1.11 mg/kg)*	*25 mg (1.18 mg/kg)*	*25 mg (1.00 mg/kg)*	*25 mg (1.17 mg/kg)*
*AUC24(µg*hr/mL)*	*49*	*58*	*28*	*18*
Cmax(µg/mL)	*3.6*	*5.2*	*2.4*	*1.5*
C24h (µg/mL)	*0.85*	*0.65*	*0.39*	*0.33*

It is unclear why significantly lower exposures were observed in this weight band. It could be due to inter-individual variability or it could potentially be due to altered absorption of tablets (including differences in food effects) in smaller children. Note that these patients are also the youngest 4 patients in Cohort IIA, Stage I. It is unlikely due to changes in metabolism as the ontogeny of UGT1A and CYP3A4 is well-characterized in this age group. In the population pharmacokinetic analysis conducted by Dr. Florian, the exposures of DTG in this weight band are marginally (~15%) lower as compared to the DTG exposures of adults.

Although population pharmacokinetic analysis results for pediatric patients weighing 15 to < 20 kg indicate that DTG exposures are comparable to those in adults, only two subjects provided samples for population pharmacokinetics and no intensive PK data were collected for this weight band.

(b) (4)

Safety Results

According to the applicant, 22 subjects (96%) in Cohort IIA reported one or more treatment-emergent clinical adverse events (AEs), the majority of which were considered to be of Grade 1 or Grade 2 intensity. The most commonly reported events were cough, nasal congestion, rash, skin lesion, and diarrhea. Sixteen (35%) subjects (n=8, Cohort I; n=8, Cohort IIA) developed drug-related AEs as assessed by the reporting investigator. Drug-related AEs reported in more than 1 subject included alanine aminotransferase increased (n=2), neutrophil count decreased (n=3), diarrhea (n=2), and dizziness (n=2). These AE counts are from both cohorts (Cohort I and IIA). The applicant stated that DTG was well tolerated and no new safety issues were identified. Refer to clinical review for detailed information.

Efficacy

The proportions of subjects with HIV-1 RNA < 400 c/mL in Cohort I (through Week 48) and IIA (through Week 24) are summarized in Table 14. In cohort I, 74% (17/23) of patients had HIV-1 RNA < 400 c/mL and 61% (14/23) of subjects had HIV-1 RNA < 50 c/mL, respectively, at Week 48. In Cohort IIA, 78% (18/23) of subjects had HIV-1 RNA < 400 c/mL and 61% (14/23) of subjects had HIV-1 RNA < 50 c/mL, respectively, at Week 24.

Table 15. Proportions of Subjects with HIV-1RNA < 400 c/mL in Cohort I and IIA

	DTG Once Daily + OBT		
	Cohort I[a] Week 24 N=23 n (%)	Cohort I[a] Week 48 N=23 n (%)	Cohort IIA[b] Week 24 N=23 n (%)
Virologic Success[c]	19 (83)	17 (74)	18 (78)
Virological Failure	4 (17)	6 (26)	4 (17)
Data in window not below threshold	4 (17)	4 (17)	4 (17)
Discontinued while not below threshold	0	2 (9)	0
No Virologic Data	0	0	1 (4)
Discontinued for Other Reasons while below threshold	0	0	1 (4)

a. Cohort I = ages ≥12 to <18 years of age
b. Cohort IIA = ages ≥6 to <12 years of age
c. Virologic success was defined as plasma HIV-1 RNA <400 c/mL; MSDF Snapshot Algorithm was used in HIV-1 RNA analysis

Subgroup analyses by weight

Proportions of subjects with HIV-1 RNA < 50 c/mL by weight are summarized in Table 15.
A numerically higher proportion of subjects with HIV-1 RNA < 50 c/mL was observed in pediatric patients weighing more than 40 kg. No definitive conclusions can be made from this analysis due to the small numbers of subjects in each group.

Table 16. Proportions of Subjects with HIV-1 RNA < 50 c/mL in Cohort I and IIA by Weight

	Proportion of subjects with HIV-1 RNA < 50 c/mL at Week 24
40 kg and above	19/24 (79%)
30 to < 40 kg	6/11 (54%)
[redacted] (b) (4)	
Adults	79% (SAILING Week 24 data)

Conclusions

- DTG exposures in pediatric patients (6 to < 18 years old) weighing 30 kg to < 40 kg are comparable to those observed in adults, thus, the proposed 35 mg dose in this weight group appears appropriate.
- [redacted] (b) (4)
- [redacted] (b) (4)
- DTG was well tolerated and no new safety issues were identified in pediatric patients (6 to < 18 years old).
- The antiviral activity of DTG in pediatric patients (6 to < 18 years old) observed in this study is acceptable.

POPULATION PHARMACOKINETIC ANALYSIS

1 RESULTS OF SPONSOR'S POPULATION PK ANALYSIS

All figures and tables, unless otherwise stated, were obtained from the Sponsor's "Population Pharmacokinetic Analysis of Dolutegravir in HIV-1 Infected Treatment-Experienced Pediatric Subjects in Study ING112578 (IMPAACT P1093)" report.

1.1 Objectives

The main objectives of the analysis were:

- To develop a population pharmacokinetic model of dolutegravir (DTG) following oral administration to HIV-1 infected pediatric subjects 6 to 12 years of age
- To evaluate subject covariates on DTG PK
- To obtain plasma DTG exposure metrics via simulation in order to evaluate the appropriateness of the current pediatric dosing regimens
- To evaluate the appropriateness of weight-band based doses of DTG tablets in children of at least 6 years of age

1.2 Datasets Used for Model Development

P1093 is an ongoing Phase I/II study of DTG in HIV-infected children and adolescents aged 6 weeks to <18 years to evaluate the PK, safety, tolerability, and efficacy of DTG when administered both prior to starting, and in combination with an optimized background regimen. Subjects are enrolled in a staggered fashion based on age. DTG doses are based on bodyweight, with the goal of achieving plasma DTG exposure similar to adults administered 50 mg QD. Doses can be adjusted based on PK and safety results of Stage I mini-cohort (N=4) and full-cohort (N=10) in each age cohort

Subjects in Cohort I (12 to 18 years) and Cohort IIA (6 to 12 years) received DTG tablet formulation of 10, 25, and 50 mg strengths. (b) (4)

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Weight-band dosing used in the trial is shown below in Table 1:

Table 1 Dolutegravir Weight-Band Dosing in P1093

Weight Band (kg)	Tablet (mg)	(b) (4)	Dispersible Tablet** (mg)
8 to <15	NA		10
15 to <20	20		15
20 to <30	25		20
30 to <40	35		30
≥40	50		NA
(b) (4)			

Source: Sponsor's Population PK report, pg 24, Table 3-2

Subjects in Stage I contribute intensive sampling from a day 5-10 visit (samples at pre-dose, 1, 2, 3, 4, 6, 8, and 24-hours) and sparse sampling at later visits (week 4 [pre- and post-dose], 12 [post-dose], and 24 [2 samples, 2-hr apart 12 to 26 hr post-dose]). Subjects in Stage II contribute sparse sampling at the same visits as the Stage 1 subjects (week 4, 12, and 24).

In the Pop PK dataset, there were 487 concentration records. A total of 99 concentration records were excluded from the analysis, including 8 BLQ concentrations, 87 samples listed as not collected or not analyzed, 1 lost sample, and 3 concentrations with no dosing records. The population PK analysis included 41 subjects that contributed a total of 388 plasma DTG concentrations. The distribution of covariates and number of subjects receiving DTG by weight band in the analysis are described in Table 2.

Table 2 Covariates and Number of Subjects Included in the Population PK Analysis

Covariate	Statistic or Category	15 to <20 kg	20 to <30 kg	30 to <40 kg	≥40 kg	Overall
Number of subjects		4	7	6	24	41
Number of samples* N (%)	Tablet Granule	7 (30) 16 (70)	51 (68) 24 (32)	59 (100) 0 (0)	231 (100) 0 (0)	348 (90) 40 (10)
Age at baseline (yrs)	Median [Min-Max] Mean (SD)	6 [6-6] 6.00 (0)	7 [6-9] 7.14 (1.07)	14 [10-15] 13.0 (2.28)	13 [10-17] 13.5 (2.27)	12 [6-17] 11.6 (3.58)
Weight at baseline (kg)	Median [Min-Max] Mean (SD)	18.5 [17.0-19.5] 18.4 (1.24)	22.1 [21.4-24.5] 22.5 (1.17)	34.4 [32.4-37.7] 34.8 (2.37)	52.3 [39.7-91.0] 56.4 (13.8)	46.4 [17.0-91.0] 43.7 (19.0)
Weight, time-varying (kg)	Median [Min-Max] Mean (SD)	19.5 [16.7-21.7] 18.7 (1.70)	22.2 [21.2-26.6] 22.8 (1.48)	33.5 [32.4-40.1] 34.7 (2.47)	51.6 [40.1-95.5] 55.8 (14.0)	45.8 [16.7-95.5] 44.0 (18.4)
Body mass index at baseline (kg/m^2)	Median [Min-Max] Mean (SD)	14.8 [14.5-16.9] 15.3 (1.12)	15.1 [14.2-16.2] 15.2 (0.691)	16.5 [14.2-18.0] 16.3 (1.31)	21.1 [18.3-39.3] 23.6 (5.57)	19.6 [14.2-39.3] 20.3 (5.85)
Body mass index, time-varying (kg/m^2)	Median [Min-Max] Mean (SD)	15.6 [14.2-17.2] 15.3 (0.960)	14.6 [13.9-17.6] 15.3 (1.11)	16.5 [14.2-18.8] 16.2 (1.44)	21.4 [18.4-41.9] 23.5 (5.04)	19.7 [13.9-41.9] 20.3 (5.55)
Body surface area at baseline (m^2)	Median [Min-Max] Mean (SD)	0.750 [0.710-0.780] 0.748 (0.0330)	0.860 [0.840-0.910] 0.867 (0.0269)	1.18 [1.11-1.25] 1.18 (0.0587)	1.53 [1.23-2.05] 1.56 (0.214)	1.39 [0.710-2.05] 1.31 (0.363)
Body surface area, time-varying (m^2)	Median [Min-Max] Mean (SD)	0.770 [0.710-0.830] 0.758 (0.0415)	0.870 [0.804-0.950] 0.874 (0.0301)	1.16 [1.11-1.30] 1.18 (0.0562)	1.52 [1.23-2.06] 1.54 (0.218)	1.36 [0.710-2.06] 1.31 (0.345)
Total bilirubin at baseline (µmol/L)	Median [Min-Max] Mean (SD)	8.60 [1.50-12.0] 7.68 (4.42)	5.10 [3.40-29.1] 8.29 (9.25)	11.2 [5.10-17.1] 10.6 (4.78)	6.80 [3.40-17.1] 7.98 (3.82)	6.80 [1.50-29.1] 8.38 (5.14)
Albumin at baseline (g/L)	Median [Min-Max] Mean (SD)	40.5 [39.0-47.0] 41.8 (3.59)	45.0 [40.0-47.0] 44.0 (2.71)	40.5 [40.0-44.0] 41.0 (1.55)	42.0 [34.0-47.0] 42.2 (3.07)	42.0 [34.0-47.0] 42.3 (2.93)
Alanine aminotransferase at baseline (IU/L)	Median [Min-Max] Mean (SD)	15.5 [11.0-87.0] 32.3 (36.7)	47.0 [12.0-304] 72.3 (103)	33.5 [12.0-43.0] 29.3 (11.5)	21.0 [7.00-244] 37.8 (50.0)	22.0 [7.00-304] 41.9 (58.0)
Aspartate aminotransferase at baseline (IU/L)	Median [Min-Max] Mean (SD)	31.0 [23.0-70.0] 38.8 (21.4)	45.0 [26.0-264] 73.7 (84.6)	39.0 [12.0-43.0] 33.0 (12.7)	29.0 [14.0-146] 40.2 (30.7)	32.0 [12.0-264] 44.7 (43.1)
Serum creatinine at baseline (mg/dL)	Median [Min-Max] Mean (SD)	0.380 [0.200-0.450] 0.353 (0.108)	0.400 [0.280-0.510] 0.391 (0.0897)	0.470 [0.340-0.600] 0.470 (0.0953)	0.530 [0.300-0.900] 0.570 (0.119)	0.500 [0.200-0.900] 0.504 (0.137)
Serum creatinine, time-varying (mg/dL)	Median [Min-Max] Mean (SD)	0.350 [0.210-0.500] 0.361 (0.126)	0.470 [0.300-0.730] 0.433 (0.103)	0.630 [0.400-0.880] 0.578 (0.136)	0.600 [0.400-1.03] 0.648 (0.119)	0.600 [0.210-1.03] 0.579 (0.154)
Creatinine clearance at baseline (mL/min/1.73 m^2)	Median [Min-Max] Mean (SD)	160 [134-296] 188 (73.5)	170 [130-238] 179 (41.3)	171 [129-244] 178 (42.0)	163 [115-256] 161 (28.8)	164 [115-296] 169 (38.3)

Creatinine clearance, time-varying (mL/min/1.73 m^2)	Median [Min-Max]	177 [124-284]	144 [92.7-224]	132 [88.4-205]	140 [89.5-193]	140 [88.4-284]
	Mean (SD)	192 (71.3)	164 (39.4)	148 (35.4)	139 (18.7)	148 (34.5)
Dose at baseline (mg)	Median [Min-Max]	16.4 [12.8-20.0]	25.0 [16.0-25.0]	35.0 [35.0-35.0]	50.0 [50.0-50.0]	50.0 [12.8-50.0]
	Mean (SD)	16.4 (4.16)	22.1 (4.25)	35.0 (0)	50.0 (0)	39.8 (13.4)
Gender N (%)	Male	4 (100)	6 (86)	1 (17)	8 (33)	19 (46)
	Female	0 (0)	1 (14)	5 (83)	16 (67)	22 (54)
Race N (%)	White	0 (0)	1 (14)	0 (0)	10 (42)	11 (27)
	Black	4 (100)	2 (29)	2 (33)	13 (54)	21 (51)
	Asian	0 (0)	1 (14)	4 (67)	1 (4)	6 (15)
	Other	0 (0)	1 (14)	0 (0)	0 (0)	1 (2)
	Unknown	0 (0)	2 (29)	0 (0)	0 (0)	2 (5)
Ethnicity N (%)	Non-Hispanic or Latino	3 (75)	4 (57)	6 (100)	16 (67)	29 (71)
	Hispanic or Latino	0 (0)	3 (43)	0 (0)	8 (33)	11 (27)
	Unknown	1 (25)	0 (0)	0 (0)	0 (0)	1 (2)
CDC classification of HIV infection N (%)	Asymptomatic or mildly symptomatic	3 (75)	4 (57)	3 (50)	7 (29)	17 (41)
	Moderately symptomatic	1 (25)	1 (14)	0 (0)	0 (0)	2 (5)
	Severely symptomatic	0 (0)	1 (14)	2 (33)	8 (33)	11 (27)
	Unknown	0 (0)	1 (14)	1 (17)	9 (38)	11 (27)
Cohort N (%)	I	0 (0)	0 (0)	4 (67)	19 (79)	23 (56)
	IIA	2 (50)	4 (57)	2 (33)	5 (21)	13 (32)
	IIB	2 (50)	3 (43)	0 (0)	0 (0)	5 (12)
Metal-cation containing products[b] N (%)	Present, Visit 1	0 (0)	2 (29)	0 (0)	0 (0)	2 (8)
	Present, Visit 2	0 (0)	2 (50)	0 (0)	1 (4)	3 (8)
	Present, Visit 3	0 (0)	2 (50)	0 (0)	1 (5)	3 (9)
	Present, Visit 4	1 (100)	2 (50)	0 (0)	1 (5)	4 (12)
Background ART as inducers N (%)	Present, Visit 1	0 (0)	0 (0)	0 (0)	1 (7)	1 (4)
	Present, Visit 2	0 (0)	1 (25)	1 (17)	15 (63)	17 (47)
	Present, Visit 3	0 (0)	1 (25)	1 (17)	14 (64)	16 (48)
	Present, Visit 4	0 (0)	1 (25)	1 (17)	14 (64)	16 (48)
Background ART as inducers classified by level of induction N (%)	Mild, Visit 1	0 (0)	0 (0)	0 (0)	1 (7)	1 (4)
	Mild, Visit 2	0 (0)	1 (25)	1 (17)	11 (46)	13 (36)
	Mild, Visit 3	0 (0)	1 (25)	1 (17)	10 (45)	12 (36)
	Mild, Visit 4	0 (0)	1 (25)	1 (17)	10 (45)	12 (36)
	Moderate-strong, Visit 1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Moderate-strong, Visit 2	0 (0)	0 (0)	0 (0)	4 (17)	4 (11)
	Moderate-strong, Visit 3	0 (0)	0 (0)	0 (0)	4 (18)	4 (12)
	Moderate-strong, Visit 4	0 (0)	0 (0)	0 (0)	4 (18)	4 (12)
Background ART as inhibitors N (%)	Present, Visit 1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Present, Visit 2	0 (0)	1 (25)	0 (0)	6 (25)	7 (19)
	Present, Visit 3	0 (0)	1 (25)	0 (0)	6 (27)	7 (21)
	Present, Visit 4	0 (0)	1 (25)	0 (0)	5 (23)	6 (18)
DTG formulation N (%)	Tablet, Visit 1	0 (0)	4 (57)	3 (100)	14 (100)	21 (81)
	Tablet, Visit 2	2 (100)	4 (100)	6 (100)	24 (100)	36 (100)
	Tablet, Visit 3	1 (100)	4 (100)	6 (100)	22 (100)	33 (100)
	Tablet, Visit 4	1 (100)	4 (100)	6 (100)	22 (100)	33 (100)

(b) (4)

Source: Sponsor's Population PK report, pg 39-41, Table 5-1

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1.3 Model Development

The Pop PK model was developed using a nonlinear mixed-effect modeling approach with NONMEM; the NONMEM VII software with the first-order conditional estimation method with interaction (FOCEI) was used.

An interim Pop PK model for DTG in pediatric subjects from P1093 using approximately 80% of the available data has previously been developed. The predictive performance of this interim model was evaluated by applying the additional data as an external validation dataset and performing simulation using a prediction-corrected visual predictive check (pcVPC) method. (b) (4) . The full model with backward deletion approach was utilized for covariate modeling.

Once the final Pop PK model was developed, the ability of the model to describe the observed data was investigated using pcVPC. The corresponding model was used to simulate 500 datasets based on the covariates, sampling times and the dosing histories contained in the dataset. Precision of the parameter estimates were evaluated using a nonparametric bootstrap procedure, generating 1000 datasets (41 subjects in each data set) through random sampling with replacement from the original data using the individual as the sampling unit.

The final Pop PK model was used to simulate plasma PK profiles of DTG in HIV-1 infected treatment-experienced pediatric subjects to assess the appropriateness of DTG dosing regimens as well as the influence of covariates. Pediatric population distributions corresponding to the six age cohorts in P1093 were constructed based on the CDC growth charts. Two hundred subjects (100 males and 100 females) were generated for each cohort for a total of 1,200 subjects. Uniform distribution of age from 6 weeks to 17 years of age was simulated for each cohort based on the study age criteria.

The simulated exposures were evaluated against the historical adult exposures. Exposure metrics included steady state AUC ($AUC_{0\text{-}tau}$), maximum concentration (C_{max}), and trough concentration (C_{tau}). All metrics were calculated assuming no intra-occasion variability. Summary statistics (geometric mean, CV%, 95% CI, median, range and percentiles (5%, 10%, 25%, 50%, 75%, 90% and 95%)) for AUC0-tau, C_{max}, and C_{tau} were computed by weight band and age cohort.

1.4 Observed Data

Observed plasma DTG concentrations versus time after dose from all subjects are displayed by weight band Figure 1.

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1.5 Population PK Model Results

In the final model, the PK of DTG following oral administration were adequately described by a one-compartment model with first-order absorption, absorption lag time and first-order elimination; absorption rate constant, absorption lag time, and relative bioavailability were formulation-specific. Random effects included inter-individual variability (IIV) as well as intra-occasion variability (IOV) on the apparent clearance (CL/F) and tablet absorption rate constant (Ka). Allometric scaling parameters for body weight were fixed to 0.75 and 1 on CL/F and V/F, respectively, as the estimates were relatively close to these value following estimation. Higher weight was associated with higher DTG CL/F and V/F. No other covariates were identified as significant in the current model. Final model parameters are summarized in Table 3. Moderate shrinkage was observed for CL/F (27.2%) and high shrinkage was observed for Ka (44.1%).

For nonparametric bootstrap analysis, 693 out of 1000 (69.3%) NONMEM runs completed successfully. Bootstrap parameter estimates (median and 95% CI) summarized from all 1000 runs are presented in Table 3. The high convergence failure rate was likely attributable to the small sample size.

The goodness-of-fit plots for the final model are shown below for all data (**Figure 2**) and for the tablet formulation (**Figure 3**). All plots demonstrate acceptable performance with no bias or trends in central tendency.

The final model was also evaluated by performing a pcVPC for all data. There was overall good agreement for the 5th, median, and 95th percentiles of DTG concentrations between observation and predictions, with slight over-predictions around absorption phase for the 5th percentile. Evaluations by weight band was difficult to interpret due to the small sample sizes

Individual model parameters were derived from the final model by an empirical Bayes estimation method. $AUC_{0\text{-}tau}$, C_{max}, and C_{tau} are summarized by body weight in Table 4.

Table 3 Parameter Estimates for the Final Dolutegravir Pediatric Population PK Model

$CL/F = 1.02 \times (WT/70)^{0.750}$
$V/F = 18.1 \times (WT/70)^{1.00}$

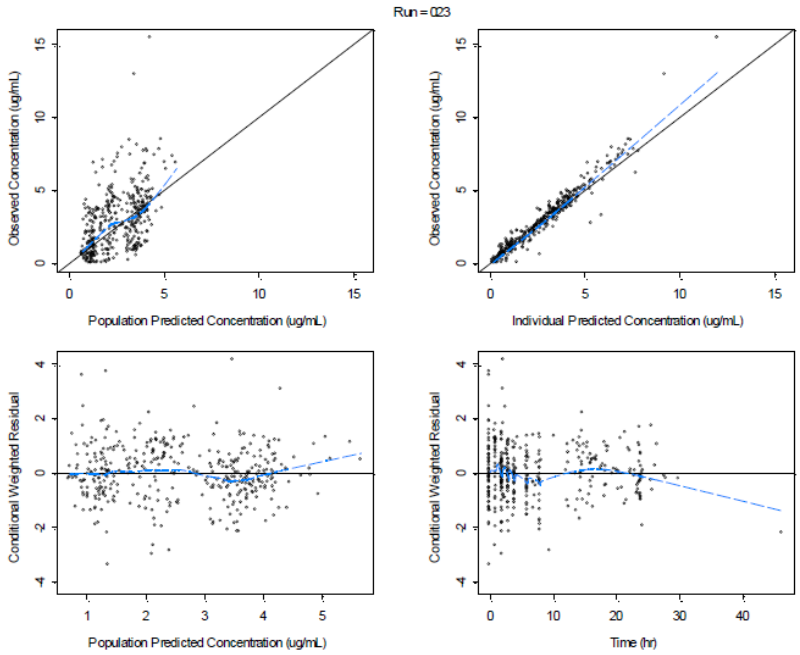
Parameter [Units]	NONMEM Estimates			Bootstrap Estimates[a]	
	Point Estimate	%RSE	95% CI	Median	95% CI
CL/F [L/hr]	1.02	8.37	0.853-1.19	1.03	0..884-1.23
V/F [L]	18.1	6.85	15.7-20.5	18.6	16.2-23.0
Ka, tablet [hr^{-1}]	0.694	35.2	0.216-1.17	0.824	0.360-3.71
					(b) (4)
ALAG, tablet [hr]	0.567	44.8	0.0692-1.06	0.565	0.00500-0.876
					(b) (4)
CL/F~WT	0.750 FIX	-	-	0.75 FIX	-
V/F~WT	1.00 FIX	-	-	1.00 FIX	-
TM_{50} [wk][b]	52.2 FIX	-	-	-	-
Hill[b]	3.43 FIX	-	-	-	-
Inter-individual or inter-occasion variability		**Shrinkage%**		**CV%***	
ω^2_{CL}	0.105	38.3	27.2	0.0262-0.184	32.4	0.105	0.0270-0.199
$\omega^2_{Ka, tablet}$	1.64	35.6	44.1	0.495-2.78	204	2.02	0.648-7.94
ω^2_{IOV-CL}	0.203	25.6	18.1-44.4	0.101-0.305	47.4	0.210	0.123-0.346
$\omega^2_{IOV-Ka, tablet}$	2.03	41.8	46.3-52.4	0.366-3.69	257	1.62	1.00E-5-4.02
Residual variability					**CV%/SD[c]**		
σ^2_{prop}	0.0188	55.3	19.6	-0.00158-0.0392	13.7	0.022	0.0029-0.0660
σ^2_{add}	0.134	45.0	19.6	0.0158-0.252	0.366	0.107	0.0131-0.240

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate*100, 95% CI = 95% confidence interval of the parameter, CL/F = apparent clearance, V/F = apparent volume of central compartment, Ka = absorption rate constant, ALAG = absorption lag time, F=relative bioavailability, WT = baseline body weight, TM_{50} = maturation half-life, Hill = slope of maturation, ω^2 = variance of inter-individual random effect, CV = coefficient of variation of proportional error ($=[\sigma^2_{prop}]^{0.5}*100$), IOV = inter-occasion variability, σ^2_{prop} = proportional component of the residual error model, σ^2_{add} = additive component of the residual error model..

The reference population is a 70 kg person.
[a] From 1000 bootstrap runs.
[b] Parameters were taken from Anderson[1] and were used in the simulation model with maturation function.
[c] Residual errors are expressed as CV% for proportional error and SD for additive error.
* $CV_{IIV_p} = \sqrt{e^{\omega^2_p} - 1}$ when ω^2_p exceeds 0.15

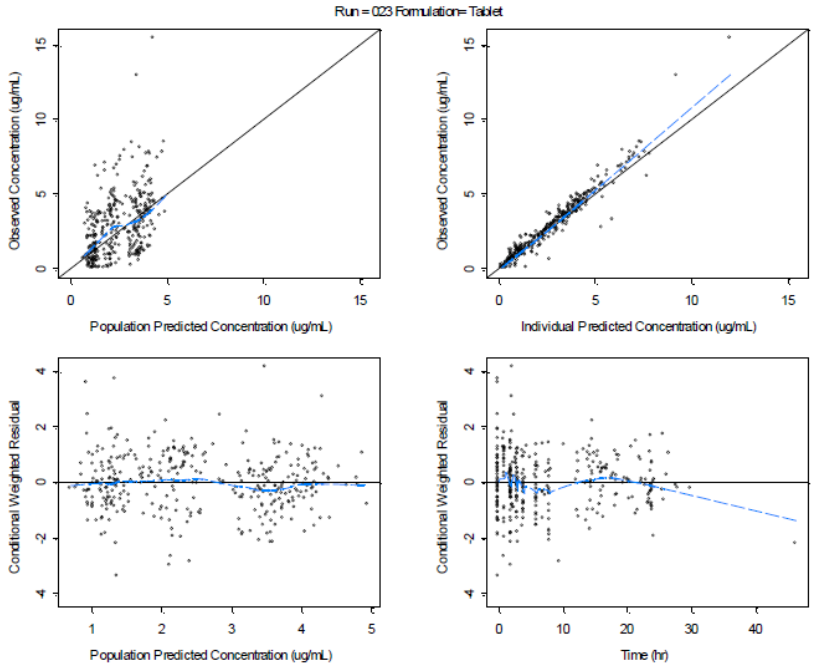
Source: Sponsor's Population PK report, pg 51, Table 5-2

Figure 2: Goodness-of-fit Plots for the Final Population PK Model, All Data (dashed blue line is Loess smoothing of data and the black line is the line of unity)



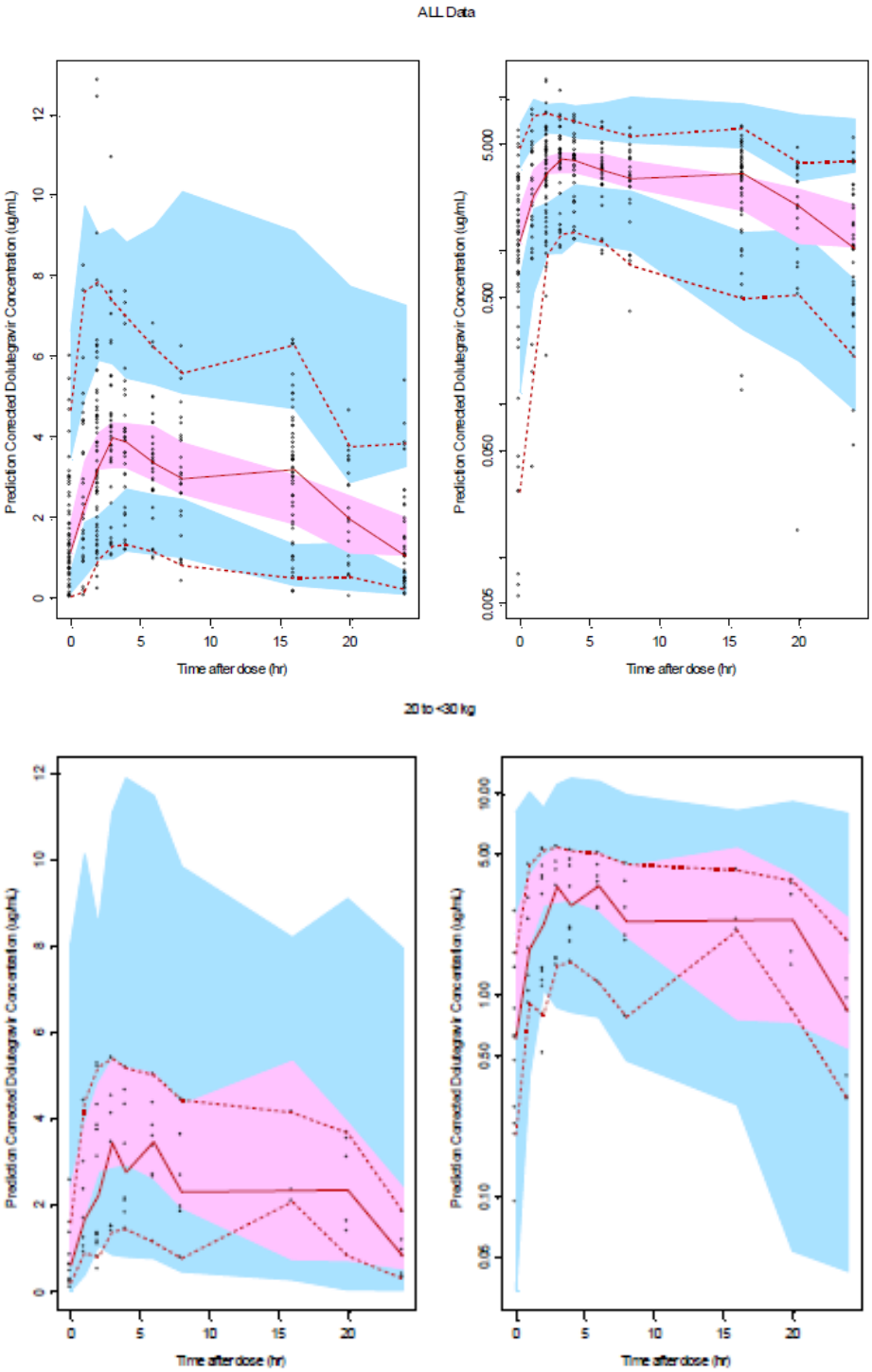
Source: Sponsor's Population PK report, pg 49, Table 5-2

Figure 3: Goodness-of-fit Plots for the Final Population PK Model, Tablet Formulation (dashed blue line is Loess smoothing of data and the black line is the line of unity)



Source: Sponsor's Population PK report, pg 106, Table 10-8

Figure 4: Predicted-Corrected Visual Predictive Check for the Final Population PK Model: All Data (top) and Pediatrics Patients 20 - <30 kg (bottom) (open circle – observed; solid line – median of observed; dashed line – 5th and 95th of observed; shaded regions – 90% prediction interval of the 5th, median, and 95th percentiles of predictions)



Source: Sponsor's Population PK report, pg 50 and 131, Figure5-3 and 10-18

Table 4 Summary of Steady-State DTG $AUC_{0\text{-}tau}$, C_{max}, and C_{tau} by Bodyweight based on EBEs

Weight Band	Statistic	C_{max} (µg/mL)	C_{τ} (µg/mL)	$AUC_{0\text{-}\tau}$ (µg·h/mL)
15 to <20 kg	N	4	4	4
	Geomean (95% CI)	4.09 (3.57-4.69)	0.903 (0.560-1.45)	55.4 (43.5-70.5)
	CV%	14.0	51.7	25.0
	Median (Min-Max)	3.91 (3.69-4.98)	0.720 (0.686-1.87)	50.1 (47.0-79.9)
	Percentiles			
	5%	3.69	0.687	47.4
	10%	3.70	0.688	47.9
	25%	3.71	0.692	49.3
	50%	3.91	0.720	50.1
	75%	4.33	1.03	57.6
	90%	4.72	1.53	71.0
	95%	4.85	1.70	75.4
20 to <30 kg	N	7	7	7
	Geomean (95% CI)	3.67 (2.97-4.53)	0.937 (0.703-1.25)	53.6 (44.6-64.4)
	CV%	29.2	40.4	25.2
	Median (Min-Max)	3.88 (2.38-5.90)	0.944 (0.599-1.66)	46.4 (43.4-80.0)
	Percentiles			
	5%	2.56	0.601	43.5
	10%	2.74	0.604	43.5
	25%	3.16	0.695	44.9
	50%	3.88	0.944	46.4
	75%	4.06	1.20	63.1
	90%	4.81	1.49	74.6
	95%	5.35	1.57	77.3
30 to <40 kg	N	6	6	6
	Geomean (95% CI)	4.01 (3.21-5.01)	1.32 (1.14-1.52)	62.2 (53.0-73.0)
	CV%	28.4	18.0	20.2
	Median (Min-Max)	4.37 (2.41-5.36)	1.32 (1.05-1.65)	65.1 (44.1-77.3)
	Percentiles			
	5%	2.72	1.07	47.1
	10%	3.04	1.09	50.1
	25%	3.80	1.15	58.1
	50%	4.37	1.32	65.1
	75%	4.59	1.51	70.3
	90%	4.99	1.60	74.6
	95%	5.17	1.62	75.9
≥40 kg	N	24	24	24
	Geomean (95% CI)	3.80 (3.42-4.21)	1.30 (1.07-1.58)	60.3 (53.4-68.2)
	CV%	26.5	52.0	31.1
	Median (Min-Max)	3.83 (2.34-7.61)	1.26 (0.422-3.59)	57.2 (32.2-132)
	Percentiles			
	5%	2.66	0.562	39.2
	10%	2.93	0.781	45.0
	25%	3.19	1.02	51.6
	50%	3.83	1.26	57.2
	75%	4.24	1.84	71.2
	90%	5.24	2.17	87.9
	95%	5.42	2.33	91.7

Source: Sponsor's Population PK report, pg 55, Table 5-4

Reviewer's comment: In general, the approach utilized by the Sponsor in the popPK model development are acceptable. However, there is a concern whether the model could be utilized for simulation in pediatric subjects weighing 20 to <30 kg. Intensive PK observations and non-compartmental analyses conducted by the sponsor suggest that $AUC_{0\text{-}tau}$ and C_{tau} in this

bodyweight band were lower than the adult target exposures and two subjects had $AUC_{o\text{-}tau}$ and C_{tau} values lower than the accepted minimum exposures. The pcVPC plot in this body weight band shows bias in the predictions for this weight band, over predicting the observed PK profile over the first 8 hours. This suggests that any simulations based on developed model would over predict exposures in this bodyweight band relative to the observed data. Data in the 30 to <40 kg bodyweight band administered 35 mg QD did not display such disparity with observations, [redacted] *in any of the weight bands.*

The reviewer conducted independent analyses to better understand the deviation between observed data in pediatrics weighing 20 to <30 kg and model predictions. Based on the model development steps provided by the Sponsor, the reviewer was able to recreate the analyses. Fixed effect parameter estimates were similar to the sponsor with less than 5% differences in all values. Similar to the Sponsor, only body weight was identified as a significant covariate in the analysis. However, the inability to identify other covariates in the pediatric popPK analysis may be due to sample size and restrictions included in the pediatric study (few subjects with concomitant medications that alter exposure). The reviewer's updated analysis did not fix scaling coefficients, and these were estimated as 0.68 and 0.96 for CL/F and V/F, respectively. These differences are not expected to substantially alter model predictions or address model performance in pediatrics 20 to <30 kg.

A comparison between intensive PK results, popPK predicted AUC from the intensive sampling period, and AUC based on individual CL predictions (removing IOV) are shown below for the seven pediatric subjects weighing 20 to <30 kg. The first four subjects were administered the tablet formulation and the last three received [redacted] *It was observed that during the intensive PK period, whether relying on NCA or popPK predictions, $AUC_{0\text{-}tau}$ for pediatrics in this bodyweight band were lower than adults, with two pediatrics having exposures less than 30 µg•hr/mL. The typical clearance predictions for these subjects, which includes sparse samples at week 4, 12, and 24 visits and which is influenced by the overall model structure, predicts values closer to the central tendency and with less variability than the observed data. This explains the conclusion in Table 4 above where combining the data from all seven pediatric subjects in this body weight band and calculating exposures based on EBEs results in median exposures higher than observed values.*

Subject ID	Conmed or Formulation	Intensive PK AUC	Early (Week 1 or 2 AUC)	PopPK AUC (typical CL)
362614		28.2	29.8	42.7
450399	Inhibitor (week 4-24)	48.7	44.5	69.6
507090	Mild inducer (week 4 to 24)	54.5	60.7	45.6
8502592		18.0	25.5	42.9
362960*	[redacted]		**69.4**	**59.1**
691120*			**65.6**	**57.2**

8505371*	(b) (4)		**35.5**	**47.7**
Geometric Mean (CV%)		34.1 (55%)	44.2 (42%)	51.3 (19%)

(b) (4)

(b) (4)

1.6 Simulations for Pediatric Dosing

To evaluate the appropriateness of the weight-band based dosing regimen for DTG tablet, individual steady-state $AUC_{0\text{-}tau}$, C_{max}, and C_{tau} for once daily dosing and the proposed pediatric dosing were simulated using the final popPK model. The entire simulation contained 1,200 subjects (200 subjects per age cohort × 6 cohorts), with equal distribution of males and females. Steady-state exposure parameters were summarized by weight band in Table 5.

Table 5 Simulated Steady-State DTG with Allometric Scaling and Maturation Function by Weight Band and Formulation

Weight Band	Statistic	C_{max} (µg/mL)		C_{τ} (µg/mL)		$AUC_{0-\tau}$ (µg·hr/mL)	
		Tablet	(b) (4)	Tablet	(b) (4)	Tablet	(b) (4)
15 to <20 kg	N	114		114		114	
	Dose (mg)	20		20		20	
	10th Median (95% PI)	2.55 (2.19, 2.97)		0.313 (0.200, 0.442)		23.9 (18.4, 30.7)	
	Geomean Median (95% PI)	4.36 (4.04, 4.70)		1.12 (0.915, 1.37)		53.2 (46.9, 60.1)	
	90th Median (95% PI)	7.15 (6.39, 8.07)		3.52 (2.92, 4.42)		111 (97.5, 129)	
	% <10th of Adult[1]	7.89		17.5		13.2	
	% >90th of Adult[1]	50.9		27.2		28.9	
	% <Min Target[2]	NA		24.6		11.4	
	% >Max Target[2]	NA		NA		18.4	
20 to <30 kg	N	226		226		226	
	Dose (mg)	25		25		25	
	10th Median (95% PI)	2.43 (2.16, 2.72)		0.319 (0.222, 0.409)		22.9 (19.3, 27.1)	
	Geomean Median (95% PI)	4.19 (3.94, 4.46)		1.15 (0.992, 1.31)		52.4 (48.2, 56.8)	
	90th Median (95% PI)	6.99 (6.39, 7.69)		3.67 (3.00, 4.21)		112 (99.4, 125)	
	% <10th of Adult[1]	8.85		16.8		13.7	
	% >90th of Adult[1]	46.2		27.9		28.3	
	% <Min Target[2]	NA		23.9		11.9	
	% >Max Target[2]	NA		NA		17.7	
30 to <40 kg	N	179		179		179	
	Dose	35		35		35	
	10th Median (95% PI)	2.54 (2.20, 2.83)		0.367 (0.240, 0.516)		25.1 (20.9, 30.6)	
	Geomean Median (95% PI)	4.34 (4.05, 4.59)		1.29 (1.10, 1.46)		56.4 (51.3, 61.3)	
	90th Median (95% PI)	7.28 (6.65, 8.16)		3.96 (3.33, 4.74)		119 (106, 137)	
	% <10th of Adult[1]	7.82		14.0		11.7	
	% >90th of Adult[1]	49.2		32.4		32.4	
	% <Min Target[2]	NA		20.7		10.1	
	% >Max Target[2]	NA		NA		20.7	
≥40 kg	N	213		213		213	
	Dose (mg)	50		50		50	
	10th Median (95% PI)	2.41 (2.15, 2.67)		0.391 (0.294, 0.529)		25.4 (21.5, 29.6)	
	Geomean Median (95% PI)	4.25 (4.05, 4.50)		1.37 (1.19, 1.56)		57.0 (53.4, 61.6)	
	90th Median (95% PI)	7.38 (6.78, 8.16)		4.14 (3.58, 4.94)		124 (112, 141)	
	% <10th of Adult[1]	8.92		12.7		11.3	
	% >90th of Adult[1]	47.4		35.2		33.8	
	% <Min Target[2]	NA		18.3		9.86	
	% >Max Target[2]	NA		NA		22.1	

Source: Sponsor's Population PK report, pg 62-63, Table 5-6

The exposure parameters were fairly consistent across the different weight bands for the tablet formulation. The median of the geometric means of C_{max}, C_{tau}, and AUC_{0-tau} were higher in the pediatric population than the respective adult exposure at 50 mg daily dose. The percentage of pediatrics AUC_{0-tau} exceeding the 90th percentile of adults was 28-34% across all weight bands, whereas 11-13% fell below the 10th percentile. Pediatric exposures had greater variability, but a similar central tendency to adults.

Reviewer's comment: Simulations based on the popPK model suggest that target $AUC_{0\text{-}tau}$ and C_{tau} would be achieved with the tablet formulation in all pediatric bodyweight bands. The reviewer agrees with this conclusion with respect to the proposed tablet dosing in pediatrics weighing 30 to <40 kg (proposed in the current submission) and ≥40 kg (already approved). The intensive PK data is in good agreement with the simulations regarding mean C_{tau} and $AUC_{0\text{-}tau}$ and support the proposed dosing of 35 mg QD in pediatrics weighing 30 to <40 kg.

(b) (4)

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/s/

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05/11/2016

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