CLINICAL PHARMACOLOGY REVIEW

sNDA # (SDN)	215413/s-02 (SDN 41) and 205551/s-31 (SDN 1000)
Submission Type	Pediatric efficacy supplement
Submission Date	12/15/2022
Applicant	ViiV Healthcare Company (ViiV)
Brand Name	NDA 215413: TRIUMEQ PD® Tablets for Oral Suspension; NDA 205551: TRIUMEQ® Tablets
Generic Name	Dolutegravir; Abacavir; Lamivudine
Dosage Form	TRIUMEQ PD tablets for oral suspension: 5 mg/60 mg/30 mg; TRIUMEQ tablets: 50 mg/600 mg/300 mg
Indication	**Approved:** Indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 10 kg.[1] **Proposed:** To expand the use of TRIUMEQ PD® Tablets for Oral Suspension to pediatric patients aged at least 3 months old and weighing at least 6 kg.
OCP Review Team	Clinical Pharmacology Reviewer Yi Zhang, MD, PhD Pharmacometrics Reviewer: Jiajun Liu, PharmD, MSc Pharmacometrics Team Leader: Justin Earp, PhD Clinical Pharmacology Team Leader: Su-Young Choi, PharmD, PhD

Table of Contents

1. Executive Summary

TRIUMEQ is a fixed dose combination (FDC) of dolutegravir (DTG, integrase strand transfer inhibitor), abacavir (ABC, nucleoside analogue reverse transcriptase inhibitor, NRTI) and lamivudine (3TC, NRTI) approved for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 10 kg.

- TRIUMEQ tablet (NDA 205551, DTG/ABC/3TC 50 mg/600 mg/300 mg) was originally approved in 2014 for adult patients, and in 2017 to include pediatric patients weighing at least 40 kg.

[1] https://www.accessdata fda.gov/drugsatfda_docs/label/2022/205551s029,215413s001lbl.pdf, action date 10/07/2022

- In 2022, efficacy supplement 205551/s-28 was approved with TRIUMEQ tablet in HIV-1 infected pediatric patients weighing 25 kg to <40 kg; and an original NDA 215413 for a new pediatric formulation, TRIUMEQ PD tablet for oral suspension (DTG/ABC/3TC 5 mg/60 mg/30 mg), was approved for pediatric patients weighing 10 kg to <25 kg. The approval was based on bridging the safety and efficacy of the individual components previously established with TIVICAY (DTG), EPIVIR (3TC), and ZIAGEN (ABC) in pediatric patients down to infants and overall benefit-risk assessment.
- **In the current efficacy supplements (215413/s-02 & 205551/s-31), ViiV proposed to extend the indication of TRIUMEQ PD to pediatric patients weighing at least 6 kg and aged at least 3 months old.** The proposed update to TRIUMEQ PD/TRIUMEQ dosing, inclusion of dosing for pediatric patients weighing 6 kg to <10 kg, is denoted by the blue shaded box in Error! Reference source not found..

Table 1. Proposed dosing regimen of TRIUMEQ PD in pediatric patients

Pediatric Population Body Weight	Number of Tablets (Once daily)	Recommended Daily Dose
TRIUMEQ PD Tablets (6 kg to <25 kg)		
6 kg to <10 kg	3	180 mg ABC, 15 mg DTG, and 90 mg 3TC
10 kg to <14 kg	4	240 mg ABC, 20 mg DTG, and 120 mg 3TC
14 kg to <20 kg	5	300 mg ABC, 25 mg DTG, and 150 mg 3TC
20 kg to <25 kg	6	360 mg ABC, 30 mg DTG, and 180 mg 3TC
TRIUMEQ Tablets (≥25 kg)		
≥25 kg	1	600 mg ABC, 50 mg DTG, and 300 mg 3TC

To support the proposed dosing regimen, the Applicant submitted the safety, antiviral activity, and pharmacokinetic (PK) results from the IMPAACT 2019 trial (Phase 1/2 Study of Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in in HIV-1-Innfected Children Less than 12 Years of Age) and a population pharmacokinetic (PopPK) analyses report. Following review of 215413/s-02, the review team concluded that the data were sufficient to approve TRIUMEQ PD for the treatment of pediatric HIV patients weighing at least 6 kg. From a clinical pharmacology perspective, the approval is primarily based on demonstrating similarity in systemic exposures of DTG, ABC, 3TC (administered as FDC) in pediatric patients 6 kg to <10 kg, pediatric patients weigh bands from 10 kg to <40 kg, and those observed at the recommended doses of individual products in adults or pediatrics.

The current applications also seek to fulfill Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs) 2768-1 and 4247-1 and the TRIUMEQ Written Request-Amendment 2 issued to NDA 205551 and NDA 215413.

PREA PMR 2768-1 (NDA 205551)/4247-1 (NDA 215413): Conduct a pediatric trial to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets and tablets for oral suspension in HIV infected pediatric participants 2 years to less than 6 years of age. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets and tablets for oral suspension in pediatric participants should be evaluated for a minimum of 24 weeks.

Written Request-Amendment 2: to investigate the potential use of ABC/DTG/3TC as part of a FDC drug product, Triumeq, in treating HIV-1 infected pediatric patients weighing 6 kg to less than 40 kg.

2. OCP Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that the application is approvable from a clinical pharmacology perspective, to extend the indication to pediatric patients aged at least 3 months and weighing at least 6 kg. In addition, PREA PMRs (2768-1 for NDA 205551, and 4247-1 for NDA 215413, respectively) and the requirements of the Written Request-Amendment 2 are fulfilled from a clinical pharmacology perspective.

3. Summary of Key Clinical Pharmacology Findings

The primary objectives of this review are:

1) to evaluate the appropriateness of the proposed dosing regimen of TRIUMEQ PD in pediatric patients weighing 6 kg to <10 kg; and
2) to assess pediatric PK data for DTG, ABC, and 3TC with the recommended dosing of TRIUMEQ PD and TRIUMEQ from Trial IMPAACT 2019.

Proposed dosing regimen of TRIUMEQ PD in pediatric patients weighing 6 kg to <10 kg

As shown in **Table 2**, the proposed dosing regimen of each component in TRIUMEQ PD is similar (identical or slightly higher) to that approved with individual products.

Table 2. Proposed dosing regimen of TRIUMEQ PD in pediatric patients 6 kg to <10 kg vs. approved daily dosing of DTG, ABC, and 3TC with individual products

Drug	TIVICAY PD (DTG)	ZIAGEN Oral Solution (ABC)	EPIVIR Oral Solution (3TC)	TRIUMEQ PD (DTG/ABC/3TC)
Dolutegravir	15 mg	N/A	N/A	15 mg (3 tablets)
Abacavir	N/A	16 mg/kg/day (96–160 mg)	N/A	180 mg (3 tablets)
Lamivudine	N/A	N/A	10 mg/kg/day (60–100 mg)	90 mg (3 tablets)

- TIVICAY PD is approved in pediatric patients aged at least 4 weeks and weighing at least 3 kg
- ZIAGEN oral solution and EPIVIR oral solution are approved in pediatric patients aged at least 3 months.

The noncompartmental analysis (NCA) estimated intensive PK parameters (i.e., $AUC_{0\text{-}24h}$, C_{max}, and C_{24h}) for DTG, ABC, and 3TC with TRIUMEQ PD and TRIUMEQ are summarized in **Table 3**.

Table 3. PK parameters of ABC, DTG and 3TC for all weigh bands in Trial IMPAACT 2019

Drug	Weight Band	N^	Pharmacokinetic Parameter[#]		
			C_{max} (mcg/mL)	$AUC_{0\text{-}24h}$ (mcg·h/mL)	C_{24h} (mcg/mL)
Abacavir	6 to <10 kg	7	7.30 (20)	17.7 (34)	0.003 (128)
	10 to <14 kg	7	8.36 (44)	19.8 (51)	0.005 (127)
	14 to <20 kg	7	6.26 (31)	15.1 (40)	0.003 (108)
	20 to <25 kg	7	6.65 (28)	17.4 (19)	0.004 (85)
	25 to <40 kg	7	9.04 (22)	25.7 (15)	0.011 (229)
Dolutegravir	6 to <10 kg	7	7.40 (28)	75.9 (34)	0.90 (68)
	10 to <14 kg	7	8.85 (21)	91.0 (36)	1.22 (77)
	14 to <20 kg	7	7.04 (17)	71.4 (23)	0.79 (44)

	20 to <25 kg	7	7.29 (17)	84.4 (26)	1.35 (95)
	25 to <40 kg	7	6.25 (21)	71.8 (14)	0.98 (28)
Lamivudine	6 to <10 kg	7	2.29 (40)	10.7 (46)	0.055 (39)
	10 to <14 kg	7	3.55 (19)	14.2 (24)	0.046 (48)
	14 to <20 kg	7	2.92 (23)	13.0 (16)	0.058 (37)
	20 to <25 kg	7	2.99 (32)	14.5 (17)	0.060 (18)
	25 to <40 kg	7	4.15 (29)	21.7 (26)	0.084 (35)

* Refer to Table 1 for dosing of ABC, DTG, 3TC in TRIUMEQ or TRIUMEQ PD

Data are expressed as geometric mean (%CV)

^ Number of participants who were dose evaluable in each weight band.

Overall, the proposed dosing regimen of TRIUMEQ PD for pediatric patients 6 to <10 kg achieved comparable exposures to those observed at the recommended doses in adults (with individual products) and in older pediatric patients (with TRIUMEQ/TRIUMEQ PD or individual products).

4. Labeling Recommendations

Clinical pharmacology related labeling recommendations are summarized as follows.

1. Addition of the new dosing regimen of TRIUMEQ PD in pediatric patients aged at least 3 months and weighing at least 6 kg (3 tablets once daily) throughout the USPI.
2. Addition of the summary of study findings from the IMPAACT 2019 trial in Sections 8 and 12.3 including pediatric intensive PK data from IMPAACT 2019 trial for all weight bands.
3. Dosing instructions in pediatric patients with renal impairment are included in the labeling: TRIUMEQ and TRIUMEQ PD are not recommended in patients with creatinine clearance (CLcr) <30 mL/min and pediatric patients with a similar degree of renal impairment with age-appropriate assessment of renal function (See Section 5.2 of this review for details).

5. Appendix

5.1. Individual Study Review: Trial IMPAACT 2019

Link of study report: GSK Document Number 2022N501029_00

Title: Phase 1/2 Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/ Lamivudine Dispersible (DT) and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Study Design: The study was designed as an open-label, multiple-dose, non-comparative PK, and safety study of DTG/ABC/3TC DTs and Tablets in antiretroviral therapy (ART)-naïve and ART-experienced children with HIV aged <12 years old and weighing 6 to <40 kg. The study was planned to be conducted among at least 50 and up to 75 children, with at least 25 children <6 years of age and at least 25 children 6 to <12 years of age. Enrolled children were to receive study drug for at least 48 weeks (through the week 48 visit) and for up to 144 weeks.

Baseline demographic characteristics by enrollment weight band in IMPAACT 2019

Demographics	≥6 to <10 kg N=9	≥10 to <14 kg N=12	≥14 to <20 kg N=15	≥20 to <25 kg N=10	≥25 kg N=11	Total N=57
Age in Years, median (range)	1.350 (0.98, 2.02)	3.555 (1.51, 4.51)	6.440 (3.88, 9.58)	8.405 (6.38, 8.91)	9.740 (8.68, 11.28)	6.380 (0.98, 11.28)
Age Category, n (%)						
<6 years	9 (100.0)	12 (100.0)	7 (46.7)	0	0	28 (49.1)
≥6 to <12 years	0	0	8 (53.3)	10 (100.0)	11 (100.0)	29 (50.9)
Sex at Birth, n (%)						
Female	5 (55.6)	7 (58.3)	5 (33.3)	3 (30.0)	6 (54.5)	26 (45.6)
Male	4 (44.4)	5 (41.7)	10 (66.7)	7 (70.0)	5 (45.5)	31 (54.4)
Baseline Weight (kg), median (range)	9.200 (8.15, 9.58)	12.900 (10.26, 13.80)	17.000 (14.40, 19.55)	21.475 (20.00, 24.60)	28.500 (25.60, 39.30)	17.000 (8.15, 39.30)
BMI (kg/m²), median (range)	14.30 (13.2, 18.9)	14.85 (13.5, 17.4)	13.90 (11.7, 15.5)	14.45 (13.4, 15.4)	15.90 (14.8, 21.6)	14.70 (11.7, 21.6)
Ethnicity, n (%)						
Hispanic or Latino	0	0	0	0	3 (27.3)	3 (5.3)
Non-Hispanic or Latino	9 (100.0)	12 (100.0)	15 (100.0)	10 (100.0)	7 (63.6)	53 (93.0)
Unknown	0	0	0	0	1 (9.1)	1 (1.8)
Race, n (%)						
Asian	3 (33.3)	1 (8.3)	7 (46.7)	4 (40.0)	3 (27.3)	18 (31.6)
Black or African American	6 (66.7)	10 (83.3)	7 (46.7)	6 (60.0)	8 (72.7)	37 (64.9)
Unknown	0	0	1 (6.7)	0	0	1 (1.8)
White	0	1 (8.3)	0	0	0	1 (1.8)
Country, n (%)						
Botswana	4 (44.4)	2 (16.7)	3 (20.0)	2 (20.0)	2 (18.2)	13 (22.8)
South Africa	2 (22.2)	7 (58.3)	4 (26.7)	3 (30.0)	1 (9.1)	17 (29.8)
Thailand	3 (33.3)	1 (8.3)	6 (40.0)	4 (40.0)	3 (27.3)	17 (29.8)
United States	0	2 (16.7)	2 (13.3)	1 (10.0)	5 (45.5)	10 (17.5)

Analysis Populations and Groups from IMPAACT 2019 by Enrollment Weight Band (All Enrolled Population)

Population/Groups	≥6 to <10 kg N=9	≥10 to <14 kg N=12	≥14 to <20 kg N=15	≥20 to <25 kg N=10	≥25 kg N=11	Total N=57
All Treated Population	9 (100.0)	12 (100.0)	15 (100.0)	10 (100.0)	11 (100.0)	57 (100.0)
Dose Evaluable Participants	7 (77.8)	7 (58.3)	7 (46.7)	7 (70.0)	7 (63.6)	35 (61.4)
CVF Participants	1 (11.1)	0	0	0	0	1 (1.8)

Dosing regimen: Table 1 gives the dose information of TRIUMEQ PD (5 mg/60 mg/30 mg) and TRIUMEQ tablet (50 mg/600 mg/300 mg) for subjects enrolled in IMPAACT 2019.

Concomitant medications: Due to interactions that decrease the concentration of DTG, etravirine, efavirenz, nevirapine, fosamprenavir/ritonavir, tipranavir/ritonavir, dofetilide, oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St. John's wort should not be coadministered. Study participants who require cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications should take these medications at least six hours before or at least two hours after taking ABC/DTG/3TC. Alternatively, ABC/DTG/3TC and supplements containing calcium or iron can be taken together with food.

Key inclusion criteria:

- Pediatric patients with confirmed HIV-1 infection who, at entry, were <12 years of age, weighing 6 to <40 kg,
- Either ART-naïve or on a stable ART regimen. The ART-experienced children were required to have a suppressed HIV viral load (HIV-1 RNA <200 c/mL) for at least 6 consecutive months prior to entry.
- eGFR ≥60 mL/min/1.73 m^2 at screening.

Key exclusion criteria:

- Known resistance to ABC, DTG, or 3TC,
- Clinical evidence of pancreatitis,
- Receiving rifampicin-containing TB treatment,
- Active AIDS-defining opportunistic infection

PK assessment: At week 1, participant underwent either intensive PK sampling (collected at pre-dose, and 1, 2, 3, 4, 6, 8, 24 hours post dose) or sparse PK sampling. Intensive PK sampling was performed on the first 5-7 children enrolled in each weight band. After week 1, all participants underwent sparse PK sampling through week 48 or study discontinuation. Two samples were collected following drug administration at week 1, at least two hours apart. At weeks 2 and 6, samples were planned to be collected 22-26 hours after the previous dose of study drug. At all visits there was no restriction on the timing of sample collection. However, across participants, samples should be collected at different times throughout the 24-hour dosing interval.

Bioanalytical site and methods: The bioanalytical site is (b) (4) (b) (4) The bioanalytical methods for the quantitation of ABC, 3TC, DTG, and ultrasensitive abacavir from human plasma were validated, and the precision and accuracy met acceptance criteria for standard curve and QC runs.

Reviewer's comment: Based on the recent inspection result for the same bioanalytical site (No Action Indicated. Refer to OSIS review dated 4/3/2020 under NDA (b) (4)) and the fact that pediatric dosing regimens of individual products have been established, the clinical pharmacology review team determined that a request for a site inspection is not needed for the current study (IMPAACT 2019).

Pharmacokinetic Results: The intensive PK results of trial IMPAACT 2019 with the final recommended doses by weight band are summarized in **Table 3**.

Comparison of PK parameters across studies

Table 4. DTG exposure in IMPAACT 2019 vs. historical adult and pediatric trials

Population/ Dose Frequency	Study, Population, Number of Participants, Dose	AUC0-24 (µg.h/mL) GM (95% CI)	C24 (µg/mL) GM (95% CI)	Cmax (µg/mL) GM (95% CI)
DTG/ABC/3TC DT & Tablet Once Daily Doses[a]	**IMPAACT 2019,** ≥6 to <10 kg, n=7, 15 mg DT	**75.9** (56.0, 102.8)	**0.91** (0.52, 1.61)	**7.40** (5.74, 9.53)
	IMPAACT 2019, ≥10 to <14 kg, n=7, 20 mg DT	**91.0** (65.6, 126.1)	**1.22** (0.65, 2.29)	**8.85** (7.28, 10.75)
	IMPAACT 2019, ≥14 to <20 kg, n=7, 25 mg DT	**71.4** (57.7, 88.5)	**0.79** (0.53, 1.16)	**7.04** (6.02, 8.23)
	IMPAACT 2019, ≥20 to <25 kg, n=7, 30 mg DT	**84.4** (66.5, 107.2)	**1.35** (0.64, 2.84)	**7.29** (6.26, 8.50)
	IMPAACT 2019, ≥25 kg, n=7, 50 mg Tablet	**71.8** (63.2, 81.6)	**0.98** (0.76, 1.26)	**6.25** (5.18, 7.55)
Historical Children Living with HIV-1 Once Daily[b]	**P1093 & ODYSSEY,** ≥6 to <10 kg, n=17, 15 mg DT	**57.2** (40.4, 80.9)	**0.71** (0.38,1.30)	**5.27** (4.14, 6.7)
	P1093 & ODYSSEY, ≥10 to <14 kg, n=13, 20 mg DT	**68.8** (52.3, 90.5)	**0.98** (0.590,1.61)	**5.99** (4.92, 7.29)
	P1093 & ODYSSEY, ≥14 to <20 kg, n=19, 25 mg DT	**59.0** (48.1, 72.4)	**0.73** (0.53, 1.00)	**5.97** (4.91, 7.26)
	P1093 & ODYSSEY, ≥20 kg, n=9, 30 mg DT	**71.5** (58.7, 87.1)	**0.76** (0.46,1.25)	**7.16** (5.90,8.69)
	P1093 & ODYSSEY, ≥20 kg, n=49, 50 mg Tablet	**54.98** (48.9, 61.9)	**0.78** (0.66, 0.92)	**4.92** (4.40, 5.49)
Historical Adults Living with HIV-1 Once Daily	Population PK Analysis in HIV-infected, treatment-naïve adults, n=449, 50 mg Tablet[c]	**53.6** (52.3, 55.0)	**1.11** (1.06, 1.15)	**3.67** (3.61, 3.74)
	Population PK Analysis in HIV-infected, treatment-experienced adults, n=371, 50 mg Tablet[d,e]	**45.1** (43.4, 47.0)	**0.83** (0.77, 0.89)	**3.26** (3.18, 3.36)

Table 5. ABC exposure in IMPAACT 2019 vs. historical adult and pediatric trials

Population/ Dose Frequency	Study, Population, Number of Participants, Dose	AUC0-24 (µg.h/mL) GM (95% CI)	Cmax (µg/mL) GM (95% CI)
DTG/ABC/3TC DT & Tablet Once Daily Doses[a]	**IMPAACT 2019,** ≥6 to <10 kg, n=7, 180 mg DT	**17.66** (13.0, 23.9)	**7.30** (6.05, 8.81)
	IMPAACT 2019, ≥10 to <14 kg, n=7, 240 mg DT	**19.77** (12.7, 30.7)	**8.36** (5.68, 12.31)
	IMPAACT 2019, ≥14 to <20 kg, n=7, 300 mg DT	**15.09** (10.5, 21.6)	**6.26** (4.73, 8.28)
	IMPAACT 2019, ≥20 to <25 kg, n=7, 360 mg DT	**17.35** (14.5, 20.7)	**6.65** (5.17, 8.56)
	IMPAACT 2019, ≥25 kg, n=7, 600 mg Tablet	**25.74** (22.5, 29.4)	**9.04** (7.40, 11.04)
Historical Children Living with HIV-1 Once Daily	**PENTA-15**, 3 to 36 months, n=18, 16mg/kg once daily[b]	**11.6** (9.89,13.5)	**4.68** (3.86, 5.67)
	PENTA-13, 2 to 12 years; n=14, 16mg/kg once daily[c]	**13.4** (11.8, 15.2)	**4.80** (4.04, 5.71)
	ARROW, 3 to 12 years; n=36, WHO once daily tablet regimen[d]	**15.3** (13.3, 17.5)	**6.84** (5.92, 7.90)
Historical Adults Living with HIV-1 Once Daily	**CAL102120**, Adults, n=27, 600mg once daily[e,f]	**8.52** (7.23, 10.0)	**3.85** (3.34, 4.42)
	CAL10001, Adults, n=25, 600mg single dose[g]	**14.2** (12.90, 15.6)	**4.69** (4.15, 5.30)

Table 6. 3TC exposure in IMPAACT 2019 vs. historical adult and pediatric trials

Population/ Dose Frequency	Study, Population, Number of Participants, Dose	AUC0-24 (µg.h/mL) GM (95% CI)	Cmax (µg/mL) GM (95% CI)
DTG/ABC/3TC DT & Tablet Once Daily Doses[a]	**IMPAACT 2019,** ≥6 to <10 kg, n=7, 90 mg DT	**10.66** (7.1, 16.0)	**2.29** (1.61, 3.27)
	IMPAACT 2019, ≥10 to <14 kg, n=7, 120 mg DT	**14.17** (11.4, 17.6)	**3.55** (2.99, 4.21)
	IMPAACT 2019, ≥14 to <20 kg, n=7, 150 mg DT	**13.02** (11.3, 15.0)	**2.92** (2.36, 3.60)
	IMPAACT 2019, ≥20 to <25 kg, n=7, 180 mg DT	**14.50** (12.5, 16.9)	**2.99** (2.24, 3.99)
	IMPAACT 2019, ≥25 kg, n=7, 300 mg Tablet	**21.73** (17.1, 27.6)	**4.15** (3.18, 5.41)
Historical Children Living with HIV-1 Once Daily	**PENTA-15**, 3 to 36 months, n=17, 8 mg/kg once daily[b]	**8.7** (7.5, 10.1)	**1.87** (1.65, 2.13)
	PENTA-13, 2 to 12 years; n=19 8 mg/kg once daily or tablets (150 mg)[c]	**9.8** (8.6, 11.1)	**2.09** (1.80, 2.42)
	ARROW, 3 to 12 years; n=35 WHO Once Daily tablet Regimen[d]	**12.9** (11.4, 14.9)	**3.17** (2.76, 3.64)
	Bruno, Adults, n=12, 300 mg Once Daily[e]	**16.6** (±4.15)	**3.46** (±0.85)
	EPV10001, Adults, n=60, 300 mg Once Daily[f]	**8.7** (8.3, 9.1)	**1.96** (1.84, 2.11)
Historical Adults Living with HIV-1 Once Daily	**NUCB1004**, Adults, n=12, 300 mg single dose[g,h]	**10.6** (9.9, 11.3)	**3.28** (2.95, 3.65)
	CAL10001, Adults, n=25, 300 mg single dose[h,i]	**12.6** (11.6, 13.6)	**2.64** (2.37, 2.95)

Reviewer's assessment

- The PK data obtained in IMPAACT 2019 support the approval of the proposed dosing regimen of TRIUMEQ PD in pediatric patients weighing 6 to < 10 kg. Exposures were primarily compared to those observed in pediatric patients following the administration of individual products in the same or similar weight bands. See below for the comparison of individual components.
- In conclusion, PK parameters ($AUC_{0\text{-}24h}$, C_{max}, and C_{24h}) for DTG, ABC, and 3TC with TRIUMEQ PD in pediatric patients demonstrated similar values across all weight bands within trial IMPAACT 2019 and considered comparable to those observed in adults and pediatric patients at the approved doses of individual products. In certain weight bands (especially for patients weighing 25 kg to < 40 kg and receiving the adult dosing regimen), pediatric exposures were higher than those observed in adults. Safety data supporting such high exposures have been previously reviewed for individual products.
- In addition, the results also confirmed the appropriateness of approved dosing regimens of TRIUMEQ PD in pediatric patients weighing 10 kg and above. In the previous efficacy supplement, the approval of TRIUMEQ PD was solely based on the relative bioavailability study results in adults and approved pediatric dosing regimens of individual products. At that time, no PK data in pediatric patients receiving TRIUMEQ PD were submitted. In this submission, the Applicant has provided PK data for all weight bands following the administration of TRIUMEQ PD.
- The PopPK analysis results are consistent with the NCA analyses and support the approval (Refer to Section 5.3 for full details).

Dolutegravir

- The proposed DTG dose of 15 mg for pediatric patients weighing 6 to < 10 kg is identical to the approved pediatric dose with TIVICAY PD in patients of the same weight band. The DTG exposures following the administration of TRIUMEQ PD (DTG 15 mg) in this weight band were slightly higher than the historical data listed in **Table 4** (combined analysis of IMPAACT 1093 and ODYSSEY), but similar to those observed in IMPAACT 1093 in the same weight band ($AUC_{0\text{-}24h}$ of 63.25 µg·h/mL in pediatric patients ≥ 6 months and $AUC_{0\text{-}24h}$ of 85.49 µg·h/mL in pediatric patients < 6 months) and PopPK predicted $AUC_{0\text{-}24h}$ of 76 µg·h/mL following the administration of the approved dose of TIVICAY PD in pediatric patients (Source: Clinical Pharmacology review of NDAs 204790/s25 and 213983, DARRTS date 5/18/2020).

Abacavir

- The proposed dosing of ABC is 180 mg in pediatric patient weighing 6 to <10 kg, which is 1.875-fold higher than the recommended ZIAGEN dose for a 6-kg subject, and >1.125-fold higher than the recommended ZIAGEN doses for subjects weighing <10 kg. The observed ABC exposures following the administration of TRIUMEQ PD in this weight band are slightly higher than those observed in pediatric patients in a similar weight band (< 14 kg) receiving the oral solution of ZIAGEN (**Table 7**). However, exposures are still within the observed exposure ranges at the recommended dose of ABC in pediatrics when comparing weight band by weight band (**Table 7**).

Table 7. ABC exposure in IMPAACT 2019 vs model-based PK parameters of ABC in historical pediatric trials by weight band

Drug	Weight Band	Pharmacokinetic Parameter		
		C_{max} (mcg/mL)	$AUC_{0\text{-}24h}$ (mcg·h/mL)	C_{24h} (mcg/mL)
Abacavir# IMPAACT 2019 trial	6 to <10 kg (n=7)	7.30 (6.05-8.81)	17.7 (13.02-23.94)	0.003 (0.001-0.007)
	10 to <14 kg (n=7)	8.36 (5.68-12.31)	19.8 (12.71-30.73)	0.005 (0.002-0.013)
	14 to <20 kg (n=7)	6.26 (4.73-8.28)	15.1 (10.54-21.61)	0.003 (0.001-0.006)
	20 to <25 kg (n=7)	6.65 (5.17-8.56)	17.4 (14.52-20.73)	0.004 (0.002-0.007)
	25 to <40 kg (n=7)	9.04 (7.40-11.04)	25.7 (22.51-29.44)	0.011 (0.003-0.037)
Abacavir* (Historical pediatric trials)	<14 kg (oral solution)	5.0 (2.1-11.3)	13.8 (5.3-34.2)	0.03 (0.001-0.22)
	14 to < 20 kg	6.6 (2.8-14.8)	16.9 (6.3-42.1)	0.021 (NQ-0.18)
	20 to < 25 kg	7.9 (3.3-17.9)	19.9 (7.5-49.9)	0.02 (NQ-0.17)
	≥25 kg	7.9 (3.2-18.5)	19.3 (7.1-50.4)	0.01 (NQ-0.13)
	Adults	4.3 (2.1-6.0)	9.3 (4.6-14.8)	NQ (NQ-0.03)

Source: Table 6 in Summary of Clinical Pharmacology; data are expressed as Geometric mean (95% CI).
* Source: Table 4 in NDA 20977/S-027 Clin Pharm review; data are expressed as Median (90% CI).

Lamivudine

- The proposed 3TC dose of 90 mg is within the range of the approved doses with EPIVIR oral solution (60–100 mg) for the 6 to <10 kg weight band. The observed 3TC exposures following the administration of TRIUMEQ PD in this weight band were slightly higher than those observed in pediatric patients in a similar weight band (< 14 kg) receiving the oral solution of EPIVIR (**Table 8**). However, exposures are still within the observed exposure ranges at the recommended dose of lamivudine in pediatrics when comparing exposures weight band by weight band (**Table 8**).

Table 8. 3TC exposure in IMPAACT 2019 vs model-based PK parameters of 3TC in historical pediatric trials by weight band

Drug	Weight Band	Pharmacokinetic Parameter		
		C_{max} (mcg/mL)	AUC_{0-24h} (mcg·h/mL)	C_{24h} (mcg/mL)
Lamivudine# IMPAACT 2019 trial	6 to <10 kg (n=7)	2.29 (1.61-3.27)	10.7 (7.10-15.99)	0.055 (0.038-0.077)
	10 to <14 kg (n=7)	3.55 (2.99-4.21)	14.2 (11.39-17.61)	0.046 (0.030-0.070)
	14 to <20 kg (n=7)	2.92 (2.36-3.60)	13.0 (11.28-15.02)	0.058 (0.042-0.081)
	20 to <25 kg (n=7)	2.99 (2.24-3.99)	14.5 (12.46-16.90)	0.060 (0.051-0.071)
	25 to <40 kg (n=7)	4.15 (3.18-5.41)	21.7 (17.13-27.58)	0.084 (0.061-0.115)
Lamivudine* (Historical pediatric trials)	<14 kg	1.8 (0.9-3.4)	7.9 (4.5-14.6)	0.05 (0.02-0.13)
	14 to < 20 kg	2.8 (1.4-5.4)	11.6 (6.3-21.9)	0.05 (0.02-0.14)
	20 to < 25 kg	3.4 (1.7-6.4)	13.8 (7.3-26.2)	0.05 (0.02-0.14)
	≥25 kg	3.4 (1.6-6.7)	13.6 (7.0-26.5)	0.05 (0.02-0.14)
	Adults	2.0 (1.3-3.0)	8.4 (7.0-11.7)	0.041 (0.025-0.067)

Source: Table 7 in Summary of Clinical Pharmacology; data are expressed as Geometric mean (95% CI).
* Source: Table 3 in NDA 20977/S-027 Clin Pharm review; data are expressed as Median (90% CI).

5.2. Summary of Renal Dosing Discussions

This section summarizes key discussion points and assessments related to our final recommendations regarding the use of TRIUMEQ and TRIUMEQ PD in pediatric patients with renal impairment.

Currently, the use of TRIUMEQ and TRIUMEQ PD in patients with CLcr <30 mL/min is not recommended due to the accumulation of 3TC (a component of TRIUMEQ and TRIUMEQ PD) which is primarily eliminated through renal excretion, and the dosage of 3TC cannot be adjusted when administered as an FDC product. There are no data available on the use of 3TC in pediatric patients with renal impairment (USPI Section 8.6[1]).

In general, kidney function maturation is considered complete at the age of 2 years. For children younger than 2 years (i.e., neonates and infants), PK of the drugs that are renally cleared can be impacted by both the maturation of kidney function and the presence/degree of renal impairment. Pediatric renal impairment is rare, abd it is not feasible to collect sufficient safety or PK data in pediatric trials to determine adequate minimum renal function for the use of TRIUMEQ and TRIUMEQ PD in pediatric patients.

Although there are no safety, efficacy, and PK data for 3TC in pediatric patients with renal impairment and limited safety data are available in children with higher exposures of 3TC (NUCA2002), the review team considers that it is reasonable to allow the use of TRIUMEQ and TRIUMEQ PD in pediatric patients with renal impairment similar to a CLcr 30mL/min in adults. However, there are challenges in identifying a pediatric renal function cutoff that orresponds to a CLcr of 30 mL/min in adults. These challenges include the fact that in pediatric patients, renal function is commonly assessed with body surface area (BSA) normalized estimated GFR (eGFR, in unit of mL/min/1.73 m^2), rather than BSA unadjusted CLcr. Therefore, additional data and analyses are required when translating CLcr in adults to BSA normalized eGFR in children. Furthermore, in children < 1 year old, there is currently no validated equation for eGFR and the definition of normal eGFR is wide and age dependent for < 2 years old. Additionally, staging of chronic kidney disease (CKD) staging is not applicable in children < 2 years old.

The agency has employed various approaches to address this review issue, and the final determination of the approach to recommend dosing in children with renal impairment was based on a case-by-case risk-benefit assessment taking into account all available data (e.g., TAMIFLU, BIKTARVY, AVYCAZ, ZERBAXA, and VALCYTE), and in many cases, it stays silent (unspecified dosing regimen in pediatrics with renal impairment).[2,3]

Applicant-proposed language regarding dosing of TRIUMEQ and TRIUMEQ PD in pediatric patients with renal impairment and review team's recommendations

The current supplement proposes to extend the indication of TRIUMEQ and TRIUMEQ PD to pediatric patients weighing ≥6 kg and aged at least 3 months old. The Applicant proposed (b) (4)

[2] Al-Khouja A, Park K, et al. Dosing Recommendations for Pediatric Patients With Renal Impairment. J Clin Pharmacol. 2020 Dec;60 (12):1551-1560 (https://www ncbi.nlm nih.gov/pmc/articles/PMC8670561/)

[3] Khurana M. Renal Impairment in Pediatric Patients: Current Approaches to Drug Dosing. J Clin Pharmacol. 2021 Jun;61 Suppl 1:S161-S164 (https://pubmed ncbi.nlm.nih.gov/34185911/)

[redacted] as shown below.

- TRIUMEQ and TRIUMEQ PD are not recommended [redacted] patients with creatinine clearance less than 30 mL/min [redacted] (8.6)

The Applicant's proposal [redacted] is not acceptable [redacted] Therefore, we concluded that it is best to individualize dosing decisions based on the degree of renal impairment and the balance between the potential benefits of administering TRIUMEQ and TRIUMEQ PD versus the potential risks with higher exposures of 3TC.

In summary, the review team concluded that a descriptive language [redacted] is appropriate for the use of TRIUMEQ and TRIUMEQ PD in pediatric patients with renal impairment. Our conclusion is based on the two factors: 1) the challenge of proposing [redacted] for pediatric patients < 2 years old as described above, and 2) the extensive experience with 3TC in pediatric patients, including the use of higher doses, and no known safety concern unique and notable in pediatric patients. Therefore, the following language is recommended by the FDA.

TRIUMEQ and TRIUMEQ PD are not recommended [redacted] patients with creatinine clearance less than 30 mL/min and pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function.

5.3. Pharmacometrics Review

5.3.1. Population PK analysis

5.3.1.1. Review Summary

This review is for the pediatric efficacy supplements for TRIUMEQ (NDA 205551, S-031) and Triumeq PD (NDA215413, S-002). The supplements seek to fulfill the TRIUMEQ Pediatric Written Request and PREA PMRs with the pharmacokinetic (PK) data from IMPAACT 2019 (Study 205860) to expand the use of fixed dose combination TRIUMEQ PD tablet for oral suspension to pediatric patients weighing at least 6 kg (6 kg to <10 kg) and who are at least 3 months of age. The Applicant conducted a study to assess the PK, safety, and antiviral activity of TRIUMEQ for a minimum of 24 weeks. TRIUMEQ and TRIUMEQ PD are fixed dose combination (FDC) of dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC) indicated for the for the treatment of HIV-1, and the respective single entities has been approved for the US market.

In general, the Applicant's population PK (popPK) analysis is considered acceptable in describing the PK of DTG, ABC, and 3TC. The derived exposure metrics of the individual components support the dosing approach when comparing to historical observed values in adults and pediatric patients (refer to Clinical Pharmacology Review Appendix 5.1). The Applicant's analyses were verified by the reviewer, with no significant discordance identified. In addition, the Applicant's popPK analysis adequately provided PK study endpoints specified in the Written Request; parameters including C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution necessary for establishing steady state for all the components of TRIUMEQ.

Of note, the PK of individual components were previously reviewed for pediatric patients. Refer to the Clinical Pharmacology Review documents of Reference ID 4610645 for DTG (by Drs. Sun, Li, Earp, and Choi, NDA 213983, 5/18/2020 in DARRTS) and Reference ID 3702679 for ABC and 3TC (by Drs. Choi, Li, Florian and Seo, NDA20977, 02/13/2015 in DARRTS).

5.3.1.2. Introduction

The primary objectives of Applicant's analysis were to:

- Evaluate the predictive performance of the popPK model in pediatric subjects
- Derive individual model-predicted exposures for DTG, ABC, and 3TC at steady-state
- Compare simulated steady-state AUC_{0-24}, C_{max}, and C24 to those from noncompartmental analysis (NCA) and Bayesian posterior predictions (post-hoc)

5.3.1.3. Model Development

Data

IMPAACT 2019 is an ongoing Phase I/II study that investigates the PK, safety, tolerability, and efficacy of TRIUMEQ FDC in pediatric patients <12 years of age with HIV-1. Study sample size and PK sampling scheme are shown in **Table 9**. A total of 55 subjects were enrolled in the study and contributed 598 DTG, 590 ABC, and 597 3TC PK observations for popPK analysis. Baseline demographics are shown in **Table 10** and **Table 11**.

Table 9. T TRIUMEQ Dose and Subject Numbers by PK Sampling Scheme and Enrollment Weight Band

Weight Band (kg)	Daily Dose (DTG/ABC/3TC)	Number of Participants		
		Intensive PK	Sparse PK	Overall
≥6 to <10	15 mg/180 mg/90 mg DT	8	1	9
≥10 to <14	20 mg/240 mg/120 mg DT	8	4	12
≥14 to <20	25 mg/300 mg/150 mg DT	7	8	15
≥20 to <25	30 mg/360 mg/180 mg DT	7	3	10
≥25	50 mg/600 mg/300 mg Tablet	7	4	11

Note: Two subjects (Subject ID 830751 in ≥6 to <10 kg and 8509054 in ≥10 to <14 kg) enrolled in the intensive PK group but discontinued from the study the first week due to palatability issues

Source: Applicant's popPK report, Table 3, page 10

Table 10. Summary of Continuous Baseline Demographics

Covariate	(N=55)
Baseline Age (years)	
Mean (SD)	5.53 (3.1)
Median [Min, Max]	6.00 [1.00, 11.0]
Baseline Body Weight (kg)	
Mean (SD)	18.64 (7.4)
Median [Min, Max]	17.00 [8.15, 39.30]
Baseline Height (cm)	
Mean (SD)	109.77 (20.2)
Median [Min, Max]	113.0 [71.0, 153.0]
Baseline Body Mass Index (kg/m²)	
Mean (SD)	14.92 (1.7)
Median [Min, Max]	14.7 [11.7, 21.6]
Baseline Body Surface Area (m²)	
Mean (SD)	0.75 (0.21)
Median [Min, Max]	0.74 [0.42, 1.25]
Baseline Serum Creatinine (umol/L)	
Mean (SD)	33.97 (11.4)
Median [Min, Max]	32.71 [15.0, 68.0]
Baseline Creatinine Clearance (mL/min)	
Mean (SD)	1.92 (0.548)
Median [Min, Max]	1.82 [0.971, 3.85]
Baseline Alanine Aminotransferase (ukat/L)	
Mean (SD)	0.29 (0.10)
Median [Min, Max]	0.28 [0.13, 0.63]
Baseline Aspartame Aminotransferase (ukat/L)	
Mean (SD)	0.55 (0.13)
Median [Min, Max]	0.53 [0.30, 0.95]
Baseline Total Bilirubin (umol/L)	
Mean (SD)	7.04 (4.1)
Median [Min, Max]	6.30 [1.40, 19.84]

Source: Applicant's popPK report, Table 9, pages 21-22

Table 11. Summary of Categorical Baseline Demographics

Demographic	Statistic	n	Percent
Gender N (%)	Female	25	45.45
	Male	30	54.55
Race N (%)	All Others	1	1.82
	Asian	17	30.91
	Black or African American	37	67.27
Ethnicity N (%)	Hispanic or Latino	3	5.45
	Non-Hispanic or Latino	52	94.55
Metal-cation containing products N (%)	No	52	94.55
	Yes	3	5.45
CYP3A inhibitors N (%)	Absent	53	96.36
	Present	2	3.64
CYP3A Inducers N (%)	Absent	55	100.00
P-gp Inhibitors N (%)	Absent	55	100.00
P-gp Inducers N (%)	Absent	55	100.00
UGT1A1 inhibitors N (%)	Absent	55	100.00
UGT1A1 Inducers N (%)	Absent	54	98.18
	Present	1	1.82
UGT1A3 inhibitors N (%)	Absent	55	100.00
UGT1A3 Inducers N (%)	Absent	55	100.00
OCT2 inhibitors N (%)	Absent	54	98.18
	Present	1	1.82
Vomit N (%)	No	55	100.00

Source: Applicant's popPK report, Appendix Table 4, page 62

Modeling methodology

The pediatric popPK models for DTG, ABC, and 3TC were previously developed with pooled pediatric data. The existing popPK models were used to predict exposures and assess current dosing approach of individual entities (external validation approach). As such, no parameter estimation was performed for this supplemental NDA submission. A brief description of the popPK models (with the Clinical Pharmacology review reference IDs) follows. Predictive performance of the existing popPK models was evaluated using standard goodness-of-fit (GoF) plots. Simulation-based diagnostics were also used including visual predictive checks (VPC) and normalized prediction distribution error (NPDE).

Simulations were performed with 1000 replicate trials of 1000 virtual subjects to support the dosing regimen of TRIUMEQ and TRIUMEQ PD. A summary of demographic characteristics of the virtual population is provided in **Table 12**.

Table 12. Demographics of Virtual Pediatric Population

Simulation Group	Number of Participants Per Trial	Body Weight (kg) Median (range)	Triumeq FDC Daily Dose (DTG/ABC/3TC)
≥6 to <10 kg	200	8.0 (6.0-9.9)	15 mg/180 mg/90 mg (DT)
≥10 to <14 kg	200	12.0(10.0 -13.9)	20 mg/240 mg/120 mg (DT)
≥14 to <20 kg	200	17.0 (14.0-19.9)	25 mg/300 mg/150 mg (DT)
≥20 to <25 kg	200	22.5 (20.0-24.9)	30 mg/360 mg/180 mg (DT)
≥25 to <40 kg	200	32.5 (25.0-39.9)	50 mg/600 mg/300 mg (Tablet)
Total	**1000**	**16.88 (6.0 -39.9)**	

Source: Applicant's popPK report, Table 8, page 20

5.3.1.4. Final Model

Respective final popPK models for each entity of TRIUMEQ and TRIUMEQ are briefly described below. An external validation approach was utilized to derive the Bayesian posterior predictions of

subjects in the IMPAACT 2019 study. Overall, the derived exposure metrics of the individual components support the dosing approach when comparing to historical observed values in adults and pediatric patients (refer to Clinical Pharmacology review Appendix 5.1).

DTG

Previously, a total of 239 pediatric patients were included, contributing 2650 plasma PK observations. The existing popPK model was a 1-compartment model with first-order absorption and first-order elimination. CL/F (apparent clearance) and V/F (apparent volume of distribution) were allometrically scaled for body weight, with exponent estimates of 0.455 and 0.556, respectively. In addition, a maturation function was applied to CL/F, where half-maximal maturation was 52 weeks PMA (post menstrual age). Gender, ALT, CRCL, race, HIV disease status, metal cation containing drugs (MCAT), and background anti-retroviral therapy (ART) as inducers were not identified as significant covariates on DTG PK in this analysis. However, DTG PK data with ART inducers and in some racial groups were limited.

*The final popPK parameters are shown in **Table 13**. NCA vs. post-hoc derived exposure metrics are summarized in **Table 14**. GoF and VPC plots are shown in **Figure 1** and **Figure 2**, respectively. **Figure 3** shows the comparison of DTG C24s derived from simulation (virtual population), NCA, and post-hoc estimates.*

Table 13. DTG Pediatric Final PopPK Model

Parameter [Units]	NONMEM Estimates				
	Point Estimate	95% CI	%RSE		
CL/F [L/h]	1.03	0.980, 1.07	2.31		
V/F [L]	13.6	13.0, 14.3	2.42		
KA, FCT [h^{-1}]	0.854	0.686, 1.06	11.2		
KA~DT and Granules [h^{-1}]	2.04	1.41, 2.67	15.7		
F, Fasted FCT (Reference)	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		
CL/F ~FMAT					
TM50 [PMA weeks][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_{Vc}, η_{KA}	0.138	-	-	R=0.598	-
ω^2_{KA}	0.762	-0.0017	0.964	107	33.2
ω^2_{IOV,CL_OCC1}	0.115	0.0220	0.171	33.9	26.6
ω^2_{IOV,CL_OCC2}	0.115	0.0314	0.0409	-	29.8
ω^2_{IOV,CL_OCC3}	0.115	-0.0213	0.0835	-	43.8
ω^2_{IOV,CL_OCC4}	0.115	-0.0306	0.0183	-	40.7
ω^2_{IOV,KA_OCC1}	0.610	0.0868	0.00415	91.7	39.9
ω^2_{IOV,KA_OCC2}	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 (μg/mL), P1093	0.00164	-0.00142, 0.0047	95.1	SD=0.0405	-
Proportional Error, ODYSSEY	0.0123	0.00787, 0.0167	18.4	11.1	16.3
Additive Error (μg/mL), ODYSSEY	0.090	0.0677, 0.112	12.7	SD=0.300	-

Covariate relationships:

- $CL/F = 1.03 \times (WT/70)^{0.455} \times FMAT$;
  where $FMAT = (PMA^{HILL}/(PMA^{HILL}+TM50^{HILL})$; and PMA (weeks) =PNA (years)*52 (weeks) + 40 (weeks)
- $V/F = 13.6*(WT/70)^{0.556}$

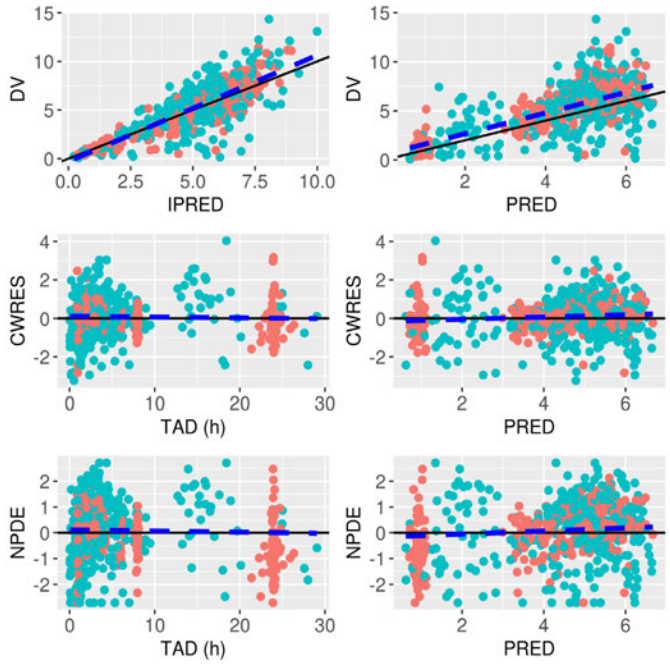
F, without regard to food for DT/Granules =1.68 (1.47-1.91), calculated as 1.10*1.53 (95% CI: 1.03*1.43-1.17*1.63)
KA for DT/Granules=1.74 (95% CI: 1.20-2.28), calculated as 0.854*2.04 (95% CI: 0.854*1.41-0.854*2.67)

Etabar is the arithmetic mean of the η estimates and the p-value for the null hypothesis that the true mean is 0.
For IIV, If ω^2 >0.15, CV% = 100 * $\sqrt{e^{\omega^2} - 1}$.

CL/F=apparent clearance after oral dosing, V/F=apparent central volume of distribution after oral dosing, KA=absorption rate constant, F=relative bioavailability (with FCT fasted as the reference), FMAT=maturation function, TM50=maturation half time, HILL=Hill coefficient related to the slope of the maturation process, PMA=post-menstrual age, PNA=post-natal age, SE=standard error; %RSE=percent relative standard error; CI=confidence interval, SD=standard deviation; CV=coefficient of variation; Shr = shrinkage; Covar=between-subject covariance; ω^2_{CL}, ω^2_V, ω^2_{KA} = variance of random effect of CL/F, V/F and KA, respectively, $\omega^2_{IOV,CL}$ = variance of random effect of IOV on CL/F, where OCC1=intensive PK, OCC2=sparse PK Week 4, OCC3=sparse PK Week 12, and OCC4=sparse PK Week 24; $\omega^2_{IOV,KA}$ = variance of random effect of IOV on Ka, where OCC1=intensive PK and OCC2=sparse PK

Source: Applicant's popPK report, Table 5, page 14

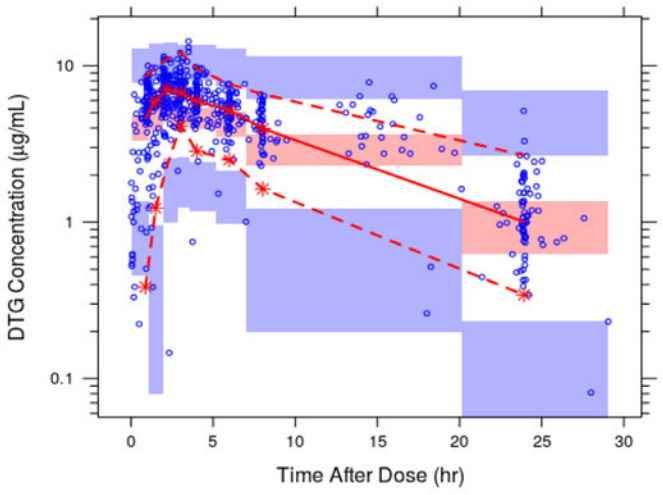
Figure 1. GoF Plots for DTG Pediatric Data



The colored symbols represent individual observations. The dashed blue line is a trend line (for population and individual predictions vs observations) or regression line (for CWRES vs population predictions and time after dose & NPDE vs population predictions and time after dose). DV= Observed concentrations (µg/mL), IPRED= Individual Predicted Concentrations (µg/mL), PRED= Population Predicted Concentrations (µg/mL), TAD= Time after Dose, CWRES: conditional weighted residuals. NPDE: Normalized prediction distribution errors. Notes: Colors of circles represent different sampling scheme, red = Serial sampling, cyan = Sparse sampling

Source: Applicant's popPK report, Figure 1, page 23

Figure 2. VPC for DTG Pediatric Data



Blue circles: observed concentrations. Red solid and red dotted lines: median and 95% quantile of observed concentrations respectively; Red and blue shaded areas: 95% confidence intervals of prediction median and 95% prediction intervals

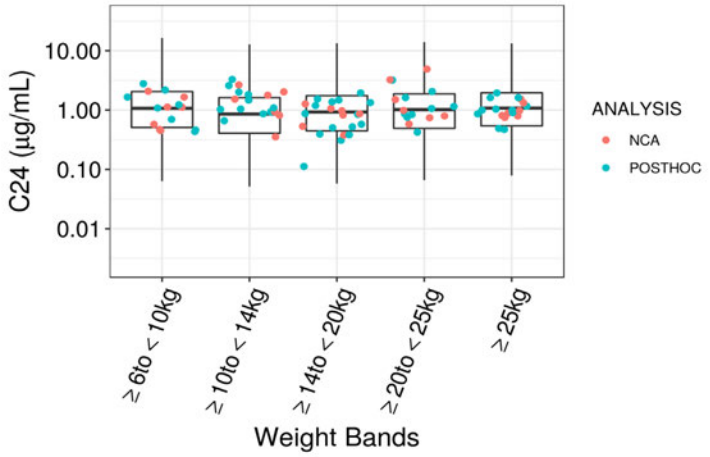
Source: Applicant's popPK report, Figure 2, page 24

Table 14. NCA vs. Post-hoc DTG PK Parameters

Weight Band (kg)	Triumeq Dosage Form	DTG Dose	N	Analysis Method	PK Parameter GM (95% CI)		
					Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10	DT	15 mg	7	PopPK[a]	6.58 (5.71 -7.59)	76.80 (62.3 -94.80)	0.94 (0.60 -1.49)
			7	NCA[b]	7.40 (5.74 - 9.53)	75.9 (56.0 - 102.8)	0.91 (0.52 -1.61)
≥10 to<14	DT	20 mg	7	PopPK[a]	7.27 (6.57 -8.04)	97.3 (82.1-115.0)	1.63 (1.08 -2.44)
			7	NCA[b]	8.85 (7.28-10.75)	91.0 (65.6 – 126.11)	1.22 (0.65 -2.29)
≥14 to <20	DT	25 mg	7	PopPK[a]	6.59 (5.95-7.30)	74.30 (63.90 -86.40)	0.85 (0.59-1.22)
			7	NCA[b]	7.04 (6.02 -8.23)	71.45 (57.66 -88.53)	0.79 (0.53 -1.16)
≥20 to <25	DT	30 mg	7	PopPK[a]	6.66 (6.13-7.25)	84.50 (71.00-101.00)	1.28 (0.85 -1.93)
			7	NCA[b]	7.29 (6.26 -8.50)	84.44 (66.49 -107.24)	1.35 (0.64 -2.84)
≥25 to <40	Tablets	50mg	7	PopPK[a]	5.86 (5.42-6.33)	78.60 (70.60 -87.50)	1.17 (0.93 -1.46)
			7	NCA[b]	6.25 (5.18 -7.55)	71.80 (63.19 -81.58)	0.98 (0.76 -1.26)

Intensive PK population only
Source: Applicant's popPK report, Figure 10, page 25

Figure 3. Comparison of Simulated DTG C24 vs. Post-hoc Estimates vs. NCA



Boxes represent median (black horizontal line in the middle), 1st quartile and 3rd quartile of predicted the data, Vertical black line through the middle of the boxes (Whiskers) represent minimum and maximum, Solid Circles: DTG (AUC0-24) post-hoc estimates and NCA estimates based on rich sampling.

Post-hoc and NCA methods include intensive PK population only
Source: Applicant's popPK report, Figure 3, page 26

Reviewer comment: the DTG popPK model predicts the observations adequately with reasonable agreements of observed and predicted concentrations as shown in the GoF and VPC plots (note a slight under-prediction at the lower quantile). Similar PK parameters are also observed when comparing the NCA and post-hoc estimated exposure metrics. This is further supported by the simulation results. In general, the popPK model for DTG reasonably predicts the data while capturing central tendency; it is acceptable for deriving exposure metrics to support dosing regimen.

ABC

Previously, a total of 169 pediatric subjects were included, contributing 1833 plasma PK observations. The existing popPK model is a 2-compartment model with interindividual variability (IIV) on CL/F following oral dosing, V2/F (central), V3/F (peripheral), intercompartmental clearance (Q/F), and inter-occasion variability (IOV) on CL/F. Covariate effects included weight on CL/F and V2/F fixed to the exponent values estimated in the 3-study model and a study-specific F1 term for tablet and solution for ARROW PK sub-study Part 2. Residual variability was described by a proportional model. The final popPK parameters are shown in ***Table 15****.*

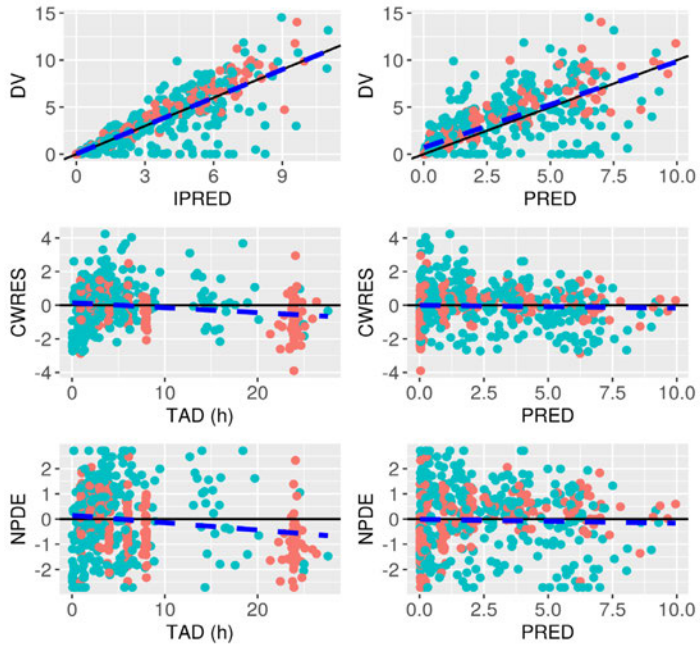
The final popPK parameters are shown in ***Table 15****. NCA vs. post-hoc derived exposure metrics are summarized in* ***Table 16****. GoF and VPC plots are shown in* ***Figure 4*** *and* ***Figure 5****, respectively.* ***Figure 6*** *shows the comparison of ABC 24-hour AUCs derived from simulation (virtual population), NCA, and post-hoc estimates.*

Table 15. ABC Pediatric Final PopPK Model

Parameter (unit)[a]	Notation	Population Estimate	RSE (%)	Bootstrap Mean (95% CI)
Absorption rate constant, Ka (1/h)	Θ1	0.85	2.31	0.85 (0.80-0.90)
Intercompartment clearance, Q/F (L/h)	Θ2	1.69	7.87	1.69 (1.40-1.98)
Apparent central volume of distribution, V2/F (L)=Θ3*(WT/15.6)^ Θ7	Θ3	10.1	7.5	10.2 (8.5-11.7)
	Θ7	0.698 FIX		
Apparent peripheral compartment volume of distribution, V3/F (L)	Θ4	23.0	17.4	23.1 (14.7-31.3)
Apparent systemic clearance, CL/F (L/h)=Θ5x (WT/15.6)^ Θ6	Θ5	16.3	3.62	16.3 (15.1-17.5)
	Θ6	0.794 FIX		
Relative bioavailability, F1				
F1 tablet ARROW PK Substudy Part 2	Θ8	1.62	8.02	1.638 (1.363-1.878)
F1 solution ARROW PK Substudy Part 2	Θ9	1.75	8.23	1.753 (1.462-2.039)
Interindividual variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
ηQ/F variance	Ω1	0.461 (67.9)[b]	18.5	0.440 (0.229-0.694)
ηV2/F variance	Ω2	0.269 (51.9)[b]	25.7	0.273 (0.110-0.429)
ηV3/F variance	Ω3	0.845 (91.9)[b]	32.2	0.830 (0.261-1.43)
ηCL/F variance	Ω4	0.132 (36.3)[b]	24.8	0.132 (0.067-0.198)
Interoccasion variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
OCCCL	Ω5	0.085 (29.2)[b]	24.9	0.085 (0.040-0.131)
Residual error		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
Proportional error (mg/L)	σ1	0.141 (37.5)	7.3	0.141 (0.122-0.161)

Source: Applicant's popPK report, Table 6, page 16

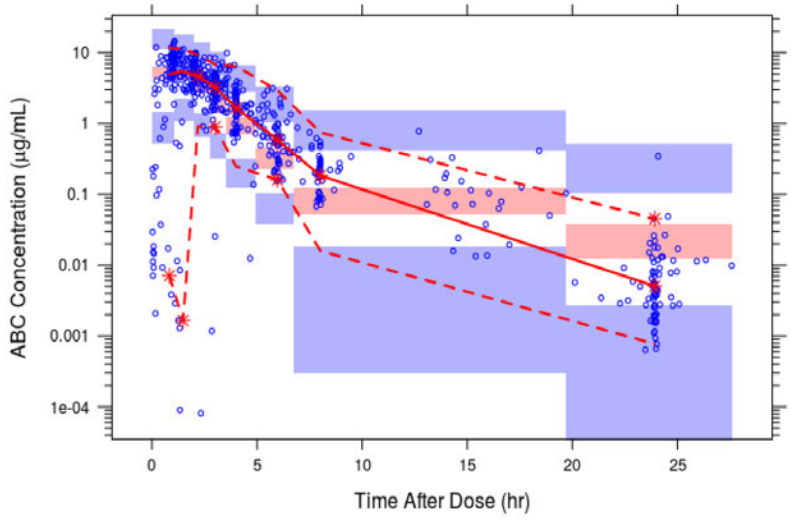
Figure 4. GoF Plots for ABC Pediatric Data



The colored symbols represent individual observations. The dashed blue line is a trend line (for population and individual predictions vs observations) or regression line (for CWRES vs population predictions and time after dose & NPDE vs population predictions and time after dose). DV= Observed concentrations (µg/mL), IPRED= Individual Predicted Concentrations (µg/mL), PRED= Population Predicted Concentrations (µg/mL), TAD= Time after Dose, CWRES: conditional weighted residuals. NPDE: Normalized prediction distribution errors. Notes: Colors of circles represent different sampling scheme, red = Serial sampling, cyan = Sparse sampling

Source: Applicant's popPK report, Figure 5, page 30

Figure 5. VPC Plot for ABC Pediatric Data



Blue circles: observed concentrations. Red solid and red dotted lines: median and 95% quantile of observed concentrations respectively; Red and blue shaded areas: 95% confidence intervals of prediction median and 95% intervals

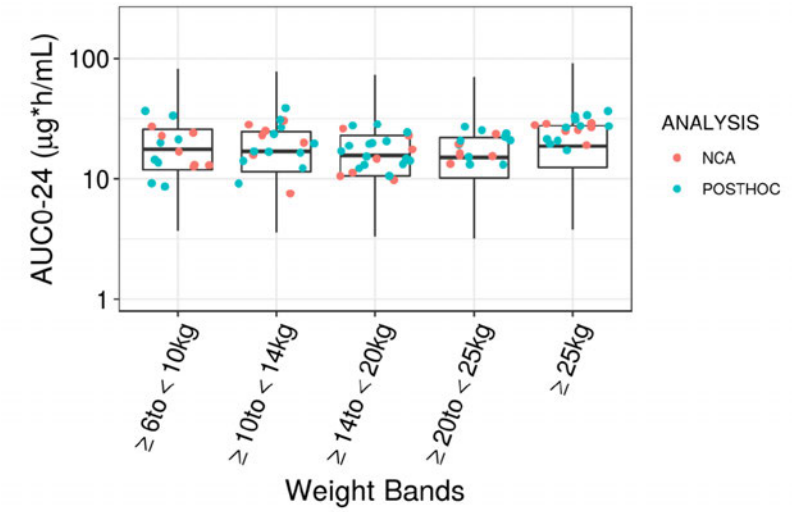
Source: Applicant's popPK report, Figure 6, page 31

Table 16. NCA vs. Post-hoc ABC PK Parameters

Weight Band (kg)	Triumeq Dosage Form	ABC Dose	N	Analysis Method	PK Parameter GM (95% CI)		
					Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10	DT	180 mg	7	PopPK[a]	5.67 (3.92 -8.19)	15.60 (10.9 -22.20)	0.004 (0.003 -0.006)
			7	NCA[b]	7.30 (6.05 – 8.81)	17.7 (13.02 – 23.94)	0.003 (0.001 -0.007)
≥10 to <14	DT	240 mg	7	PopPK[a]	8.06 (6.11 -10.60)	19.20 (14.90 -24.80)	0.012 (0.004 -0.040)
			7	NCA[b]	8.36 (5.68 -12.31)	19.8 (12.71 - 30.73)	0.005 (0.002 -0.013)
≥14 to <20	DT	300 mg	7	PopPK[a]	6.30 (5.42-7.32)	14.60 (12.30 - 17.40)	0.004 (0.002 -0.007)
			7	NCA[b]	6.26 (4.73 -8.28)	15.1 (10.54 - 21.61)	0.003 (0.001 -0.006)
≥20 to <25	DT	360 mg	7	PopPK[a]	8.70 (6.18-12.30)	18.30 (14.90 - 22.50)	0.004 (0.003 -0.008)
			7	NCA[b]	6.65 (5.17 -8.56)	17.35 (14.52 - 20.73)	0.004 (0.002 -0.007)
≥25 to <40	Tablets	600 mg	7	PopPK[a]	9.86 (8.01-12.10)	24.40 (20.70 - 28.70)	0.011 (0.005-0.025)
			7	NCA[b]	9.04 (7.40 -11.04)	25.74 (22.51 - 29.44)	0.011 (0.003 -0.037)

Source: Applicant's popPK report, Table 13, page 32

Figure 6. Comparison of Simulated ABC AUC0-24 vs. Post-hoc Estimates vs. NCA



Boxes represent median (black horizontal line in the middle), 1st quartile and 3rd quartile of the data, Vertical black line through the middle of the boxes (Whiskers) represent minimum and maximum, Solid Circles: ABC AUC0-24. Post-hoc estimates and NCA estimates

Source: Applicant's popPK report, Figure 8, page 35

Reviewer comment: the ABC popPK model predicts the observations adequately with reasonable agreements of observed and predicted concentrations as shown in the GoF and VPC plots. The reviewer noted some over-predictions at the lower quantile during absorption phase; however, central tendency is captured considering the confrontation-time profile in VPC. NCA derived Cmax is slightly higher than Bayesian posterior-predicted Cmax. Overall, similar PK parameters are observed between the two methods. This is further supported by the simulation results. In general, the popPK model for ABC captures central tendency and is acceptable for deriving exposure metrics to support the dosing regimen.

3TC

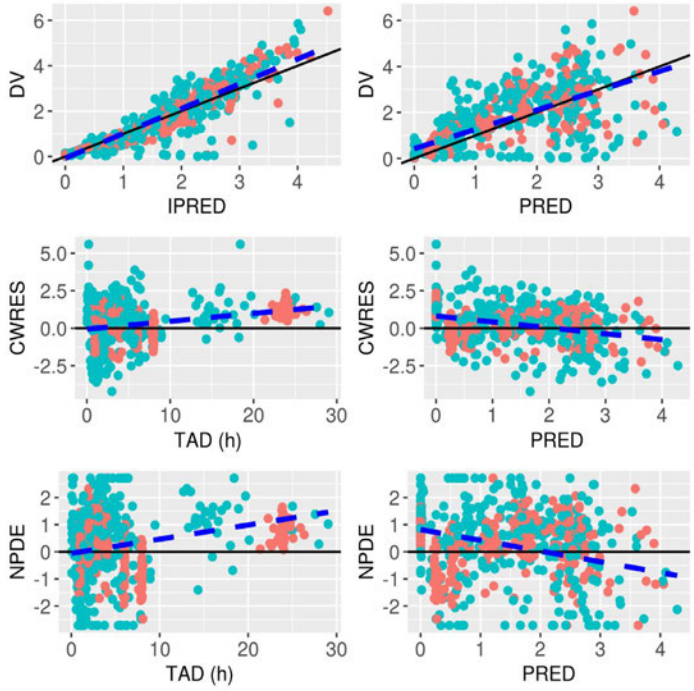
Previously, 209 pediatric subjects were included, contributing 3023 plasma PK observations (note that the Applicant's descriptive sample size of 210 is incorrect as one subject was excluded due to no oral formulation record; n=209 is consistent with previous Clinical Pharmacology Review of ZIAGEN® and EPIVIR® per referenced document above). The existing popPK model is a 1-compartment model with first-order absorption rate constant (Ka) and lag time (for absorption). IIV and IOV were estimated for CL/F, V/F, and Ka. Covariate effects included weight on CL and V. Residual variability was described by an additive error model with a proportional weighting factor on the variance estimate. The final popPK parameters are shown in ***Table 17****.*

The final popPK parameters are shown in ***Table 17****. NCA vs. post-hoc derived exposure metrics are summarized in* ***Table 18****.* ***Table 19*** *summarizes the post-hoc exposure metrics for all PK subjects. GoF and VPC plots are shown in* ***Figure 7****and* ***Figure 8****, respectively.* ***Figure 9*** *shows the comparison of 3TC 24-hour AUCs derived from simulation (virtual population), NCA, and post-hoc estimates.*

Table 17. 3TC Pediatric Final PopPK Model

Parameter (unit)[a]	Notation	Population Estimate	RSE (%)	Bootstrap Mean (95% CI)
Absorption rate constant (Ka) (1/h)	Θ3	2.08	9.76	2.12 (1.57-2.59)
Lag time ALAG1 (h)	Θ4	0.297	12.1	0.299 (0.218-0.376)
Volume of distribution (V)=Θ2*(WT/18.5)^Θ7 (L)	Θ2 Θ7	23.1 0.677	4.68 8.98	23.2 (21.0-25.2) 0.680 (0.555-0.799)
Clearance (CL)=Θ1*(WT/18.5)^Θ6 (L/h)	Θ1 Θ6	9.16 0.758	4.49 7.07	9.17 (8.37-9.95) 0.758 (0.652-0.864)
Absolute bioavailability (F1) solution PO	Θ8	0.496	5.36	0.498 (0.445-0.547)
Absolute bioavailability (F1) tablet PO	Θ9	0.609	5.35	0.612 (0.544-0.674)
Interindividual variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
ηCL variance	Ω1	0.082 (28.6%)[a]	20.2	0.081 (0.049-0.115)
ηV variance	Ω2	0.107 (32.7%)[a]	17.6	0.104 (0.071-0.143)
ηKA variance	Ω3	0.585 (76.5%)[a]	23.6	0.613 (0.265-0.907)
Interoccasion variability		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
OCCCL	Ω4-6	0.0619 (24.9%)[a]	14.9	0.062 (0.044-0.079)
OCCKA	Ω7-9	0.360 (60.0%)[a]	26.9	0.360 (0.129-0.591)
OCCV	Ω10-12	0.0387 (19.7%)[a]	23.5	0.040 (0.021-0.056)
Residual error		**Population Estimate (CV%)**	**RSE (%)**	**Bootstrap Mean (95% CI)**
Additive error [mg/L]	σ1	0.003	9.17	0.003 (0.002-0.004)
Weighing factor for residual error	Θ5	4.72	7.22	4.68 (4.06-5.38)

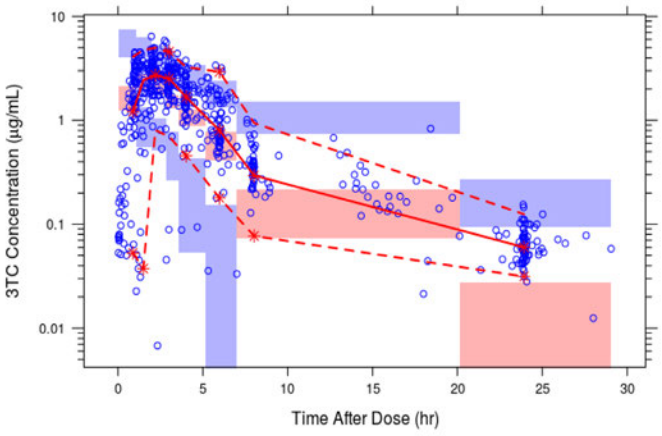
Figure 7. GoF Plots for 3TC Pediatric Data



The colored symbols represent individual observations. The dashed blue line is a trend line (for population and individual predictions vs observations) or regression line (for CWRES vs population predictions and time after dose & NPDE vs population predictions and time after dose). DV= Observed concentrations (µg/mL), IPRED= Individual Predicted Concentrations (µg/mL), PRED= Population Predicted Concentrations (µg/mL), TAD= Time after Dose, CWRES: conditional weighted residuals. NPDE: Normalized prediction distribution errors. Notes: Colors of circles represent different sampling scheme, red = Serial sampling, cyan = Sparse sampling

Source: Applicant's popPK report, Figure 9, page 37

Figure 8. VPC for 3TC Pediatric Data



Blue circles: observed concentrations. Red solid and blue dotted lines: median and 95% quantile of observed concentrations respectively; Red and blue shaded areas: 95% confidence intervals of prediction median and 95% intervals

Source: Applicant's popPK report, Figure 10, page 38

Table 18. NCA vs. Post-hoc 3TC PK Parameters

Weight Band (kg)	Triumeq Dosage Form	3TC Dose	N	Analysis Method	PK Parameter GM (%CV)		
					Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (ng/mL)
≥6 to <10	DT	90 mg	7	PopPK[a]	2.27 (1.75 -2.96)	9.42 (6.53 – 13.60)	0.017 (0.004 - 0.065)
			7	NCA[b]	2.29 (1.61 – 3.27)	10.7 (7.10 – 15.99)	0.055 (0.038 - 0.077)
≥10 to <14	DT	120 mg	7	PopPK[a]	3.22 (2.75 -3.78)	14.10 (11.90 –16.90)	0.010 (0.003-0.036)
			7	NCA[b]	3.55 (2.99 – 4.21)	14.2 (11.39 -17.61)	0.046 (0.030 - 0.070)
≥14 to <20	DT	180 mg	7	PopPK[a]	2.67 (2.26 – 3.17)	11.30 (9.71 – 13.2)	0.005 (0.002 - 0.011)
			7	NCA[b]	2.92 (2.36 -3.60)	13.02 (11.28 -15.02)	0.058 (0.042 - 0.081)
≥20 to <25	DT	150 mg	7	PopPK[a]	2.80 (2.11 – 3.72)	12.50 (10.30 –15.10)	0.023 (0.009 - 0.059)
			7	NCA[b]	2.99 (2.24 -3.99)	14.51 (12.46 -16.90)	0.060 (0.051 –0.071)
≥25 to <40	Tablets	300 mg	7	PopPK[a]	3.94 (3.29 – 4.72)	19.20 (15.30 - 24.00)	0.012 (0.003-0.053)
			7	NCA[b]	4.15 (3.18 -5.41)	21.73 (17.13 -27.58)	0.084 (0.061 –0.115)

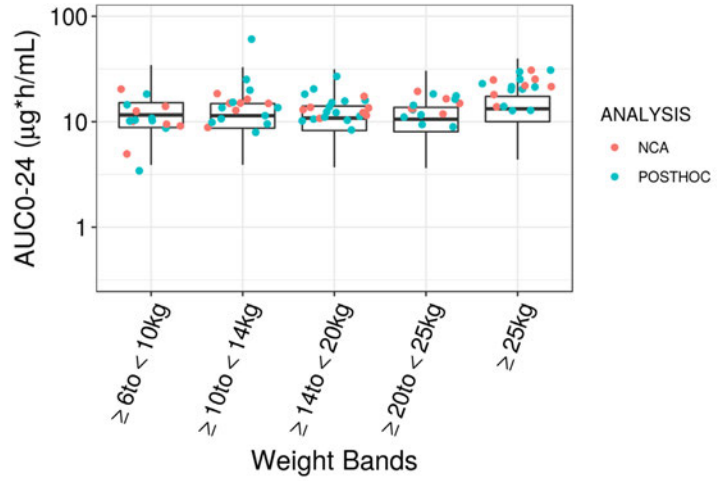
Source: Applicant's popPK report, Table 16, page 39

Table 19. Post-hoc 3TC PK Parameters for All Subjects

Weight Band (kg)	Triumeq Dosage Form	3TC Dose	N	PK Parameter GM (95% CI)		
				Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10	DT	90 mg	8	2.29 (1.82 -2.88)	9.97 (7.12 – 14.00)	0.013 (0.004 – 0.047)
≥10 to <14	DT	120 mg	11	2.64 (2.12 – 3.29)	14.90 (10.60 – 20.9)	0.017 (0.005 – 0.053)
≥14 to <20	DT	150 mg	15	2.98 (2.65 – 3.35)	13.60 (11.60 -15.80)	0.010 (0.005 -0.021)
≥20 to <25	DT	180 mg	10	2.65 (2.16 – 3.25)	13.10 (11.20 -15.20)	0.017 (0.007 – 0.043)
≥25 to <40	Tablets	600 mg	11	3.59 (2.89 – 4.45)	20.30 (16.90 – 24.30)	0.026 (0.008 – 0.081)

Source: Applicant's popPK report, Table 17, page 41

Figure 9. Comparison of Simulated 3TC AUC0-24 vs. Post-hoc Estimates vs. NCA



Boxes represent median (black horizontal line in the middle), 1st quartile and 3rd quartile of the data, Vertical black line through the middle of the boxes (Whiskers) represent minimum and maximum, Solid Circles: 3TC AUC0-24. Post-hoc estimates and NCA estimates

Source: Applicant's popPK report, Figure 12, page 42

Reviewer comment: while reasonable agreement is shown between observed vs. predicted 3TC PK data, the residual plots are less than ideal. This is likely due to a higher variability for concentrations at the end of the dosing interval and/or those at lower end of the concentration range (compared to the higher concentrations earlier on after a dose) are more problematic in terms of predictions. This latter explanation is also described by the Applicant in the popPK report, particularly referring to the sparse PK data. Additionally, the reviewer noted that the sparse data may also drive the misspecification as shown in the VPC beyond 8-10 hours.

*Nevertheless, the exposure metrics of AUC_{0-24}, C_{max}, and C24 are comparable between those that are: 1) NCA derived, 2) popPK derived with the NCA population, and 3) popPK derived with all subjects as shown in **Table 18** and **Table 19**. Lastly, the simulation exercise (**Figure 9**) also supports that the popPK model is generally acceptable for deriving exposure metrics to support dosing regimen.*

<u>Additional analysis for individual subjects with notable safety and efficacy issues</u>
Using the Bayesian posterior predictions from the respective final popPK models, the reviewer examined the exposure profiles (AUC_{0-24}, C_{max}, and C24) of DTG, 3TC, and ABC for 2 subjects: one subject with confirmed virologic failure (CVF) at Week 24, and the other with drug-induced liver injury (DILI). Considering the limited overall and subgroup sample sizes, the exposures of these subjects did not differ from the others.

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