CLINICAL PHARMACOLOGY REVIEW

NDA	205551/S-28 (SDN-964) 215413 (SDN-01, 05, 09)
Submission dates	09/30/2021 02/04/2022 (Response to IR) 03/01/2022 (Response to IR)
Submission type	Efficacy supplement Original submission
Drug	Dolutegravir (DTG)/Abacavir (ABC)/Lamivudine (3TC) Tablets, 50 mg/600 mg/300 mg (NDA-205551/S-28) Dolutegravir/Abacavir/Lamivudine Dispersible Tablets for Oral Suspension, 5 mg/60 mg/30 mg (NDA-215413)
Applicant	ViiV Healthcare Company
Indication	Approved indication: treatment of HIV-1 infection in adults and in pediatric patients weighing at least 40 kg; Proposed indication: treatment of HIV-1 infection in adults and in pediatric patients weighing at least 14 kg;
OCP Division	DIDP
OND Division	DAV
Review Team	Yang Zhao, Ph.D., Su-Young Choi, Pharm.D., Ph.D.

1. Executive Summary

The applicant submitted a supplemental New Drug Application (sNDA) for Triumeq Tablets (sNDA 205551) and an original NDA for Triumeq Dispersible Tablets for Oral Suspension (Triumeq PD) (NDA 215413) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients weighing at least 14 kg.

The Applicant submitted the following studies to support their proposal:

- A relative bioavailability study (205894) that compared Triumeq PD tablets (at Dolutegravir/Abacavir/Lamivudine 50 mg/600 mg/300 mg dose) to Triumeq tablets in healthy adults,
- A food effect study (216149) with Triumeq PD tablets,
- A relative bioavailability study (200402) comparing Dolutegravir/Abacavir/Lamivudine Dispersible tablets when dispersed and consumed under different dosing conditions to an oral dose of the combination of Tivicay and Epzicom tablets,
- Population pharmacokinetic (PopPK) analysis report supporting dosing in pediatric participants weighing ≥14 kg (2021N471578).

In this application, no new clinical trial data in pediatric patients were submitted. Instead, the proposed approach for the approval of Triumeq PD is bridging the safety and efficacy of the individual products that was previously established, by demonstrating comparable relative

bioavailability for the individual components between Triumeq PD and the individual products. While the Applicant initially proposed the approval in pediatric patients weighing 14 kg and above, the review team concluded that the available data also support the approval in pediatric patients weighing ≥10 to < 14 kg.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in the submission. The Applications are approvable from a Clinical Pharmacology perspective.

2. Relevant Regulatory History and Product Description

Triumeq PD tablet for oral suspension, is a Fixed Dose Combination (FDC) of DTG/ABC/3TC 5 mg/60 mg/30 mg. All the components (DTG, ABC, and 3TC) have been approved in pediatric patients down to infants as single active ingredients. In the current submission, the Applicant proposes the use of Triumeq PD for the treatment of HIV-1 infection in pediatric patients <25 kg.

Triumeq tablet is an FDC of DTG/ABC/3TC 50 mg/600 mg/300 mg approved in 2014. In support of the approval of Triumeq tablets, the Applicant conducted a relative bioavailability study (ING114580) comparing the PK of Triumeq tablet and the combination of Tivicay tablet plus Epzicom tablet (link). The exposure of DTG, ABC and 3TC with the Triumeq tablets was comparable to those with Tivicay tablet and Epzicom tablet at the same dosage.

DTG is an HIV integrase strand transfer inhibitor (INSTI) approved for use in combination with other antiretroviral (ARV) agents for treatment-naïve and treatment-experienced HIV infected adults and pediatric patients ≥4 weeks of age weighing ≥3 kg. DTG was initially approved in 2013 and is marketed as Tivicay tablet (NDA-204790) in strengths of 10 mg, 25 mg, and 50 mg. Tivicay PD 5 mg (NDA-213983) was approved in 2020. Of note, the relative bioavailability of Tivicay PD is approximately 1.6-fold higher than that of Tivicay tablet (Study 205893). As such, Tivicay PD and Tivicay tablet are not interchangeable on a milligram-per-milligram basis.

ABC is a guanosine nucleoside analog approved for use in combination with other ARV agents for the treatment of HIV-1 infection in adults and pediatric patients ≥3 months of age. ABC was initially approved in 1998 and is available as Ziagen tablet 300 mg (NDA-020977) and Ziagen oral solution 20 mg/mL (NDA-020978) formulations. The tablet formulation is approved for once daily dosing in adult and pediatric patients who weigh at least 14 kg, while the oral solution can be administered to pediatric patients ≥3 months of age.

3TC is a cytidine nucleoside analog HIV-1 reverse transcriptase inhibitor approved in combination with other ARV agents for the treatment of HIV-1 infection. 3TC was initially approved in 1995 and is available as Epivir tablet (150 mg and 300 mg, NDA-020564) and Epivir oral solution 10 mg/mL (NDA-020596). The tablet formulation is approved for adult and pediatric patients who weigh at least 14 kg while the oral solution can be administered to pediatric patients ≥3 months of age.

Epzicom tablets is an FDC of ABC/3TC 600 mg/300 mg approved in 2004. In support of the approval of Epzicom tablets, the Applicant conducted a relative bioavailability study (CAL10001) bridging Epzicom tablets and equivalent doses of Ziagen tablets and Epivir tablets (link). Bioequivalence was achieved for both ABC and 3TC following administration of FDC Epzicom tablets compared to administration of the individual product combination, Ziagen and Epivir.

3. Summary of Clinical Pharmacology Assessment

As described in Section 2, the individual components of Triumeq PD (DTG, ABC, and 3TC) are approved in children. The proposed approach for the approval of Triumeq PD is bridging the safety and efficacy of the individual products that was previously established by demonstrating comparable relative bioavailability for the individual components between Triumeq PD and the individual products.

Establishing comparable relative bioavailability between Triumeq PD and individual products (Tivicay PD, Ziagen, and Epivir)

The pivotal relative bioavailability study (205894) demonstrated that the exposure of DTG with Triumeq PD administrated as a dispersion was approximately 1.7-fold higher than that with Triumeq tablet. This magnitude of difference is similar to the magnitude of difference that was observed with Tivicay PD vs. Tivicay. Comparable relative bioavailability between Tivicay tablet and Triumeq tablet for DTG was previously demonstrated in study (ING114580). As such, with respect to DTG exposure, it can be concluded that Triumeq PD and Tivicay PD have comparable relative bioavailability.

For ABC and 3TC, comparable relative bioavailability was demonstrated between Triumeq PD and Triumeq tablet in this study. Further, comparable relative bioavailability has been previously demonstrated between Triumeq vs. Epzicom, and between Epzicom vs. Ziagen/Epivir.

As such, the pediatric dosing regimens of Tivicay PD, Epzicom (or Ziagen/Epivir) can be translated to the pediatric dosing regimens of Triumeq PD without adjusting for potential differences in relative bioavailability among those formulations.

Comparison of proposed dosing regimen of Triumeq PD, Triumeq tablets and approved dosing regimens of individual products

The proposed dosing regimens of Triumeq PD and Triumeq tablets for pediatric patients and the approved dosing regimens of the individual products are summarized in Table 1.

Table 1: Proposed dosing regimen of Triumeq PD and Triumeq tablets in pediatric patients weighing ≥10 kg and approved daily dosing of DTG, ABC, and 3TC with individual products

Body weight	Proposed daily dosing with Triumeq PD or Triumeq	Approved daily dosing with individual tablet products	Approved daily dosing with individual ABC, 3TC solution products
≥10 to < 14 kg	4 PD tablets DTG: 20 mg ABC: 240 mg 3TC: 120 mg	–	DTG: 20 mg (Tivicay PD) ABC: 160–224 mg (Ziagen solution) 3TC: 100–140 mg (Epivir solution)
≥14 to < 20 kg	5 PD tablets DTG: 25 mg ABC: 300 mg 3TC: 150 mg	DTG: 25 mg (Tivicay PD) ABC: 300 mg (Ziagen tablet) 3TC: 150 mg (Epivir tablet)	DTG: 25 mg (Tivicay PD) ABC: 224–320 mg (Ziagen solution) 3TC: 140–200 mg (Epivir solution)
≥20 to < 25 kg	6 PD tablets DTG: 30 mg ABC: 360 mg 3TC: 180 mg	DTG: 30 mg (Tivicay PD) ABC: 450 mg (Ziagen tablet) 3TC: 225 mg (Epivir tablet)	DTG: 30 mg (Tivicay PD) ABC: 320–400 mg (Ziagen solution) 3TC: 200–250 mg (Epivir solution)
≥ 25 kg	1 Triumeq tablet DTG: 50 mg ABC: 600 mg 3TC: 300 mg	DTG: 50 mg (Tivicay) ABC: 600 mg (Ziagen tablet or solution) 3TC: 300 mg (Epivir tablet or solution)	

For DTG, the proposed dosing regimens for all weight bands with Triumeq PD (< 25 kg) or Triumeq (≥ 25 kg) are identical to those approved with Tivicay PD or Tivicay.

For ABC and 3TC, the proposed dosing regimens are identical to those approved with individual products for ≥ 25 kg and ≥ 14 to < 20 kg. For ≥ 20 to < 25 kg, the proposed doses (360 mg for ABC and 180 mg for 3TC) with Triumeq PD are slightly lower than the approved doses with the individual products (450 mg with Ziagen tablet and 225 mg with Epivir tablet). However, predicted concentrations of ABC and 3TC with the proposed dosing regimens are within the range of the observed exposures at the recommended doses of approved products in both pediatrics and adults. For ≥10 to < 14 kg, the proposed dose for ABC (240 mg) with Triumeq PD is slightly higher than the approved dose of ABC (160–224 mg with Ziagen solution), but the predicted exposures do not exceed those observed in pediatric patients of other weight bands.

Effects of food

In the food effect study (216149), no clinically meaningful differences in the exposures of DTG, ABC, and 3TC were observed between fed and fasted conditions. Therefore, Triumeq PD may be taken with or without food.

4. Clinical Pharmacology Related Labeling Recommendations

Clinical Pharmacology related labeling recommendations, as of the date of this review is finalized, are summarized below. See the approved USPI for the finalized labeling.

Section	Updates (Bold)
1 INDICATIONS AND USAGE	TRIUMEQ **and TRIUMEQ PD** are indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least **10** kg.
2 DOSAGE AND ADMINISTRATION	In addition to the new dosing regimens, the overview of TRIUMEQ Dosage Forms (2.3) has been added to outline distinctions in the two dosage forms, Triumeq tablets and Triumeq PD tablets: **TRIUMEQ is available in two dosage forms. Do not interchange TRIUMEQ tablets and TRIUMEQ PD tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles for the dolutegravir component [see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)].** **• TRIUMEQ tablets: 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine.** **o TRIUMEQ is recommended in adults and pediatric patients weighing at least 25 kg [see Dosage and Administration (2.4, 2.5)].** **• TRIUMEQ PD tablets for oral suspension: 60 mg of abacavir, 5 mg of dolutegravir, and 30 mg of lamivudine.** **o TRIUMEQ PD is recommended in pediatric patients weighing 10 kg to less than 25 kg.** **o Because TRIUMEQ PD is a fixed-dose tablet and the dosage of individual components cannot be adjusted, it may lead to a suboptimal dosing for patients weighing >25 kg.**
7 DRUG INTERACTIONS	In Table 6, with Concomitant Drugs of Non-nucleoside reverse transcriptase inhibitor: Efavirenz, Protease inhibitor: Fosamprenavir/ritonavir, Tipranavir/ritonavir, Carbamazepine, Rifampin, 10 to <14 kg: administer an additional 20-mg dose of dolutegravir (4 TIVICAY PD tablets for oral suspension), 12 hours after TRIUMEQ PD, 14 to <20 kg: administer an additional 25-mg dose of dolutegravir (5 TIVICAY PD tablets for oral suspension), 12 hours after TRIUMEQ PD, 20 to <25 kg: administer an additional 30-mg dose of dolutegravir (6 TIVICAY PD tablets for oral suspension), 12 hours after TRIUMEQ PD.
8.4 Pediatric Use	The clinical data supporting use of TRIUMEQ and **TRIUMEQ PD** in pediatric patients with HIV-1 infection weighing **at least 10 kg** is derived from the following previously conducted pediatric trials using the individual components of TRIUMEQ and TRIUMEQ PD: • The safety and efficacy of once-daily abacavir and lamivudine using either the combination of EPIVIR and ZIAGEN or EPZICOM; • The safety, pharmacokinetics, and antiviral activity (efficacy) of TIVICAY and **TIVICAY PD**; • Additional pharmacokinetics data; Overall, the safety, and efficacy profile of TRIUMEQ and **TRIUMEQ PD** in pediatric patients is comparable to that observed in adults. **There are no data available on the use of lamivudine in pediatric patients with renal impairment** [see Warnings and Precautions (5.4), Adverse Reactions (6.1), Use in Specific Populations (8.6), Clinical Pharmacology (12.3), Clinical Studies (14.2)]. **Safety and effectiveness of TRIUMEQ PD have not been established in pediatric patients weighing <10 kg.**

8.6 Patients with Impaired Renal Function	**TRIUMEQ and TRIUMEQ PD are not recommended for patients with creatinine clearance <30 mL/min,** because TRIUMEQ and TRIUMEQ PD are fixed-dose combinations and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of TRIUMEQ and **TRIUMEQ PD**, is required for patients with creatinine clearance <30 mL/min, then the individual components should be used [see Clinical Pharmacology (12.3)]. There are no data available on the use of lamivudine in pediatric patients with renal impairment. Patients with a creatinine clearance between 30 and 49 mL/min receiving TRIUMEQ may experience a 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥ 50 mL/min. There are no safety data from randomized, controlled trials comparing TRIUMEQ to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of hematologic toxicities (neutropenia and anemia), although discontinuations due to neutropenia or anemia each occurred in <1% of subjects. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive TRIUMEQ or **TRIUMEQ PD** should be monitored for hematologic toxicities.
12.3 Pharmacokinetics	One TRIUMEQ tablet was bioequivalent to one dolutegravir (TIVICAY) tablet (50 mg) plus one abacavir and lamivudine fixed-dose combination tablet (EPZICOM) under fasted conditions in healthy subjects (n = 62). **TRIUMEQ tablets and TRIUMEQ PD tablets for oral suspension are bioequivalent for the abacavir and lamivudine components, but not for the dolutegravir component. The relative dolutegravir bioavailability of TRIUMEQ PD is approximately 1.7-fold higher than TRIUMEQ; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis** [see Dosage and Administration (2.3), Warnings and Precautions (5.8)].

5. Appendix

5.1 Bioanalysis

A bioanalytical site inspection was requested for the Study 205894. The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time as the previous inspection falls within the surveillance interval and the final classification of the inspection was No Action Indicated (NAI) (link).

Bioanalytical method and validation results are summarized below.

Table 2: Summary of Bioanalytical Method Validation and Performance for the study 205894

Analyte	DTG	ABC	3TC
Method	UPLC-MS/MS	UPLC-MS/MS	UPLC-MS/MS
Matrix	Human plasma (EDTA K2)	Human plasma (EDTA K2)	Human plasma (EDTA K2)
Validation report	Provided and acceptable	Provided and acceptable	Provided and acceptable
Performance report	Provided	Provided	Provided
Samples analyzed within established stability period	☒Yes ☐No	☒Yes ☐No	☒Yes ☐No
Quality control (QC) samples range acceptable	☒Yes ☐No	☒Yes ☐No	☒Yes ☐No
Chromatograms provided	☒Yes ☐No	☒Yes ☐No	☒Yes ☐No
Accuracy and precision of the calibration curve acceptable	☒Yes ☐No	☒Yes ☐No	☒Yes ☐No
Accuracy and precision of the quality control samples acceptable	☒Yes ☐No	☒Yes ☐No	☒Yes ☐No
Linearity, ng/mL	20–20000	2.5–2500	2.5–2500
Lower limit of quantification (LLOQ)	20 ng/mL	2.5 ng/mL	2.5 ng/mL
Incurred sample reanalysis (ISR)	Acceptable	Acceptable	Acceptable
Overall performance	**Acceptable**	**Acceptable**	**Acceptable**

5.2 Study 205894: A 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric Triumeq Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared with Adult Tablets in Healthy Volunteers

1. Study Design:

Study 205894 is a 2-part, open-label, single-dose, 3-period, randomized, crossover study to compare the relative bioavailability (BA) of pediatric Triumeq PD with Triumeq conventional tablet formulation (Part 1) and compare the relative BA of pediatric FDC DTG/3TC dispersible tablets with combination treatment of individual DTG and 3TC conventional tablet formulation (Part 2) in healthy volunteers under fasted conditions. There were at least 7 days washout between each dose of study drug. Study 205894 Part 2 (pertinent to DOVATO® pediatric formulation) results are not evaluated in this review.

Part 1: Part 1 was a 3-period, randomized, crossover study to compare the relative BA of pediatric Triumeq PD administered both as a dispersion and direct to mouth vs. Triumeq Tablet formulation, in 18 planned healthy subjects (baseline demographics shown in Table 3). Seventeen subjects completed Part 1.

- Treatment A: Triumeq tablet (1 tablet) administered as direct to mouth (reference).
- Treatment B: Pediatric Triumeq PD (10 dispersible tablets) administered as a dispersion and taken immediately (test).
- Treatment C: Pediatric Triumeq PD (10 dispersible tablets) administered as direct to mouth (test).

2. Pharmacokinetic Sampling:

Intensive blood samples were collected for PK analysis of DTG, ABC, and 3TC. Samples were collected up to 72 hours post doses for each period.

3. Baseline Demographics of Part 1 subjects:

Table 3: Baseline demographic data (Part 1 only)

Age, years	Body weight, kg	Body Mass Index (BMI)	Sex	Race
34.9±10.1 (mean±SD)	74.9±14.0 (mean±SD)	25.9±3.06 (mean±SD)	9 females+9 males	12 white+5 african american+1 native hawaiian

4. Clinical Pharmacology Results on Part 1:

(1) For DTG, geometric mean values of $AUC_{0-\infty}$ and Cmax following a single oral administration of 10 Triumeq PD as a dispersion (the proposed route of administration, Treatment B) were approximately 70% higher than those observed following a single oral administration of 1 Triumeq Tablet (Treatment A, Table 4). DTG exposure following oral administration of 10 Triumeq PD taken direct to mouth (Treatment C) were approximately 35% higher than Treatment A.

(2) For ABC and 3TC, geometric mean values of $AUC_{0-\infty}$ and Cmax following a single oral administration of 10 Triumeq PD as a dispersion or direct to mouth (Treatments B or C) were similar to those after administration of 1 Triumeq Tablet (Treatment A) (Table 4). The 90% CIs of the geometric mean ratios of $AUC_{0-\infty}$ and Cmax for Treatment B/Treatment A and Treatment C/Treatment A were within the predefined range of 0.80−1.25.

Table 4: Plasma PK parameters of DTG, ABC, and 3TC and statistical analysis (Part 1 only)

PK parameters	Treatments			Ratio of Geometric Least Squares (GLS) Means [90% CI]	
	A (n = 17)	B (n = 17)	C (n = 17)	B vs A	C vs A
DTG					
AUCt, mean (SD), h•µg/mL	59.74 (16.95)	99.89 (22.51)	77.51 (18.64)	1.70 [1.57, 1.84]	1.35 [1.25, 1.47]
AUC∞, mean (SD), h•µg/mL	62.38 (19.30)	103.60 (24.52)	80.57 (20.71)	1.69 [1.56, 1.84]	1.35 [1.25, 1.46]
Cmax, mean (SD), µg/mL	3.15 (0.59)	5.43 (0.82)	4.21 (0.82)	1.74 [1.60, 1.89]	1.36 [1.25, 1.48]
Tmax, median (range) h	3.00 (1.50, 4.08)	2.50 (1.00, 6.00)	3.00 (1.00, 6.00)	–	–
ABC					
AUCt, mean (SD), h•µg/mL	16.95 (3.62)	17.63 (3.60)	17.13 (3.92)	1.04 [1.01, 1.07]	1.02 [0.99, 1.05]
AUC∞, mean (SD), h•µg/mL	16.98 (3.63)	17.65 (3.60)	17.15 (3.92)	1.04 [1.01, 1.07]	1.02 [0.99, 1.05]
Cmax, mean (SD), µg/mL	5.18 (1.09)	5.45 (1.04)	5.01 (1.11)	1.05 [0.99, 1.12]	0.98 [0.92, 1.04]
Tmax, median (range) h	1.50 (0.50, 2.57)	1.00 (0.25, 2.00)	1.00 (0.25, 2.00)	–	–
3TC					
AUCt, mean (SD), h•µg/mL	13.26 (3.54)	13.18 (3.32)	12.39 (3.88)	1.00 [0.95, 1.05]	0.94 [0.90, 0.99]
AUC∞, mean (SD), h•µg/mL	13.52 (3.69)	13.42 (3.36)	12.68 (3.98)	1.00 [0.95, 1.05]	0.95 [0.90, 0.99]
Cmax, mean (SD), µg/mL	2.28 (0.69)	2.17 (0.76)	2.06 (0.78)	0.94 [0.87, 1.01]	0.91 [0.84, 0.98]
Tmax, median (range) h	2.50 (1.50, 5.05)	2.50 (1.00, 4.00)	2.50 (1.50, 4.08)	–	–

Source: summarized by the reviewer based on Tables 8, 10, 12, 14, 16, 17 in CSR 205894
Treatment A: 1 Triumeq tablet administered as direct to mouth;
Treatment B: 10 Triumeq PD administered as a dispersion and taken immediately (test);
Treatment C: 10 Triumeq PD administered as direct to mouth (test).

Conclusions

- For DTG, AUC and Cmax following administration of Triumeq PD as a dispersion (the proposed route of administration) were approximately 70% higher than those observed after administration of Triumeq Tablet at the same dosage. The difference is similar to that observed between Tivicay PD vs. Tivicay tablet.
- For ABC and 3TC, AUC and Cmax following administration of 10 tablets of Triumeq PD were similar to those observed after administration of 1 Triumeq Tablet.

5.3 Study 216149: A Randomized, 2-Cohort, 2-Period, Single Dose, Crossover Clinical Study to Assess the Effect of Food on the Pediatric Dispersible Tablet Formulations of Triumeq (Dolutegravir/Abacavir/Lamivudine) and Dovato (Dolutegravir/Lamivudine) in Healthy Adult Participants

1. Study Design:

Study 216149 is a 2-cohort, single-center, randomized, open-label, single-dose, crossover study. The study has 2 cohorts and each study cohort has 16 subjects. For fed conditions, after an overnight fast for at least 10 hours, participants received a high-fat and high-calorie meal (fat contributes approximately 50% of total caloric content of the meal with 800−1000 calories) 30 minutes prior to drug administration. Drugs were administered within 5 minutes after completion of the meal consumption. There were at least 7 days washout between each dose of study drug. Study 216149 Cohort 2 results are not evaluated in this review.

Cohort 1: A total of 16 subjects (baseline demographics shown in Table 5) were enrolled and completed.

- Treatment A: 6 Triumeq PD tablets dispersed in 20 mL water and taken immediately under fed condition (with a total water volume of 240 mL).
- Treatment B: 6 Triumeq PD tablets dispersed in 20 mL water and taken immediately under fasted condition (with a total water volume of 240 mL).

2. Pharmacokinetic Sampling:

Intensive blood samples were collected for PK analysis of DTG, ABC, and 3TC. Samples were collected up to 72 hours post doses for each period.

3. Baseline Demographics:

Table 5: Baseline demographic data (Cohort 1 only)

Age, years	Body weight, kg	Body Mass Index (BMI)	Sex	Race
34.9±8.1 (mean±SD)	80.2±12.4 (mean±SD)	27.7±1.9 (mean±SD)	6 females+10 males	9 white+5 african american+1 white–arabic+1 multiple

4. Clinical Pharmacology Results on the Cohort 1:

(1) For DTG, the geometric mean value of AUC0–∞ following administration of Triumeq PD under fed condition was similar to that under fasted condition. The geometric mean value of Cmax under fed condition was approximately 29% lower than that under fasted condition.

(2) For ABC and 3TC, the geometric mean values of AUC0–∞ following administration of Triumeq PD under fed condition were similar to those under fasted condition. However, the geometric mean values of Cmax for ABC and 3TC under fed condition were approximately 55% and 36% lower than those under fasted condition.

(3) The median Tmax values under fed condition (5 hours, 2.8 hours, 3.5 hour for DTG, ABC, and 3TC, respectively) were longer than those under fasted condition (1.3 hours, 0.5 hours, 1.5 hours for DTG, ABC, and 3TC, respectively).

Table 6: Plasma PK parameters of DTG, ABC, and 3TC and statistical analysis (Cohort 1 only)

PK Parameter	GLS Mean		Ratio of GLS Means [90% CI]
	Triumeq DT Treatment A (n = 16)	Triumeq DT Treatment B (n = 16)	DT Fed vs DT Fasted
DTG PK Parameters			
AUC(0-∞) (μg.h/mL)	59.14	67.21	0.88 [0.83 – 0.93]
AUC(0-t) (μg.h/mL)	55.80	63.80	0.87 [0.83 – 0.92]
Cmax (μg/mL)	2.36	3.32	0.71 [0.66 – 0.76]
ABC PK Parameters			
AUC(0-∞) (μg.h/mL)	8.57	9.99	0.86 [0.82 – 0.90]
AUC(0-t) (μg.h/mL)	8.50	9.92	0.86 [0.82 – 0.90]
Cmax (μg/mL)	1.84	4.08	0.45 [0.40 – 0.51]
3TC PK Parameters			
AUC(0-∞) (μg.h/mL)	6.51	7.30	0.89 [0.83 – 0.96]
AUC(0-t) (μg.h/mL)	6.32	7.18	0.88 [0.82 – 0.94]
Cmax (μg/mL)	0.89	1.39	0.64 [0.56 – 0.73]

DTG = dolutegravir; ABC=abacavir, 3TC= lamivudine
Treatment A = 6 Triumeq PD dispersed in 20 mL water and taken immediately under fed condition;
Treatment B = 6 Triumeq PD dispersed in 20 mL water and taken immediately under fasted condition.

Reviewer Comments:
The review team concluded that the lower Cmax values observed for all components with a high fat meal are not considered clinically relevant based on the following:

(1) Across all products (manufactured by the same Applicant) containing ABC and 3TC, Cmax of ABC and 3TC were lower under fed conditions as compared to fasted conditions (Table 7). The observed magnitude of reduction in Cmax in this trial overlaps the range observed with other products. The food effects for these drugs were not considered clinically meaningful and all of the listed products can be taken without regard to food. Since the effects were similar for Triumeq PD to the approved drugs, the food effect is also not clinically relevant.

Table 7: Food effects on PK of ABC and 3TC with various products

Clinical Study	Subjects	Evaluated formulation	Component	AUC ratio of fed/fasted (90% CI)	Cmax ratio of fed/fasted (90% CI)
ING114580	Healthy adults	Triumeq	ABC	0.93 (0.90–0.95)	0.77 (0.66–0.91)
			3TC	1.04 (0.97–1.12)	0.96 (0.88–1.05)
131-001	Healthy adults	Ziagen 300 mg	ABC	0.95 (0.87–1.03)	0.65 (0.53–0.79)
CNAA1009	Adults with HIV	Ziagen 300 mg	ABC	0.97 (0.90–1.04)	0.74 (0.65–0.84)
CAL10001	Healthy adults	Epzicom	ABC	0.90 (0.86–0.95)	0.76 (0.68–0.84)
			3TC	0.96 (0.92–1.01)	0.86 (0.80–0.92)
NUCA1001	Adults with HIV	Epivir 25 mg*2	3TC	0.94 (0.86–1.03)	0.57 (0.47–0.69)
NZTA1001	Healthy adults	3TC/zidovudine, 150 mg/300 mg	3TC	0.99 (0.94–1.04)	0.85 (0.76–0.96)
204994	Healthy adults	Dovato	3TC	0.91 (0.87–0.96)	0.68 (0.59–0.80)
AZL10001	Healthy adults	ABC/3TC/zidovudine, 300 mg/150 mg/300 mg	ABC	0.91 (0.88–0.95)	0.68 (0.62–0.76)
			3TC	0.92 (0.88–0.97)	0.82 (0.75–0.90)

(2) In addition, there are clinical data suggesting that Cmax is not an exposure metric relevant to efficacy for the single entity products (Ziagen and Epivir). Rather, AUC is considered relevant, because comparable efficacy has been demonstrated between once daily dosing and twice daily dosing both in adults and pediatrics despite approximately 50% lower Cmax with twice daily dosing. Refer to USPIs for Ziagen and Epivir for details. Also, it has been shown that similar intracellular triphosphate metabolites (active metabolites, carbovir-triphosphate for ABC, and lamivudine-triphosphate for 3TC) exposure at steady state were achieved following QD vs. BID oral administration at steady state were achieved following QD vs. BID oral administration of ABC (link) or 3TC (link);

(3) For DTG (or any other directly acting antivirals for HIV not requiring intracellular conversion), AUC and/or Ctau are considered more clinically relevant exposure metrics for efficacy. Therefore, lower DTG Cmax under fed condition is also considered not clinically relevant.

Conclusions

- The AUC of DTG, ABC and 3TC following administration of Triumeq PD with a high fat meal were similar to those under fasted conditions.
- The Cmax of DTG, ABC and 3TC when Triumeq PD was administered with a high fat meal were lower than those under fasted condition; however, these lower Cmax are considered not clinically relevant.
- Therefore, Triumeq PD may be taken with or without food.

5.4 Study 200402: A Phase 1, Single Dose, Five-Period Crossover Relative Bioavailability Study of a Fixed-Dose Combination Dolutegravir/Abacavir/Lamivudine Dispersible Tablet as Compared to a co-dose of TIVICAY and EPZICOM in Healthy Subjects

1. Study Design:

Study 200402 is an open label, 5-treatment, single-dose, crossover study to evaluate the relative BA of Triumeq dispersible tablets when dispersed and consumed under four different dosing conditions in comparison to an oral dose of the combination of Tivicay and Epzicom non-dispersible tablets. The dispersible tablets used in this study (a strength of DTG 10 mg/ABC 150 mg/3TC 75 mg), are not the to-be-marketed formulation. There were at least 7 days washout between each dose of study drug. A total of 20 subjects (baseline demographics shown in Table 8) were enrolled, and 19 subjects completed this study.

- Treatment A: 4 Tivicay tablets (DTG 10 mg) plus 1 Epzicom tablet (ABC 600 mg/3TC 300 mg) taken with purified water.
- Treatment B: 4 Triumeq dispersible tablets (DTG 10 mg/ABC 150 mg/3TC 75 mg) dispersed with high mineral content water plus flavor & sweeteners and taken immediately.
- Treatment C: 4 Triumeq dispersible tablets (DTG 10 mg/ABC 150 mg/3TC 75 mg) dispersed with high mineral content water plus flavor & sweeteners and taken after 30 minutes.
- Treatment D: 4 Triumeq dispersible tablets (DTG 10 mg/ABC 150 mg/3TC 75 mg) dispersed with purified water plus flavor & sweeteners and taken immediately.
- Treatment E: 4 Triumeq dispersible tablets (DTG 10 mg/ABC 150 mg/3TC 75 mg) dispersed with purified water plus flavor & sweeteners and taken after 30 minutes.

Reviewer Comments:

DTG inhibition of HIV-1 integrase requires chelating of the magnesium ion cofactor required for integrase activity. As an intrinsic metal-binding molecule, the solubility of DTG is impacted by the presence of divalent metals (e.g., calcium) in the dispersion medium which may result in the reduction in the bioavailability of DTG. The study was not conducted with the to be marketed formulation. As this effect is mainly related to the characteristics of the drug substance, the results will be likely applicable to the to be marketed formulation.

2. Pharmacokinetic Sampling:

Intensive blood samples were collected for PK analysis of DTG, ABC, and 3TC. Samples were collected up to 72 hours post doses for each period.

3. Baseline Demographics:

Table 8: Baseline demographic data

Age, years	Body weight, kg	Body Mass Index (BMI)	Sex	Race
44.8±15.9 (mean±SD)	79.5±12.2 (mean±SD)	26.7±3.0 (mean±SD)	6 females+14 males	15 white+5 african american

4. Clinical Pharmacology Results:

(1) AUC∞ and Cmax of DTG, ABC, and 3TC from Triumeq dispersible tablets when dispersed with high mineral content water (treatments B and C) were similar to drug exposures when dispersed with purified water (treatments D and E).

(2) AUC∞ and Cmax of DTG, ABC, and 3TC when the dispersion of Triumeq dispersible tablets was withheld for 30 minutes before consumption (treatments C and E) were similar to immediate consumption of dispersion (treatments B and D).

(3) For ABC and 3TC, AUC∞, Cmax, and C24 from treatments B, C, D, and E were similar to those from treatment A and the 90% CI of geometric mean ratios were within the range of 0.80–1.25.

Table 9: Plasma PK parameters of DTG, ABC, and 3TC and statistical analysis

PK parameters	Treatments					Ratio of Geometric Least Squares (GLS) Means [90% CI]			
	A (n =20)	B (n =20)	C (n =20)	D (n =20)	E (n =19)	B vs A	C vs A	D vs A	E vs A
DTG									
AUC∞, mean (cv%), h•µg/mL	48.4 (26.1)	75.7 (17.5)	74.1 (16.0)	76.3 (21.0)	75.4 (17.6)	1.56 [1.49, 1.64]	1.53 [1.46, 1.6]	1.58 [1.50, 1.65]	1.54 [1.47, 1.62]
Cmax, mean (cv%), µg/mL	2.5 (28.0)	4.0 (12.8)	3.9 (14.3)	3.9 (17.4)	4.0 (17.6)	1.59 [1.50, 1.70]	1.56 [1.46, 1.66]	1.56 [1.46, 1.66]	1.58 [1.48, 1.68]
Tmax, median (range), h	2.5 (0.5, 5.0)	2.0 (1.0, 4.0)	2.3 (0.5, 4.0)	2.0 (1.5, 5.0)	2.5 (1.0, 4.1)	–	–	–	–
ABC									
AUC∞, mean (cv%), h•µg/mL	16.6 (23.3)	16.0 (27.2)	16.2 (25.3)	16.5 (28.0)	16.7 (22.6)	0.97 [0.93, 1.01]	0.98 [0.94, 1.02]	1.00 [0.96, 1.04]	0.99 [0.95, 1.03]
Cmax, mean (cv%), µg/mL	5.68 (26.7)	5.75 (32.4)	5.37 (29.0)	5.53 (25.2)	5.78 (24.3)	1.01 [0.93, 1.10]	0.95 [0.87, 1.03]	0.97 [0.89, 1.06]	1.01 [0.93, 1.10]
Tmax, median (range), h	1.0 (0.5, 3.0)	1.0 (0.5, 2.5)	1.0 (0.5, 4.0)	1.0 (0.5, 3.0)	1.0 (0.5, 2.5)	–	–	–	–
3TC									
AUC∞, mean (cv%), h•µg/mL	15.1 (27.2)	14.8 (28.5)	15.4 (28.0)	15.3 (27.0)	14.6 (28.5)	0.99 [0.94, 1.04]	1.04 [0.98, 1.10]	1.02 [0.97, 1.08]	0.98 [0.93, 1.03]
Cmax, mean (cv%), µg/mL	2.6 (27.4)	2.4 (29.7)	2.5 (25.9)	2.3 (28.7)	2.4 (32.2)	0.93 [0.85, 1.01]	0.95 [0.88, 1.04]	0.90 [0.83, 0.98]	0.92 [0.84, 1.01]
Tmax, median (range), h	2.0 (1.0, 4.1)	2.0 (1.0, 4.0)	2.3 (1.5, 4.0)	2.0 (0.5, 4.0)	2.0 (1.0, 3.0)	–	–	–	–

Source: summarized by the reviewer based on Tables 9, 10, 11, 12 in CSR 200402

Conclusions

- Pharmacokinetics of DTG, ABC, and 3TC following a single dose oral administration of Triumeq dispersible tablets after dispersion with high mineral content water were similar to dispersion with purified water.
- Withholding the dispersion for 30 minutes or immediate consumption produced similar pharmacokinetic profiles for DTG, ABC, and 3TC.

5.5 Detailed approach and supporting data for the proposed dosing regimen of Triumeq PD and Triumeq in pediatric patients weighing at least 10 kg

The proposed dosing regimens of Triumeq and Triumeq PD in pediatric patients and the approved dosing regimens with individual products are shown in Table 10. The Applicant initially proposed the dosing regimens in pediatric patients weighing ≥14 kg. However, the review team considered that the available safety, PK, and efficacy data of individual components may support the approval of Triumeq PD in pediatric patients weighing ≥10 to < 14 kg as well. In the Response dated 02/04/2022 to FDA's IR dated 01/14/2022, the Applicant proposed for pediatric patients weighing ≥10 kg and submitted additional simulation data.

When comparing the proposed dosing regimens of Triumeq and Triumeq PD with the approved dosing regimens of individual products in pediatric patients, the dosing regiments of the following weight bands/components are identical. Therefore, the approval is supported by established comparable relative bioavailability between Triumeq vs. Tivicay+Epzicom (or Ziagen/Epivir), Triumeq PD vs. Tivicay PD+Epzicom (or Ziagen/Epivir) without further simulations.

- DTG for all weight bands
- ABC/3TC for ≥25 kg and ABC/3TC for ≥14 to < 20 kg.

Table 10: Proposed dosing regimen of Triumeq PD and Triumeq tablets in pediatric patients living with HIV-1 weighing ≥10 kg and approved daily dosing of DTG, ABC, and 3TC with individual products

Body weight	Proposed daily dosing with Triumeq PD or Triumeq	Approved daily dosing with individual tablet products	Approved daily dosing with individual ABC, 3TC solution products
≥10 to < 14 kg	4 PD tablets DTG: 20 mg ABC: 240 mg 3TC: 120 mg	–	DTG: 20 mg (Tivicay PD) ABC: 160–224 mg (Ziagen solution) 3TC: 100–140 mg (Epivir solution)
≥14 to < 20 kg	5 PD tablets DTG: 25 mg ABC: 300 mg 3TC: 150 mg	DTG: 25 mg (Tivicay PD) ABC: 300 mg (Ziagen tablet) 3TC: 150 mg (Epivir tablet)	DTG: 25 mg (Tivicay PD) ABC: 224–320 mg (Ziagen solution) 3TC: 140–200 mg (Epivir solution)
≥20 to < 25 kg	6 PD tablets DTG: 30 mg ABC: 360 mg 3TC: 180 mg	DTG: 30 mg (Tivicay PD) ABC: 450 mg (Ziagen tablet) 3TC: 225 mg (Epivir tablet)	DTG: 30 mg (Tivicay PD) ABC: 320–400 mg (Ziagen solution) 3TC: 200–250 mg (Epivir solution)
≥ 25 kg	1 Triumeq tablet DTG: 50 mg ABC: 600 mg 3TC: 300 mg	DTG: 50 mg (Tivicay) ABC: 600 mg (Ziagen tablet or solution) 3TC: 300 mg (Epivir tablet or solution)	

Therefore, this review section will focus on data supporting weight bands/components where the proposed dosing regimens are slightly different from those approved with individual products. To support the proposed dosing regimens, the Applicant provided a summary of pop-PK based simulation results. Of note, all popPK models were previously submitted and reviewed to support the approval of the individual products as described below.

1. PopPK Models and Simulation:

The Applicant performed simulations using NONMEM software (version 7.3.0, ICON Development Solutions) via Pirana (version 2.9.7). The simulated clinical trial population consisted of 390 participants with different number of participants across the body weight range (demographics shown in Table 11). In total, 1000 replicate trials of 390 participants each were simulated and plasma AUC0-24, Cmax, and C24 were calculated for each component, DTG, ABC, 3TC.

Table 11: Demographic characteristics of the simulated pediatric population

Simulation Group	Number of Participants Per Trial	Body Weight (kg) Median (range)
≥6 to <10 kg	50	8.0 (6.0-9.9)
≥10 to <14 kg	50	12.0 (10.0-13.9)
≥14 to <20 kg	70	17.0 (14.0-19.9)
≥20 to <25 kg	60	22.5 (20.0-24.9)
≥25 to <40 kg	160	32.5 (25.0-39.9)
Total	**390**	**22.0 (6.0-39.9)**

DTG popPK model was developed based on the data from IMPAACT P1093 (ING112578) and the ODYSSEY PK sub-studies (201296). This model has been assessed by FDA in NDA-204790/S-025 (link). In brief, pediatric PopPK model for DTG follows 1-compartment PK model. The PopPK model accounts for differences in bioavailability across formulations and the impact of food on DTG exposures. The CL/F and V/F were scaled for body weight and a maturation function was applied to CL/F.

ABC popPK model was developed based on the data from studies of ARROW PK Substudy Part 1, PENTA 13, PENTA 15, ARROW PK Substudy Part 2, CNAA1001, and CNAA1013 (ACTG330). This model has been assessed by FDA in NDA-020977/S-027 (link). In brief, pediatric PopPK model for ABC follows 2-compartment PK model. ABC popPK model considers a study specific F1 term for tablet and solution.

3TC popPK model was developed with the data from pediatric studies ARROW PK Substudy Part 1, PENTA 13, PENTA 15, ARROW PK Substudy Part 2, and historical studies NUCA2002 and NUCA2005. This model has been assessed by FDA in NDA-020977/S-027 (link) and NDA-020564/S-033 (link). In brief, pediatric PopPK model for 3TC follows 1-compartment PK model. 3TC PopPK model accounted for a higher bioavailability estimate for solid dosage forms (tablet and capsule) than for the oral solution in pediatric participants (link).

2. Proposed ABC Dosing regimen and Prediction of ABC Exposure in Pediatrics:

(1) For pediatric patients weighting ≥10 to <14 kg, the proposed ABC dosing regimen (240 mg with Triumeq PD) are higher than the approved dosing regimen with Ziagen solution (224 mg). However, the simulated AUC at the proposed 240 mg dose for patients weighing ≥10 to < 14 kg (16.45 μg·hr/mL) is comparable to the simulated exposure at other weight bands (14.85–18.37 μg·hr/mL) (Table 12).

(2) For pediatric patients weighting ≥20 to <25 kg, the proposed ABC dosing regimen (360 mg from Triumeq PD) is lower than the approved regimen with Ziagen Tablet (450 mg). However, it is within the approved dose range with Ziagen solution (320–400 mg).

(3) The simulated ABC AUC values at the proposed dose regimens across different weight bands are comparable to historically observed ABC exposures in pediatrics and adults (Table 13).

Table 12: Simulated plasma ABC exposure at the proposed dosing and at the currently approved dosing

Predicted exposures of ABC with the approved single component dosing regimen				
Weight Bands	**Approved Daily Dose**	**AUC0-24 (μg.h/mL)**	**Cmax (μg/mL)**	**C24 (ng/mL)**
≥6 to <10 kg	16 mg/kg ABC Oral Solution	12.08 (4.98-28.53)	4.59 (2.11 - 9.89)	26.37 (1.25 – 205.7)
≥10 to <14 kg	16 mg/kg ABC Oral Solution	13.05 (5.34-30.98)	5.21 (2.36 - 11.19)	20.70 (1.25-168.1)
≥14 to <20 kg	300 mg ABC Tablet	15.46 (6.11-37.47)	6.41 (2.80 - 14.17)	18.41 (1.25- 166.4)
≥20 to <25 kg	450 mg ABC Tablet	18.55 (7.57-44.48)	7.85 (3.50 - 17.24)	17.44 (1.25 -156.9)
≥25 to <40 kg	600 mg ABC Tablet	18.37 (7.09-46.22)	7.99 (3.34 - 18.43)	13.37 (1.25 -129.0)
Predicted exposures of ABC with the proposed Triumeq DT and Triumeq Tablet dosing regimen				
Weight Bands	**Proposed Daily Dose**	**AUC0-24 (μg.h/mL)**	**Cmax (μg/mL)**	**C24 (ng/mL)**
≥10 to <14 kg	240 mg DT	16.45 (6.70 -39.35)	6.57 (2.95 -14.24)	25.74 (1.25 -215.5)
≥14 to <20 kg	300 mg DT	15.47 (6.11-37.47)	6.41 (2.80 - 14.17)	18.41 (1.25- 166.4)
≥20 to <25 kg	360 mg DT	14.85 (6.05-35.59)	6.28 (2.80 -13.80)	14.24 (1.25 -122.5)
≥25 to <40 kg	600 mg Tablet	18.37 (7.09-46.22)	7.99 (3.34 -18.43)	13.37 (1.25 -129.0)

Source: response to FDA IR, dated 02/04/2022

Table 13: Simulated plasma ABC exposure at the proposed dosing and historically observed ABC exposure in pediatrics and adults

Population/ Dose Frequency	Study, Dose, Age, Number of Participants, [Reference Source]	AUC (0-24) (µg.h/mL) GM (95% CI)	Cmax (µg/mL) GM (95 % CI)
Proposed Triumeq DT & Tablet Once Daily Doses[a]	Simulations, proposed once daily dose for ≥10 to <14 kg weight band (240 mg DT)	16.45 (14.10, 19.17)	6.57 (5.72, 7.53)
	Simulations, proposed once daily dose for ≥14 to <20 kg weight band (300 mg DT)	15.45 (13.4,17.9)	6.41 (5.63, 7.25)
	Simulations, proposed once daily dose for ≥20 to <25 kg weight band (360 mg DT)	14.9 (12.9,17.2)	6.28 (5.52, 7.14)
	Simulations, proposed once daily dose ≥25 kg weight band (600 mg Tablet)	18.4 (16.8,20.1)	7.99 (7.38, 8.67)
Historical Children Living with HIV-1 Once Daily	**PENTA-15**, 16mg/kg once daily 3 to 36 mos, n=18 [PENTA, 2010]	11.6 (9.89,13.5)	4.68 (3.86, 5.67)
	PENTA-13, 16mg/kg once daily 2 to 12 years; n=14 [Bergshoeff, 2005]	13.4 (11.8, 15.2)	4.80 (4.04, 5.71)
	ARROW, WHO once daily tablet regimen 3 to 12 years; n=36 [GSK Document Number RM2009/00368/00]	15.3 (13.3, 17.5)	6.84 (5.92, 7.90)
Historical Adults Living with HIV-1 Once Daily	**CAL102120**, 600mg once daily [b] Adults, n=27 [GSK Document Number GM2006/00416/00]	8.52 (7.23, 10.0)	3.85 (3.34, 4.24)
	CAL10001, 600mg single dose Adults, n=25 [GSK Document Number RM2002/00116/01]	14.2 (12.90, 15.6)	4.69 (4.15, 5.30)

Source: response to FDA IR, dated 02/04/2022

Conclusions on the proposed ABC dosing regimen in pediatric patients:

The proposed ABC dosing regimens (Table 10) for Triumeq PD or Triumeq tablets are acceptable for all weight bands.

3. Proposed 3TC Dosing regimen and Prediction of 3TC Exposure in Pediatrics:

(1) For pediatric patients weighting ≥10 to <14 kg, the proposed 3TC dosing regimen (120 mg from Triumeq PD) are within the approved dose range from Epivir solution (100−140 mg).

(2) For pediatric patients weighting ≥20 to < 25 kg, the proposed 3TC dosing regimen (180 mg from Triumeq PD) is lower than the approved regimen with Epivir Tablet (225 mg) or from solution (200–250 mg). However, the simulated AUC at the proposed 180 mg dose for pediatric patients weighing ≥20 to < 25 kg (8.50 µg·hr/mL) is comparable to the simulated exposure at other weight bands (8.81−10.70 µg·hr/mL) (Table 14).

(3) The simulated 3TC AUC values at the proposed dose regimens across different weight bands are comparable to historically observed ABC exposures in pediatrics and adults (Table 15).

Table 14: Simulated plasma 3TC exposure at the proposed dosing and at the currently approved dosing

Predicted exposures of 3TC with the approved single component dosing regimen				
Weight Bands	**Approved Daily Dose**	**AUC0-24 (µg.h/mL)**	**Cmax (µg/mL)**	**C24 (ng/mL)**
≥6 to <10 kg	10 mg/kg 3TC Oral Solution	8.22 (4.44 -15.04)	2.00 (1.07 – 3.68)	8.19 (1.25 – 108.9)
≥10 to <14 kg	10 mg/kg 3TC Oral Solution	9.04 (4.82 – 16.51)	2.26 (1.21 – 4.16)	8.19 (1.25 – 108.3)
≥14 to <20 kg	150 mg 3TC Tablet	8.81 (4.63 – 16.45)	2.25 (1.17 – 4.21)	8.02 (1.25 – 109.5)
≥20 to <25 kg	225 mg 3TC Tablet	10.55 (5.67 – 19.43)	2.74 (1.46 – 5.10)	8.14 (1.25 – 111.1)
≥25 to < 40 kg	300 mg 3TC Tablet	10.70 (5.41 – 20.46)	2.83 (1.43 – 5.46)	8.06 (1.25 – 113.3)
Predicted exposures of 3TC with the proposed Triumeq DT and Triumeq Tablet dosing regimen				
Weight Bands	**Proposed Daily Dose**	**AUC0-24 (µg.h/mL)**	**Cmax (µg/mL)**	**C24 (ng/mL)**
≥10 to <14 kg	120 mg DT	9.11 (4.81 -16.90)	2.28 (1.21 -4.27)	8.17 (1.25 -108.7)
≥14 to <20 kg	150 mg DT	8.81 (4.63 – 16.45)	2.25 (1.17 – 4.22)	8.02 (1.25 – 109.5)
≥20 to <25 kg	180 mg DT	8.50 (4.48 – 15.62)	2.20 (1.17 – 4.08)	7.77 (1.25 – 105.00)
≥25 to <40 kg	300 mg Tablet	10.70 (5.41 – 20.46)	2.82 (1.43 – 5.46)	8.06 (1.25 – 113.2)

Source: response to FDA IR, dated 02/04/2022

Table 15: Simulated plasma 3TC exposure at the proposed dosing and historically observed 3TC exposure in adults and pediatrics

Population/ Dose Frequency	Study, Dose, Age, Number of Participants, [Reference Source]	AUC (0-24) (µg.h/mL) GM (95% CI)	Cmax (µg/mL) GM (95 % CI)
Proposed Triumeq DT & Tablet Dose[a]	Simulations, proposed once daily dose for ≥10 to <14 kg weight band (120 mg DT)	9.11 (8.20, 10.18)	2.28 (2.04, 2.56)
	Simulations, proposed once daily dose for ≥14 to <20 kg weight band (150 mg DT)	8.81 (8.0, 9.6)	2.25 (2.04, 2.46)
	Simulations, proposed once daily dose for ≥20 to <25 kg weight band (180 mg DT)	8.5 (7.7-9.4)	2.20 (1.96, 2.44)
	Simulations, proposed once daily dose ≥25 kg weight band (300 mg Tablet)	10.7 (10.1-11.4)	2.82 (2.66, 2.99)
Historical Children Living with HIV-1 Once Daily	**PENTA-15**, 8 mg/kg once daily 3 to 36 mos, n=17 [PENTA, 2010]	8.7 (7.5, 10.1)	1.87 (1.65, 2.13)
	PENTA-13, 8 mg/kg once daily or tablets (150 mg) 2 to 12 years; n=19 [Bergshoeff, 2005]	9.8 (8.6, 11.1)	2.09 (1.80, 2.42)
	ARROW, WHO Once Daily tablet Regimen 3 to 12 years; n=35 [GSK Document Number RM2009/00368/00]	12.9 (11.4, 14.9)	3.17 (2.76, 3.64)
Historical Adults Living with HIV-1 Once Daily	Bruno[b] 300 mg Once Daily Adults, n=12 [Bruno, 2001]	16.6 (±4.15) [25%]	3.46 (±0.85)
	EPV10001, 300 mg Once Daily Adults, n=60 [GSK Document Number RM2000/00258/00]	8.7 (8.3, 9.1)	1.96 (1.84, 2.11)
	NUCB1004[c], 300 mg single dose Adults, n=12 [GSK Document Number GCP/93/086]	10.6 (9.9, 11.3)	3.28 (2.95, 3.65)
	CAL10001[c], 300 mg single dose Adults, n=25 [GSK Document Number RM2002/00116/01]	12.6 (11.6, 13.6)	2.64 (2.37, 2.95)

Source: response to FDA IR, dated 02/04/2022

Conclusions on the proposed 3TC dosing regimen in pediatric patients:

The proposed 3TC dosing regimens (Table 10) for Triumeq PD or Triumeq tablets are acceptable for all weight bands.

The proposed dosing regimen with Triumeq and Triumeq PD are being evaluated in an ongoing trial, IMPAACT 2019 (Study 205860). The Applicant submitted the topline summary of PK data (noncompartmental analysis) for DTG, ABC, and 3TC at different weight bands. (b) (4)

(b) (4)

5.6 Assessment on creatinine clearance (CLcr) cutoff value of 30 mL/min

Current labeling states that Triumeq is not recommended in patients with creatinine clearance (CLcr <30 mL/min) because for fixed-dose combination tablets the dosage of the individual components cannot be adjusted. Of all components, 3TC is the only one renally eliminated, thus this review focuses on 3TC exposures in patients with renal impairment. 3TC dosage adjustment is recommended for patients with CLcr <50 mL/min, as per the EPIVIR (3TC) label.

The Applicant originally proposed the following labeling: "TRIUMEQ and TRIUMEQ PD are not recommended in patients with creatinine clearance <30 mL/min (b) (4) Based on the safety profile of 3TC and ranges of doses/exposures of 3TC evaluated in children and adults, the review team considered the creatinine clearance cutoff value of 30 mL/min may be justified for all children, therefore, in an IR dated 02/15/2022, the review team requested the Applicant to provide assessments and supporting data on creatinine clearance cutoff value.

In the response dated 03/01/2022, the Applicant submitted supporting information/data for CLcr cutoff value of 30 mL/min for all children and revised labeling to "TRIUMEQ and TRIUMEQ PD are not recommended for patients with creatinine clearance <30 mL/min." The submitted supporting information/data include:

(1) The Applicant predicted 3TC exposures in children by weight band with CLcr ≥30-49 mL/min and stated that the predicted 3TC exposure in children with renal impairment is overall lower than the observed exposure data in adults with renal impairment.

Table 16: Predicted plasma 3TC exposure at the proposed Triumeq PD regimen in pediatrics with moderate renal impairment vs. observed exposure in adults

Population/ Dose Frequency	Study, Subjects, Dose	AUC (0-24) (µg.h/mL) GM (95% CI)	Cmax (µg/mL) GM (95 % CI)
Proposed Triumeq DT & Tablet Dose[a] (No Renal Impairment)	Simulations, proposed once daily dose for ≥10 to <14 kg weight band, 120 mg DT	9.11 (8.20, 10.18)	2.28 (2.04, 2.56)
	Simulations, proposed once daily dose for ≥14 to <20 kg weight band, 150 mg DT	8.81 (8.0, 9.6)	2.25 (2.04, 2.46)
	Simulations, proposed once daily dose for ≥20 to <25 kg weight band, 180 mg DT	8.5 (7.7, 9.4)	2.20 (1.96, 2.44)
	Simulations, proposed once daily dose ≥25 to <40 kg weight band, 300 mg Tablet	10.7 (10.1-11.4)	2.82 (2.66, 2.99)
Proposed Triumeq DT & Tablet Dose (Moderate Impairment, CLcr: 30 to 49 ml/min)	Simulations, proposed once daily dose for ≥10 to <14 kg weight band, 120 mg DT	17.7 (9.6, 33.4)	2.94 (1.66, 5.23)
	Simulations, proposed once daily dose for ≥14 to <20 kg weight band, 150 mg DT	17.16 (9.2, 32.4)	2.88 (1.61, 5.16)
	Simulations, proposed once daily dose for ≥20 to <25 kg weight band, 180 mg DT	16.59 (9.0, 30.7)	2.82 (1.60, 4.98)
	Simulations, proposed once daily dose ≥25 to <40 kg weight band, 300 mg Tablet	21.0 (10.9, 40.4)	3.64 (1.97, 6.6)
Adults (Moderate renal impairment, CLcr: 30 to 49 ml/min)[b]	NUCB 1003 & NUCA 1004 Adults, n=8, 300 mg Once Daily	38.5 (32.7,45.4)	4.84 (3.62,6.47)

a. Exposures at the proposed Triumeq regimen is based on PopPK simulations [GSK Document Number 2021N471578_01].
b. Table 7, GSK Document Number 2018N378487_00 (NUCB 1003 & 1004 assumes AUC0-24 once daily dosing= AUCinf single dose)

Source: response to FDA IR, dated 03/01/2022

(2) The Applicant identified 2 participants (at reduced 3TC doses) with baseline CLcr ≥30-49 mL/min in previously conducted pediatric trials (ODYSSEY and P1093) and reported that their renal function was improved with the DTG/ABC/3TC-based treatment.

Therefore, the Applicant concluded that a CLcr cutoff value of 30 mL/min can be justified across pediatric weight bands for children taking Triumeq or Triumeq PD. These additional data do not directly support the safety of 3TC in the setting of renal impairment where 3TC exposure is approximately 2-fold higher than those observed in pediatric subjects with normal renal function. Also, safety data from two participants are insufficient to make any assessment. However, based on the overall safety profile of 3TC in children and adults, ranges of doses/exposures of 3TC observed in children and adults, and the benefit of having an FDC in pediatric patients, the review team considers that an inclusive recommendation is suitable in this case.

5.7 Additional PK data from individual studies

Simulated plasma DTG exposure at the proposed dosing regimen and historically observed DTG exposure in pediatrics and adults

Population/ Dose Frequency	Study, Dose, Age, Number of Participants, [Reference Source]	AUC (0-24) (µg.h/mL) GM (95 % CI)	C24h (ng/mL) GM (95 % CI)	Cmax (µg/mL) GM (95 % CI)
Proposed Triumeq DT & Tablet Dose[a]	Simulations, proposed once daily dose for ≥10 to <14 kg weight band (20 mg DT)	64.6 (56.33, 74.57)	729 (512, 1021)	6.8 (6.21, 7.49)
	Simulations, proposed once daily dose for ≥14 to <20 kg weight band (25 mg DT)	68.8 (61.9, 76.9)	819 (608, 1049)	7.12 (6.54, 7.73)
	Simulations, proposed once daily dose for ≥20 to <25 kg weight band (30 mg DT)	71.9 (64.6, 80.9)	878 (656, 1139)	7.39 (6.76, 8.05)
	Simulations, proposed once daily dose ≥25 kg weight band (50 mg Tablet)	66.57 (61.99, 71.7)	951 (804, 1116)	6.22 (5.87, 6.59)
Historical Children Living with HIV-1 Once Daily	P1093 & ODYSSEY (≥10 to <14 kg) n=13 (20 mg DT) [GSK Document Number 2019N422597_00]	68.8 (52.3, 90.5)	976.5 (590.5,1614.6)	5.99 (4.92, 7.29)
Historical Children Living with HIV-1 Once Daily	P1093 & ODYSSEY (≥14 to <20 kg) n=19 (25 mg DT) [GSK Document Number 2019N422597_00]	59.0 (48.1, 72.4)	725.2 (525.9, 1000)	5.97 (4.91, 7.26)
	P1093 & ODYSSEY (≥20 kg) n=49 (50 mg Tablet) [GSK Document Number 2019N422597_00]	54.98 (48.9, 61.9)	777.5 (659.5, 916.6)	4.92 (4.40, 5.49)
Historical Adults Living with HIV-1 Once Daily	Population PK Analysis in HIV-infected, treatment-naïve adults (n=403) (50 mg Tablet) [GSK Document Number 2012N149219_00]	53.6 (52.3-55.0)	1100 (1050, 1150)	3.67 (3.6, 3.74)
	Population PK Analysis in HIV-infected, treatment-experienced adults (n=371) (50 mg Tablet) [GSK Document Number 2012N149456_01][b]	45.1 (43.4-47.0)	832 (774, 893)	3.26 (3.18, 3.36)

Source: response to FDA IR, dated 02/04/2022

a. DTG exposures is based on PopPK simulations.

b. Data shown for the overall population which includes participants on mild or moderate background ARV therapies as inducers

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/s/

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03/07/2022 09:15:38 PM

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