25 April 2024
EMA/CHMP/136294/2024
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Triumeq

International non-proprietary name: Dolutegravir / Abacavir / Lamivudine

Procedure No. EMEA/H/C/002754/II/0116

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

µg	Microgram
3TC	lamivudine, GR109714
ABC	abacavir, GI265235
AE	Adverse event
AESI	Adverse Event of Special Interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
BE	Bioequivalence
BMI	Body mass index
c/mL	Copies per milliliter
CI	Confidence interval
CSR	Clinical study report
CV	Coefficient of variation
CVF	Confirmed virologic failure
DAIDS	Division of AIDS (United States)
DILI	Drug-induced liver injury
DT	Dispersible tablet
DTG	dolutegravir, GSK1349572
eGFR	Estimated glomerular filtration rate
EU	European Union
FDC	Fixed dose combination
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GM	Geometric Mean
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1

IMPAACT	*International Maternal Paediatric Adolescent AIDS Clinical Trials (Network)*
INSTI	*Integrase strand transfer inhibitor*
IRIS	*Immune Reconstitution Inflammatory Syndrome*
kg	*Kilogram*
LLOQ	*Lower limit of quantification*
mg	*Milligram*
NRTI	*Nucleoside reverse transcriptase inhibitor*
PK	*Pharmacokinetic*
PT	*Preferred term*
RNA	*Ribonucleic acid*
SAE	*Serious Adverse Event*
SE	*Single entities*
SOC	*System Organ Class*
US(A)	*United States of America*
WHO	*World Health Organization*

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, ViiV Healthcare B.V. submitted to the European Medicines Agency on 21 September 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients from 6 kg to less than 25 kg for Triumeq Dispersible Tablets, based on PK, safety, and efficacy data observed in the final results of study 205860 (IMPAACT 2019), further supported by extrapolation to data generated in adults and additional data in paediatric patients with the single entities. IMPAACT 2019 is a Phase 1/2 open-label, multicenter, multiple dose study of dolutegravir/lamivudine/abacavir fixed dose combination tablets in treatment-experienced and treatment-naïve HIV-1-infected children less than 12 years of age. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 22.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0038/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0038/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0038/2023, EMEA-001219PIP01-11-M06.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur : Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	21 September 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	19 December 2023
PRAC Rapporteur Assessment Report	3 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 January 2024
Request for supplementary information (RSI)	25 January 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC members comments	28 February 2024
CHMP Rapporteur Assessment Report	6 March 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	09 April 2024
PRAC Rapporteur Assessment Report	09 April 2024
PRAC members comments	15 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	N/a
Updated PRAC Rapporteur Assessment Report	N/A
Opinion	25 April 2024

2. Scientific discussion

2.1. Introduction

Triumeq (DTG/ABC/3TC) is a fixed dose combination (FDC) of three previously authorised antiretrovirals, specifically the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) with the two nucleoside reverse transcriptase inhibitors (NRTI) abacavir (ABC) and lamivudine (3TC). DTG/ABC/3TC film-coated tablets (50/600/300mg) are already approved for use for the treatment of HIV-1 infection in adult and paediatric patients weighing at least 25 kg, while DTG/ABC/3TC dispersible tablets (DT) (5/60/30mg) are authorised for paediatric patients weighing from 14 to less than 25 kg.

The proposed extension of indication covers the use of DTG/ABC/3TC DTs in paediatric patients weighting at least 6 kg, with the following dosing recommendations:

Table 1. DTG/ABC/3TC Dosing Recommendations for Paediatric Patients Living with HIV-1 Weighing 6kg or Greater

Weight Band (kg)	Total Daily Dose (DTG/ABC/3TC)	Number of Tablets Formulation	Dispersion Volume
≥6 to <10	15 mg/180 mg/90 mg	3 DTs	15 mL
≥10 to <14	20 mg/240 mg/120 mg	4 DTs	20 mL

Note: While the relative bioavailability of ABC and 3TC administered in DTG/ABC/3TC DTs are not different from the DTG/ABC/3TC Tablets, the bioavailability of the DTG component of the DTG/ABC/3TC DT is approximately 1.7-fold greater than (m2.7.1 Section 2.1) that of the DTG/ABC/3TC Tablet. Thus, the 2 dosage forms are not interchangeable on a mg-per-mg basis and preclude switching between the 2 dosage forms.

The application for regulatory approval in paediatric patients weighing ≥6 kg is based on PK, safety and tolerability data from the completed Phase 1/2 IMPAACT 2019 study (Study 205860), supported by with extrapolation of clinical efficacy as already established in adults for the FDC and in the paediatric population for the single entities, through a PK-bridging approach.

2.1.1. Problem statement

Combination antiviral therapy with human immunodeficiency virus type-1 (HIV-1) protease and reverse transcriptase inhibitors has significantly reduced acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality. However, emerging multi-class drug-resistant HIV strains as well as potential long-term toxicities warrant development of new antiretroviral therapies without or with limited cross-resistance to available drugs.

DTG is a preferred agent for the initial treatment of HIV, and ABC and 3TC form the backbone of several recommended first line ART regimens. Global guidelines for the management of HIV-1 infection recommend an INSTI (specifically DTG) plus 2 NRTIs as part of preferred first line therapy for adults and children. DTG/ABC/3TC as an FDC is a preferred regimen and access to DTG/ABC/3TC DT remains a priority for children globally as was described in the Paediatric Antiretroviral Drug Optimization (PADO) group's list of priority medications for children.

There is an ongoing need for age-appropriate treatment options for children living with HIV. Specifically, single-tablet, once daily regimens provide several advantages to adults and children living with HIV because having a lower pill burden is associated with improved adherence, lower healthcare costs, increased viral suppression, and higher patient satisfaction.

2.1.2. About the product

Triumeq (DTG/ABC/3TC) is a fixed dose combination (FDC) of three previously authorised single entities. DTG/ABC/3TC film-coated tablets (50/600/300mg) are already approved for use for the treatment of HIV-1 infection in adult and paediatric patients weighing at least 25 kg, while DTG/ABC/3TC dispersible tablets (DT) (5/60/30mg) are authorised for paediatric patients weighing from 14 to less than 25 kg.

The DTG/ABC/3TC dispersible tablet (DT) and tablet formulations used in paediatric clinical IMPAACT 2019 study were the currently marketed formulations. No new biopharmaceutical information is provided in this Application. Formulation development and in vitro dissolution data for the DTG/ABC/3TC dispersible tablet formulation have been previously submitted and assessed.

Dolutegravir (DTG) is an HIV INSTI approved for use in combination with other ARV agents for treatment-naïve and treatment-experienced adults and paediatric patients living with HIV who are ≥4 weeks of age

and weigh ≥3 kg. DTG was initially approved in 2013 and is marketed globally as Tivicay in Tablet (10 mg, 25 mg, and 50 mg) and DT (5 mg) formulations.

Abacavir (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 paediatric patients ≥3 months of age. ABC was initially approved in 1998 and is available globally as scored tablet (300 mg) for patients weighing at least 14 kg and oral solution (20 mg/mL) for paediatric patients ≥3 months of age.

Lamivudine (3TC) is a cytidine nucleoside analog HIV-1 reverse transcriptase inhibitor approved for use in combination with other ARV agents for the treatment of HIV-1 in adults and paediatric patients ≥3 months of age. 3TC was initially approved in 1995 and is available globally as Epivir tablet (300 mg) and scored tablet (150 mg) for patients weighing at least 14 kg and oral solution (10 mg/mL) for paediatric patients ≥3 months of age.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A CHMP guideline (CPMP/EWP/633/02 Rev. 3) on the clinical development of medicinal products for treatment of HIV infection is available.

The development program for Triumeq has been formally discussed with key regulatory agencies at various milestones throughout the development program.

The IMPAACT 2019 study was included as a clinical measure in the agreed Paediatric Investigation Plan (PIP) for Triumeq.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. The present procedure proposed to lower the acceptable weight limit of paediatric patients from 14 to 6 kg for TRIUMEQ Dispersible Tablets.

An overview of existing non-clinical studies of relevance to postnatal and juvenile developmental toxicity for the three active substances (DTG, ABC, and 3TC) has been provided which corresponds to the previous non-clinical assessment of Triumeq. Uncertainties remain about the actual interactions (i.e., leading to possible mixture toxicity) in young animals but this is not further pursued as no such studies are available. Overall, the provided non-clinical overview is acceptable.

An updated environmental risk assessment (ERA) has also been provided (see below).

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has submitted an updated ERA where it is stated that the previously approved TRIUMEQ ERA dated to 22-February-2017 (report 2017N317214) is considered to be robust and complete.

The composition of the dispersible tablets for the proposed paediatric dosing regimen (i.e., patients weighing under 25 kg) contains 10% (5/60/30 mg vs 50/600/300 mg) of the amounts of DTG/ABC/3TC to that of the adult population. The total daily dose amount for paediatric patients weighing under 25 kg is estimated to be 30% to 60% of the total daily dose for adult patients and paediatric patients weighing greater than 25 kg.

This ERA reported risk quotients (PEC/PNEC) based on scenarios phase I PEC (based on maximum daily dose), phase II PEC (based on consumption data) and a PEC based on worst case predicted forecast. All

scenarios, including the most conservative worst-case phase I PEC, indicated that the use of TRIUMEQ is unlikely to be a risk to the environment (PEC/PNEC < 1). The MAH argues for, and the Committee agrees, that the increase in patient population for the proposed indication is deemed to generate a negligible increase in PEC for the different APIs. Also, DTG, ABC and 3TC are not persistent, bio accumulative and toxic (PBT) substances.

2.2.2. Discussion on non-clinical aspects

It was noted in the TRIUMEQ EPAR from 2022 (15 December 2022; EMA/CHMP/915669/2022) that overall, in the context of reducing the lower limit of patient body weight to 14 kg, DTG and ABC seem to manifest some form of general toxicity (growth-reduction related) at low exposure margins (0.5x—3.2x, Cmax-based) after pre-weaning exposure in rat (where rodents tend to particular sensitive to toxicological exposure). A human body weight of 14 kg tends to correspond to an age range slightly around or after 2 years of age which roughly corresponds to the immediate post-weaning period in rat which is likely less sensitive than the pre-weaning period. It was then considered that, combined with previous clinical experience, the weight range of >14kg was unlikely to result in novel Triumeq-generated toxicity but it was also noted that any further reduction of these indication (age or body weight) limits would be accompanied with increasingly greater toxicological uncertainty.

The present procedure aims at reducing the body weight limit even further to 6 kg (>6 kg which roughly corresponds to infants of around 5-6 months of age and older) - meaning that the developmental toxicity impact potential has shifted into an age range where certain organs/organ system are still undergoing some degree of development/maturation which have not previously been considered when the body weight limit >14 kg.

In the current procedure, the MAH indicates that the safety of DTG, ABC, and 3TC has been well characterized in a comprehensive battery of nonclinical studies previously submitted with the original dossiers for each SE. These studies have previously supported the marketing approvals of the SEs as well as FDC products containing them. In their view, the overall nonclinical data are considered adequate to support the use of DTG/ABC/3TC Tablets and DTG/ABC/3TC DTs in the treatment of HIV-1 infection in patients weighing at least 6 kg at the recommended doses".

An overview of existing non-clinical studies of relevance to postnatal and juvenile developmental toxicity for the three active substances (DTG, ABC, and 3TC) provided which corresponds to the previous non-clinical assessment of Triumeq. Uncertainties remain about the actual interactions (i.e., leading to possible mixture toxicity) in young animals but this is not further pursued as no such studies are available. Overall, the provided non-clinical overview is acceptable.

2.2.3. Conclusion on the non-clinical aspects

Overall, the provided non-clinical overview is acceptable.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of *DTG/ABC/3TC.*

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The IMPAACT 2019 study was conducted in Botswana, South Africa, Thailand and USA.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

IMPAACT 2019 (Study 205860) Phase 1/2, multi-center, open-label study that investigates the PK, safety, tolerability, and efficacy of DTG/ABC/3TC FDC (Tablets and DTs) in ART-naïve and ART-experienced children living with HIV-1 who were <12 years of age and weighed ≥6 kg to <40 kg.

2.3.2. Pharmacokinetics

The pharmacokinetic (PK) results consisted of both intensive PK sampling and sparse PK sampling from IMPAACT 2019. Intensive PK sampling was performed in a subset of the patients and were analysed using non-compartmental analysis. Sparse PK sampling was to be performed in all patients in IMPAACT 2019 and the sparse PK data were analysed using population PK analysis (also including the intensive PK sampling data).

PK was included as a primary objective according to the IMPAACT2019 protocol, as follows:

- Determine the steady-state area under the plasma concentration-time curve from time 0 to 24 hours (AUC0-24h), maximum concentration (Cmax), and drug concentration at 24 hours post-dose (C24h) of DTG, ABC, and 3TC and confirm the dosing of DTG/ABC/3TC dispersible tablets (DTs) and Tablets that achieves protocol-defined pharmacokinetic (PK) targets for DTG, ABC, and 3TC in children <12 years of age.

PK was also included as a secondary objective according to the IMPAACT2019 protocol, as follows:

- Determine the PK of DTG, ABC, and 3TC, and clinical covariates that influence PK disposition, among children <12 years of age using population PK (PopPK) analysis of intensive and sparse PK samples collected over 48 weeks of treatment with DTG/ABC/3TC DTs and Tablets.

IMPAACT 2019

IMPAACT 2019 (Study 205860) is a Phase 1/2, multi-center, open-label study that investigates the PK, safety, tolerability, and efficacy of DTG/ABC/3TC FDC (Tablets and DTs) in ART-naïve and ART-experienced children living with HIV-1 who were <12 years of age and weighed ≥6 kg to <40 kg. Paediatric participants were enrolled concurrently in 5 separate weight bands (see *Table 2* below)).

Table 2. DTG/ABC/3TC Dosing for Paediatric Patients Living with HIV-1 in IMPAACT 2019 Study

DTG/ABC/3TC DT		
Weight Band (kg)	**Total Daily Dose (DTG/ABC/3TC)**	**Number of 5 mg/60 mg/30 mg DTs**
≥6 to <10	15 mg/180 mg/90 mg	3
≥10 to <14	20 mg/240 mg/120 mg	4
≥14 to <20	25 mg/300 mg/150 mg	5
≥20 to <25	30 mg/360 mg/180 mg	6
DTG/ABC/3TC Tablet		
Weight Band (kg)	**Total Daily Dose (DTG/ABC/3TC)**	**Number of 50 mg/600 mg/300 mg Tablets**
≥25 kg	50 mg/600 mg/300 mg	1

Intensive PK sampling was performed in the first 7 paediatric participants enrolled in each of the weight bands at the Week 1 (Days 5-10) study visit. There were 57 participants (see table below) enrolled in IMPAACT 2019 and 35 participants (7 in each weight band) provided dose evaluable intensive PK samples. Sparse PK samples were collected across all participants at Weeks 1 (in participants not undergoing intensive PK sampling at Week 1), 4, 12, 24, 36, and 48.

Intensive plasma PK samples for analysis of DTG, ABC, and 3TC were collected up to 24 hours after dosing (pre-dose, 1, 2, 3, 4, 6, 8, and 24 hours post-dose) within 5 to 10 days of starting DTG/ABC/3TC in these participants. Intensive PK samples were collected following administration of DTG/ABC/3TC in a modified-fasted condition as defined in the protocol. On the day of the intensive PK visit, paediatric participants were allowed to eat a low-fat light snack (approximately 100-150 calories) at least 2 hours prior to study drug dosing at the study site. During the 2 hours prior to study drug dosing, and the first hour after study drug dosing, only water was allowed in these participants.

In addition, participants were required to have at least 4 consecutive days of observed dosing prior to the intensive PK visit to ensure steady state had been achieved and that the appropriate doses were administered. This analysis includes data from 55 study participants who provided intensive and/or sparse plasma PK samples. Out of these 55 participants, 35 participants provided intensive and sparse PK samples and the remaining 20 participants only provided sparse PK samples. These data on DTG/ABC/3TC PK parameters (DTG, ABC, and 3TC) are provided to support weight band-based once daily doses proposed for marketing authorization.

Table 3. IMPAACT 2019 Baseline Demographics

Demographics	**Total N=55**
Baseline Age (years)	
Mean (SD)	5.53 (3.1)
Median (range)	6.00 (1.00, 11.00)
Baseline Weight (kg)	
Mean (SD)	18.64 (7.4)
Median (range)	17.0 (8.15, 39.30)
Baseline Height (cm)	
Mean (SD)	109.77 (20.2)
Median (range)	113.0 (71.0, 153.0)
Gender, n (%)	
Male	30 (54.5)
Female	25 (45.5)
Race, n (%)	
Asian	17 (30.9)
Black or African American	37 (67.3)
Unknown	1 (1.8)

Source: IMPAACT 2019 PopPK Report

The dose confirmation for the each of the weight bands was achieved based on IMPAACT 2019 protocol-defined PK targets for DTG, ABC, and 3TC (see table below) among participants who underwent intensive PK sampling and met dose-evaluable criteria. As per the protocol, geometric means of the targeted PK parameters for each of the weight bands must fall within the pre-defined range. The DTG AUC0-24 and C24 target values used in this analysis are similar to those previously used in the DTG SE paediatric-related applications.

Table 4. DTG, ABC, and 3TC PK Targets

PK Parameter	DTG[a]		ABC[b]		3TC[b]	
	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
AUC0-24 (µg.h/mL)	37	134	6.3	50.4	6.3	26.5
C24 (µg/mL)	0.697	2.260	--	—	--	--

Source: IMPAACT 2019 PopPK Report Table 4

The DTG targets were based on adult study data. C24=The lower limit reflects the 70% of GM (0.697 µg/mL= 0.995 µg/mL * 0.7) and the upper limit (2.260 µg/mL) is the upper 90th percentile observed in adults following 50 mg QD dosing. AUC0-24=The lower limit reflects the 80% of the target GM observed in adults (46 µg.h/mL *0.8 = 37 µg*h/mL) following 50 mg QD dosing while upper limit (134 µg*h/mL) is the upper 95th percentile of AUC obtained at steady state following 50 mg BID dosing.

The ABC and 3TC AUC0-24 targets are based on PopPK modelling. The lower bound and upper bounds are of the 90% CIs for predicted exposures with once-daily ABC/3TC weight band dosing with the Tablet formulation in children.

Additional information concerning the exposure targets were included in the extension for the Triumeq dispersible tablets (EMEA/H/C/002754/X/0101/G). For ABC and 3TC, target ranges for Cmax were derived and the corresponding adult geometric mean AUC and Cmax were provided. For DTG, target ranges for Cmax were derived and the corresponding adult geometric mean Cmax were provided (see the 3 tables below).

Table 5. ABC PK targets

	AUC0-24h (µg*h/mL)	Cmax (µg/mL)
Pediatric Targets GM (Range)[a]	16.1 (6.3-50.4)	6.16 (2.75 -18.5)
Adult Corresponding Exposure GM (%CV)[b]	8.52 (43)	3.85 (37)

[a]AUC0-24h= The GM target (16.1 µg*h/mL) is the overall median predicted exposure in pediatric subjects with approved QD dosing. The lower bound (6.3 µg*h/mL) and upper bounds (50.4 µg*h/mL) are of the 90% PI for predicted exposures with once-daily ABC weight band dosing with the tablet formulation in children (GSK Document Number 2013N181066_00).

[a]Cmax= The GM target (6.1 µg/mL) is the overall median predicted exposure in pediatric subjects with approved QD dosing. The lower bound (2.75 µg/mL) and upper bounds (18.5 µg/mL) are of the 90% PI for predicted exposures with once-daily ABC weight band dosing with the tablet formulation in children (GSK Document Number 2013N181066_00).

[b]Adult Exposure= ABC exposure observed after 600 mg QD dosing in adults (Study CAL102120, GSK Document Number GM2006/00416/00).

Table 6. 3TC PK targets

	AUC0-24h (µg*h/mL)	Cmax (µg/mL)
Pediatric Targets GM (Range)[a]	10.2 (6.3-26.5)	2.4 (1.39 -6.74)
Adult Corresponding Exposure GM (%CV)[b]	8.7 (21)	1.96 (26)

[a]AUC0-24h= The GM target (10.2 µg*h/mL) is the overall median predicted exposure in pediatric subjects with approved QD dosing. The lower bound (6.3 µg*h/mL) and upper bounds (26.5 µg*h/mL) are of the 90% CI for predicted exposures with once-daily ABC weight band dosing with the tablet formulation in children (GSK Document Number 2013N181170_00).

[a]Cmax= The GM target (2.4 µg/mL) is the overall median predicted exposure in pediatric subjects with approved QD dosing. The lower bound (1.39 µg/mL) and upper bounds (6.74 µg/mL) are of the 90% CI for predicted exposures with once-daily ABC weight band dosing with the tablet formulation in children (GSK Document Number 2013N181170_00).

[b]Adult Exposure= 3TC exposure observed after 300 mg QD dosing in adults (Study EPV10001, GSK Document Number RM2000/00258/01)

Table 7. DTG Cmax targets

	Cmax (µg/mL)
Pediatric Targets GM (Range)	5.32 (2.12 -13.3)[a]
Adult Corresponding Exposure GM (%CV)	3.67 (20)[b]

[a]Cmax= The GM target of 5.32 µg/mL represents an overall GM estimate in pediatric participants following approved DT and Tablet QD DTG dosing [GSK Document Number 2019N422597_00]. The lower limit (2.12 µg/mL) is selected as 5th percentile of GM Cmax after 5 mg DT dosing. The upper limit (13.3 µg/mL) represents the 95th percentile of GM in pediatric participants following 50 mg Tablet dosing (GSK Document Number 2019N424147_00 & Tivicay Latest SmPC)

[b]Adult Exposure= DTG post-hoc estimates based on population pharmacokinetic analyses using data (n=449) from SPRING-1 (ING112276) and SPRING-2 (ING113086) following 50 mg Tablet dosing (GSK Document Number 2012N149219_00).

Bioanalysis

Plasma samples were analysed at Antiviral Pharmacology Laboratory, University of Alabama at Birmingham.

ABC/3TC Method Description (GSK Report number 2022N509615_00): Abacavir and lamivudine were extracted from human plasma using a protein precipitation followed by hydrophilic interaction chromatography (HILIC) HPLC, paired with MS-MS detection for all curves, QC samples, and patient samples.

Dolutegravir Method Description (GSK Report number 2022N509614_00): Dolutegravir was extracted from human plasma using a protein precipitation followed by reversed phase HPLC, paired with MS-MS detection for all curves, QC samples, and patient samples.

Ultrasensitive ABC Method Description (GSK Report Number 2022N509617_00): Ultrasensitive abacavir was extracted from human plasma using a protein precipitation followed by reversed phase HPLC, paired with MS-MS detection for all curves, QC samples, and patient samples.

Non-compartmental PK analysis

Methods

Steady-state intensive PK parameters for all three agents were calculated using noncompartmental method (Phoenix WinNonlin v7.0).

DTG, ABC, and 3TC AUC 0-24h will be determined using linear up-log down trapezoidal method. In the absence of adequate PK data to perform non-compartmental analyses (NCA), other appropriate compartmental analyses may be undertaken to describe the plasma PK of these three moieties. Pharmacokinetic analyses will be carried out using actual sampling times. AUC 0-tau with tau set to 24 hours will be reported as the measurement for the primary outcome of AUC 0-24h for weight band dose confirmation as these participants are at steady-state.

Results

An overview of selected DTG, ABC, and 3TC PK parameters is included in the table below, also including the exposure target ranges. The DTG, ABC, and 3TC PK parameters are detailed further below.

Table 8. Overall summary of PK parameters (Dose evaluable population)

Weight Bands (kg)	DTG/ABC /3TC Dosage Form	DTG/ABC/ 3TC Dose (mg)	n	PK Parameter GM (%CVb)			
				DTG		ABC	3TC
				AUC0-24 (µg*h/mL)	C24 (µg /mL)	AUC0-24 (µg*h/mL)	AUC0-24 (µg*h/mL)
≥6 to <10	DT	15/180/90	7	75.9 (34)	0.91 (68)	17.7 (34)	10.7 (46)
≥10 to <14	DT	20/240/120	7	91.0 (36)	1.22 (77)	19.8 (51)	14.2 (24)
≥14 to <20	DT	25/300/150	7	71.4 (23)	0.79 (44)	15.1 (40)	13.0 (16)
≥20 to <25	DT	30/360/180	7	84.4 (26)	1.35 (95)	17.4 (19)	14.5 (17)
≥25	Tablet	50/600/300	7	71.8 (14)	0.98 (28)	25.7 (15)	21.7 (26)
Target GM Range				**37 to 134**	**0.697 to 2.26**	**6.3 to 50.4**	**6.3 to 26.5**

Source: IMPAACT 2019 CSR Table 4.5, Table 4.4, Table 4.6
Note: n = Number of participants who were dose evaluable in each weight band
Note: CVb is between participant coefficient of variation calculated for log transformed data as: CVb: 100 * (sqrt(exp(SD^2)-1))
Note: Target GM ranges are presented in IMPAACT 2019 PopPK Report In-text Table 4

DTG

The DTG Cmax, AUC and C24 for all 5 weight bands are listed below. The observed plasma DTG C24h , AUC0-24 , and Cmax values following administration of Triumeq FDC in the IMPAACT 2019 were consistent with historically observed exposures in adults and paediatrics following single entity QD dosing (see figures below).

Table 9. Pharmacokinetic Parameters of DTG after Administration of DTG/ABC/3TC

PK Parameter	Weight Band (kg)				
	≥6 to <10 (N=7)	**≥10 to <14 (N=7)**	**≥14 to <20 (N=7)**	**≥20 to <25 (N=7)**	**≥25 (N=7)**
Dosage Form	DT	DT	DT	DT	Tablet
DTG Dose	15 mg	20 mg	25 mg	30 mg	50 mg
Cmax (µg/mL)					
Geometric Mean (%CVb)	7.40 (28)	8.85 (21)	7.04 (17)	7.29 (17)	6.25 (21)
95% CI	5.74, 9.53	7.28, 10.75	6.02, 8.23	6.26, 8.50	5.18, 7.55
Min, Max	5.11, 11.15	6.18, 11.45	5.73, 9.77	6.01, 9.59	4.36, 7.83
AUC0-24 (µg*h/mL)					
Geometric Mean (%CVb)	75.9 (34)	91.0 (36)	71.4 (23)	84.4 (26)	71.8 (14)
95% CI	56.0, 102.8	65.6, 126.1	57.7, 88.5	66.5, 107.2	63.2, 81.6
Min, Max	48.5, 124.9	46.6, 125.6	48.6, 101.9	68.0, 138.8	63.2, 90.8
C24 (µg/mL)					
Geometric Mean (%CVb)	0.91 (68)	1.22 (77)	0.79 (44)	1.35 (95)	0.98 (28)
95% CI	0.52, 1.61	0.64, 2.29	0.53, 1.16	0.64, 2.84	0.76, 1.26
Min, Max	0.45, 2.08	0.35, 2.65	0.38, 1.27	0.58, 4.90	0.75, 1.53

Source: IMPAACT 2019 CSR Table 4.5
Note: CVb is between participant coefficient of variation calculated for log transformed data as: CVb: 100 * (sqrt(exp(SD^2)-1))

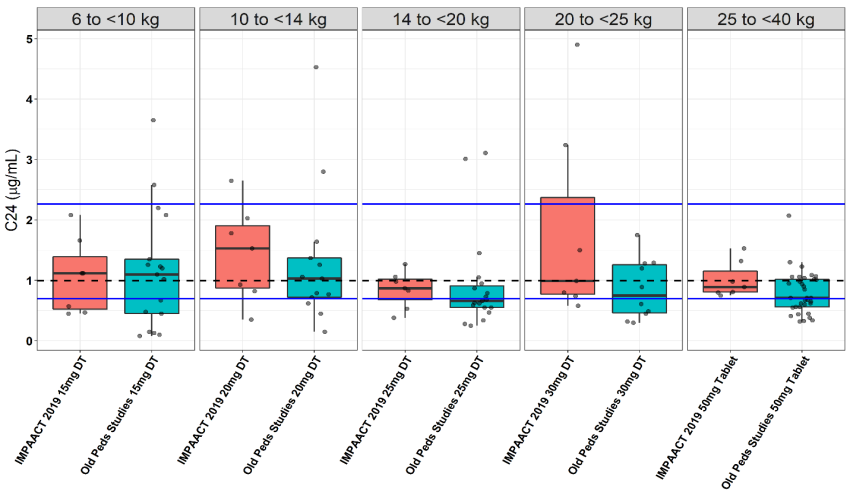


*Figure 1. Comparison of observed DTG C24h in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line in the middle of the boxes (Whiskers) represent 1.5*IQR (inter-quartile range)., Circles represents observed C24h values. Blue solid horizontal lines: Geometric mean C24h target range (0.697 to 2.26 µg/mL). Black dashed horizontal line: Geometric mean C24h exposure with 50mg QD dosing in adults (0.995 µg/mL). IMPAACT 2019= DTG exposures with Triumeq FDC doses. Old Paeds Studies= DTG PK data from P1093 & ODDYSSEY studies combined (⩾6 to <40 kg) for this analysis.*

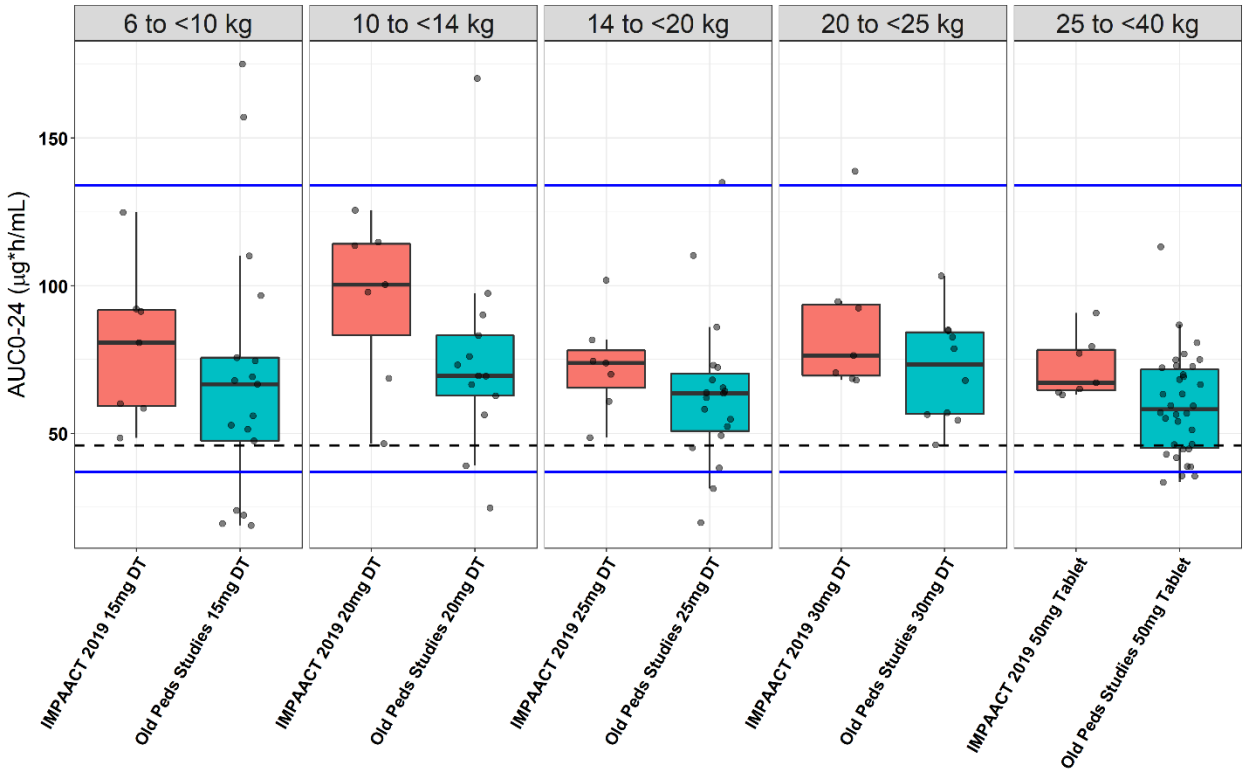


*Figure 2. Comparison of observed DTG AUC0-24h in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line in the middle of the boxes (Whiskers) represent 1.5*IQR, Circles represents observed AUC0-24h values. Blue solid horizontal lines: Geometric mean AUC0-24h target range (37 to 134 µg*h/mL). Black dashed horizontal line: Target Geometric mean AUC0-24h exposure (46 µg*h/mL). IMPAACT 2019= DTG exposures with Triumeq FDC doses. Old Peds Studies= DTG PK data from P1093 & ODDYSSEY studies combined (⩾6to <40 kg) for this analysis.*

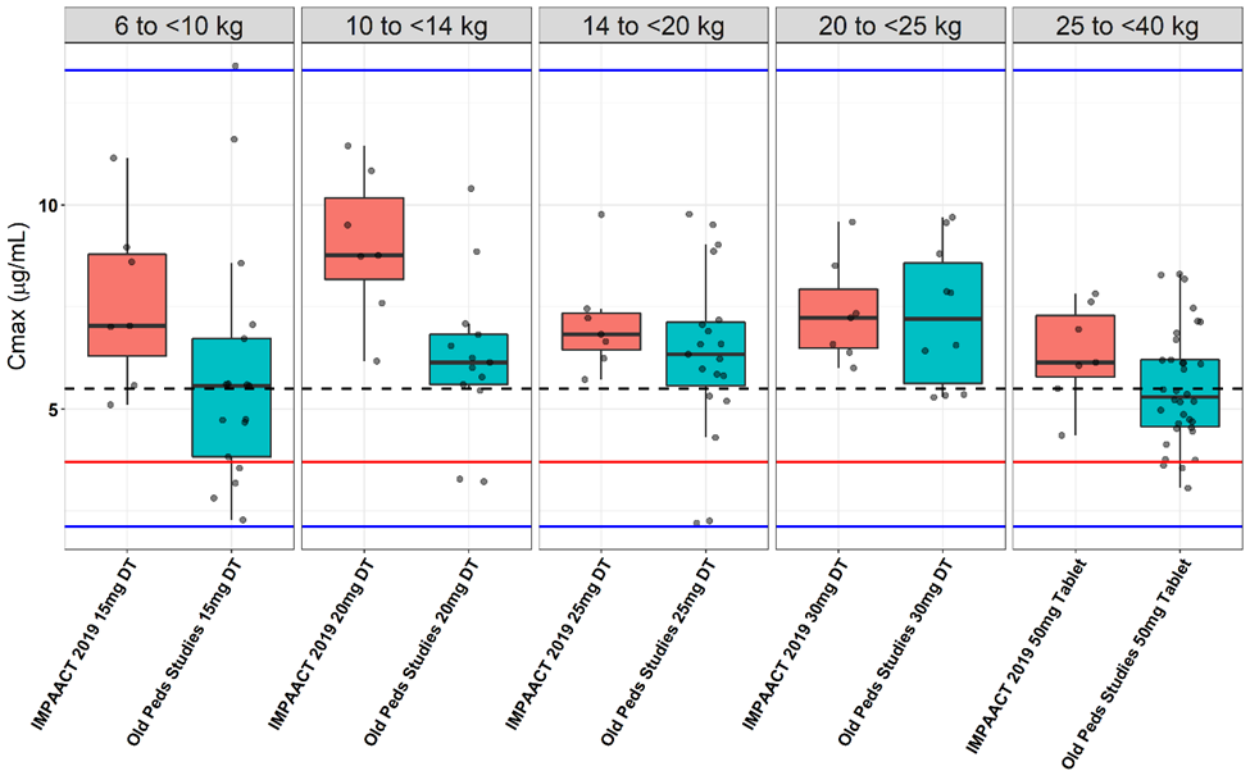


*Figure 3. Comparison of observed DTG Cmax in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line through the middle of the boxes (Whiskers) represent 1.5*IQR, Circles represents observed Cmax values. Blue solid horizontal lines: Geometric mean Cmax target range (2.12 to 13.3 µ g/mL). Black dashed horizontal line: Geometric mean Cmax exposure with DT and FCT dosing in Paediatrics (5.32 µg/mL). solid red horizontal line: Geometric mean observed in adults after 50 mg FCT (3.7 µg/mL). IMPAACT 2019= DTG exposures with Triumeq FDC doses. Old Peds Studies= DTG PK data from P1093 & ODDYSSEY studies combined (≥6 to <40 kg) for this analysis.*

ABC

The ABC Cmax, AUC and C24 for all 5 weight bands are listed below. The observed plasma ABC AUC0-24 and Cmax values following administration of Triumeq FDC in the IMPAACT 2019 study were consistent with that historically observed in adults and paediatrics with single entity QD dosing (see table and figures below)

Table 10. Pharmacokinetic Parameters of ABC after Administration of DTG/ABC/3TC

PK Parameter	Weight Band (kg)				
	≥6 to <10 (N=7)	**≥10 to <14 (N=7)**	**≥14 to <20 (N=7)**	**≥20 to <25 (N=7)**	**≥25 (N=7)**
Dosage Form	DT	DT	DT	DT	Tablet
ABC Dose	180 mg	240 mg	300 mg	360 mg	600 mg
Cmax (μg/mL)					
Geometric Mean (%CVb)	7.30 (20)	8.36 (44)	6.26 (31)	6.65 (28)	9.04 (22)
95% CI	6.05, 8.81	5.68, 12.31	4.73, 8.28	5.17, 8.56	7.40, 11.04
Min, Max	5.31, 9.51	3.79, 14.04	4.27, 9.24	4.58, 8.82	5.83, 11.78
AUC0-24 (μg*h/mL)					
Geometric Mean (%CVb)	17.7 (34)	19.8 (51)	15.1 (40)	17.4 (19)	25.7 (15)
95% CI	13.02, 23.94	12.71, 30.73	10.54, 21.61	14.52, 20.73	22.51, 29.44
Min, Max	12.58, 27.23	7.55, 30.53	9.78, 26.14	13.36, 23.52	19.03, 29.03
C24 (μg/mL)					
Geometric Mean (%CVb)	0.003 (128)	0.005 (127)	0.003 (108)	0.004 (85)	0.011 (229)
95% CI	0.001, 0.007	0.002, 0.013	0.001, 0.006	0.002, 0.007	0.003, 0.037
Min, Max	0.005, 0.009	0.001, 0.015	0.001, 0.013	0.002, 0.014	0.001, 0.043

Source: IMPAACT 2019 CSR Table 4.4

Note: CVb is between participant coefficient of variation calculated for log transformed data as: CVb: 100 * (sqrt(exp(SD^2)-1))

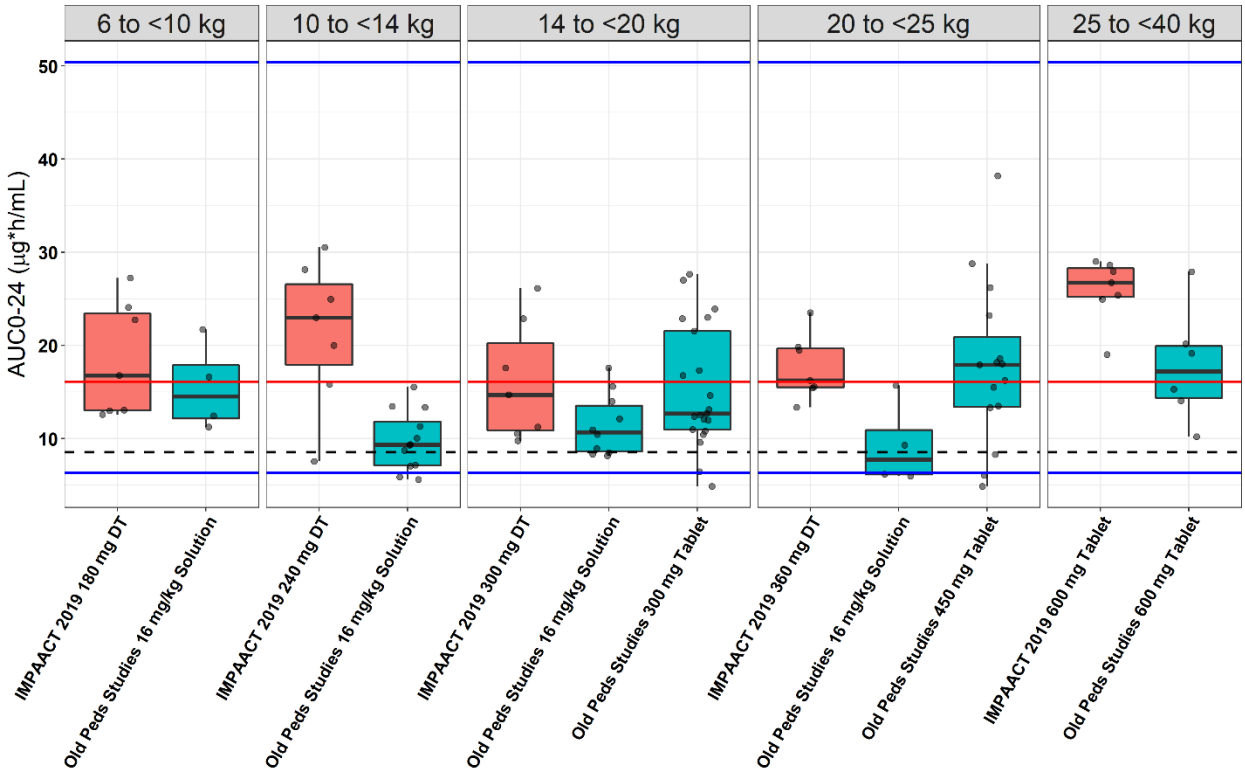


*Figure 4. Comparison of observed ABC AUC0-24h in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line in the middle of the boxes (Whiskers) represent 1.5*IQR, Circles represents observed AUC0-24 values. Blue solid horizontal lines: Geometric mean AUC0-24 target range (6.3 to 50.4 µg*h/mL). Black dashed lines: Adult geometric mean AUC0-24 exposure with 600 mg QD dosing (8.52 µg*h/mL). Red Solid line: Overall PopPK predicted median concentration with approved single entity dosing (16.1 µg*h/mL). IMPAACT 2019= ABC exposures with Triumeq FDC doses. Old Peds Studies= ABC PK data from ARROW PK Substudy, PENTA 13, and PENTA 15 combined divided into weight bands (≥6to <40 kg) for this analysis.*

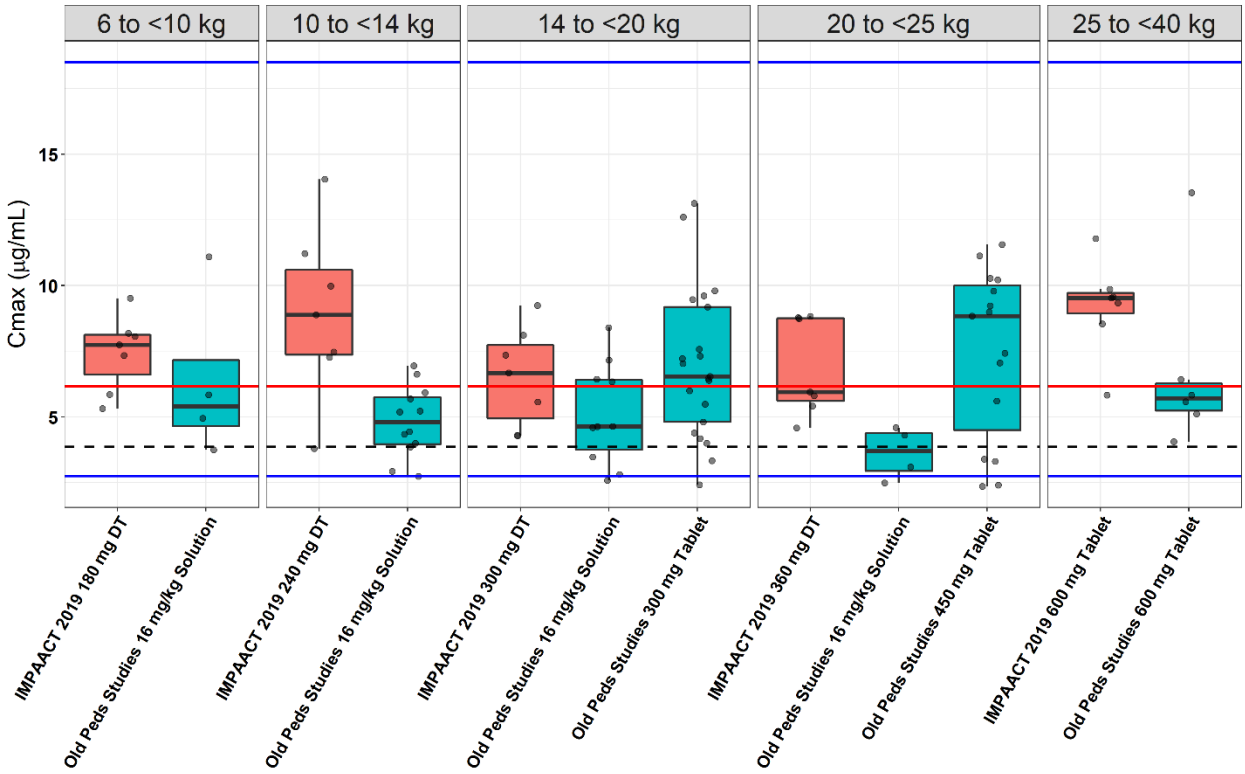


*Figure 5. Comparison of observed ABC Cmax in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line in the middle of the boxes (Whiskers) represent 1.5*IQR, Circles represents observed Cmax values. Blue solid lines: PopPK based 90% prediction intervals of Cmax with once-daily ABC dosing in Paediatrics (2.75 to 18.5 µg/mL). Black dashed line: Adult geometric mean Cmax exposure with 600 mg QD dosing (3.85 µg /mL). Red Solid line: Overall PopPK predicted median concentration with approved single entity dosing (6.1 µg/mL). IMPAACT 2019= ABC exposures with Triumeq FDC doses. Old Peds Studies= ABC PK data from ARROW PK Substudy, PENTA 13, and PENTA 15 combined divided into weight bands (≥6 to <40 kg) for this analysis.*

3TC

The 3TC Cmax, AUC and C24 for all 5 weight bands are listed below. The observed plasma 3TC AUC0-24 and Cmax values following administration of Triumeq FDC in the IMPAACT 2019 study were consistent with historically observed values in adults and paediatrics with single entity QD dosing (see figures below).

Table 11. Pharmacokinetic Parameters of 3TC after Administration of DTG/ABC/3TC

PK Parameter	Weight Band (kg)				
	≥6 to <10 (N=7)	**≥10 to <14 (N=7)**	**≥14 to <20 (N=7)**	**≥20 to <25 (N=7)**	**≥25 (N=7)**
Dosage Form	DT	DT	DT	DT	Tablet
3TC Dose	90 mg	120 mg	150 mg	180 mg	300 mg
Cmax (μg/mL)					
Geometric Mean (%CVb)	2.29 (40)	3.55 (19)	2.92 (23)	2.99 (32)	4.15 (29)
95% CI	1.61, 3.27	2.99, 4.21	2.36, 3.60	2.24, 3.99	3.18, 5.41
Min, Max	1.12, 3.70	2.72, 4.41	2.27, 4.51	1.93, 4.76	2.79, 6.42
AUC0-24 (μg*h/mL)					
Geometric Mean (%CVb)	10.7 (46)	14.2 (24)	13.0 (16)	14.5 (17)	21.7 (26)
95% CI	7.10, 15.99	11.39, 17.61	11.28, 15.02	12.46, 16.90	17.13, 27.58
Min, Max	4.95, 20.39	8.83, 18.48	10.77, 17.42	11.85, 19.39	13.86, 30.78
C24 (μg/mL)					
Geometric Mean (%CVb)	0.055 (39)	0.046 (48)	0.058 (37)	0.060 (18)	0.084 (35)
95% CI	0.038, 0.077	0.030, 0.070	0.042, 0.081	0.051, 0.071	0.061, 0.115
Min, Max	0.034, 0.102	0.029, 0.106	0.036, 0.105	0.044, 0.073	0.052, 0.140

Source: IMPAACT 2019 CSR Table 4.6

Note: CVb is between participant coefficient of variation calculated for loge transformed data as: CVb: 100 * (sqrt(exp(SD^2)-1))

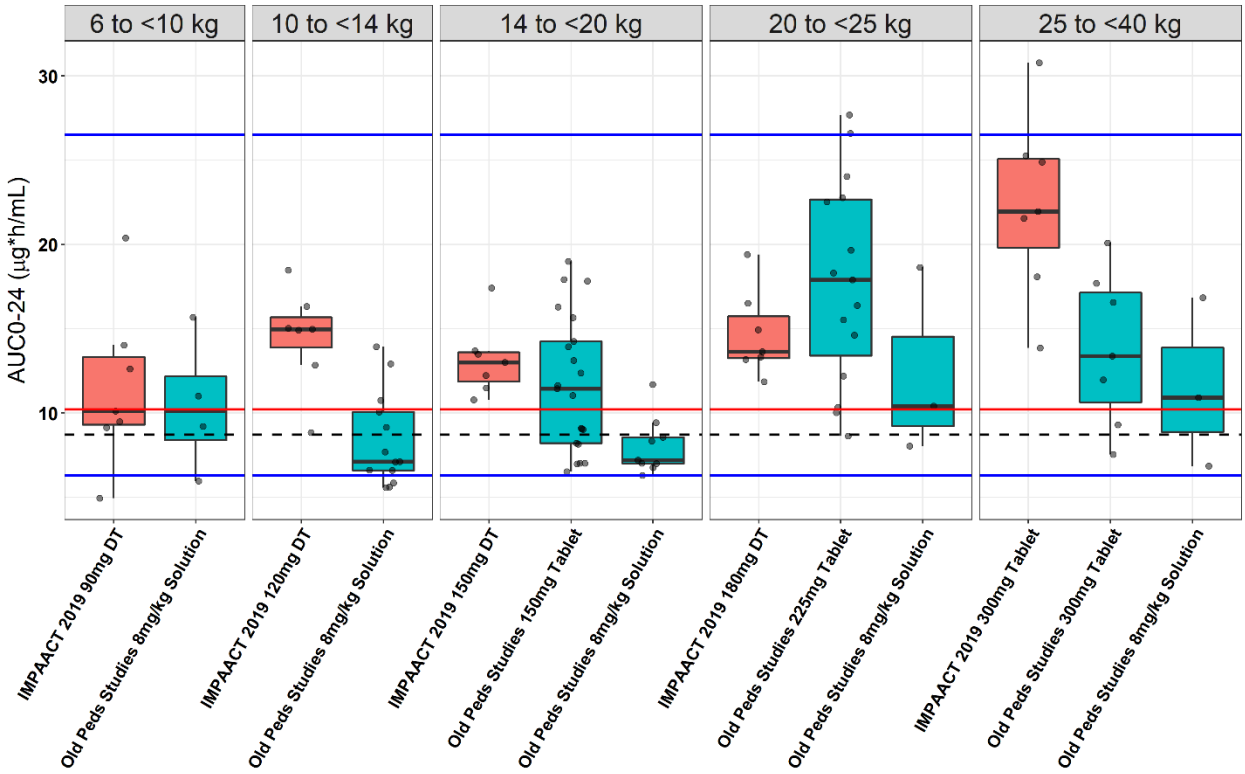


*Figure 6. Comparison of observed 3TC AUC0-24h in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line through the middle of the boxes (Whiskers) represent 1.5*IQR, Circles represents observed AUC0-24 values. Blue solid lines: Geometric mean AUC0-24 target range (6.3 to 26.5 µg*h/mL). Black dashed line: Adult geometric mean AUC0-24 exposure with 300 mg QD dosing (8.7 µg*h/mL). Red Solid line: Overall PopPK predicted median concentration with approved single entity dosing (10.2 µg*h/mL). IMPAACT 2019= 3TC exposures with Triumeq FDC doses. Old Peds Studies= 3TC PK data from ARROW PK Substudy, PENTA 13, and PENTA 15 combined divided into weight bands (≥6 to <40 kg) for this analysis.*

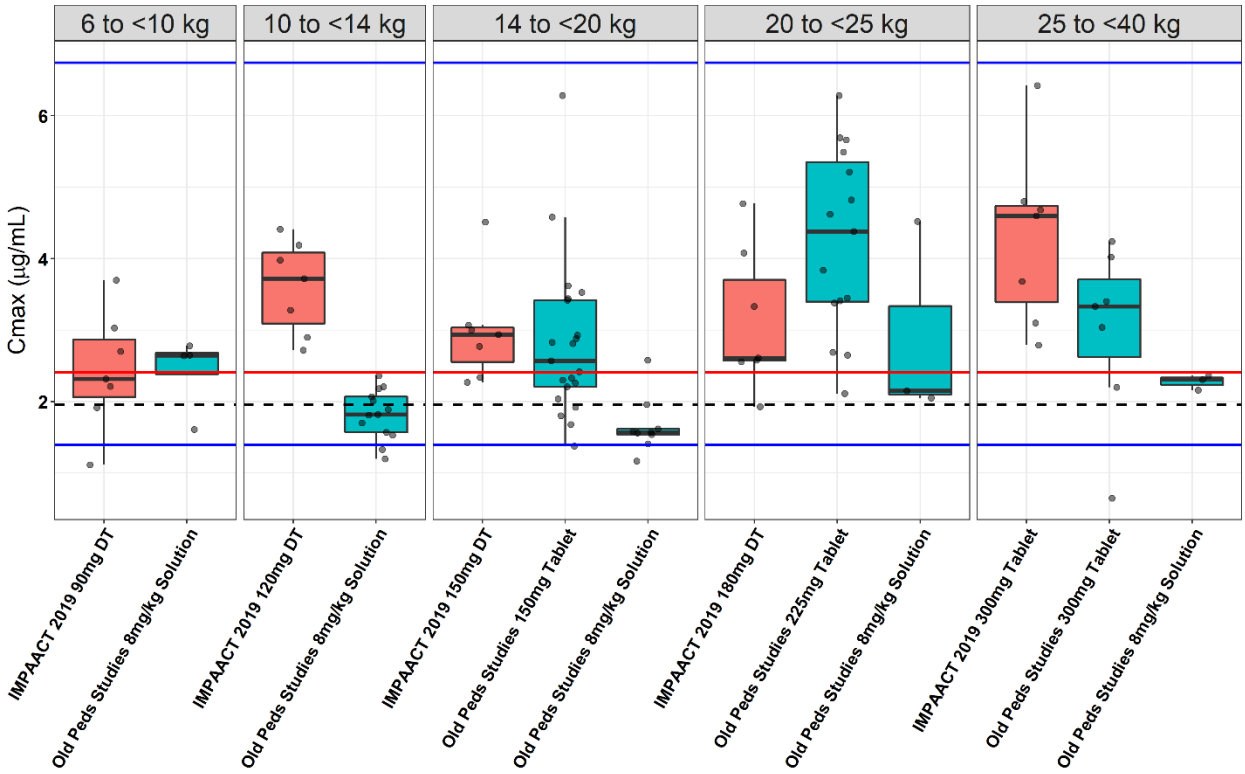


*Figure 7. Comparison of observed 3TC Cmax in Paediatrics with Triumeq FDC and Previously Observed Exposures in Paediatric Subjects. Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line through the middle of the boxes (Whiskers) represent 1.5*IQR, Circles represents observed Cmax values. Blue solid lines: PopPK based 90% predicted intervals of Cmax with once-daily ABC dosing in Paediatrics (1.39 to 6.74 µg/mL). Black dashed line: Adult geometric mean Cmax exposure with 300 mg QD dosing (1.96 µg /mL). Red Solid line: Overall PopPK predicted median concentration with approved single entity dosing (2.4 µg/mL). IMPAACT 2019= 3TC exposures with Triumeq FDC doses. Old Peds Studies= 3TC PK data from ARROW PK Substudy, PENTA 13, and PENTA 15 combined divided into weight bands (≥14 to <40 kg) for this analysis.*

The MAH's NCA PK conclusions from intensive PK sampling data are:

- The estimated PK parameters for DTG, ABC, and 3TC with the DTG/ABC/3TC DTs and Tablets at the originally proposed doses were within the pre-defined target ranges. These ranges were selected based on PK of SEs in adults and paediatric participants.
- The ABC and 3TC PK parameters were marginally higher in the ≥25 kg weight band (n=7) compared to the other 4 weight bands (combined n=28), which might be because the actual participants enrolled in the IMPAACT 2019 study were concentrated between 25 to 30 kg weight (n=5) with higher mg/kg dose (~20 mg/kg and ~10 mg/kg). As a result, the geometric means shifted slightly higher as compared to the other 4 weight bands, but the exposures were still within the pre-defined ABC and 3TC target ranges.
- Overall, DTG, ABC, and 3TC PK exposures following once-daily DTG/ABC/3TC DT and Tablet dosing were comparable to those observed in paediatrics and adults with SEs.

Population PK analysis

Objectives

The objectives were to:

- To evaluate the predictive performance of the previously developed paediatric PopPK models for describing and predicting DTG, ABC, and 3TC PK in paediatric subjects receiving Triumeq doses (DT & Tablet) in Study 205860.
- To derive individual model-based DTG, ABC, and 3TC steady-state exposure in plasma for Study 205860 using post hoc PK parameters in paediatric subjects to compare with NCA estimates.
- To perform clinical trial simulations (CTS) of exposure metrics AUC0-24, Cmax, and C24.

Data

PK data from 55 patients from IMPAACT 2019 were used for the PopPK analysing including:

- 598 DTG observations
- 590 ABC observations
- 597 3TC observations

All samples below the quantifiable limit/not quantifiable (BQL/NQ) kept as missing values (8 and 1 ABC and 3TC samples, respectively). Concentrations without corresponding dosing information were commented out and excluded from the analysis (5 samples each for DTG, ABC, and 3TC).

Methods

The PopPK analysis was performed using NONMEM software, Version 7.3.0 (ICON Development Solutions).

The paediatric PopPK models for each of the respective single entities (DTG, ABC, and 3TC) were developed with pooled rich paediatric data. These existing PopPK models were previously used to support the current dosing of each constituent compound and were used for this analysis. A brief description of each of the models follows in subsequent sections.

An external model validation was applied to evaluate the adequacy of the existing paediatric PopPK models to describe the PK and variability in paediatric subjects receiving Triumeq DT & Tablet Study 205860. A sequential modelling approach was employed.

The existing paediatric PopPK models were applied to the PK dataset from Study 205860 without re-estimation of PopPK parameters (MAXEVAL=0). The external predictive performance of the existing paediatric PopPK models was evaluated using prediction- and simulation-based diagnostics.

Dolutegravir

Previously, intensive, and sparse plasma DTG concentration data obtained from 239 paediatric HIV-1 infected participants in P1093 & ODYSSEY studies were pooled for the PopPK analysis using a non-linear mixed effect modelling approach [GSK Document Number 2019N424147_00]. 2,650 were included in the PopPK analysis.

Across the 239 participants included in the PopPK analysis, the median (min-max) baseline age and weight were 6.00 years (0.170 to 17.5 years) and 17.6 kg (3.90 to 91.0 kg), respectively. There were

equal proportions of female and male participants; the majority (79.5%) of the population was Black, with 6.3% and 7.5% being White and Asian, respectively. The remaining race groups accounted for 6.7% of the population. Similar amounts of data were collected for DTG film coated tablets (FCT) (48.5%) and DT (41.4%) and a lesser amount with granules (16.3%).

The final PopPK model was a 1-compartment model with first-order absorption and first order elimination.

In the PopPK model, the bioavailability of DTG DT/Granules was 1.53-fold (95% CI 1.43- to 1.63-fold) the bioavailability of FCT. The higher bioavailability of the DT/Granule estimated in the PopPK analysis is comparable to results from adult relative bioavailability studies (AUC ratio: 1.62 for DT/FCT). For each dosage form, bioavailability was approximately 10% (95% CI: 3 to 17%) higher when DTG was administered without regard to food vs. fasted (as defined in each protocol). Ka was higher for DTG DT/granule vs. FCT. CL/F and V/F 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 (12 weeks PNA).

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.

All PopPK parameters were estimated with good precision, as measured by RSE <20% for both fixed and random effects, with the exception of additive residual error (RE) for Study P1093 (RSE=95.1%), (see table below); this high RSE is not relevant because the additive RE for P1093 was very low (less than the LLQ). IIV and IOV for CL/F and IIV for V/F were moderate (table below); whereas IIV and IOV were high for Ka.

Residual variabilities (proportional and additive) were estimated separately for P1093 and ODYSSEY because the analyses of plasma samples were conducted using different bioanalytical methods. The proportional REs were low to moderate. The additive RE was less than LLQ for P1093 (1.64 ng/mL; LLQ=5 ng/mL) while it was relatively higher for ODYSSEY (90 ng/mL).

Table 12. DTG paediatric PopPK Parameter Estimates

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 x $(WT/70)^{0.455}$ x 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					

Data Source:- GSK Document Number 2019N424147_00Table 5.6-1

[a]Anderson, 2009

Abacavir

Previously, the PopPK data set included 169 paediatric participants and 1833 plasma ABC concentrations for once- and twice-daily regimens. The age across all studies ranged from 0.42 years (5 months) to 13.6 years and weight ranged from 4.6 to 61.3 kg. The data set was balanced for sex and the majority of participants were black. Of the 169 participants included in the PopPK analysis, 75% received ABC oral solution and 42% received ABC tablets.

Plasma ABC exposure in paediatric participants aged 5 months to 13 years of age was well described by a 2-compartment model, with interindividual variability (IIV) on apparent clearance following oral dosing (CL/F), apparent volume of distribution of the central compartment (V2/F), apparent peripheral compartment volume of distribution (V3/F), intercompartmental clearance (Q/F), and interoccasion 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 Substudy Part 2 (table below). Residual variability was described by a proportional model. All parameters were well estimated without significant correlations between parameters. Fixed-effect parameters were estimated with good precision (% relative standard error [RSE] <18%) as were the IIV and IOV (% RSE <33%).

Table 13. ABC Paediatric PopPK Parameter estimates

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)

Data Source: GSK Document Number 2013N181066_00, Table 10.
CI = confidence interval; CV = coefficient of variation; FIX = fixed to estimates from 3-study model; OCCCL=inter-occasion variability in CL/F; PK = pharmacokinetic; RSE = relative standard error; WT = body weight; Θ = PK parameter estimation; η = inter-individual variability; Ω = inter-individual or inter-occasion variability in population PK parameter; σ = population variance.

a. Population parameter point-estimates for the full 2-compartment model and 95% CI and %CV from a non-parametric bootstrap are presented.
b. Value in parentheses represents either the inter-individual or inter-occasion variability of the PK parameters calculated as the square root of Ω x 100%.

Lamivudine

Previously, the PopPK dataset included 210 children and 3023 plasma 3TC concentrations for once-daily and twice-daily regimens. The age across all studies ranged from 0.33 years (4 months) to 19.2 years and weight ranged from 5.1 to 66.4 kg. The dataset was balanced for sex. Approximately 59% of subjects received lamivudine oral solution and 54% of subjects received lamivudine as a solid dosage form (tablet or capsule).

Plasma 3TC exposure in paediatric participants aged 4 months to 19 years of age were well described by a 1-compartment model. Oral absorption was characterized by a first-order absorption rate constant (Ka) with a lag time for absorption (ALAG1). A higher absolute bioavailability (F1) estimate was identified for solid dosage forms (tablet and capsule) than for the oral solution, consistent with the results of a 3TC relative bioavailability study conducted in children [Kasirye, 2012]. Interindividual variability (IIV) and inter-occasion variability (IOV) were estimated for clearance (CL/F), volume of distribution (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. All parameters were well estimated good precision (*Table 14* below).

Table 14. 3TC Paediatric PopPK parameter estimates

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)

Data Source: GSK Document Number 2013N181170_00, Table 10.
ALAG1 = lag time for absorption; CI = confidence interval; CV = coefficient of variation; OCCCL = interoccasion variability in clearance; OCCKA = interoccasion variability in Ka; OCCV = interoccasion variability in V;

RSE = relative standard error; WT = body weight; Θ = PK parameter estimation; η = interindividual variability; Ω = interindividual or interoccasion variability in population pharmacokinetic parameter; σ = population variance.

a. Population parameter point-estimates for the full 1-compartment model and 95% CI and CV% from a nonparametric bootstrap are presented.
b. Value in parentheses represents either the interindividual or inter-occasion variability of the PK parameters calculated as the square root of Ω x 100%.

Individual predictions

The final paediatric PopPK models were used to compute individual predictions of AUC0-24, Cmax and C24 for each of the individual components of Triumeq following a steady-state dose for each subject included in the population PK analysis. The individual estimates of all model parameters were obtained from the final models by an empirical Bayes estimation method.

These model-based steady state post-hoc PK parameters were compared with NCA PK parameters from clinical study report (GSK Document Number 2022N501029_00) to assess predictive performance of these established models.

Simulations

Simulations were performed to evaluate the appropriateness of Triumeq DT and Tablet dosing regimen in the paediatric population. The simulations aimed at confirming the anticipated exposure across a wider range of body weights and age range. The DTG, ABC and 3TC concentrations were predicted at 0, 1, 2, 3, 4, 6, 8, and 24 hours following steady-state weight based once daily doses of Triumeq DT and Tablet for one occasion. Paediatric population distributions corresponding to weight bands were constructed based on CDC growth charts. The simulated clinical trial population consisted of 1000 participants with 200 participants in each of the weight bands ensuring distribution of the weights and age in the simulation. The demographic characteristics of the simulated population and Triumeq doses are presented in the *Table 15*. In total, 1000 replicate trials were simulated of 1000 participants with the once daily Triumeq dosing regimen and plasma AUC0-24, Cmax, and C24 were calculated for each of the entities.

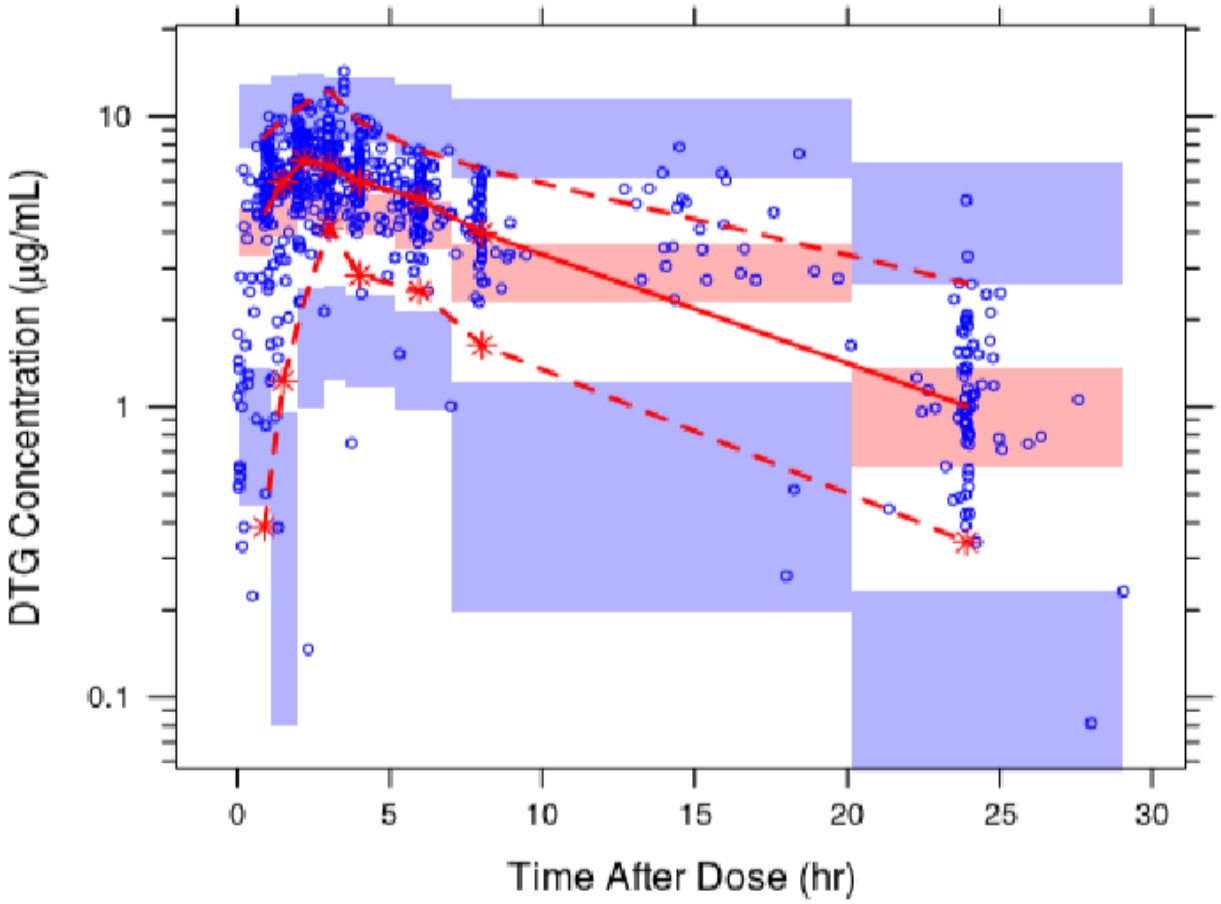
Table 15. Demographic characteristics of the simulated paediatric population

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)**	

Results

Dolutegravir

The goodness-of-fit for the DTG model showed good agreement between observed and predicted concentrations (not shown). This is also reflected in the VPC plot, showing that the data also is well predicted over time. However, there is some overprediction of variability, likely due to the relatively lower number of subjects in each of the weight bands. Also, there is a slight model misspecification specially with some of the sparse PK data. The observed DTG PK data in the Study 205860 fell well within the 95% prediction interval (figure below). Overall, the model predicts well and was considered sufficient for the current analysis, therefore no refitting was attempted.



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

Figure 8. Visual predictive check for the DTG model

A summary of the individual predicted exposure metrics is shown in the table below.

Table 16. Individual Post-hoc DTG Steady-State PK parameters Following once daily oral dosing of Triumeq in IMPAACT 2019 Study

Weight Band (kg)	Triumeq Dosage Form	DTG Dose	N	PK Parameter GM (95% CI)		
				Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10	DT	15 mg	8	6.79 (5.92 -7.80)	82.20 (65.60 -103.0)	1.08 (0.67 -1.74)
≥10 to <14	DT	20 mg	11	6.63 (5.96 -7.37)	86.90 (75.30 -100.00)	1.36 (1.01 -1.82)
≥14 to <20	DT	25 mg	15	6.36 (5.90-6.85)	71.50 (62.10 -82.20)	0.71 (0.48 -1.05)
≥20 to <25	DT	30 mg	10	6.59 (6.13-7.09)	81.60 (70.8-94.20)	1.09 (0.76-1.56)
≥25 to <40	Tablets	50mg	11	5.43 (4.91 -6.02)	72.60 (64.90-81.10)	1.01 (0.77-1.32)

Source: Appendix Table 6

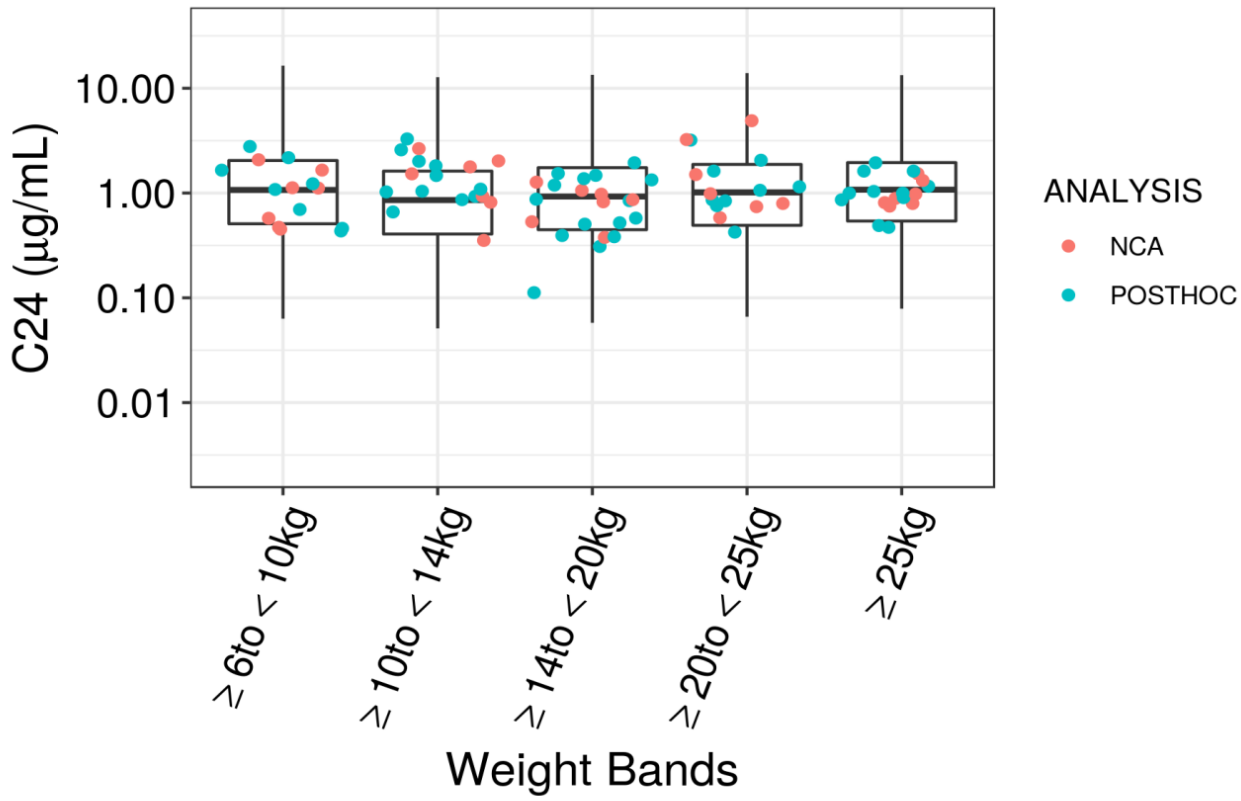
The predicted DTG exposures with the proposed doses of Triumeq (DT and Tablet formulations) across different weight bands are provided in the table below.Box-and-whisker plots of steady-state predicted C24 estimates for each cohort overlaid by the observed individual post-hoc estimates and NCA estimates are shown in Figure 9. The C24 values were consistent with observed data and demonstrate that the target plasma DTG concentrations described in the figure below, are achieved with the proposed once daily doses for paediatric patients across the weight bands. Overall, majority of the individual model predicted post-hoc estimates and NCA calculated PK parameters were within the interquartile range (IQR) of simulations.

Table 17. Simulated Steady State DTG PK Parameters in HIV-infected children based on proposed Triumeq DT and Triumeq Tablet dosing

Weight Bands	Proposed Daily Dose	Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10 kg	15 mg DT	6.99 (3.83 - 13.05)	70.55 (30.5 - 166.4)	0.94 (0.13 - 4.60)
≥10 to <14 kg	20 mg DT	6.88 (3.90 - 12.13)	65.36 (29.69 - 142.6)	0.74 (0.10 - 3.54)
≥14 to <20 kg	25 mg DT	7.12 (4.03 - 12.59)	68.57 (31.33 - 150.4)	0.81 (0.11 - 3.78)
≥20 to <25 kg	30 mg DT	7.42 (4.21 - 13.15)	72.36 (33.03 - 158.3)	0.88 (0.13 - 4.03)
≥25 kg	50 mg Tablet	6.24 (3.41 - 11.38)	66.75 (30.49 - 146.1)	0.95 (0.15 - 4.11)

Source: Appendix Table 7

Note: AUC0-24, Cmax and C24 presented as a GM (90% prediction interval).



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.

Figure 9. Comparison of simulated DTG C24 with Post-hoc estimates and NCA estimates

To better understand the impact of glucuronidation maturation on DTG PK, simulations were performed for the ⩾6 to <10kg weight band especially in ⩾3 to <6 months of age. These simulations demonstrate that the predicted DTG exposures for the proposed Triumeq DT dose in the ⩾6 to <10kg weight band are comparable to IMPAACT 2019 study data and are within predefined target ranges (see Table 18 below).

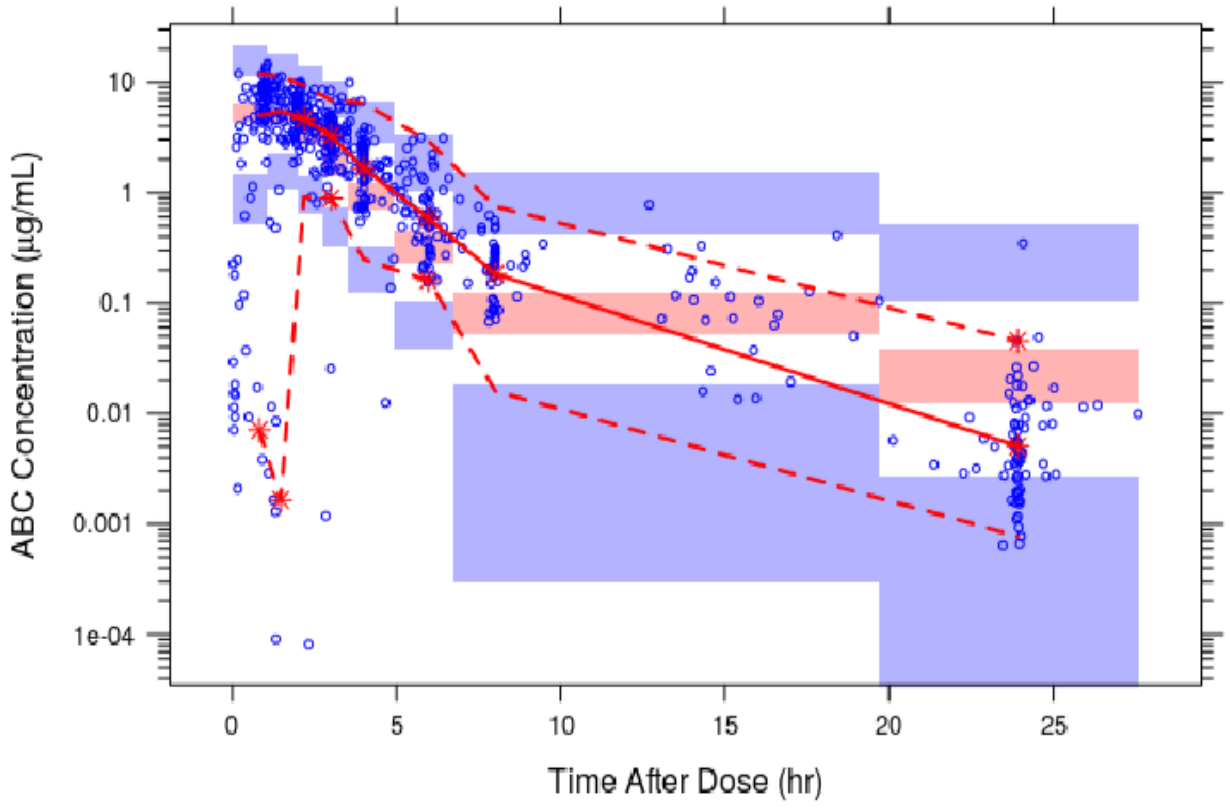
Table 18. Comparison of Predicted Plasma DTG Exposure for Proposed Triumeq Dose in ⩾6 to <10 kg (⩾ 3 to <6 months of age) and Observed Exposure in IMPAACT 2019 Study

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)
Simulated Exposures				
Proposed Triumeq DT Dosing in ≥3 months	**Simulations,** ≥6 to <10 kg weight band (≥3 to <6 months of age),15 mg DT	**95.53** (87.82 - 102.5)	**1.80** (1.53, 2.06)	**8.27** (7.78 - 8.78)
Observed Exposures in IMPAACT 2019 Study				
Triumeq 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)
Target GM Range[b]		**37 to 134**	**0.697 to 2.260**	**2.12 to 13.3**

[a]Source: IMPAACT 2019 CSR
[b]DTG target range described previously in the EPAR of Triumeq-H-C-002754-X-0101

Abacavir

The GOF plots for the abacavir model show good agreement between the observed and predicted concentrations (not shown). This can also be seen in the VPC, with some overprediction of variability, likely due to the lower number of subjects in each weight category. Similar to DTG, there is a slight model misspecification specially with some of the sparse PK data. The observed ABC PK data in Study 205860 fell mostly within the 95% prediction interval. There was some overprediction of the trough concentrations as well (see figure below). However, as the absolute difference was relatively small, this is not expected to have any significant impact on AUC0-24 which is the primary marker for antiviral activity of ABC. Overall, the model predicts adequately and was considered sufficient for the current analysis.



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

Figure 10. Visual Predictive Check for the ABC model

A summary of the individual predicted exposure metrics is shown in the table below.

Table 19. Individual Post-hoc ABC Steady-State PK parameters following once daily oral dosing of Triumeq in IMPAACT 2019 Study

Weight Band (kg)	Triumeq Dosage Form	ABC Dose	N	PK Parameter GM (95% CI)		
				Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10	DT	180 mg	8	6.04 (4.29 -8.51)	17.30 (11.90 -25.10)	0.007 (0.003 -0.018)
≥10 to <14	DT	240 mg	11	7.42 (5.75 -9.57)	18.90 (14.7 -24.20)	0.017 (0.007 -0.042)
≥14 to <20	DT	300 mg	15	7.07 (5.73-8.73)	17.20 (14.80 -20.00)	0.013 (0.007-0.024)
≥20 to <25	DT	360 mg	10	8.04 (6.27-10.3)	19.50 (16.60-22.90)	0.008 (0.004-0.018)
≥25 to <40	Tablets	600mg	11	9.60 (8.03-11.5)	26.10 (22.50-30.20)	0.020 (0.010-0.040)

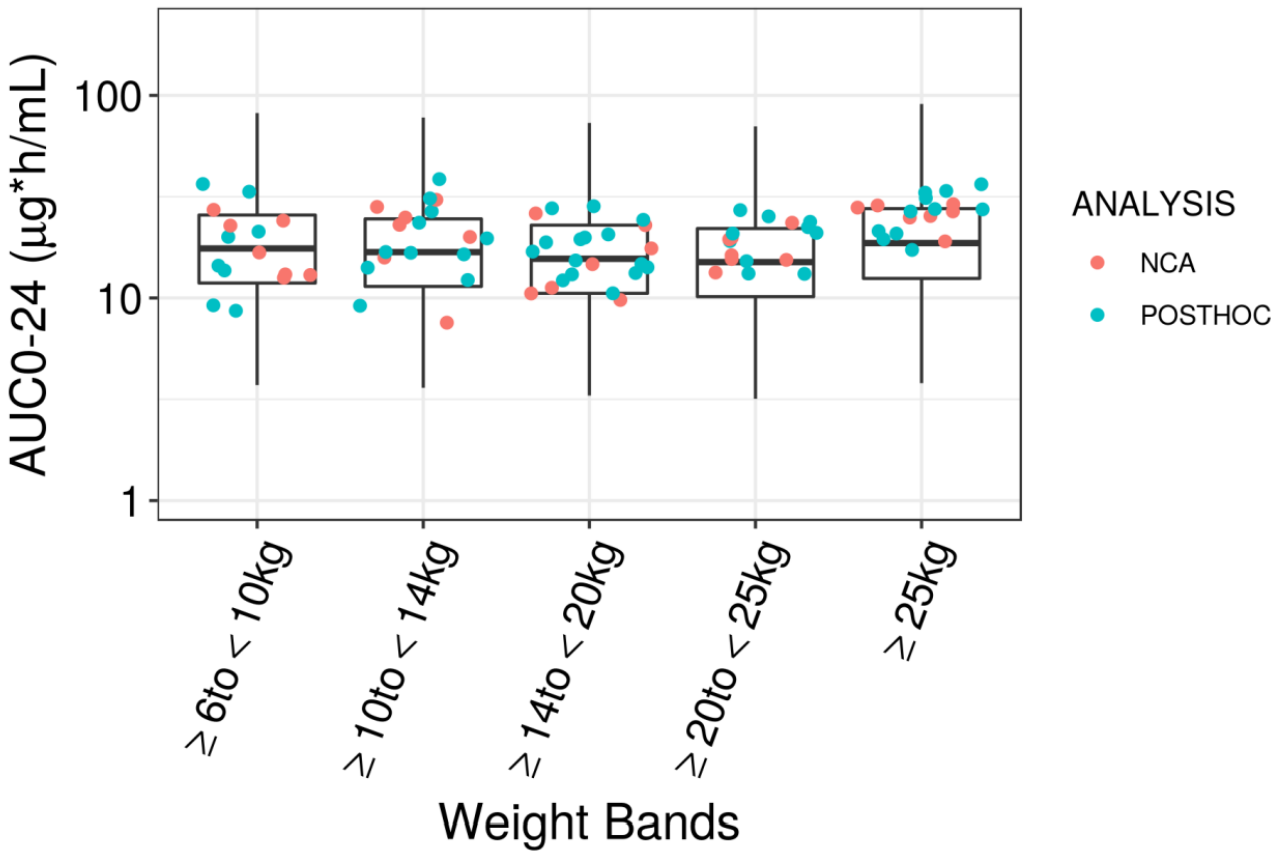
Source: Appendix Table 9

The predicted ABC exposures with the proposed doses of Triumeq (DT and Tablet formulations) across different weight bands are provided in Table 20. Box-and-whisker plots of steady-state predicted AUC0-24 for each weight band overlaid by the observed individual post-hoc estimates and NCA estimates are shown in *Figure 11*. The ABC PK exposures observed in the IMPAACT 2019 study are higher compared to the simulated data primarily in ≥25 to <40 kg weight band, which might be because actual participants enrolled in the IMPAACT 2019 study to date were concentrated between 25 to 30 kg weight with higher mg/kg dose (~20 mg/kg) resulting in slightly higher exposure. Overall, majority of the individual model predicted post-hoc estimates and NCA calculated PK parameters were within the IQR of simulations (figure below) and within the predefined target range.

Table 20. Simulated steady state ABC PK parameters in children with HIV-1 infection based on proposed Triumeq DT and Triumeq tablet dosing

Weight Bands	Proposed Daily Dose	Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10 kg	180 mg DT	6.63 (2.84 - 14.96)	17.36 (6.66 - 43.70)	0.039 (0.003 - 0.344)
≥10 to <14 kg	240 mg DT	6.66 (2.85 - 15.04)	16.66 (6.43- 41.62)	0.027 (0.003 - 0.246)
≥14 to <20 kg	300 mg DT	6.41 (2.71 - 14.71)	15.47 (5.94 - 39.12)	0.020 (0.003- 0.178)
≥20 to <25 kg	360 mg DT	6.31 (2.65 - 14.43)	14.89 (5.72 - 37.49)	0.016 (0.003 - 0.138)
≥25 kg	600 mg Tablet	8.06 (3.31- 18.85)	18.50 (7.00 – 47.70)	0.014 (0.003 - 0.136)

Source: Appendix Table 10
Note: AUC0-24, Cmax and C24 presented as a GM (90% prediction interval).

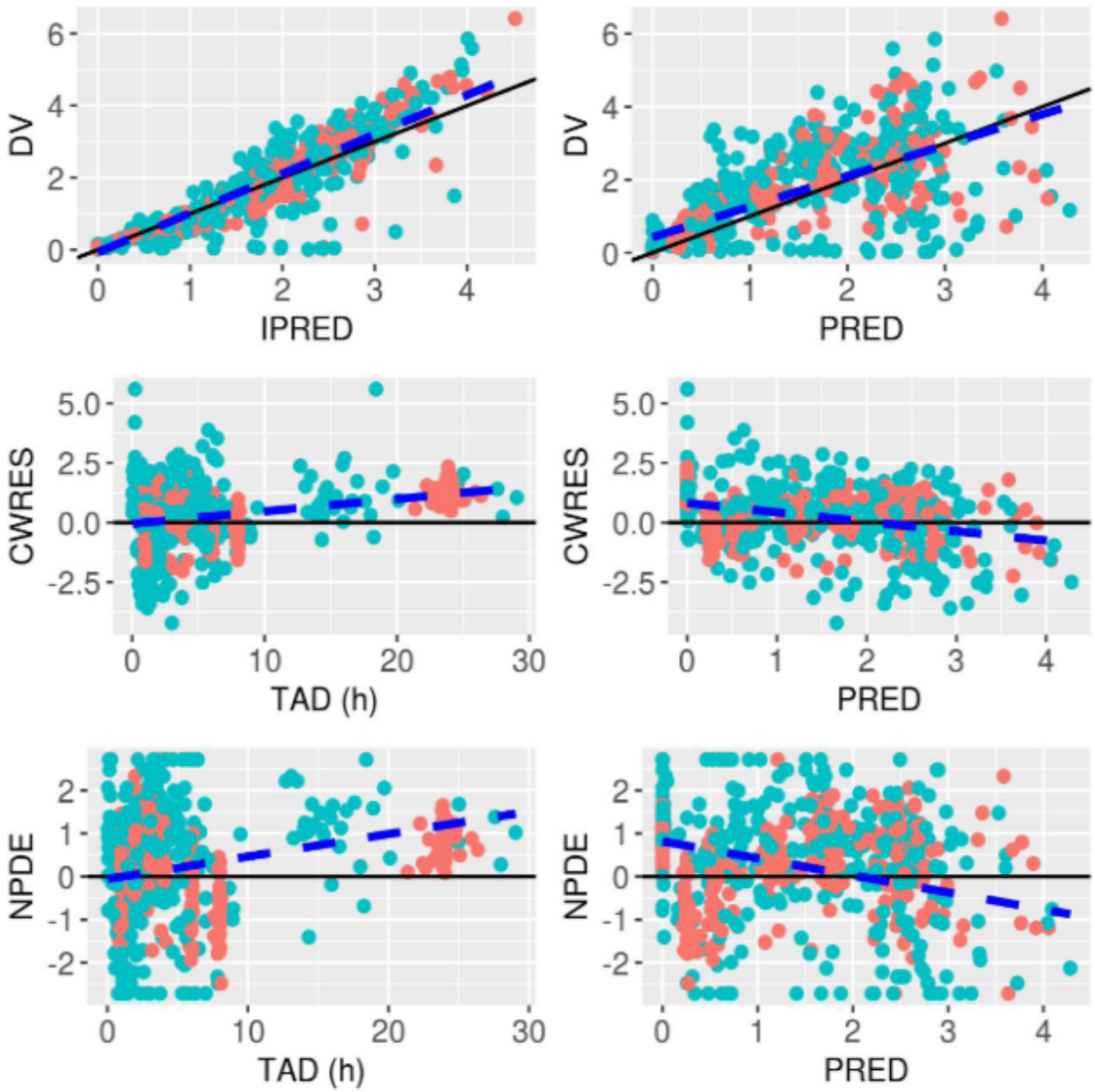


Boxes represent median (black horizontal line in the middle), 1st quartile and 3rd quartile of the data, Vertical black line through the middle of the boxes (Whiskers) represent minimum and maximum, Solid Circles: ABC AUC0-24. Post-hoc estimates and NCA estimates

Figure 11. Comparison of simulated ABC AUC0-24h with post-hoc estimates and NCA estimates

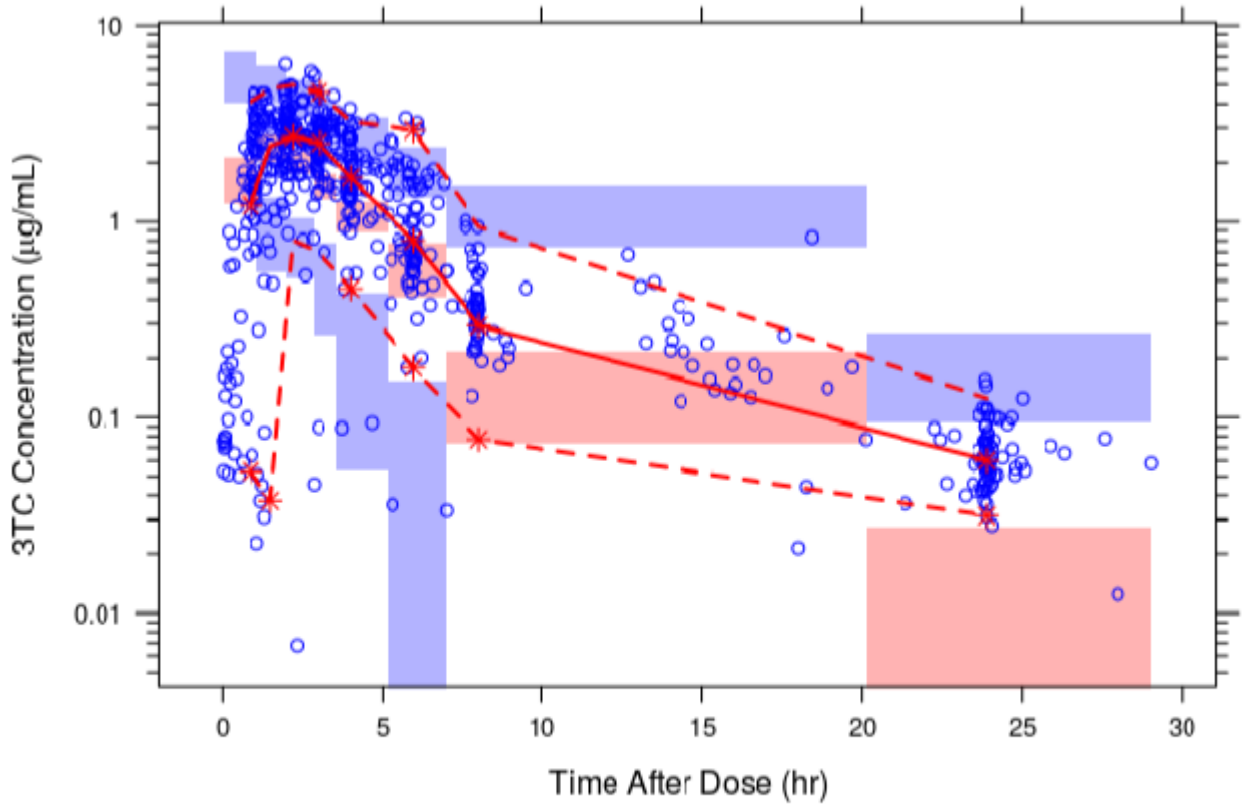
Lamivudine

The GOF plots for 3TC show good agreement between observed and predicted concentrations. There is some mismatch in the lower concentration range at the end of the dosing interval, most evident in the bottom plots in Figure 12. However, as this only occurs at the end of the dosing interval where concentrations are low, this does not significantly affect the predictions of the overall exposure (AUC0-24). Similar to other two components (DTG & ABC), there is a slight model misspecification specially with some of the sparse PK data. As can be seen from VPC plot, overall observed 3TC PK data in the Study 205860 fell mostly within the 95% prediction interval, and this model can be used for predictions (see figure below).



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

Figure 12. Goodness-of-fit plot for the 3TC model



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

Figure 13. Visual predictive check for the 3TC model

A summary of the individual predicted exposure metrics is shown in the table below.

Table 21. Individual Post-hoc 3TC steady-state PK parameters following once daily oral dosing of Triumeq in IMPAACT 2019 Study

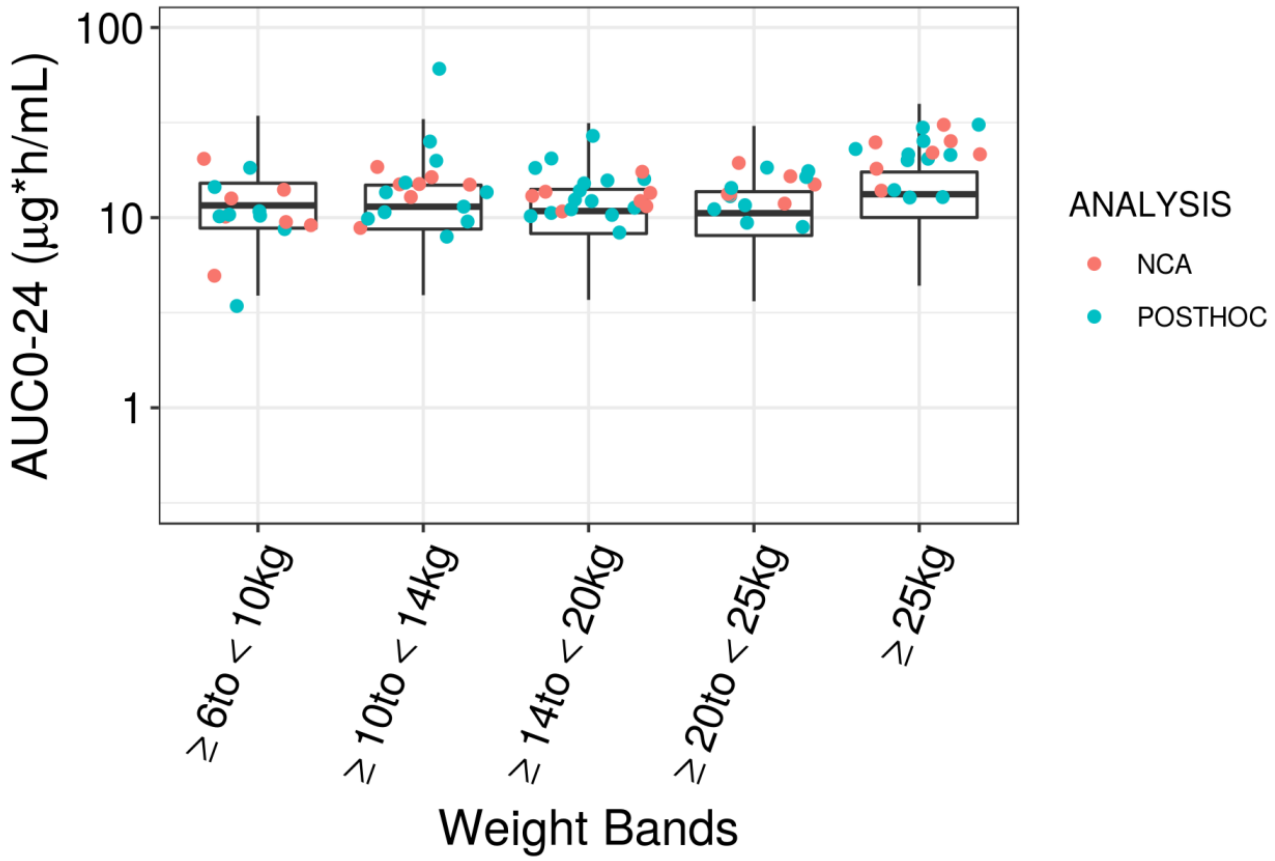
Weight Band (kg)	Triumeq Dosage Form	3TC Dose	N	PK Parameter GM (95% CI)		
				Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10	DT	90 mg	8	2.29 (1.82 -2.88)	9.97 (7.12 – 14.00)	0.013 (0.004 – 0.047)
≥10 to <14	DT	120 mg	11	2.64 (2.12 – 3.29)	14.90 (10.60 – 20.9)	0.017 (0.005 – 0.053)
≥14 to <20	DT	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)

The predicted 3TC exposures with the proposed doses of Triumeq (DT and Tablet formulations) across different weight bands are provided in the table below. Box-and-whisker plots of predicted steady-state AUC0-24 estimates for each weight band overlaid by the observed individual post-hoc estimates and NCA estimates are shown in the figure below. The 3TC PK exposures observed in the IMPAACT 2019 study are higher compared to the simulated data primarily in ≥25 to <40 kg weight band, which might be because actual participants enrolled in the IMPAACT 2019 study to date were concentrated between 25 to 30 kg weight with higher mg/kg dose (~10 mg/kg) resulting in slightly higher exposure. Overall, majority of the individual model predicted post-hoc estimates and NCA calculated PK parameters were within the IQR of simulations (see figure below) and within the predefined target range.

Table 22. Simulated steady state 3TC PK parameters in HIV-infected children based on proposed Triumeq DT and Triumeq tablet dosing

Weight Bands	Proposed Daily Dose	Cmax (µg/mL)	AUC0-24 (µg*h/mL)	C24 (µg/mL)
≥6 to <10 kg	90 mg DT	2.83 (1.43 - 5.48)	11.57 (5.82 - 22.36)	0.012 (0.003 - 0.132)
≥10 to <14 kg	120 mg DT	2.84 (1.45- 5.44)	11.40 (5.79 - 21.66)	0.0118 (0.003 - 0.127)
≥14 to <20 kg	150 mg DT	2.74 (1.39 - 5.28)	10.78 (5.49 - 20.6)	0.0114 (0.003 - 0.121)
≥20 to <25 kg	180 mg DT	2.70 (1.37 - 5.20)	10.50 (5.34 - 19.96)	0.0112 (0.003 - 0.119)
≥25 kg	300 mg Tablet	3.48 (1.73 - 6.80)	13.20 (6.59 - 25.65)	0.0115 (0.003 - 0.125)

Source: Appendix Table 13
Note: AUC0-24, Cmax and C24 presented as a GM (90% prediction interval).



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

Figure 14. Comparison of simulated 3TC AUC0-24 with post-hoc estimates and NCA estimates

MAH conclusion

- Overall, the models were able to describe and predict the observed data, and the post-hoc estimates were in agreement with the NCA parameter estimates which made it unnecessary to re-evaluate covariate relationships, or to develop new PopPK models specifically for only Study 205860 data.
- Model-predicted values of C24 were within the predefined target range for DTG and model-predicted values of AUC0-24 were within the predefined target range for both ABC and 3TC

Pharmacokinetic interaction studies

No new PK interaction studies were submitted in the current procedure.

2.3.3. Discussion on clinical pharmacology

Discussion on clinical pharmacology

PK has high impact in the current procedure as the paediatric program was designed based on PK matching. The IMPAACT 2019 protocol includes PK as a primary objective. There is limited efficacy and safety data available in IMPAACT2019. The efficacy and safety will be established in children with body weight between 6-14 kg based on extrapolation from adult data, i.e. exposure matching. The included active components of Triumeq (dolutegravir [DTG], abacavir [ABC] and lamivudine [3TC]), also referred to as single entities have histories of being used in adults and children. The main principle for the exposure matching will consist of comparisons to adult data, any exposure comparisons to other paediatric data will be considered as supportive.

In the two paediatric weight-bands of interest for this procedure (6-10kg and 10-14kg), there were 7 patients in each weight band with intensive PK sampling which were analysed using NCA methods. For the population PK analysis, there were 9 and 12 patients included in the 6-10kg and 10-14kg weight bands, respectively. Of note, the minimum weight in the IMPAACT2019 is 8kg which is higher than 6kg which is stated in the proposed indication. Having no observed data at all between 6-8 kg patients is an uncertainty. PopPK model-based simulations can be used to predict the exposure in this subset of patients (6-8kg) which means that PopPK will provide important support for the overall benefit-risk assessment.

The PK targets were pre-specified according to the IMPAACT 2019 protocol. For DTG, targets were defined both in terms of AUC and C24 (i.e. Ctrough) and were based on adult targets which is reasonable.

For ABC and 3TC, the target range was based on AUC and not C24 which is considered acceptable. However, targets based on paediatric data were used which is not acceptable since the current procedure is mainly based on exposure matching compared to adults. In the procedure EMEA/H/C/002754/X/0101/G, adult corresponding exposures were presented which is relevant to include also in the current procedure (see Tables above for PK for ABC and 3TC).

No target for Cmax has been provided for any of the entities which would be relevant from a safety perspective. However, Cmax targets were derived for all entities in procedure EMEA/H/C/002754/X/0101/G which will be considered also in the current procedure (see Tables above for PK for DTG, ABC and 3TC). The analytical methods used in this study were already assessed and found acceptable in previous regulatory procedures.

Standard methods were used to calculate the PK metrics using NCA, which is acceptable.

The MAH concludes that the proposed posology in the 6-10kg and 10-14kg weight bands are acceptable, based on comparisons of observed (NCA) and simulated exposure metrics with PK exposure in adults and children. This is accepted.

The observed (NCA) and simulated exposures for the 6-10 and 10-14kg were within the target exposure range for the most critical exposure metrics in adults (DTG: Cmax, AUC and C24, ABC+3TC: Cmax and AUC). As supportive evidence, it was noted that the simulated and observed exposures were also within the exposure range in children. This includes a comparison of exposure between the 6-10 and 10-14kg weight band with the other paediatric weight bands in IMPAACT 2019 (14-20kg, 20-25kg and ≥25kg).

The Applicant provided paediatric exposures stratified by weight group in the form of box plots. This graphical comparison confirmed that there were not many extreme individuals/outliers which fell outside of the target range.

The simulated and observed PK exposures were comparable for the 6-10 and 10-14kg weight bands in IMPAACT 2019, for the most critical exposure metrics; C24 was not similar between the simulations and

observations for ABC and 3TC, however, C24 is not considered clinically relevant (Cmax and AUC are more important for ABC and 3TC). The simulations are considered important since they explore the exposure down to 6kg, whereas the observed PK data was only available for patients down to 8kg. The simulations confirmed that the PK exposure seems acceptable down to 6kg.

The proposed doses of Triumeq (DTG/ABC/3TC) are 15 mg/180 mg/90 mg and 20 mg/240 mg/120 mg once daily for the 6-10kg and 10-14kg weight bands, respectively. This is in line with the dose recommendations for DTG (Tivicay dispersable tablet SmPC) for the 10-14kg weight band but not for the 6-10kg weight band. The corresponding DTG single-entity product Tivicay SmPC states that patients between 6-10kg are dosed based on weight *and age* (10 mg if below 6 months of age).

A major reason for this recommendation is that the metabolising enzymes responsible for eliminating DTG is not sufficiently matured in patients below 6 months. This results in a reduced capacity for very young children to eliminate DTG and the consequence is over-exposure of DTG with risk of adverse events.

Based on the maturation function included in the PopPK model , the elimination capacity reduces gradually with age and a very heavy child in relation to its age may be considerably younger than 6 months.

Based on CDC growth curves, an extreme yet possible scenario is that a 1.5-month-old boy could have a body weight above 6 kg and would have considerable reduced elimination capacity compared to a 6 month old (a 1.5-month-old will have ~40% lower clearance than a 6-month-old based on the maturation function in the DTG PopPK model. Due to the known impact of maturation on glucuronidation capacity, the Applicant included a 3-month age restriction for the use of Triumeq in SmPC section 4.1 and section 4.2 for patients weighing 6-10 kg. The 3-month age restriction was supported by PK simulations which indicated that the expected dolutegravir PK exposure in children between 3-6 months of age and weighing 6-10 kg fall within the corresponding target exposure range based on adult data. In addition, the PK exposure did not deviate significantly from the observed PK exposure in IMPAACT 2019.

A 3-month age restriction is thus considered acceptable. Of note, the PopPK model(s) have limitations and it is not acceptable for support dosing recommendations in patients younger than 3 months. The IMPAACT 2019 study only studied patients ≥1 year of age (and ≥8 kg) which is an important limitation. This procedure concerns a triple FDC where the elimination of one of the active components (DTG) goes through considerable maturation <1 year of age which adds further complexity and uncertainty. As outlined in the first round, the maturation function in the DTG PopPK model predicts that a 1.5-month-old have ~40% lower clearance than a 6-month-old whereas the model predicts ~20% lower clearance for a 3-month-old than a 6-month-old which is more reasonable.

The applied popPK models were not developed on Triumeq data which is a limitation since this assumes that the absorption characteristics (absorption rate and relative bioavailability) of the active components in Triumeq were assumed to be the same as for corresponding single entity formulations. According to the pcVPCs for each respective entity, there was a slight tendency to underpredict Cmax which could be a sign that the assumed rate and/or relative bioavailability differs somewhat from that of Triumeq. Underprediction of Cmax implies that the model predictions are not regarded as conservative from a safety aspect.

Taken together, the predictions in patients younger than 6 months might be reasonable but is associated with uncertainties which should be considered when deciding on which exact age restriction to include for Triumeq. Also, the PopPK modelling is not considered acceptable for supporting dosing recommendations < 3 months of age.

A lower dose of Triumeq in a subset of younger patients is not an option, since the exposure of ABC and 3TC would become suboptimal.

For ABC, a corresponding single entity product is Ziagen, whose SmPC states a dose of 16 mg/kg once daily for patients weighing 6-14 kg which is lower than the ABC doses proposed for Triumeq for patients between 6-14kg. According to the Applicant, it was not practically possible to use a similar ABC dose as in

the corresponding single entity product Ziagen since the relative bioavailabilities of the individual components are not similar between Triumeq and the corresponding single entity products. This is acknowledged and similar doses between Triumeq and the corresponding single entity products is not a requirement. An important aspect to consider is that the PK exposure is acceptable. The Applicant refers to the observed ABC PK data in IMPAACT 2019 and the comparison with previous paediatric PK data and the adult reference range. It is agreed that despite the higher ABC dose in Triumeq compared to Ziagen, the ABC PK exposure falls within an acceptable range. For 3TC, a corresponding single entity product is Epivir, whose SmPC states a dose of 10 mg/kg once daily for patients weighing 6-14 kg which is generally in line with the doses proposed for Triumeq.

The Applicant also provided VPCs stratified by weight group which confirmed reasonable predictive performance across weight range.

2.3.4. Conclusions on clinical pharmacology

PK has impact in the current procedure. The observed (NCA) and simulated exposures in the 6-10kg and 10-14 kg weight bands indicates that the proposed posology in these weight bands are overall acceptable. The PopPK model(s) have limitations and it is not acceptable for support dosing recommendations in patients younger than 3 months. This cut off is accepted by the applicant. A 3-month age restriction is thus considered acceptable.

2.3.5. Dose response study

No separate dose response study was conducted to support the extension of indication to paediatric patients weighing ≥6 kg.

The DTG dosing recommendations previously established for the single entity are not expected to differ when DTG was administered in an FDC. The doses of ABC/3TC used in IMPAACT 2019 were consistent with WHO recommended doses of approximately 16 mg/kg for ABC and approximately 8 mg/kg for 3TC in children.

Nevertheless, a subset of children in each weight band underwent intensive PK approximately 1 week after initiating DTG/ABC/3TC in the main IMPAACT 2019 study, to confirm dosing based on similar exposures to DTG, ABC, and 3TC. Enrolment continued while intensive PK evaluations were performed and the appropriateness of each weight band dose was determined, because the PK, safety, and efficacy of DTG, ABC, and 3TC have been previously established and there was no evidence to suggest that these should differ with administration as part of an FDC. This was a reasonable approach.

2.3.6. Main study

Study 205860: Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age (IMPAACT 2019)

Methods

Study participants

ART-naïve and ART-experienced children living with HIV-1 infection who were <12 years of age and weighed ≥6 to <40 kg. ART-experienced children (on a stable ART regimen) were required to have a suppressed HIV viral load (HIV-1 RNA <200 c/mL) for at least 6 consecutive months prior to entry.

Main inclusion criteria

- Hepatitis B surface antigen (HBsAg) negative test within 30 days of study entry.
- Normal, Grade 1 or Grade 2 laboratory test results within 30 days of study entry for Hb, neutrophils, platelets, eGFR, liver function tests (LFT).
- HLA-B*5701-negative based on documented testing at any time prior to entry. (Abacavir should not be used in patients known to carry the HLA-B*5701 allele.)

Main exclusion criteria

- Documented resistance to ABC, DTG, or 3TC.
- History of malignancy, hypersensitivity to ABC, prohibited medications (excluding prednisolone up to 2mg/kg for replacement or short course, but including systemic interferon or any chronic systemic immunosuppressant, or rifampicin-containing tuberculosis treatment) within 30 days of study entry.
- Evidence of current pancreatitis, active tuberculosis, AIDS-defining opportunistic infection.

Treatments

ART-naïve children began treatment with DTG/ABC/3TC at enrolment. ART- experienced children were switched from their pre-study ART regimen to DTG/ABC/3TC at enrolment.

Children were enrolled concurrently in five weight bands and received the according study drug dose once daily, with or without food, as shown in the tables below.

Table 23. IMPAACT 2019 Weight Band Dosing of Study Drug

Group	Weight Band	Number of Tablets Formulation	DTG/ABC/3TC Daily Dose
1	≥6 to <10 kg	3 DTs	15/180/90 mg
2	≥10 to <14 kg	4 DTs	20/240/120 mg
3	≥14 to <20 kg	5 DTs	25/300/150 mg
4	≥20 to <25 kg	6 DTs	30/360/180 mg
5	≥25 kg	1 Tablet	50/600/300 mg

Table 24. Dispersion Volumes for ABC/DTG/3TC Dispersible Tablets

Weight Band		Number of Dispersible Tablets per Dose	Dispersion Volume
#1	6 to less than 10 kg	3	15 mL
#2	10 to less than 14 kg	4	20 mL
#3	14 to less than 20 kg	5	20 mL
#4	20 to less than 25 kg	6	20 mL

The dose of DTG/ABC/3TC that was initiated by each participant was based on the participant's weight at study entry; this dose was continued through at least Week 4 and then adjusted, if indicated, based on the participant's growth and weight gain over time.

Objectives

Primary

Pharmacokinetic

- Determine the steady-state AUC0-24h, Cmax, and C24h of DTG, ABC, and 3TC and confirm the dosing of DTG/ABC/3TC DTs and Tablets that achieves protocol- defined PK targets for DTG, ABC, and 3TC in children <12 years of age.

Safety

- Evaluate the safety profile of 24 weeks of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age.

Secondary

Pharmacokinetic

- Determine the PK of DTG, ABC, and 3TC, and clinical covariates that influence PK disposition, among children <12 years of age using population PK analysis of intensive and sparse PK samples collected over 48 weeks of treatment with DTG/ABC/3TC DTs and Tablets.

Safety

- Evaluate the safety profile of 48 weeks, and additionally up to 144 weeks, of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age.
- Evaluate changes in lipid profiles at 24 and 48 weeks of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age.

Efficacy

- Evaluate antiviral (virologic) and immunologic responses at 4, 24, and 48 weeks, and additionally up to 144 weeks, of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age.
- Evaluate HIV-1 genotypes and phenotypes among children <12 years of age who experience virologic failure while receiving treatment with DTG/ABC/3TC DTs or DTG/ABC/3TC Tablets.

Palatability

- Evaluate adherence to and palatability and acceptability of DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age at 4, 24 and 48 weeks of treatment.

Outcomes/endpoints

Primary

Pharmacokinetic

- GM AUC0-24h, Cmax, and C24h for ABC, DTG, and 3TC.

Safety

- All AEs occurring through Week 24.
- Participants with the following through Week 24:
    - Grade 3 or Grade 4 AEs assessed as related to study drug
    - Grade 5 AEs assessed as related to study drug
    - Life-threatening AEs assessed as related to study drug
    - SAEs assessed as related to study drug
    - AEs assessed as related to study drug that led to permanent discontinuation of study drug.

Secondary

Pharmacokinetic

- AUC0-24h, C0h, C24h, Cmax, Tmax, CL/F, and t1/2 derived from PopPK modelling with sampling through Week 48.

Safety

- All AEs occurring through Week 48.
- Participants with the following through Week 48 and Week 144:
    - Grade 3 or Grade 4 AEs assessed as related to study drug
    - Grade 5 AEs assessed as related to study drug
    - Life-threatening AEs assessed as related to study drug
    - SAEs assessed as related to study drug
    - AEs assessed as related to study drug that led to permanent discontinuation of study drug.

- Total cholesterol, HDL, LDL, and triglycerides at Weeks 24 and 48.

Efficacy

- HIV-1 RNA through Week 48 and Week 144.
- The proportion of participants with:
    - HIV-1 RNA ≥200 c/mL at Weeks 4, 24, and 48.
    - HIV-1 RNA ≥50 c/mL at Weeks 4, 24, and 48.
- CD4+ cell count and percentage at Weeks 4, 24, 48 and 144.
- HIV-1 genotypes and phenotypes of participants who experienced confirmed virologic failure (CVF; 2 consecutive plasma HIV-1 RNA test results ≥200 c/mL, at or after Week 24 in ART-naïve participants and at any time after enrolment in ART-experienced participants).

Palatability

- Parent/guardian reported adherence to study drug at Weeks 4, 24, and 48.
- Parent/guardian reported tolerability (i.e., palatability and acceptability) of study drug at Weeks 4, 12, 24, and 48.

Use of DTG/ABC/3TC and evaluations to assess safety, adherence, tolerability (i.e., palatability and acceptability), antiviral (virologic), and immunologic response, and lipid profiles continued through 48 weeks of follow-up. Safety findings were also presented for the 10 participants (all in Thailand, all ≥14 kg) who continued past Week 48 through their final (Week 60) visit due to unavailability of study drug outside of study setting.

Specimen collection for PK evaluations was also continued through 48 weeks of follow-up.

Safety and efficacy analyses were based on the All Treated Population.

Safety analyses were typically done by enrolment weight band. However, to better understand exposure to weight band doses over time, some analyses were also performed by the actual weight band and dose the participant received at the time of the AE. Additionally, the primary safety outcome measure was evaluated by age group at enrolment (<6 years vs ≥6 to <12 years) and formulation (DTs vs Tablets). AEs were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (Corrected Version 2.1 – July 2017).

Missing CD4 count data were imputed using baseline value.

Plasma HIV-1 RNA results below the LLOQ were imputed as LLOQ – 1.

HIV-1 resistance testing (genotype and/or phenotype) was not required for study inclusion. Participants with M184V resistance mutations known from historic testing had additional study visits conducted leading up to Week 24 to allow for closer virologic monitoring.

Sample size

The sample size target of at least 50 children, with at least 25 children <6 years of age and at least 25 children ≥6 to <12 years of age, was selected based on agreements with regulatory authorities. At least 5 dose-evaluable (meaning both safety-evaluable and PK-evaluable) participants were required for each weight band (see table above) and a total sample size of up to 75 children was permitted to ensure that the accrual requirements were met and to permit additional enrolment if needed to adjust and/or verify doses. The study was not powered for inferential testing.

Randomisation/ Blinding (masking)

This was a single-arm, open-label study.

Statistical methods

Pharmacokinetics: see previous section

Safety and Efficacy: Descriptive statistic was performed.

Results

Participant flow

A total of 69 participants were screened and 57 participants enrolled. Reasons for screening failure were logistical and administrative issues and not meeting inclusion/exclusion criteria.

Two participants (1 each in the ≥6 to <10 kg and ≥10 to <14 kg enrolment weight bands) discontinued study drug and study participation during the first week due to palatability issues. In addition, 1 participant discontinued study drug at Week 36 due to an AE of DILI (see **Clinical Safety** below). This participant remained in the study until completion of the Week 48 visit. Thus, 55 participants completed 48 weeks of study, and all of these remained on study treatment for the intended duration.

There were 19 reportable protocol deviations documented across 18 participants. Notably amongst these, enrolment of an ineligible participant who changed their background ARV within weeks of study entry. This deviation was not captured until data analysis was underway. The participant completed study treatment and remained virologically suppressed throughout the study. This deviation is considered, if anything, to present a potential disadvantage for the product/sponsor in terms of effect on safety and efficacy analyses and thus from a regulatory point of view is unproblematic. It was determined by the Clinical Management Committee that none of the reportable deviations would affect the integrity of the primary data analyses of IMPAACT 2019, and this can be agreed.

There were 7 dose-evaluable (meaning both safety-evaluable and PK-evaluable) participants available in each weight band for final dose-confirmation analysis.

Recruitment

Participants enrolled in IMPAACT 2019 reflected the global HIV paediatric population with just over half the participants enrolled from Botswana and South Africa, approximately one third from Thailand, and the remainder enrolled in the US.

Conduct of the study

Initiated: 26 August 2020

Last Site Last Visit: 31 May 2022.

Database lock: 09 September 2022.

CSR: 01 November 2022

All study activities have occurred under Version 2.0 of the protocol (dated 04 September 2019).

Baseline data

The predominant race was Black or African American, females comprised roughly half of the population, and the majority of participants were ART-experienced (only 3 of 57 participants were ART-naive). The

number of participants enrolled was mostly balanced across the weight bands, and the age-based quotas of enrolling at least 25 participants in each age group (i.e., <6 years vs ≥6 to <12 years) were met.

At baseline, the majority of participants were ART-experienced (94.7%), had a WHO clinical stage classification of Stage 1 (75.4%), and no known M184V mutation (93.0%). The median (range) viral load at baseline was 1.59 (1.3, 3.5) log10 HIV-1 RNA in participants who were ART-experienced and 5.70 (5.3, 6.5) log10 HIV-1 RNA in participants who were ART-naïve. The median (range) CD4% at baseline was similar (within 5%) across the 5 weight bands.

Most participants switched from PI- and NRTI-containing regimens to the study drug at entry. In line with first line therapies recommended for this population, prior ARV regimens most commonly contained 3TC, ABC, and ZDV. No participants switched to the study drug regimen from an NNRTI based regimen.

The use of concomitant non-ARTs was as expected for the paediatric population with commonly co-administered medications including paracetamol, antibiotics, topical antifungals, childhood vaccines, multivitamins, minerals, salbutamol, ibuprofen, and antihistamines. Reported medical history was varied and much as expected for the paediatric population.

Table 25. Baseline Demographic Characteristics by Enrolment Weight Band in IMPAACT 2019 (All Enrolled Population)

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)

Table 26. Additional Baseline Characteristics by Enrolment Weight Band in IMPAACT 2019 (All Enrolled Population)

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
CD4+%	34.00	33.90	32.90	32.55	37.70	35.05
Median (range)[a]	(18.0, 55.0)	(23.9, 49.0)	(25.3, 47.6)	(25.8, 46.7)	(32.2, 49.5)	(18.0, 55.0)
CD4+ (cells/mm^3)	2321.0	1452.0	886.0	1155.0	915.0	1201.0
Median (range)[a]	(663.0, 4636.0)	(1038.0, 3073.0)	(522.0, 2374.0)	(479.0, 1480.0)	(320.0, 1530.0)	(320.0, 4636.0)
WHO Clinical Stage, n (%)						
Stage 1	8 (88.9)	8 (66.7)	12 (80.0)	8 (80.0)	7 (63.6)	43 (75.4)
Stage 2	0	1 (8.3)	0	0	1 (9.1)	2 (3.5)
Stage 3	1 (11.1)	1 (8.3)	3 (20.0)	1 (10.0)	3 (27.3)	9 (15.8)
Stage 4	0	2 (16.7)	0	1 (10.0)	0	3 (5.3)
log10 HIV-RNA c/mL						
n	9	12	15	10	11	57
Median,	1.59	1.59	1.59	1.59	1.59	1.59
range (min, max)	(1.6, 6.5)	(1.3, 1.6)	(1.3, 2.3)	(1.3, 2.3)	(1.3, 1.6)	(1.3, 6.5)
log10 HIV-RNA in ART-naïve						
n	3					3
Median,	5.70	0	0	0	0	5.70
range (min, max)	(5.3, 6.5)					(5.3, 6.5)
log10 HIV-RNA in ART-experienced						
n	6	12	15	10	11	54
Median,	1.59	1.59	1.59	1.59	1.59	1.59
range (min, max)	(1.6, 3.5)	(1.3, 1.6)	(1.3, 2.3)	(1.3, 2.3)	(1.3, 1.6)	(1.3, 3.5)
Known M184V mutation, n (%)						
Yes	0	0	2 (13.3)	0	2 (18.2)	4 (7.0)
No	9 (100.0)	12 (100.0)	13 (86.7)	10 (100.0)	9 (81.8)	53 (93.0)

Source: IMPAACT 2019 CSR Table 1.7

Note: N = Number of participants in each weight band. n(%) = Number (percent) of participants in each subcategory in each weight band (with respect to the number of participants in each weight band).

Note: HIV-1 RNA viral loads below LLOQ were represented as LLOQ - 1.

a. 1 participant from the ≥10 to <14 kg enrollment weight band was missing baseline values for CD4+ cells.

Table 27. Prior Antiretroviral Experience by Enrolment Weight Band (All Enrolled Population)

	≥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
ART Status, n (%)						
ART-experienced	6 (67.7)	12 (100)	15 (100)	10 (100)	11 (100)	54 (94.7)
ART-naïve	3 (33.3)	0	0	0	0	3 (5.3)
ART Experience by Class, n (%)						
INSTI- and NRTI-experienced	0	2 (16.7)	4 (26.7)	2 (20.0)	5 (45.5)	13 (22.8)
NRTI-experienced	0	0	0	0	1 (9.1)	1 (1.8)
PI- and NRTI-experienced	6 (66.7)	10 (83.3)	10 (66.7)	8 (80.0)	4 (36.4)	38 (66.7)
PI-, INSTI-, and NRTI-experienced	0	0	1 (6.7)	0	1 (9.1)	2 (3.5)

Source: IMPAACT 2019 CSR Table 1.7

Table 28. Prior Antiretroviral Medications All Enrolled Population

	Weight Band					
Antiretroviral Medication	1 6 to <10 kg (N=9) n (%)	2 10 to <14 kg (N=12) n (%)	3 14 to <20 kg (N=15) n (%)	4 20 to <25 kg (N=10) n (%)	5 ≥25 kg (N=11) n (%)	Total (N=57) n (%)
Number of participants who took one or more antiretroviral drugs prior to the treatment initiation	**6 (66.7)**	**12 (100.0)**	**15 (100.0)**	**10 (100.0)**	**11 (100.0)**	**54 (94.7)**
ABACAVIR	2 (22.2)	7 (58.3)	7 (46.7)	3 (30.0)	3 (27.3)	22 (38.6)
ABACAVIR SULFATE	0	1 (8.3)	0	0	1 (9.1)	2 (3.5)
ABACAVIR SULFATE;LAMIVUDINE	0	0	0	0	1 (9.1)	1 (1.8)
ABACAVIR;LAMIVUDINE	3 (33.3)	1 (8.3)	2 (13.3)	0	0	6 (10.5)
DARUNAVIR	0	0	0	0	1 (9.1)	1 (1.8)
DOLUTEGRAVIR	0	0	4 (26.7)	1 (10.0)	3 (27.3)	8 (14.0)
EMTRICITABINE	0	1 (8.3)	0	0	0	1 (1.8)
EMTRICITABINE;TENOFOVIR DISOPROXIL FUMARATE	0	0	1 (6.7)	0	2 (18.2)	3 (5.3)
LAMIVUDINE	3 (33.3)	10 (83.3)	7 (46.7)	5 (50.0)	2 (18.2)	27 (47.4)
LAMIVUDINE;ZIDOVUDINE	1 (11.1)	0	5 (33.3)	6 (60.0)	5 (45.5)	17 (29.8)
LOPINAVIR;RITONAVIR	6 (66.7)	10 (83.3)	11 (73.3)	8 (80.0)	4 (36.4)	39 (68.4)
RALTEGRAVIR	0	2 (16.7)	1 (6.7)	1 (10.0)	3 (27.3)	7 (12.3)
RITONAVIR	0	0	0	0	1 (9.1)	1 (1.8)
ZIDOVUDINE	2 (22.2)	3 (25.0)	2 (13.3)	2 (20.0)	1 (9.1)	10 (17.5)

N = Number of participants in each weight band
n (%) = Number (percent) of participants in each subcategory (with respect to the number of participants in each weight band)

Numbers analysed

A total of 57 participants were enrolled across all weight bands. Only three ART-naïve participants were recruited, all in the lowest weight band (≥6 to <10 kg).

Table 29. All treated population by Weight Band

Population	Weight band					Total
	≥6 to <10 kg	≥10 to <14 kg	≥14 to <20 kg	≥20 to <25 kg	≥25 kg	
All Treated Population (N)	9	12	15	10	11	57

Continuation beyond Week 48 was not necessary for most participants because they were able to access the drug through a non-study source upon completion of the Week 48 visit. Some participants (10/57 [17.5%], all in Thailand, all ≥14 kg) continued in the study after Week 48, pending local availability of study drug. All of these participants completed a Week 60 safety visit (i.e., 1 additional visit after Week 48) and then transferred to a non-study source of study drug.

Exposure

Patient exposure

Table 30. Summary of Exposure to Study Drug in Weeks through End of Study, by Enrolment Weight Band (All Treated Population)

	≥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
n	9	12	15	10	11	57
Exposure, weeks						
Mean (SD)	42.03 (15.515)	43.99 (13.540)	50.99 (5.551)	50.04 (7.217)	50.60 (4.556)	47.86 (10.188)
Median	47.00	48.00	48.14	47.79	48.14	48.14
(Q1, Q3)	(46.29, 48.00)	(46.93, 48.57)	(47.14, 58.14)	(46.86, 58.14)	(48.00, 55.14)	(46.86, 49.14)
(Min, Max)	(0.7, 48.3)	(1.1, 49.7)	(45.9, 62.0)	(37.0, 61.1)	(46.6, 59.0)	(0.7, 62.0)

Source: IMPAACT 2019 CSR Table 1.9
Note: N = Number of participants in each weight band.
Note: Duration is calculated starting at treatment start until treatment end. Any time off treatment but on study is not counted in treatment duration.

Table 31. Summary of Exposure through End of Study, by Actual Weight Band (All Treated Population)

DTG/ABC/3TC Daily Dose (mg)[a]	15/180/90	20/240/120	25/300/150	30/360/180	50/600/300
Formulation Administered	DTs	DTs	DTs	DTs	Tablets
Weight Band at Time of Actual Dosing	≥6 to <10 kg	≥10 to <14 kg	≥14 to <20 kg	≥20 to <25 kg	≥25 kg
n	9	19	24	15	18
Exposure, weeks					
Mean (SD)	19.21 (16.251)	23.74 (15.543)	36.69 (14.810)	37.87 (12.469)	36.41 (19.464)
Median	12.14	24.71	40.43	36.00	47.43
(Q1, Q3)	(12.00, 36.00)	(12.00, 36.00)	(29.86, 47.29)	(24.14, 47.43)	(23.00, 49.00)
(Min, Max)	(0.7, 47.0)	(1.1, 48.1)	(4.1, 59.0)	(23.0, 58.1)	(3.0, 59.0)

Source: IMPAACT 2019 CSR Table 1.15

Note: n = Number of participants in each weight band by actual dosing.

Note: Duration is calculated starting at treatment start until treatment end. Any time off treatment but on study is not counted in treatment duration. Treatment start and end dates are for the actual weight band by dosing. Participants may move from 1 weight band dosing to the next throughout study participation and therefore may be counted in more than 1 weight band.

a. Daily dose of DTG/ABC/3TC received based on actual weight band at the time of the actual exposure to study drug.

Overall, 26 participants changed weight bands once and 1 participant changed weight bands twice. Further, there were 7 participants who switched from taking dispersible tablets to film-coated tablets during the study. No dose adjustments requiring the use of the single entities (required, for example, when co-administered with medications perpetrating DDI) were necessary.

The difference in average exposure between weight bands reflects the expected progression of participants into the next weight category during the course of the study and before the completion of total 48 weeks' treatment, driven by natural growth patterns during early childhood.

Treatment adherence

Adherence data were available for all participants except the 2 who discontinued study drug due to palatability issues (55 of 57 participants). For 1 participant, adherence data are only available through Week 24 because of study drug discontinuation due to an SAE.

All but 2 caregivers reported that participants received at least 90% of their study drug within the last 30 days. The most common reasons for missed doses were related to caregivers forgetting or being too busy to administer the medication. Nevertheless, these patients remained virologically suppressed through Week 48. Most patients took the formulations as directed, with 3 caregivers reporting administration of split/broken film-coated tablets.

Outcomes and estimation

Primary analyses

For Pharmacokinetics see section above.

For safety, see Clinical safety section.

Secondary analyses

Antiviral (virologic) response

Snapshot outcomes by Week and Enrolment Weight Band were presented for the All Treated population through Week 48 using both HIV-1 RNA 200 and 50 c/mL cutoffs for successful virological suppression:

Table 32. Snapshot Outcomes by Week and Enrolment Weight Band – Standard Snapshot Analysis (All Treated Population)

Analysis Visit	Weight Band ≥6 to <10 kg (N=9) n (%)	≥10 to <14 kg (N=12) n (%)	≥14 to <20 kg (N=15) n (%)	≥20 to <25 kg (N=10) n (%)	≥25 kg (N=11) n (%)	Total (N=57) n (%)
Week 24						
HIV-1 RNA <200 c/mL	7 (77.8)	11 (91.7)	15 (100.0)	10 (100.0)	11 (100.0)	54 (94.7)
HIV-1 RNA ≥200 c/mL	1 (11.1)	0	0	0	0	1 (1.8)
HIV-1 RNA <50 c/mL	7 (77.8)	10 (83.3)	14 (93.3)	10 (100.0)	11 (100.0)	52 (91.2)
HIV-1 RNA ≥50 c/mL	1 (11.1)	1 (8.3)	1 (6.7)	0	0	3 (5.3)[a]
No Virologic Data	**1 (11.1)**	**1 (8.3)**	**0**	**0**	**0**	**2 (3.5)**
Discontinued study drug due to AE or death	0	0	0	0	0	0
Discontinued study drug due to other reasons and HIV-1 RNA at time of discontinuation is missing or <200 c/mL (or <50 c/mL)	1 (11.1)	1 (8.3)	0	0	0	2 (3.5)
Week 48						
HIV-1 RNA <200 c/mL	8 (88.9)	11 (91.7)	15 (100.0)	9 (90.0)	11 (100.0)	54 (94.7)
HIV-1 RNA ≥200 c/mL	0	0	0	0	0	0
HIV-1 RNA <50 c/mL	7 (77.8)	8 (66.7)	13 (86.7)	7 (70.0)	10 (90.9)	45 (78.9)
HIV-1 RNA ≥50 c/mL	1 (11.1)	3 (25.0)	2 (13.3)	2 (20.0)	1 (9.1)	9 (15.8)[a]
No Virologic Data	**1 (11.1)**	**1 (8.3)**	**0**	**1 (10.0)**	**0**	**3 (5.3)**
Discontinued study drug due to AE or death	0	0	0	1 (10.0)	0	1 (1.8)
Discontinued study drug due to other reasons and HIV-1 RNA at time of discontinuation is missing or <200 c/mL (or 50 c/mL)	1 (11.1)	1 (8.3)	0	0	0	2 (3.5)

Source: Table 2.24, Table 2.25, Table 2.27, Table 2.28

Note: N = Number of participants in each weight band. n (%) = Number (percent) of participants in each subcategory in each weight band (with respect to the number of participants with results available at that visit in each weight band).

Note: Participants can be included in more than 1 row (<200 c/mL and <50 c/mL; ≥200 c/mL and ≥50 c/mL).

Note: 95% CI = Exact 95% CI (Clopper-Pearson) are included in the source tables.

Note: Week 4 data are included in the source tables.

Note: No participant discontinued study drug due to virologic failure.

Note: No participant discontinued study drug due to other reasons and HIV-1 RNA at time of discontinuation ≥threshold.

Note: No participant had missing data during the window and on study drug.

Note: Virologic success included HIV-1 RNA under the threshold for virologic suppression (<200 c/mL or <50 c/mL); Plasma HIV-1 RNA results below the LLOQ were imputed as LLOQ - 1.

a. Additional context for these participants with HIV-1 RNA ≥50 c/mL is presented in Section 8.1.2.1.

Sensitivity analyses for the snapshot algorithm summary were also done, categorizing results less than a hypothetical LLOQ of 50 c/mL or 200 c/mL, respectively, as a virologic success if the target was not detected, or as 'No Virologic Data' if the target was detected (composite snapshot). This approach essentially simulates the study outcome in a clinical setting where the LLOQ for HIV-1 RNA testing could be above 50 c/mL and even up to 200 c/mL. Study outcomes for the composite snapshot approach were similar to the standard snapshot approach.

All 4 ART-experienced participants with a known M184V mutation at study entry (from historic testing) had a viral load <50 c/mL at both Week 24 and 48.

No participants had known treatment emergent NRTI or INSTI associated resistance through Week 48.

The 3 ART-naïve participants had high viral loads at study entry and had a rapid response, with suppression as early as Week 4. Of these participants, one met protocol criteria for confirmed virological failure (CVF) due to not being suppressed to <200 c/mL at Week 24, although all 3 were suppressed to <200 c/mL at Week 48:

Table 33. HIV-1 RNA Results of ART-naïve Participants

Timepoint	HIV-1 RNA (c/mL)		
	PID 6073921	PID 3041436	PID 830750
Baseline	186 419	3 519 602	500 885
Week 4	625	14 155	108
Week 24	46	419[a]	<40
Week 48	<40	76	<40

Source: Listing 29

a. CVF confirmed at 358 c/mL

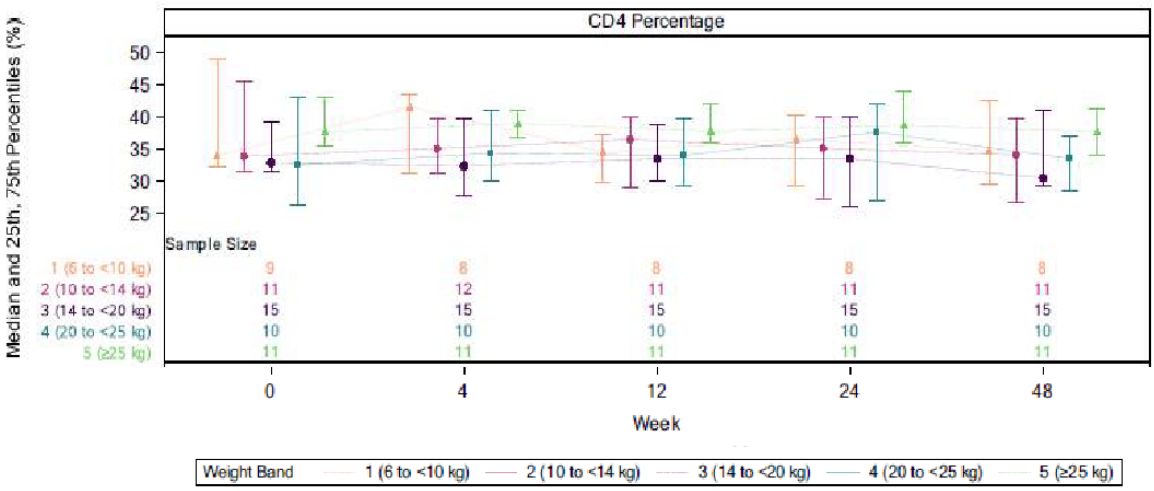
Summary of case narrative – confirmed virological failure

A one-year-old male ART-naïve participant with a baseline HIV-1 RNA of 519 602 c/mL and a CD4% of 25% was enrolled into the ≥6 to <10 kg weight band. On study, the participant met the criteria for CVF at Week 24 with an HIV-1 RNA of 419 c/mL and a CD4% of 38%.

The baseline genotypic and phenotypic testing showed evidence of one pre-existing polymorphic position in integrase, L74I, identified in the IN coding region of HIV pol. Samples drawn at CVF failed to amplify due to low HIV-1 RNA. As a result, no genotypic or phenotypic data are available for the CVF timepoint.

The participant remained on study and on study drug through Week 48. Around Week 36 the viral load crossed below the 200 c/mL threshold and at Week 48 the HIV-1 RNA viral load was 76 c/mL.

Immunologic response



Source: Figure 2.4

Figure 15. Median (Q1, Q3) CD4% by Visit and Enrolment Weight Band Through Week 48 (All treated population)

In practice, laboratory measures of CD4 lymphocyte count were successfully collected at every planned study timepoint and data were imputed only for one participant (20 to <25 kg enrolment weight band) at one timepoint (Week 48).

CD4% remained generally stable through Week 48.

Palatability

Acceptability was assessed at Week 4, Week 12, Week 24, and Week 48. For DTG/ABC/3TC DTs, measures of acceptability included happiness with the number of DTs, the amount of water to be used, and the amount of the liquid medicine to be swallowed.

At Week 4, the acceptability of the dispersion volumes was evaluated with special emphasis on the palatability of these volumes for the ≥14 to <20 kg and ≥20 to <25 kg weight bands. For DTG/ABC/3TC Tablets, acceptability was assessed by questions focused on determining if the Tablets were swallowed whole.

Across all measures, the use of DTG/ABC/3TC DTs was reported as acceptable (>90% positive responses) throughout the course of the study. A total of 2 (3.5%) participants (1 each in the ≥6 to <10 kg and ≥10 to <14 kg enrolment weight bands) discontinued study drug and study participation during the first week due to palatability issues. The reasons as described in the study listings were "The Child Is Continuously Refusing To Take The Study Treatment" (participant in ≥6 to <10 kg enrolment weight band) and "Continued Spitting Up With Each Dose" (participant in ≥10 to <14 kg enrolment weight band).

For 2 participants, the caregiver reported administration with cut or broken DTG/ABC/3TC Tablets.

All cases where caregivers reported that the child did not take the study drug easily (with or without minimal help) occurred for the DTs, i.e. in the younger age/weight participants. It is not unexpected that administration issues are higher amongst the youngest paediatric population.

Table 34. Summary of Efficacy for trial

<table>
<tr><th colspan="5">Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age</th></tr>
<tr><td>Study identifier</td><td colspan="4">NCT03760458</td></tr>
<tr><td rowspan="3">Design</td><td colspan="4"><table>
<tr><th>Weight Band (kg)</th><th>Total Daily Dose (DTG/ABC/3TC)</th><th>Number of Tablets Formulation</th><th>Dispersion Volume</th></tr>
<tr><td>≥6 to <10</td><td>15 mg/180 mg/90 mg</td><td>3 DTs</td><td>15 mL</td></tr>
<tr><td>≥10 to <14</td><td>20 mg/240 mg/120 mg</td><td>4 DTs</td><td>20 mL</td></tr>
<tr><td>≥14 to <20</td><td>25 mg/300 mg/150 mg</td><td>5 DTs</td><td>20 mL</td></tr>
<tr><td>≥20 to <25</td><td>30 mg/360 mg/180 mg</td><td>6 DTs</td><td>20 mL</td></tr>
<tr><td>≥25 kg</td><td>50 mg/600 mg/300 mg</td><td>1 Tablet</td><td>N/A</td></tr>
</table></td></tr>
<tr><td colspan="4">Note: While the relative bioavailability of ABC and 3TC administered in DTG/ABC/3TC DTs are not different from the DTG/ABC/3TC Tablets, the bioavailability of the DTG component of the DTG/ABC/3TC DT is approximately 1.7-fold greater than that of the DTG/ABC/3TC Tablet. Thus, the 2 dosage forms are not interchangeable on a mg-per-mg basis and preclude switching between the 2 dosage forms.</td></tr>
<tr><td colspan="4"><table>
<tr><td>Duration of main phase:</td><td>48 weeks</td></tr>
<tr><td>Duration of Extension phase:</td><td>Following completion of the Week 48 Visit, children who are deriving benefit from DTG/ABC/ 3TC may remain on-study for up to an additional 96 weeks if DTG/ABC/ 3TC is not otherwise available from a non-study source.</td></tr>
</table></td></tr>
<tr><td>Hypothesis</td><td colspan="4">The hypotheses of this study are:
• Selected doses of DTG/ABC/3TC dispersible and immediate release tablets will achieve protocol-defined PK targets for DTG, ABC, and 3TC in children less than 12 years of age
• DTG/ABC/ 3TC DTs and DTG/ABC/ 3TC Tablets will be described as safe for treatment in children less than 12 years of age</td></tr>
<tr><td></td><td>≥6 to <10 kg</td><td colspan="3">15 mg DTG/180 mg ABC/90 3TC mg DT Once Daily, 48 Weeks, 9 Participants</td></tr>
</table>

Treatment groups	≥10 to <14 kg	20 mg DTG/240 mg ABC/120 3TC mg DT Once Daily, 48 Weeks, 12 Participants
	³14 to <20 kg	25 mg DTG/300 mg ABC/1503TC mg DT Once Daily, 48 Weeks, 15 Participants
	³20 to <25 kg	30 mg DTG/360 mg ABC/180 3TC mg DT Once Daily, 48 Weeks, 10 Participants
	³25 kg	50 mg DTG/600 mg ABC/300 3TC mg Tablet Once Daily, 48 Weeks, 11 Participants
Endpoints and definitions	Primary endpoints	• Geometric Mean (GM) AUC0-24h, Cmax, and C24h for ABC, DTG, and 3TC based on analysis of • intensive PK samples collected at Week 1 (AUC0-24h and C24h to be compared within each weight band to the PK targets specified in Study Protocol) • All adverse events (AEs) occurring through Week 24
	Secondary endpoints	• AUC0-24h, C0h, C24h, Cmax, Tmax, CL/F, and t1/2 derived from PopPK modeling with sampling through Week 48 • All AEs occurring through Week 48 • All AEs occurring through Week 144 • HIV-1 RNA through Week 48 • HIV-1 RNA through Week 144 • CD4+ cell count and percentage at Weeks 4, 24, and 48 • CD4+ cell count and percentage through Week 144
Database lock	09 September 2022	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	The dose confirmation for each of the weight bands was achieved based on IMPAACT 2019 protocol-defined PK targets for DTG, ABC, and 3TC among participants who underwent intensive PK sampling and met dose-evaluable criteria. As per the protocol, GM of the targeted PK parameters for each of the weight bands must fall within the pre-defined range.	

Descriptive statistics and estimate variability

Overall Summary of PK Parameters (Intensive PK Group)

Weight Bands (kg)	DTG/ABC/3TC Dosage Form	DTG/ABC/3TC Dose (mg)	n	PK Parameter GM (%CVb)			
				DTG		ABC	3TC
				AUC0-24 (µg*h/mL)	C24 (µg /mL)	AUC0-24 (µg*h/mL)	AUC 0-24 (µg*h/mL)
≥ 6 to <10	DT	15/180/90	7	75.9 (34)	0.91 (68)	17.7 (34)	10.7 (46)
≥10 to <14	DT	20/240/120	7	91.0 (36)	1.22 (77)	19.8 (51)	14.2 (24)
≥ 14 to <20	DT	25/300/150	7	71.4 (23)	0.79 (44)	15.1 (40)	13.0 (16)
≥ 20 to <25	DT	30/360/180	7	84.4 (26)	1.35 (95)	17.4 (19)	14.5 (17)
≥ 25	Tablet	50/600/300	7	71.8 (14)	0.98 (28)	25.7 (15)	21.7 (26)
Target GM Range				**37 to 134**	**0.697 to 2.26**	**6.3 to 50.4**	**6.3 to 26.5**

Notes	• The estimated intensive PK parameters for DTG, ABC, and 3TC with the DTG/ABC/3TC DTs and Tablets at the originally proposed doses were within the protocol-defined target ranges. • Overall, DTG, ABC, and 3TC PK exposures following once-daily DTG/ABC/3TC DT and Tablet dosing were comparable to those observed in paediatric and adult populations with single drug entity data.
Analysis description	**Safety Analysis** IMPAACT 2019 safety data presented herein are from the All Treated Population, which is defined as all participants who received at least 1 dose of study drug. No participants were excluded from the All Treated Population.

Overall Summary of AEs through Week 24 and Week 48 for All Weight Bands (All Treated Population)*

	Total (N=57) n (%)	
	Week 24	**Week 48[a]**
Any AE	50 (87.7)	53 (93.0)
AE related to study drug	11 (19.3)	15 (26.3)
≥Grade 3 AE	8 (14.0)	15 (26.3)
Grade 5 AE (death)[b]	0	0
Grade 3 or Grade 4 AE related to study drug	0	2 (3.5)
Grade 5 AE (death) related to study drug	0	0
Any SAE[b,c]	2 (3.5)	3 (5.3)
SAE related to study drug[c]	0	1 (1.8)
Any life-threatening AE[b]	0	0
Life-threatening AE related to study drug	0	0
Any AE that led to permanent discontinuation of study drug[b]	0	1 (1.8)
AE related to study drug that led to permanent discontinuation of study drug	0	1 (1.8)

- Note: N= Number of all treated participants. n (%) = Number (percent) of participants in each subcategory who experienced at least 1 such event (with respect to the number of all treated participants).
  a. Although additional AEs were reported between Week 48 and the End of Study, the number and proportion of participants experiencing each category of AEs was unchanged, and therefore a separate "End of Study" column is not presented.
  b. The number (n) of participants with any Grade 5 AE, SAE, life-threatening AE, or AE that led to permanent discontinuation of study drug was identified from source listings, and the % was tabulated based on n/N for the group.
  c. The SAEs up to Week 24 were Grade 3 gastroenteritis (not related to study drug) and Grade 3 pneumonia (not related to study drug); the additional SAE after Week 24 was Grade 4 DILI (related to study drug).

2.3.7. Discussion on clinical efficacy

This was a Phase 1/2, multi-site, open-label, multiple dose, non-comparative PK and safety study of DTG/ABC/3TC DTs and Tablets in ART-naïve and ART-experienced children living with HIV who were <12 years of age and weighed ≥6 kg to <40 kg. Enrolled children were to receive DTG/ABC/3TC DTs or DTG/ABC/3TC Tablets (according to weight band) for at least 48 weeks (through the Week 48 visit) and for up to 144 weeks, if needed.

The 57 paediatric participants enrolled in IMPAACT 2019 reflected the global HIV paediatric population with just over half the participants enrolled from Botswana and South Africa, approximately one third from Thailand, and the remainder enrolled in the US. The predominant race was Black or African American, females comprised roughly half of the population.

At baseline, the majority of participants were ART-experienced (94.7%), had a WHO clinical stage classification of Stage 1 (75.4%), no known M184V mutation (93.0%) and a suppressed viral load at baseline. Only three ART-naïve participants were recruited, all in the lowest weight band (≥6 to <10 kg). Patients with significant renal, liver or autoimmune dysfunction or concurrent malignancy, active tuberculosis or hepatitis B infection were excluded from the study.

In line with first line therapies recommended for this population, prior ARV regimens most commonly contained 3TC, ABC, and ZDV. No participants switched to the study drug regimen from an NNRTI based regimen. The concomitant non-ART medications and medical history were varied and as expected for the study population.

A total of 7 dose-evaluable (meaning both safety-evaluable and PK-evaluable) participants in each weight band underwent intensive PK sampling for the purposes of final dose-confirmation analysis.

Palatability and acceptability of DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age at 4, 24 and 48 weeks of treatment was a secondary objective of IMPAACT 2019.

Efficacy data and additional analyses

Snapshot outcomes by Week and Enrolment Weight Band were presented for the All Treated population through Week 48 using both HIV-1 RNA 200 and 50 c/mL cutoffs for successful virological suppression. The antiviral (virologic) response was favourable in all weight bands. Sensitivity analyses for the snapshot algorithm summary using hypothetical LLOQ of 50 c/mL or 200 c/mL gave results similar to the standard snapshot approach.

All 4 ART-experienced participants with a known M184V mutation at study entry (from historic testing) had a viral load <50 c/mL at both Week 24 and 48.

No participants had known treatment emergent NRTI or INSTI associated resistance through Week 48.

The 3 ART-naïve participants had high viral loads at study entry and had a rapid response, with suppression as early as Week 4. Of these participants, one met protocol criteria for confirmed virological failure (CVF) due to not being suppressed to <200 c/mL at Week 24, although all 3 were successfully virologically suppressed to <200 c/mL at Week 48. The case of CVF occurred in a one-year-old male ART-naïve participant with a baseline HIV-1 RNA of 519 602 c/mL and a CD4% of 25% was enrolled into the ≥ 6 to <10 kg weight band. The baseline genotypic and phenotypic testing showed evidence of one pre-existing polymorphic position in integrase, L74I, identified in the IN coding region of HIV pol. No genotypic or phenotypic data are available for the CVF timepoint.

Two participants (1 each in the ≥6 to <10 kg and ≥10 to <14 kg enrolment weight bands) discontinued study drug and study participation during the first week due to palatability issues. The DT and Tablet formulations were otherwise considered adequately palatable and administration generally acceptable for the majority of children/caregivers, with no major concerns were identified across the weight band.

2.3.8. Conclusions on the clinical efficacy

The descriptive paediatric efficacy data presented from the now-completed IMPAACT 2019 study are in line with what has been observed for the FDC in adults. However, this study was not designed to permit inferential testing of efficacy endpoints.

The application for regulatory approval in paediatric patients weighing ≥6 kg relies on extrapolation of clinical efficacy as already established in adults for the FDC and in the paediatric population for the single entities, based on PK-bridging. This aligns with current EMA guidance and regulatory precedent.

Given that exposure achieved in paediatric patients is comparable to that shown to be effective in adults, Triumeq is expected to be effective in the treatment of HIV-1 infection in paediatric patients.

2.4. Clinical safety

Introduction

Triumeq (DTG/ABC/3TC) is a fixed dose combination (FDC) of three previously authorised antiretrovirals for which the clinical safety profiles are well established. There is no pre-existing evidence to suggest that these should differ with administration as part of an FDC. The safety data generated within the IMPAACT 2019 study comprised 48 weeks' study duration for 55 patients and an additional Week 60 safety follow up visit for 10 patients who remained on study drug past Week 48.

Adverse events

Summary tables of treatment-emergent adverse events (TEAEs) were presented through 24 and 48 weeks of treatment, and beyond for those patients who continued to receive study drug. The picture at 24 weeks is very similar to that at 48 weeks, which is therefore presented below.

Table 35. Overall Summary of Adverse Events through Week 48, by Enrolment Weight Band (All Treated Population)

	≥6 to <10 kg (N=9) n (%)	≥10 to <14 kg (N=12) n (%)	≥14 to <20 kg (N=15) n (%)	≥20 to <25 kg (N=10) n (%)	≥25 kg (N=11) n (%)	Total (N=57) n (%)
Any AE	8 (88.9)	10 (83.3)	15 (100.0)	10 (100.0)	10 (90.9)	53 (93.0)
AE related to study drug	4 (44.4)	2 (16.7)	1 (6.7)	4 (40.0)	4 (36.4)	15 (26.3)
≥Grade 3 AE	3 (33.3)	4 (33.3)	5 (33.3)	3 (30.0)	0	15 (26.3)
Grade 5 AE (death)[a]	0	0	0	0	0	0
Grade 3 or Grade 4 AE related to study drug	0	0	0	2 (20.0)	0	2 (3.5)
Grade 5 AE (death) related to study drug	0	0	0	0	0	0
Any SAE[a]	1 (11.1)[b]	1 (8.3)[c]	0	1 (10.0)[d]	0	3 (5.3)
SAE related to study drug	0	0	0	1 (10.0)[d]	0	1 (1.8)
Any life-threatening AE[a]	0	0	0	0	0	0
Life-threatening AE related to study drug	0	0	0	0	0	0
Any AE that led to permanent discontinuation of study drug[a]	0	0	0	1 (10.0)[d]	0	1 (1.8)
AE related to study drug that led to permanent discontinuation of study drug	0	0	0	1 (10.0)[d]	0	1 (1.8)

Source: Table 3.64, Table 3.65, Listing 10, Listing 12, Listing 14, Listing 15

Note: N = Number of treated participants in each weight band group. n (%) = Number (percent) of participants in each subcategory (with respect to the number of all treated participants in each weight band group).

a. The number (n) of participants with any Grade 5 AE, SAE, life-threatening AE, or AE that led to permanent discontinuation of study drug was identified from source listings, and the % was tabulated based on n/N for the group.

b. (≥6 to <10 kg enrollment weight band) experienced a Grade 3 SAE of gastroenteritis during Week 25.

c. (≥10 to <14 kg enrollment weight band) experienced a Grade 3 SAE of pneumonia during Week 23.

d. (≥20 to <25 kg enrollment weight band) experienced a Grade 4 SAE of DILI during Week 36 as well as non-serious AEs of Grade 4 ALT increased, Grade 3 AST increased, and Grade 1 blood bilirubin increased at the same time; all of these AEs were assessed as related to study drug and all led to permanent discontinuation of study drug. These PTs were subsequently reported at various times during follow-up, including Grade 4 AST increased.

Table 36. Most Common AEs (Reported for 3 or More Participants Total) through week 48, by enrolment Weight Band (All Treated Population)

Preferred Term	≥6 to <10 kg (N=9) n (%)	≥10 to <14 kg (N=12) n (%)	≥14 to <20 kg (N=15) n (%)	≥20 to <25 kg (N=10) n (%)	≥25 kg (N=11) n (%)	Total (N=57) n (%)
GFR decreased	6 (66.7)	5 (41.7)	9 (60.0)	9 (90.0)	7 (63.6)	36 (63.2)
Blood creatinine increased	4 (44.4)	6 (50.0)	6 (40.0)	5 (50.0)	5 (45.5)	26 (45.6)
ALT increased	2 (22.2)	3 (25.0)	8 (53.3)	7 (70.0)	1 (9.1)	21 (36.8)
Cough	6 (66.7)	6 (50.0)	5 (33.3)	1 (10.0)	2 (18.2)	20 (35.1)
AST increased	0	2 (16.7)	5 (33.3)	4 (40.0)	2 (18.2)	13 (22.8)
Rhinorrhoea	4 (44.4)	3 (25.0)	3 (20.0)	1 (10.0)	2 (18.2)	13 (22.8)
Blood cholesterol increased	1 (11.1)	0	3 (20.0)	3 (30.0)	2 (18.2)	9 (15.8)
Decreased appetite	4 (44.4)	2 (16.7)	1 (6.7)	0	0	7 (12.3)
Neutropenia	1 (11.1)	1 (8.3)	2 (13.3)	0	3 (27.3)	7 (12.3)
Pyrexia	2 (22.2)	2 (16.7)	2 (13.3)	1 (10.0)	0	7 (12.3)
Nasal congestion	2 (22.2)	2 (16.7)	1 (6.7)	1 (10.0)	0	6 (10.5)
Underweight	2 (22.2)	0	4 (26.7)	0	0	6 (10.5)
URTI	2 (22.2)	3 (25.0)	0	1 (10.0)	0	6 (10.5)
LDL increased	1 (11.1)	0	1 (6.7)	2 (20.0)	1 (9.1)	5 (8.8)
Nasopharyngitis	1 (11.1)	0	3 (20.0)	1 (10.0)	0	5 (8.8)
Productive cough	1 (11.1)	1 (8.3)	2 (13.3)	1 (10.0)	0	5 (8.8)
COVID-19	1 (11.1)	1 (8.3)	0	1 (10.0)	1 (9.1)	4 (7.0)
Haemoglobin decreased	2 (22.2)	0	0	1 (10.0)	1 (9.1)	4 (7.0)
Neutrophil count decreased	1 (11.1)	1 (8.3)	2 (13.3)	0	0	4 (7.0)
Blood bilirubin increased	0	0	2 (13.3)	1 (10.0)	0	3 (5.3)
Creatinine renal clearance decreased[a]	0	3 (25.0)	0	0	0	3 (5.3)
Headache	0	0	2 (13.3)	0	1 (9.1)	3 (5.3)
Tonsillitis	1 (11.1)	0	2 (13.3)	0	0	3 (5.3)
Vomiting	1 (11.1)	1 (8.3)	0	1 (10.0)	0	3 (5.3)

Source: IMPAACT 2019 CSR Table 3.68, Table 3.69, Table 3.70, Table 3.71, Table 3.72, Table 3.73

Note: The End of Study data were compared with Week 48 data presented in this table, and there is no change from Week 48 to End of Study in the n (%) of each PT for any weight band or the total, and there were no additional PTs meeting the cut-off of being reported for 3 or more total participants (Source: IMPAACT 2019 CSR Table 3.104, Table 3.105, Table 3.106, Table 3.107, Table 3.108, Table 3.109).

Note: N = Number of treated participants in each weight band group. n (%) = Number (percent) of participants in each subcategory (with respect to the number of all treated participants in each weight band group).

Note: Included AEs started between treatment initiation and either the end of the Week 48 analysis visit window or the end of treatment date +1, whichever was earlier.

Note: Participants may have reported more than 1 event within each PT.

Note: PTs are sorted according to highest frequency for the Total group, then alphabetically.

a. For 3 participants, decreases in eGFR identified per DAIDS grading criteria were reported under the PT of "creatinine renal clearance decreased" instead of "glomerular filtration rate decreased".

For both enrolment weight bands and actual weight bands (at time of event), most events were reported from the Investigations System Organ Class (SOC), with the most commonly reported PTs being GFR decreased, blood creatinine increased and ALT increased.

Overall, the reported TEAEs reflect what is expected for the target population, concomitant conditions and known safety profile of the SEs.

AEs such as cough, rhinorrhoea, decreased appetite, pyrexia, nasal congestion, and neutrophil count decreased were predominant amongst younger children (<6 years) with lower body weight through Week 48, as might be expected in this population. A higher proportion of older children (≥6 to <12 years) with higher body weight experienced AST increased, blood creatinine increased, GFR decreased, and blood cholesterol increased. Due to the small number of participants, any differences between age groups should be interpreted with caution. Rigorous comparison of the frequency of reporting of PTs per enrolment weight band versus actual weight bands is hampered by small absolute numbers.

Throughout the study, the majority (three quarters) of participants experienced AEs with a maximum severity of Grade 1 or Grade 2. There was a higher proportion of participants (n=15; 26.3%) with ≥Grade 3 AEs at Week 48, compared to Week 24 (n=8; 14.0%). These events were spread amongst enrolment weight bands, but all occurred in participants receiving the DT formulation. No Grade 5 (fatal) events were reported during the study.

The interpretation of drug-relatedness in the course of the study is confounded by the open-label design and such assignment should be interpreted with caution.

Although the proportion of participants experiencing any AE was similar between the 2 drug formulation groups, the pattern of the specific AE PTs varied between the two groups, with many more PTs reported across the group of participants taking the DT formulation compared with those taking the Tablet formulation. Rigorous comparison of the safety data collected for the tablet and DT formulations is precluded by relatively low numbers (n=11 in the tablet group). In any case, the weight-based dosing regimen means their use and thus safety profile correlates with weight (and, therefore, age for the most part) in the IMPAACT 2019 study.

No new safety issues arise from the additional data collected in 10 patients who continued on treatment to 60 weeks.

Serious adverse event/deaths/other significant events

No deaths or life-threatening events occurred during IMPAACT 2019.

Across the 57 participants, a total of 3 participants each experienced 1 non-fatal SAE. There were 2 SAEs reported from the Infections and infestations SOC (gastroenteritis and pneumonia, both reported within the Week 24 analysis window) and 1 SAE reported from the Hepatobiliary disorders SOC (DILI, reported after Week 24, within the Week 48 analysis window), which was considered drug-related by the site investigator and led to withdrawal from study treatment. No SAEs were reported after Week 48 through End of Study.

Adverse Events of Special Interest (AESI) have previously been determined for DTG (gastrointestinal disorders, renal disorders, hepatobiliary disorders), ABC (suspected ABC hypersensitivity), and 3TC (psychiatric disorders, rhabdomyolysis and myositis, serious rash and/or hypersensitivity); as well as incidence of Immune Reconstitution Inflammatory Syndrome (IRIS) for DTG/ABC/3TC. During this study, there were no unexpected safety findings related to identified DTG/ABC/3TC FDC-related risks of IRIS events, hypersensitivity and rash, psychiatric disorders, gastrointestinal disorders, and musculoskeletal disorders.

Hepatobiliary-related events were consistent with product labelling; one case of DILI reported during the IMPAACT 2019 study is the first in the DTG or DTG/ABC/3TC development programs for a paediatric participant, although DILI cases have previously been reported in adults:

The majority of reported renal-related events were apparently due to the way creatinine and eGFR grading was performed (see **Laboratory findings**).

Laboratory findings

Liver parameters

Although post-baseline increases in ALT or AST were frequently reported (36.8% and 22.8% of participants, respectively), these were mostly Grade 1 and generally resolved on continued treatment:

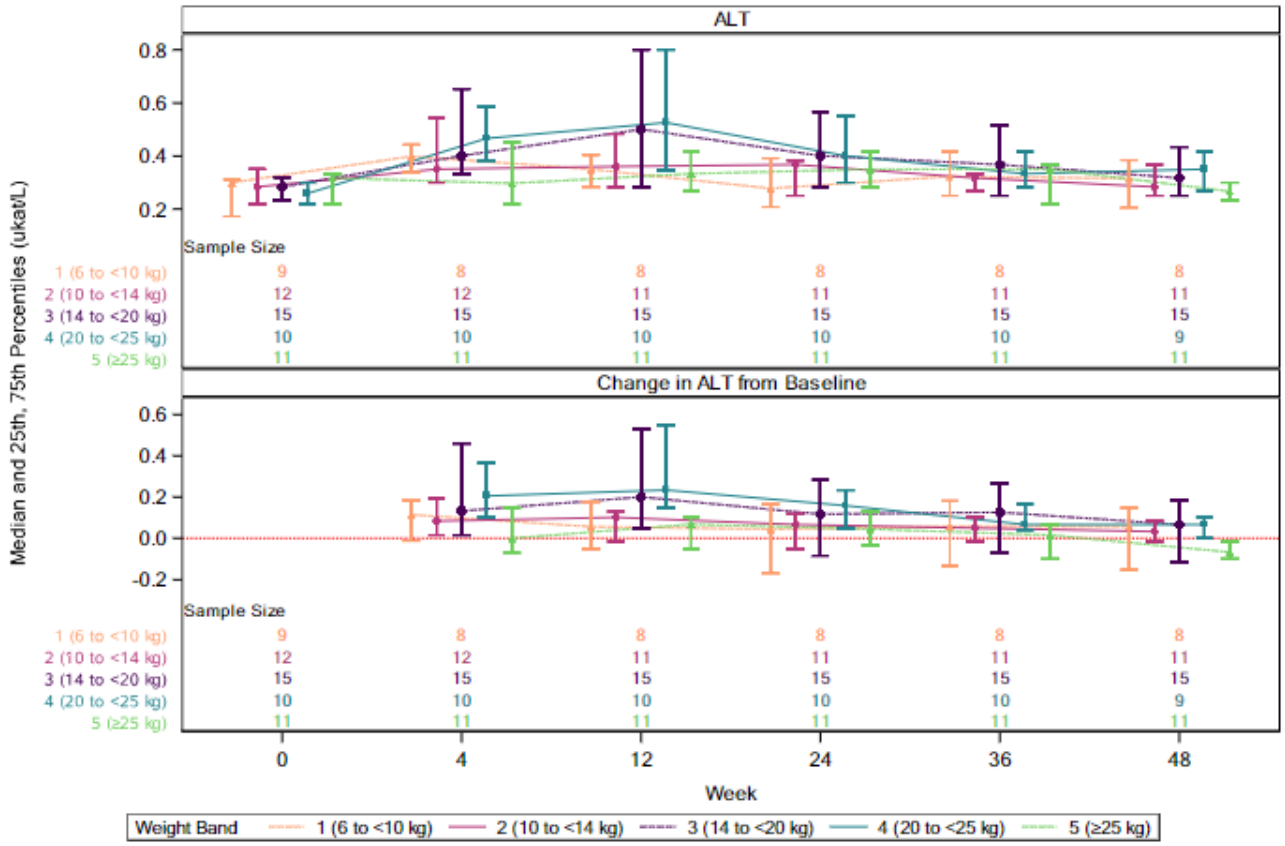


Figure 16. Median (Q1, Q3) ALT by Visit and Weight Band All Treated Population

Only 3 participants experienced ≥Grade 2 severity AEs: 1 participant with Grade 2 ALT increased; 1 participant with Grade 3 ALT increased; and 1 participant with Grade 4 DILI and associated Grade 4 increases in ALT and AST (see **Serious adverse event/deaths/other significant events** above).

Renal parameters

A notable finding was the high proportion of participants reporting creatinine and eGFR abnormalities, which were mostly due to a relative change from baseline of creatinine or creatinine-derived eGFR reported according to the relevant DAIDs grade. Most changes in creatinine or eGFR reported in this study had a maximum severity of Grade 2 based on DAIDS grading criteria. There were 8 participants who reported ≥Grade 3 decreases in eGFR with (5) or without (3) concurrent ≥Grade 3 increases in creatinine based on change from baseline. However, these reflected mainly a normalisation of a previously higher-than-normal eGFR, and the absolute laboratory-measured values for creatinine and eGFR were actually normal in 6/8 cases. Two participants experienced abnormal absolute eGFR values categorised as Grade 2. Review of the case details reveals that one of these participants experienced a concomitant event (pneumonia managed with gentamycin and ampicillin) that clearly confounds the assessment of causality for DTG/ABC/3TC. These participants did not have clinical symptoms indicating renal dysfunction/toxicity and no changes to study drug were made.

The small mean and median increases in creatinine (3.27 µmol/L [IQR -2.65 to 8.00 µmol/L]), with associated mean and median decreases in eGFR, observed across all weight bands at Week 48 were within the range seen in previous studies in adults and in children receiving DTG-containing regimens in a previous paediatric study (IMPAACT P1093):

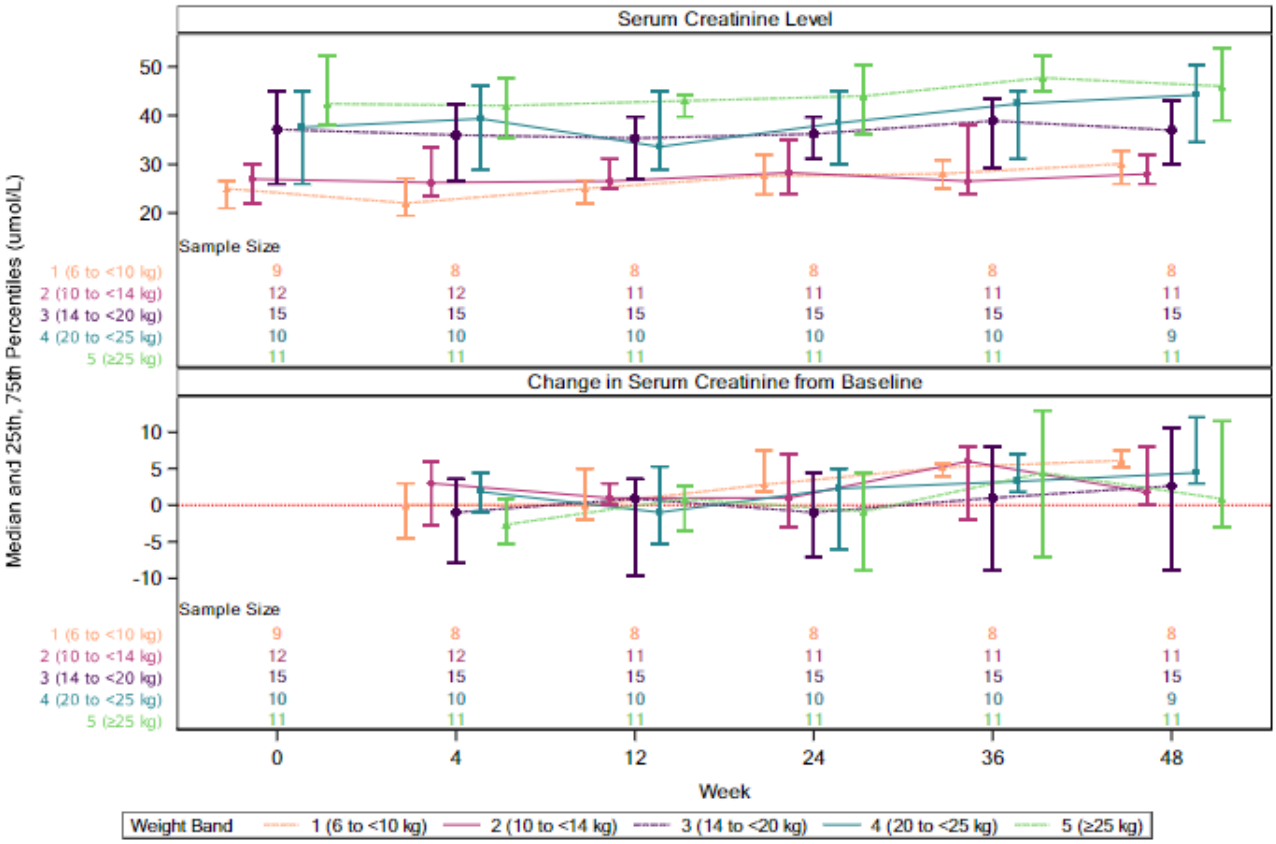


Figure 17. Median (Q1, Q3) Serum Creatinine by Visit and Weight Band All Treated Population

Although in IMPAACT P1093 and adult studies the changes in creatinine were usually apparent by Week 4 and stabilized thereafter, in this study, early changes in serum creatinine were less evident and changes in creatinine were more variable over time. Based on current product labelling for DTG-containing regimens, small mean increases in serum creatinine are expected due to non-pathological inhibition of OCT2 in the proximal renal tubules, which typically become evident early after initiation of treatment with study drug (within the first few weeks) and then remain stable over time. This increase in serum creatinine conversely leads to small decreases in the creatinine-derived creatinine clearance. The Applicant asserts that substantial variability in the observed creatinine values within the normal range is expected in the studied paediatric population from ≥6 k to <14 kg, and is most likely due to factors such as the growth, local creatinine assay variability, maturation or inhibition of transporters (e.g., OCT2), and the fact that creatinine levels vary throughout the day and following intake of food (e.g., after a recent meat meal). Thus, in addition to any potential OCT2 inhibition from DTG, children may experience larger change from baseline in creatinine and creatinine-based eGFR over 48 weeks of treatment compared with adults due to their growth and development.

Haematology parameters

Through the End of Study, there were 10 participants who experienced AEs related to decreased ANC (reported as the PT of either "neutropenia" or "neutrophil count decreased"). None of these AEs were serious or led to discontinuation of study drug. The majority of participants who experienced decreased ANC had events of Grade 1 or Grade 2 severity, while 2 participants had Grade 3 events. All the participants with neutropenia/neutrophil count decreased were of Black/African American race, which can be associated with a lower normal neutrophil count. Most of AEs related to decreased ANC occurred after 24 weeks of treatment. Time to onset for the first occurrence of low ANC decreased ranged from 85 to

337 days. At the End of Study, the events related to decreased ANC had resolved in 5 out of 10 of the participants and were ongoing in the remaining participants.

Lipid profile

AEs that were reported due to changes in lipid parameters were mostly reported in participants from higher enrolment weight bands (≥14 kg). None of the lipid-related clinical AE PTs were of ≥Grade 3 severity, serious, or considered drug-related by the site investigator. Of note, fasting was not required prior to lipid evaluations. Per the DAIDS AE grading tables, lipid values were only graded if the participant was fasting at the time of evaluation. Few participants had evaluations that were graded, and thus, the proportions of participants with abnormal (Grade 1 or higher) lipid values must be interpreted with caution. For all 4 lipid parameters, small median decreases from baseline were observed for most enrolment weight bands.

Safety in special populations

Sub-group analyses from prior adult studies did not reveal any meaningful differences in safety findings based on gender, age, or race. Safety analyses of data by gender, race, or HBV co-infection were not conducted as part of the IMPAACT 2019 analyses.

Patients with significant renal or hepatic impairment were excluded from the IMPAACT 2019 study and thus no new information is provided in this submission regarding use of Triumeq in these patient groups.

No pregnancies occurred in IMPAACT 2019 through End of Study.

No new information on the use of DTG/ABC/3TC in patients with HBV co-infection is provided in this submission.

Safety related to drug-drug interactions and other interactions

A summary of drug interactions and their impact on dosing recommendations for the DTG/ABC/3TC FDC product was previously submitted. This drug-drug interaction information applies to the DTG/ABC/3TC Tablet and DT formulations.

Safety related to medication errors

No medication errors or protocol deviations related to medication errors were reported in IMPAACT 2019.

DTG/ABC/3TC Tablets and DTG/ABC/3TC DTs are not interchangeable, as the relative bioavailability of DTG administered in the DT formulation is approximately 1.7-fold higher as compared to DTG administered in Tablets. Therefore, DTG/ABC/3TC Tablets and DTG/ABC/3TC DTs cannot be used as direct replacements. The risk of incorrect dosing to children will be minimized through use of clear instructions to indicate the weight dependent dose/number of tablets for each weight band. Furthermore, DTG/ABC/3TC DTs will be clearly marked as different from DTG/ABC/3TC Tablets.

Discontinuation due to adverse events

Two participants (1 each in the ≥6 to <10 kg and ≥10 to <14 kg enrolment weight bands) discontinued study drug and study participation during the first week due to palatability issues (see **Clinical Efficacy**

above). In addition, 1 participant discontinued study drug at Week 36 due to an AE of DILI (see **Serious adverse event/deaths/other significant events** above).

Post marketing experience

An overview was provided of the global post-marketing experience with DTG/ABC/3TC in children <12 years of age (an age threshold has been used because weight is infrequently reported in post-marketing data). As DTG/ABC/3TC (including the DT formulation) has only recently been approved for use in children weighing at least 14 kg to less than 25 kg, an overview of global post-marketing experience of DTG administered in combination with ABC and 3TC (as SEs or FDC) in children was also provided.

For Triumeq, the best estimates of total post-marketing experience, assuming all patients take a single tablet of Triumeq per day, from licensure (22 August 2014) to 31 March 2023 is estimated to be 1 401 593 patient years. There are currently no sales data available for Triumeq DTs, which are indicated in the paediatric population weighing at least 14 kg to less than 25 kg.

The GSK Safety database was searched for spontaneous and post-marketing surveillance reports involving Triumeq as a suspect drug reported through 15 May 2023. A total of 10 932 cases were retrieved cumulatively, of which 10 (received between 2016 and 2023) were identified in children <12 years of age (excluding cases where exposure to Triumeq was in utero or via breastmilk). All 10 reports were non-serious. 9 of the 10 reports occurred in countries prior to approval of Triumeq in this population and it is assumed that all the children were taking Triumeq Tablets (DTG 50 mg/ABC 600 mg/3TC 300 mg), rather than Triumeq DTs, as this formulation would not have been available at the time of the report. The remaining case involved a child (age not specified) in the United States taking Triumeq tablets for oral suspension (approved in the US in paediatric patients aged at least 3 months and weighing at least 6 kg). Overall, 5 of the 10 cases reported medication error terms or off-label use without any associated AEs, 2 cases concerned administration errors, and the remaining 3 cases concerned non-serious AEs, specifically musculoskeletal chest pain, headache, and nightmares. Nightmares and headache are described in the current product labelling for Triumeq, either with DTG/ABC/3TC FDC or the SEs. Additionally, arthralgia and myalgia are described in the current product labelling for Triumeq as uncommon adverse reactions with DTG, whilst arthralgia and muscle disorders are listed as common AEs with 3TC.

The GSK Safety database was also searched for spontaneous and post-marketing surveillance reports involving Tivicay as a suspect drug and cases were reviewed to identify those reported in children <12 years of age and where both ABC and 3TC (given either as SEs or FDC) were reported as co-suspect drugs. A total of 13 201 cases were retrieved cumulatively for Tivicay, 7 of which (received between 2019 and 2022) were identified in children <12 years of age (excluding cases where exposure to Tivicay was in utero or via breastmilk), and where both ABC and 3TC were reported as co-suspect medication, and all 3 products were taken at the same time. Two of the 7 cases reported off-label use of Tivicay in an unapproved age group. Both of these reports were non-serious and concerned the use of Tivicay with ABC and 3TC (given as Kivexa in 1 case) in 4-year-old males. Only 1 of the 2 cases was associated with AEs (unspecified behavioral issues).

The other 5 cases reported clinical AEs following exposure to Tivicay plus Kivexa, or with ABC and 3TC given as the SEs. In 3 of these 5 cases, the reported AEs were non-serious and included abnormal sweat odor, constipation, and headache and sleep problems. Headache and insomnia are known adverse drug reactions for Tivicay and Kivexa, whilst abnormal sweat odor and constipation are not recognized adverse drug reactions with either of these products. Two of these 3 cases did not provide sufficient clinical context to be able to assess causality, whilst in the third case the event (constipation) was resolving on continued treatment with Tivicay and Kivexa.

The other 2 cases reported SAEs. Review of both cases identifies a plausible alternative cause of the reported SAE in the first instance (vomiting) and unclear causality in the second (myopathy). Vomiting is already listed as an ADR for DTG and 3TC Myalgia is already listed as an ADR for DTG and muscle disorders for 3TC.

In summary, post-marketing experience with the DTG/ABC/3TC FDC in children is limited and does not add meaningfully to the benefit risk assessment. Post-marketing reports concerning co-administration of the relevant Ses in children are sparse. Notwithstanding the known problem with under-reporting in the post-marketing setting, the reviewed reports do not raise any new safety issues pertinent to the FDC.

Literature

Review of the literature did not identify any published articles relating to the safety of Triumeq in young children beyond the conference abstracts related to IMPAACT 2019.

A brief summary of publications including safety information regarding use of DTG in combination with both ABC and 3TC in children <12 years of age was provided by the Applicant. Review of the publications raises no new safety issues pertinent to the benefit-risk profile or safe use of the FDC in the proposed paediatric population weighing at last 6 kg.

2.4.1. Discussion on clinical safety

The safety database provided from the IMPAACT 2019 is modest (55 participants completing 48 weeksof study treatment). At the time of assessment of the original Paediatric Investigation Plan, a waiver for the development of Triumeq in paediatric patients <2 years of age was agreed on the grounds that the specific medicinal product did not represent a significant therapeutic benefit over existing treatments. However, in view of the recommendations of most guidelines of this FDC as a first line regimen for adult and children, the Applicant permitted enrolment <2 years of age into the IMPAACT 2019 study (a reasonable approach), and indeed 8 of the 9 participants enrolled in the lowest weight band were <2 years of age (median 1.35; Q1,Q3 1.05, 1.91; Min, Max 0.98, 2.02 years) but still largely towards the upper end of the weight band (median 9.2; Q1, Q3 8.45, 9.51; Min, Max, 8.15, 9.58). Thus, there are no clinical data for the FDC available in patients aged <1 year or weighing <8 kg.

Reassuringly, no new safety issues for DTG/ABC/3TC FDC were identified in these paediatric participants that had not been previously observed in adults or for the SEs in a paediatric population. The nature of AEs reported and timing of reporting were consistent with the established safety profile of DTG/ABC/3TC and are reflective of the population under study. There were few participants in any weight band with a drug-related AE that was either ≥Grade 3 or serious. A single participant experienced an SAE (DILI) that led to permanent discontinuation of study drug. The majority of observed reports of AEs related to GFR decreased, creatinine renal clearance decreased, and blood creatinine increased appear to be an artefact of the use of the DAIDS grading system for creatinine and eGFR, and there was no true indication of clinical renal toxicity. There were no life-threatening or fatal AEs.

Only three ART-naïve participants were recruited, all in the lowest weight band (≥6 to <10 kg). Status in terms of being ART-naïve or experienced is not anticipated to confer a meaningful difference in clinical safety profile.

Patients with significant renal, liver or autoimmune dysfunction or concurrent malignancy, active tuberculosis or hepatitis B infection were excluded from the study. This is consistent with the registrational studies for Triumeq in adults.

Whilst no dosage adjustment of DTG or ABC is necessary in patients with renal impairment, a dose reduction of 3TC is required due to decreased clearance. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia). DTG/ABC/3TC dispersible tablets are therefore not recommended for use in adolescents or children with a creatinine clearance less than 50 mL/min. This is already reflected in the authorised Triumeq DT Product Information. Based on historical PK data, DTG/ABC/3TC dispersible tablets are not recommended in patients with moderate or severe hepatic impairment. This is already reflected in the authorised Triumeq DT Product Information.

Patients with pre-existing liver dysfunction, including chronic active hepatitis B infection, have an increased risk of severe and potentially fatal liver adverse reactions during combination antiretroviral therapy and should be monitored according to standard practice according to the authorised Triumeq DT Product Information.

To some extent, clinical safety must be partially extrapolated from the SEs as already authorised for use in paediatric patients, particularly with regards to patients aged <1 year or weighing <8 kg, who are not represented in the IMPAACT 2019 study. This approach reasonable since the safety profile of Triumeq is expected to be consistent with the safety profile of the individual components used at comparable exposures. The population reflected by the proposed indication is qualified by weight but not age, at a lowest weight cut-off of 6 kg being equivalent to between 6 weeks and 6 months for girls, or 5 weeks and 5 months for boys, using WHO standard weight-for-age 97th and 3rd centiles. In other words, the lowest weight limit proposed for Triumeq reflects fairly well the youngest/ lightest paediatric population in which the single entities ABC and 3TC already have authorised indications (≥3 months of age). As such, the safety profiles previously established for the SEs can be reasonably considered to predict clinical safety of the FDC in the youngest/lightest paediatric subgroups. Indeed, there is no existing evidence to suggest that these should differ with administration as part of an FDC.

2.4.2. Conclusions on clinical safety

The paediatric safety data presented from the now-completed IMPAACT 2019 study are reassuring and in line with what has been observed for the FDC in adults. No new safety issues have been identified.

Given the modest safety database for the FDC provided by the IMPAACT 2019 study, safety must be to some extent be extrapolated from the SEs as already authorised for use in paediatric patients. This approach reasonable since the safety profile of Triumeq is expected to be consistent with the safety profile of the individual components used at comparable exposures. To date, no patient younger than ~5 months appears to have been treated with 15 mg DTG as a single entity in a clinical study. Furthermore, the oral solutions available for the separate entities ABC and 3TC are authorised in the EU only down to 3 months of age, below which there are insufficient data to support dosing recommendations. Thus, clinical safety of Triumeq below 3 months of age is supported neither by clinical safety data for the FDC, nor by extrapolation of clinical safety of the single entities.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP 22 version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 22 is acceptable.

The CHMP endorsed the Risk Management Plan version 22 with the following content:

Safety concerns

Summary of safety concerns The safety profile of DTG taken in combination with ABC and 3TC is consistent with the safety profiles of the single agents, and no additional risks or safety issues due to combination therapy have been identified.	
Important identified risks	**ABC** • Hypersensitivity reactions
Important potential risks	**DTG** • Neural tube defects
Missing information	• Use in pregnancy/ breastfeeding

Pharmacovigilance plan

Part II.1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry Ongoing	Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnancy NTDs	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR is presented in the PBRER.	-
Study 208613 DOLOMITE EPPICC Ongoing	Assess "real-world" maternal and foetal outcomes following DTG use during pregnancy and to describe patterns of DTG utilization using data from the EPPICC in order to increase knowledge of the safety profile of DTG in	Use in pregnancy, NTDs: DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.	Protocol effective date	14 February 2018
			Study start	08 March 2018

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	pregnancy. DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.		Final Report	June 2023
Study 208759 DOLOMITE NEAT ID Network Ongoing	To assess the safety and effectiveness of DTG in pregnancy in the NEAT-ID network of approximately 40 sites across Europe	Use in pregnancy, NTDs DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.	Protocol effective date	13 November 2018
			Study start	01 March 2019 or after EC approval
			Expected Final Report	October 2023

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern (risk/ missing information)	Risk minimization measures	Pharmacovigilance activities
Hypersensitivity reactions (Important identified risk for ABC)	**Routine risk minimization measures:** Sections 4.3, 4.4 and 4.8 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** Each pack of TRIUMEQ medication contains an Alert Card for patients and information on the risk of HSR with ABC in the Patient Information Leaflet.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Neural tube defects (Important potential risk for DTG)	**Routine risk minimization measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** Direct health care professional communication completed in 2018	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Target Follow-up questionnaire Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy **Additional pharmacovigilance activities:** Review of the APR Study 208613 -DOLOMITE EPPICC Study 208759- DOLOMITE NEAT ID Network Study

Safety concern (risk/ missing information)	Risk minimization measures	Pharmacovigilance activities
Pregnant/ breastfeeding women (missing information)	**Routine risk minimization measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Review of the APR Study 208613 -DOLOMITE EPPICC Study 208759- DOLOMITE NEAT ID Network Study

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The proposed changes are minor and not considered to significantly affect the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in paediatric patients weighing at least 6 kg.

3.1.2. Available therapies and unmet medical need

HIV-1 infection remains a major public health concern. In a 2020 report, the World Health Organization (WHO) estimated that in 2019 there were 1.7 million [1.2 million-2.2 million] new HIV-1 infections worldwide, of which 150,000 [94,000-240,000] were in children less than 15 years of age. Approximately 84% of child infections occurred in sub-Saharan Africa. HIV-infected children may have more rapid disease progression and accelerated damage of the developing immune system compared to adults, with higher viral loads and less effective immunological responses to HIV-1 infection than their adult counterparts.

Treatment of HIV requires use of combination antiretroviral therapy. Treatment options in children are more limited compared to adults. The most commonly used guidelines are those developed by the World Health Organization (WHO) [World Health Organization, 2019], the European AIDS Clinical Society (EACS) [EACS, 2019], the Department of Health and Human Services (DHHS) in the USA [Department of Health and Human Services, 2019] and the PENTA (for use in children and adolescents) [PENTA2019].

Single-tablet, once daily regimens provide several advantages to people living with HIV because having a lower pill burden is associated with improved adherence, lower healthcare costs, increased viral suppression, and higher patient satisfaction. There is an ongoing need for age-appropriate treatment options for children living with HIV.

3.1.3. Main clinical studies

3.2. Favourable effects

The efficacy of Triumeq have been established in adult and adolescent patients ≥40 kg. The efficacy demonstration in children is based on PK bridging, whereby efficacy is inferred through achievement of exposures similar to those that have been shown to be effective in adults.

Given that exposure achieved in paediatric patients appears comparable to that shown to be effective in adults, Triumeq is expected to be effective in the treatment of HIV-1 infection in paediatric patients.

Both Tablets and DTs were considered overall to be tolerable and palatable in the course of the IMPAACT 2019 study, with no major issues identified across any of the age or weight sub-groups.

3.3. Uncertainties and limitations about favourable effects

The efficacy demonstration in children is based on PK bridging, whereby efficacy is inferred through achievement of exposures similar to those that have been shown to be effective in adults. The clinical efficacy data generated in paediatric study participants is not intended to permit independent conclusions on clinical efficacy in this population. This aligns with current EMA guidance and regulatory precedent.

The PK data from 55 patients (35 rich PK sampling and 20 with sparse PK sampling), including 21 patients in the 6-10 and 10-14kg weight bands are considered sufficient. The provided popPK analysis as well as the observed (NCA) PK data generally support the PK bridge.

The observed (NCA) and simulated exposures in the 6-10kg and 10-14 kg weight bands indicates that the proposed posology in these weight bands are overall acceptable. However, the PopPK model(s) have limitations and it is not acceptable for support dosing recommendations in patients younger than 3 months. For that reason, a 3-month age restriction is added to the indication in addition to the weight.

3.4. Unfavourable effects

The safety profile of Triumeq is expected to be consistent with the safety profile of the individual components used in children at their licensed doses. The safety profiles of the individual components and FDCs are already described in approved product labelling.

Predicted exposures for the FDC appear to be comparable to predicted paediatric exposures of the individual components at approved doses and are also comparable to observed data for the FDC in adults.

No new safety issues were identified in the IMPAACT 2019 single-arm, open-label study of 57 paediatric participants with HIV-1 infection weighing at least 6 kg. TEAEs were generally mild and self-resolving and

did not lead to discontinuation of study drug. The reported preferred terms reflect the target population and expected concurrent conditions.

One case of DILI reported during the IMPAACT 2019 study is the first in the DTG or DTG/ABC/3TC development programs for a paediatric participant, although DILI cases have previously been reported in adults.

3.5. Uncertainties and limitations about unfavourable effects

The safety database provided from the IMPAACT 2019 is modest (57 participants). There are no clinical data for the FDC available in patients aged <1 year or weighing <8 kg. To some extent, clinical safety must be partially extrapolated from the SEs as already authorised for use in paediatric patients. This approach is reasonable since the safety profile of Triumeq is expected to be consistent with the safety profile of the individual components used at comparable exposures.

The lightest patient in IMPAACT 2019 had a body weight of 8 kg whereas the indication covers body weight down to 6 kg. The observed (NCA) PK data is therefore limited to 8 kg. However, PopPK-based simulations were provided and included simulation of PK exposure down to 6 kg for all entities which support that a positive B/R can be concluded down to 6 kg.

The ABC dose in Triumeq is higher than in a corresponding single entity product. The Applicant refers to the observed ABC PK data in IMPAACT 2019 and the comparison with previous paediatric PK data and the adult reference range. It is agreed that despite the higher ABC dose in Triumeq compared to Ziagen, the ABC PK exposure falls within an acceptable range and thus there is support for paediatric clinical safety of the FDC from the ABC single entity.

Only three ART-naïve participants were recruited, all in the lowest weight band (≥6 to <10 kg). Status in terms of being ART-naïve or experienced is not anticipated to confer a meaningful difference in terms of clinical safety profile.

Patients with significant renal, liver or autoimmune dysfunction or concurrent malignancy, active tuberculosis or hepatitis B infection were excluded from the IMPAACT 2019 study. This is consistent with the registrational studies for Triumeq in adults. As per the already-authorised Triumeq DT Product Information, DTG/ABC/3TC dispersible tablets are not recommended for use in adolescents or children with a creatinine clearance less than 50 mL/min or with moderate or severe hepatic impairment, as no safety data are available. Furthermore, a warning exists regarding the possible increased risk of severe and potentially fatal liver adverse reactions during combination antiretroviral therapy in patients with pre-existing liver dysfunction, including chronic active hepatitis B infection, who should be monitored according to standard practice.

3.6. Effects Table

Table 37. Triumeq -for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infected children of at least 3 months of age and weighing at least 6 kg to less than 25 kg.

Favourable effects table in paediatric patients.

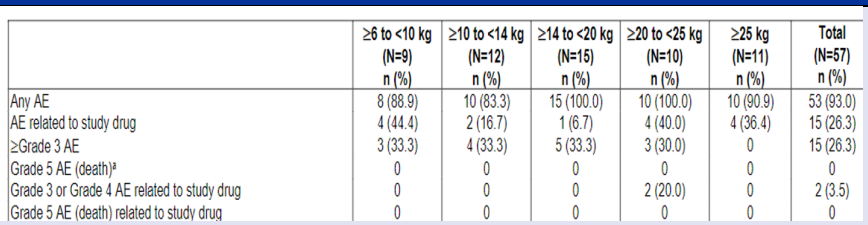
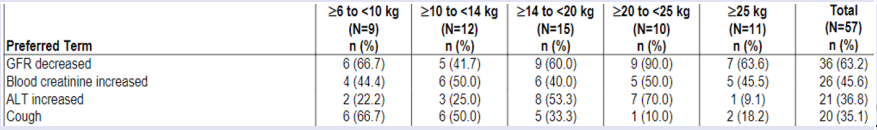
Favourable effects Triumeq DTG/ABC/3TC							
		Geometric mean (%CV)			%GMR (90% CI)		
					Paediatric vs Adult[c]		
Analyte	PK Parameter	Paediatric Subjects ≥6< 10 kg (n=8)[a]	Paediatric Subjects ≥ 10 < 14 kg (n=11)[a]	Adult Target exposure[b]	≥6< 10 kg	≥ 10 < 14 kg	Uncertainties / Strength of evidence Model predicted
ABC	AUC_{tau} (h•µg /mL)	17.3 (58)	18.9 (44)	8.52 (43)	203	222	Robust paediatric PopPK models, which were developed with extensive data across different weight ranges (3.90 to 91.0 kg for DTG, 4.6 to 61.3 kg for ABC, and 5.1 to 66.4 kg for 3TC) and several different formulations (dispersible tablet, solution, tablet, and granules) across the studies (DTG (n=239 subjects from 2 studies, ABC (n=169 subjects from 6 studies), 3TC (n=209 subjects from 6 studies)) accurately able to describe and predict the observed data (≥ 6kg to <14 kg) in the IMPAACT 2019 study
	C_{max} (µg /mL)	6.04 (53)	7.42 (45)	3.85 (37)	157	193	
3TC	AUC_{tau} (h•µg /mL)	9.97 (52)	14.9 (62)	8.7 (21)	115	171	
	C_{max} (µg /mL)	2.29 (34)	2.64 (38)	1.96 (26)	117	135	
DTG	AUC_{tau} (h•µg/mL)	82.2 (33)	86.9 (25)	53.6 (27)	153	162	
	C_{max} (µg /mL)	6.79 (20)	6.63 (18)	3.67 (20)	185	181	
	C_{tau} (µg /mL)	1.08 (78)	1.35 (53)	1.11 (46)	97	122	

[a]*Paediatric Exposure: - Model Predicted individual post-hoc estimates in the ongoing IMPAACT 2019 study- (GSK Document Number GSK Document Number TMF- 16152904, Appendix Tables 6, 9, and 12)*

[b]*Adult Exposure- ABC exposure observed after 600 mg QD (n=27) dosing in adults (Study CAL102120, GSK Document Number GM2006/00416/00). 3TC exposure observed after 300 mg QD (n=60) dosing in adults (Study EPV10001, GSK Document Number RM2000/00258/01). DTG post-hoc estimates based on population pharmacokinetic analyses using data (n=449) from SPRING-1 and SPRING-2 following 50 mg Tablet dosing (GSK Document Number 2012N149219_00)*

[c]*Geometric Mean Ratio (GMR) calculation- Paediatric GM post-hoc estimates for individual weight bands compared with corresponding adult GM mean (%GMR= Paediatric GM PK parameter for particular weight band/Adult GM PK parameter*100). The 90% CI was not calculated due to difference in the subject numbers in adults and Paediatrics.*

Unfavourable effects table in paediatric patients.

Effect	Short description and percentages	Uncertainties / Strength of evidence
AEs related to the study drug		Safety sample size of IMPAACT 2019 is modest (55 participants completing 48 weeks of study treatment)
Most common AEs	 Patients < 6 years with lower bodyweight (week 48): Cough, rhinorrhoea, decreased appetite, pyrexia, nasal congestion, and neutrophil count decreased more predominant in this group of age. atients ≥6 to <12 years with higher bodyweight (week 48): AST, blood creatinine or cholesterol increased, or GFR decreased, more predominant in this group of age. 1 case of Grade 4 DILI SAE considered related to study drug was reported (that led to permanent discontinuation of study drug, and the patient recovered)	Overall, the reported TEAEs reflect what is expected for the target population, concomitant conditions and known safety profile. Due to the small number of participants, any differences between age groups should be interpreted with caution.
Deaths or life-threatening events occurred	None	

	≥6 to <10 kg (N=9) n (%)	≥10 to <14 kg (N=12) n (%)	≥14 to <20 kg (N=15) n (%)	≥20 to <25 kg (N=10) n (%)	≥25 kg (N=11) n (%)	Total (N=57) n (%)
Any AE	8 (88.9)	10 (83.3)	15 (100.0)	10 (100.0)	10 (90.9)	53 (93.0)
AE related to study drug	4 (44.4)	2 (16.7)	1 (6.7)	4 (40.0)	4 (36.4)	15 (26.3)
≥Grade 3 AE	3 (33.3)	4 (33.3)	5 (33.3)	3 (30.0)	0	15 (26.3)
Grade 5 AE (death)[a]	0	0	0	0	0	0
Grade 3 or Grade 4 AE related to study drug	0	0	0	2 (20.0)	0	2 (3.5)
Grade 5 AE (death) related to study drug	0	0	0	0	0	0

Preferred Term	≥6 to <10 kg (N=9) n (%)	≥10 to <14 kg (N=12) n (%)	≥14 to <20 kg (N=15) n (%)	≥20 to <25 kg (N=10) n (%)	≥25 kg (N=11) n (%)	Total (N=57) n (%)
GFR decreased	6 (66.7)	5 (41.7)	9 (60.0)	9 (90.0)	7 (63.6)	36 (63.2)
Blood creatinine increased	4 (44.4)	6 (50.0)	6 (40.0)	5 (50.0)	5 (45.5)	26 (45.6)
ALT increased	2 (22.2)	3 (25.0)	8 (53.3)	7 (70.0)	1 (9.1)	21 (36.8)
Cough	6 (66.7)	6 (50.0)	5 (33.3)	1 (10.0)	2 (18.2)	20 (35.1)

Abbreviations: SAE: serious adverse events, AE: adverse events, DILI: Drug-induced liver injury

Notes: Source IMPAACT 2019 CSR

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The extrapolation of efficacy adults to paediatric patients is in accordance with regulatory practice in the field of HIV. The ability to administer this first line ART regimen in a single tablet or dispersion is considered to offer an additional therapeutic advantage in reducing pill burden.

The safety profile of the FDC in paediatric patients at least 1 year of age and weighing at least 8 kg, albeit based on a limited dataset from the IMPAACT 2019 trial, appears to be consistent with the safety profile as established for the FDC in adults and for the SEs in paediatrics patients. Indeed, the safety profile of the FDC is not expected to differ significantly from administration of the SEs, which are already authorised for paediatric patients from 3 months of age.

Predicted exposures in this FDC (Tablet and DT formulations) appears comparable to predicted paediatric exposures of the individual components at approved doses and are also comparable to observed data in adults. However, due to the known impact of maturation on glucuronidation capacity for DTG an age

restriction for the use of Triumeq is needed in SmPC section 4.1 and section 4.2 for patients weighing 6-10 kg. The applicant proposed a 3-month cut-off which was justified with PK simulations in children aged 3-6 months weighing 6-10 kg which demonstrated that the DTG exposure were within an acceptable range.

3.7.2. Balance of benefits and risks

The benefit-risk profile for Triumeq for the final indication *Treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in paediatric patients of at least 3 months of age and weighing at least 6 kg* is positive.

3.8. Conclusions

The overall B/R of Triumeq is positive

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of paediatric patients from at least 3 months of age and weighting at least 6 kg to less than 25 kg for Triumeq Dispersible Tablets, based on PK, safety, and efficacy data observed in the final results of study 205860 (IMPAACT 2019) As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 22 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0038/2023and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet