15 December 2022
EMA/CHMP/915669/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of extensions of marketing authorisation and an extension of indication variation

Triumeq

International non-proprietary name: dolutegravir / abacavir / lamivudine

Procedure No. EMEA/H/C/002754/X/0101/G

Note

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

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List of abbreviations

3TC	lamivudine, GR109714
3TC TP	Lamivudine Triphosphate
ABC	abacavir, GI265235
AE	Adverse Events
AIDS	Acquired Immunodeficiency Syndrome
ANC	Absolute Neutrophil Count
API	Active Pharmaceutical Ingredient
ARROW	AntiRetroviral Research fOr Watoto
ART	Antiretroviral therapy
ARV	Antiretroviral
AT	All Treatment
AUC24h	Area under the concentration-time curve over the dosing interval
AUC0-24h	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose or over 24 hours
BID	Twice daily
BMI	Body Mass Index
BR	Background regimen
C24h	Concentration at the end of the 24-hour dosing interval
CBV TP	Carbovir Triphosphate
CD4+	Cluster of differentiation 4
Cmax	Maximum plasma concentration
CHMP	Committee for Medicinal Products for Human Use
CPP	Critical process parameter
CQA	Critical Quality Attribute
dGTP	deoxyguanosine 5′ triphosphate
DHHS	Department of Health and Human Services
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic acid
DS	Design space
DoE	Design of Experiments
DT	Dispersible tablet
DTG	dolutegravir, GSK1349572

EACS	European AIDS Clinical Society
EAIR	Exposure-Adjusted Incidence Rates
EC	European Commission
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
FCT	Film-coated tablet
FDA	Food and Drug Administration (US)
FDC	Fixed dose combination
FMEA	Failure mode effect analysis
GSK	GlaxoSmithKline
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HPLC	High performance liquid chromatoghraphy
ICH	International Council for Harmonisation
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials (Network)
INI	Integrase Inhibitor
INSTI	Integrase strand transfer inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
LC	Label Claim
LDPE	Low density polyethylene
MAH	Marketing Authorisation Holder
MRHD	Maximum Recommended Human Dose
NCA	Non-Compartmental Analysis
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NOAEL	No Observed Adverse Effect Level
PAR	Proven acceptable range
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
PENTA	Paediatric European Network for Treatment of AIDS
PI	Product Information

PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PopPK	Population PK
pp	postpartum
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
QbD	Quality by Design
QTPP	Quality Target Product Profile
RBA	Relative bioavailability
RH	Relative Humidity
RMP	Risk Management Plan
RQ	Risk Quotients
RT	Reverse Transcriptase
SE	Single entity
SGF	Simulated gastric fluid
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TCRVβ	T cell receptor Vβ
TDAR	T cell dependent antibody response
TDF	Tenofovir disoproxil fumarate
USA	United States of America
UV	Ultraviolet
VPC	Visual Predictive Checks
XRPD	X-ray powder diffraction
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

ViiV Healthcare B.V. submitted on 16 December 2021 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
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	II

Extension application to introduce a new pharmaceutical form associated with new strength (5 mg/60 mg/30 mg dispersible tablet). The new presentation is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected children weighing at least 14 kg to less than 25 kg.
This extension application is grouped with a type II variation (C.I.6.a) to include treatment of children weighing at least 25kg for the already approved film-coated tablets for Triumeq (EU/1/14/940/001-002); as a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.
The RMP (version 19) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0116/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0116/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson

PRAC Rapporteur: Martin Huber

The application was received by the EMA on	16 December 2021
The procedure started on	20 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2022

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	19 May 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	08 Aug 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	13 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	13 October 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 November 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Triumeq on	15 December 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The HIV targets the immune system and weakens people's defence against many infections and some types of cancer that people with healthy immune systems can fight off. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. Immune function is typically measured by CD4 cell count. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS), which can take many years to develop if not treated, depending on the individual. AIDS is defined by the development of certain cancers, infections or other severe long-term clinical manifestations.

2.1.2. Epidemiology

HIV infection remains a major public health concern. The World Health Organization (WHO) estimated that in 2019 there were 1.7 million [1.2 million-2.2 million] new infections worldwide. Of the 1.7 million estimated new infections, 1.5 million [1.1 million-2.0 million] were adults and 150,000 [94,000-240,000] were in children (<15 years old). Approximately 84% of child infections occurred in sub-Saharan Africa. Overall, the global incidence of new infections among children less than 15 years of age has decreased over the past decade due to improved access to mother-to-child prevention services. Of all global deaths in 2019, 95,000 [61,000–150,000] were in children less than 15 years of age.

People living with HIV who are aware of their status, take antiretroviral therapy (ART) as prescribed, and get and keep an undetectable viral load can live healthy lives with no risk of sexually transmitting HIV. Combination antiviral therapy with HIV-1 protease and reverse transcriptase inhibitors has significantly reduced AIDS-related morbidity and mortality.

2.1.3. Clinical presentation, diagnosis

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months after being infected, many are unaware of their status until the later stages. In the first few weeks after initial infection people may experience no symptoms or an influenza-like illness including fever, headache, rash, or sore throat. As the infection progressively weakens the immune system, they can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea, and cough. Without treatment, they could also develop severe illnesses such as tuberculosis, cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma.

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 infection than adults.

2.1.4. Management

Standard of care for the treatment of HIV-1 requires use of combination ART to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. The choice of the combination regimen depends on the status of the patient, particularly in terms of plasma HIV viral load, CD4 cell counts, any previous treatments and prior treatment failure/intolerance. Commonly used guidelines are those developed by the WHO, the European AIDS Clinical Society (EACS), the Department of Health and Human Services (DHHS) in the USA and the Paediatric European Network for Treatment of AIDS (PENTA), for use in children and adolescents.

Treatment options in children are more limited compared to adults.

2.2. About the product

Triumeq is currently approved for use in adults and adolescents above 12 years of age and weighing at least 40 kg for the treatment of HIV infection. Triumeq film-coated tablets contain 50 mg of dolutegravir (DTG), 600 mg of abacavir (ABC), and 300 mg of lamivudine (3TC) and are administered orally once daily as fixed drug combination (FDC) single tablet regimen.

DTG is an HIV integrase strand transfer inhibitor (INSTI) approved for use in combination with other antiretroviral (ARV) agents for treatment-naïve and treatment-experienced adults and paediatric patients living with HIV from 4 weeks of age and weighing at least 3 kg by competent authorities including the US FDA and the EMA. DTG was initially approved in 2013 and is marketed globally as Tivicay. It is currently available in both film-coated tablet (10 mg, 25 mg, and 50 mg) and dispersible tablet (5 mg) formulations.

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 over 3 months of age. ABC was initially approved in 1998 and is available globally as scored film coated tablet (300 mg) and oral solution (20 mg/mL) formulations. The tablet formulation is approved for once daily dosing in adults and paediatric patients who weigh at least 14 kg while the oral solution can be administered to paediatric patients over 3 months of age.

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 over 3 months of age. 3TC was initially approved in 1995 and is available globally as scored film-coated tablet (150 mg and 300 mg), and oral solution (10 mg/mL) formulations. The tablet formulation is approved for adult and paediatric patients who weigh at least 14 kg while the oral solution can be administered to paediatric patients from 3 months of age.

2.3. Type of Application and aspects on development

The MAH submitted an application under Article 19, Annex I and Article 7.2 of Commission Regulation (EC) No 1234/2008 to extend the Triumeq marketing authorisation with the introduction of a new pharmaceutical form associated with a new strength (5 mg/60 mg/30 mg dispersible tablet) indicated for the treatment of HIV infected children weighing at least 14 kg to less than 25 kg, grouped with a type II C.I.6.a variation to include treatment of children weighing at least 25kg for the already approved film-coated tablets.

The Triumeq PIP includes the IMPAACT 2019 study, with the aim to evaluate pharmacokinetic (PK) and safety of Triumeq for both the DT and film-coated tablet formulations in children living with HIV from 2 to less than 12 years of age. With the completion of IMPAACT 2019 (Study 205860), the MAH will fulfil its PIP obligation. However, in the interim, the PK and safety data from the previously approved weight-based doses of the single entities of Triumeq (DTG, ABC, 3TC) are used to support the submission of a Type II Variation (C.I.6.a) and a Line Extension to include the therapeutic indication in children weighing from 14 kg to <40 kg.

In addition, interim PK data from IMPAACT 2019 was also included in this submission along with modelling and simulation. Efficacy is extrapolated from adults to paediatric population based on similar exposure (PK bridge).

Each of the single entities of this FDC are already approved for use in paediatric patients weighing at least 14 kg and the proposed doses for the Triumeq formulations (DT and FCT) are the same or similar to those currently approved.

2.4. Quality aspects

2.4.1. Introduction

The additional formulation and strength of the finished product is a FDC, film-coated dispersible tablet, intended for children weighing at least 14 kg to less than 25 kg, containing 5 mg DTG, 60 mg ABC and 30 mg 3TC as active substances.

Other ingredients are:

- In the tablet core: acesulfame potassium, crospovidone, mannitol (E421), microcrystalline cellulose, povidone, silicified microcrystalline cellulose (cellulose, microcrystalline; silica, colloidal anhydrous), sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavour and sucralose.
- In the tablet coating: iron oxide yellow (E172), macrogol, polyvinyl alcohol partially hydrolysed, talc and titanium dioxide (E171).

As described in section 6.5 of the SmPC, the product is available in opaque, white high-density polyethylene (HDPE) bottles closed with polypropylene child-resistant closures, with a polyethylene faced induction heat seal liner. Each bottle contains 90 dispersible tablets and a desiccant. A plastic dosing cup with graduation marks at 5 mL intervals, between 15 mL and 40 mL, is co-packed.

2.4.2. Active Substance

The active substances dolutegravir sodium, abacavir sulphate and lamivudine are manufactured and controlled by the same manufacturers as for the approved Triumeq film-coated tablets. No new information is provided.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Triumeq dispersible tablets are yellow, biconvex, capsule shaped tablets debossed with 'SV WTU' on one side. The tablets are designed to be dispersed in 20 mL of water prior to administration. Sweetener and strawberry cream flavour are included in the formulation to enhance the palatability of the dispersion.

The tablets are packed in HDPE bottles with child-resistant closure. Each bottle contains a silica gel desiccant. To facilitate the dispersion procedure, a plastic CE marked dosing cup with graduation marks is co-packed. A Declaration of Conformity for the dosing cup in accordance with Medical Device Directive 93/42/EEC is provided. This is acceptable since the transitional provisions of the Medical Device Regulation (EU) 2017/745 are applicable.

DTG/ABC/3TC dispersible tablets, 5 mg/60 mg/30 mg, contain dolutegravir sodium, abacavir sulphate and lamivudine as active substances which are previously approved for Triumeq film-coated tablets. Dolutegravir sodium is also used for Tivicay, Juluca and Dovato film-coated tablets.

Pharmaceutical development of the finished product contains QbD elements and is also based on prior knowledge of the existing products such as Tivicay (dolutegravir sodium), Triumeq

(dolutegravir/abacavir/lamivudine), Juluca (dolutegravir/rilpivirine) and Dovato (dolutegravir/lamivudine).

The DT is a FDC, film-coated tablet. The tablets are coated with a cosmetic film-coat.

The quality target product profile (QTPP) was defined as:

Dosage Form and Strength	A dispersible tablet (tablet for oral suspension), (film coated with a colour coat) containing 5 mg dolutegravir as the sodium salt, 60mg of abacavir provided as the sulfate salt, 30mg of lamivudine provided as the free base, for once daily dosing is required. The tablet size is to be kept to a minimum in order to minimise excipients dosed to children and aid swallowing if dosed as a conventional tablet. A dosing cup (convenience kit) may be allowed as part of the patient instruction to deliver the full dose if required. A film-coated tablet is preferred to facilitate the swallowing of tablets, if taken as conventional tablets. A maximum of six tablets for older/higher weight children is required.
Finished Product Quality Criteria	The product components (active and inactive ingredients) must have the required functional characteristics. The dosage form must meet compendial and any other relevant quality standards at the time of manufacture and over the proposed shelf-life. This includes meeting the finished product critical quality attributes (CQAs) to ensure patient safety, quality and efficacy. The manufacturing process needs to be robust, reproducible and suitable for the use of dolutegravir sodium, and existing abacavir and lamivudine active substance sources. The excipients should be selected to aid patient compliance in the subject group. The tablet should contain flavour (strawberry cream) and sweeteners (sucralose and acesulfame potassium).
Drug Delivery and Release Considerations	The paediatric dispersible tablet will use the same three active substance forms that are contained in already approved products e.g., TIVICAY and TRIUMEQ Tablets. Primarily the dolutegravir, abacavir and lamivudine will be delivered as a dispersion from the dispersible tablet.
Container Closure System and Convenience kit	The finished product must be packaged in a container closure system that provides adequate protection from light and moisture vapour. The pack will be a HDPE bottle containing a desiccant (quantity of tablets in pack will be 90). A dosing cup will be supplied with the tablets for preparation of the dispersion.
Stability Criteria	Components of the finished product (active and inactive ingredients) must be physically and chemically compatible with the required functional characteristics to ensure appropriate stability of the finished product over the proposed shelf life. The product will aim to achieve a global shelf life of at least 24 months . As a minimum the product must have a commercially acceptable shelf life.

Dolutegravir sodium

- Solubility

The solubilities of non-micronised dolutegravir sodium in various media at 25°C indicates that it is very slightly soluble in simulated intestinal fluids (FaSSIF, FeSSIF) and practically insoluble in simulated gastric fluid (SGF). Based on the solubility data along with its high permeability, dolutegravir sodium is considered to be a Class 2 compound in the Biopharmaceutical Classification System.

- Particle size distribution

During the development of Tivicay film-coated tablets, 50 mg, a human in-vivo study (ING113068) was conducted to evaluate the effect of active substance particle size on pharmacokinetics.

- Solid state form

The anhydrous Form 1 is generated by the commercial dolutegravir sodium manufacturing process.

- Drug-related impurities

The impurity content of dolutegravir sodium is controlled as part of the synthetic process. As a result of the controls applied during synthesis the manufacturing process conditions consistently deliver dolutegravir sodium with low total impurity content. The level of impurities present in the drug is directly related to the drug-related impurity content in the finished product at batch release.

Abacavir sulphate

- Solubility

Solubility data indicate that abacavir sulphate is highly soluble and has been classified as a Class 3 compound in the Biopharmaceutical Classification System.

- Particle size distribution

Various particle size distributions of abacavir sulphate from the commercial manufacturing process have been used in DTG/ABC/3TC dispersible tablets during development.

- Solid state form

Crystalline abacavir sulphate is generated by the commercial process.

- Drug-related impurities

The impurity content of abacavir sulphate is controlled as part of the synthetic process. As a result of the controls applied during synthesis, the manufacturing process conditions consistently deliver abacavir sulphate with consistent total impurity content. The level of impurities present in the finished product is directly related to the drug-related impurity content in the active substance at batch release.

Lamivudine

- Solubility

Solubility data indicate that lamivudine is highly soluble and has been classified as a Class 3 compound in the Biopharmaceutical Classification System.

- Particle size distribution

Various particle size distributions of lamivudine from the commercial manufacturing process have been used in DTG/ABC/3TC dispersible tablets during development.

- Solid state form

The crystalline Form II solid state form of lamivudine is generated by the commercial process.

- Drug-related impurities

The impurity content of lamivudine is controlled as part of the synthetic process. As a result of the controls applied during synthesis, the manufacturing process conditions consistently deliver lamivudine with consistent total impurity content. The level of impurities present in the finished product is directly related to the drug-related impurity content in the active substance at batch release.

Drug : drug compatibility

Triumeq film-coated tablets 50/600/300 mg successfully combined the three active substances together.

Excipients

All excipients are well-known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. and/or USNF standards (except strawberry cream flavour and the Opadry II Yellow (85F220169) coating, for which in-house specifications were established). The list of excipients is included in section 6.1 of the SmPC. The excipients were chosen based on ICH E11 and EMA/CHMP/QWP/805880/ 2012 Rev. 2 "Guideline on pharmaceutical development of medicines for paediatric use" as well as scientific and prior knowledge.
There are no materials of human or animal origin. There are no novel excipients.

Clinical formulations

The relative bioavailability Study 200402 was performed early in development and used a higher strength tablet containing 10 mg DTG/150 mg ABC/75 mg 3TC. This formulation includes the same excipients with the difference that sucralose, acesulfame potassium and strawberry cream flavour were added extemporaneously, by incorporation into the dispersions prepared in the study.

The formulation used in relative bioavailability Study 205894 is identical in composition to the proposed commercial formulation with some minor differences which have no finished product impact.

The formulation used in food effect Study 216149 is the intended commercial formulation.

In vitro dissolution method

The development of the dissolution method has been adequately presented. The dissolution method has been demonstrated to discriminate between critical manufacturing process parameters for dolutegravir, and to adequately detect changes in the stability of DTG/ABC/3TC dispersible tablets on open/exposed storage for dolutegravir. The method is not discriminatory for abacavir or lamivudine as they dissolve very rapidly.

CQAs and manufacturing process development

The CQAs were identified.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments (DoE) to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

Design spaces (DS) have been developed for the unit operations of dolutegravir granulation and tablet compression. The DS are described as the multivariate combination of ranges for critical process parameters (CPP) and associated process parameters as applicable. The DS have been developed in conjunction with control of relevant attributes of input active substance and excipients as applicable as part of the overall control strategy. The proposed DS are sufficiently verified and accepted.

Proven Acceptable Ranges (PAR) are identified in the process description for which the operation within this range, while keeping other parameters constant, results in finished product meeting relevant quality criteria. Only a single parameter was varied while other parameters within the unit operation were maintained at target values.

Primary packaging

The primary packaging is a white HDPE bottle closed with polypropylene child-resistant closure, with a polyethylene faced induction heat seal liner. The material complies with Ph.Eur. and EC requirements. Each bottle contains a silica gel HDPE desiccant canister. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of the following main steps: manufacture of DTG granules, manufacture of compression blend, tablet compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

DS have been proposed for the following steps of the manufacturing process of the medicinal product: dolutegravir wet granulation and tablet compression.

The DS were developed at commercial scale.

PARs have been defined for the relevant manufacturing steps of the medicinal product.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space and PARs.

CPP and in-process material CQA, and their target values or ranges, were included in the process description. The in-process controls are adequate for this type of manufacturing process for dispersible tablets.

The film-coated tablets may be stored in suitable bulk containers until required for packaging. Bulk product is stored up to 25°C and is packed in the final market pack within the defined hold time. The hold time comprises part of the overall shelf-life of the finished product.

Process validation will be performed on three consecutive production scale batches. An acceptable validation scheme is provided, and the validation will be completed prior to marketing. All data met the acceptance criteria, demonstrating that the manufacturing process is robust and provide dispersible tablets with desired quality.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), assay content (HPLC), uniformity of dosage units (Ph. Eur., HPLC), drug related impurities (HPLC), fineness of dispersion (Ph. Eur.), dissolution (Ph. Eur., HPLC), disintegration (Ph. Eur.), and microbial limit test (Ph. Eur.).

The specification for DTG/ABC/3TC DTs has been defined taking into account manufacturing experience and process capability, ICH guidance, batch data and stability data. The test parameters and acceptance criteria are considered sufficiently justified. The acceptance limit for assay content at shelf-life for all three active substances was tightened during the procedure, as requested.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and

answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches and three smaller scale clinical batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH), and from one commercial scale batch of finished product stored for up to 24 months at 5°C / ambient humidity, according to the ICH guidelines, were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay content, drug-related impurities, fineness of dispersion, dissolution, disintegration, microbial limit test. The analytical procedures used are stability indicating.

The results of long-term and accelerated stability studies demonstrate chemical and physical stability. No significant changes were observed in description, fineness of dispersion, disintegration, microbial enumeration tests or for content, drug related impurities or dissolution for any of the three active components, and all results comply with specification.

Data have been generated following short-term storage of one batch under stress conditions of 50°C / ambient humidity for three months, a freeze/thaw cycle (-20°C/30°C) for one month and exposed photostability testing in accordance with ICH Q1B (Option 2). The results demonstrate the chemical and physical stability at all storage conditions. No significant changes were observed.

No significant change in the stability data for two commercial size bulk batches stored in the simulated bulk container was observed when stored for the defined hold time at 25°C/60% RH.

Simulated patient in-use stability data are presented for two batches following in-use storage. The results demonstrate chemical and physical stability when stored for up to 30 or 90 days at 30°C/75% RH when subjected to the simulated patient use regime expected for the finished product. In-use studies will be conducted on tablets at the end of the proposed shelf-life.

Dose delivery testing was conducted with the dosing cup. All individual dose delivered results met the criteria of the label claim (LC) for dolutegravir, abacavir and lamivudine. The stability of the dispersion in the dosing cup was evaluated. The data demonstrates satisfactory chemical stability of dolutegravir, abacavir and lamivudine in water.

Based on available stability data, the proposed shelf-life of 36 months and the following storage conditions as stated in the SmPC (section 6.3) are acceptable:

- Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant.

- This medicinal product does not require any special temperature storage conditions.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. No new information was presented for the three active substances. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied Quality by Design (QbD) principles in the development of the manufacturing process of the finished product. Design spaces have been proposed for two steps in the manufacture of the finished product. The design spaces have been adequately verified.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the product information. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were investigated and were controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

See clinical conclusions and recommendation(s).

2.5. Non-clinical aspects

2.5.1. Introduction

The information on non-clinical aspects is mainly derived from the submitted non-clinical overview. No new experimental studies were submitted for this procedure. Besides some general pharmacological details, only an overview/discussion on toxicological studies relevant for the juvenile age range was provided.

2.5.2. Pharmacology

Dolutegravir

DTG is a 2-metal binding integrase inhibitor (INI) developed for use in combination ART for the treatment of HIV infection. It is a potent, low nanomolar inhibitor of HIV integrase that provides the excellent antiviral activity and tolerability demonstrated for the INI class, while also offering once-daily dosing without the need for pharmacokinetic (PK) boosting.

Abacavir

ABC is a carbocyclic synthetic nucleoside analogue converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV TP), an analogue of deoxyguanosine 5′ triphosphate (dGTP). CBV TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′ hydroxyl group in the incorporated nucleotide analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Lamivudine

3TC is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC TP). The principal mode of action of 3TC TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. 3TC TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

2.5.3. Toxicology

2.5.3.1. Reproductive and developmental toxicity

Dolutegravir

In a pre-and post-natal development study, DTG was administered to female rats at doses of 5, 50 or 1000 mg/kg/day from Day 6 of gestation to Day 20 of lactation [Report 2011N121663]. Suppressed body weight gain and decreased food consumption were noted in dams (F0) in the 1000 mg/kg/day group during the lactation period, which were associated with mild decreases in body weights in the offspring in the 1000 mg/kg/day group from pre-weaning until adolescence. There were no adverse effects on maternal pregnancy, parturition, lactation, or offspring (F1) survival, behavioural or reproductive function. The no observed adverse effect level (NOAEL) for maternal reproductive function was 1000 mg/kg/day (23 times above the exposure at the maximum recommended human clinical dose (MRHD), based on exposures achieved in female rats in the 4-week toxicity study). Due to the decreased body weights of the offspring observed at higher doses, the NOAEL for pre- and post-natal development of the offspring (F1) was 50 mg/kg/day. At this dose, the exposure was 18 times above the exposure at the MRHD, extrapolated from gender mean exposures achieved in the rat 14-day toxicity study.

A juvenile toxicity study in rats was conducted with DTG at oral doses of 0.5, 2 or 75 mg/kg/day from Day 4 to 66 postpartum (pp) [Report CD2010/00023]. Two pre-weanling deaths were considered test article related at 75 mg/kg/day. Over the preweaning treatment period (Day 4 to 21 pp), mean body weight gain decreased (0.86 times control mean gain) for males and females in the 75 mg/kg/day group and the decrease persisted throughout the entire study for females during the postweaning period. There were no test article-related differences among the groups for the age at which offspring attained physical signs of sexual maturation (vaginal opening or balano-preputial skinfold separation). There were no changes considered related to DTG administration in stage-dependent evaluation of spermatogenesis. There were no new target organs identified in juveniles compared to adults. There were no test article-related effects on T cell dependent antibody response (TDAR) measured on Day 67, and no effects on lymphocyte subsets (T cells, both CD4 and CD8 subsets, and B cells) and CD4 or CD8 T cell receptor Vβ (TCRVβ) usage in peripheral blood. Therefore, the NOAEL in juvenile rats was 2 mg/kg/day (Day 32 pp gender mean AUC0-24 = 90ug.h/mL and Cmax = 7.6ug/mL), corresponding to a Cmax-based margin of ~3.2 times, based on a human adult dose of 50mg.

Abacavir

At a dose of 500 mg/kg/day, ABC sulfate was toxic to the F0 parental female rats, causing transient decreases in body weight during treatment, and was associated with an increase in stillbirths. In addition, reductions in body weight were recorded in both male and female F1 offspring during lactation and throughout the remainder of post-natal life, through mating to birth of the F2 litters [Report RD1997/04208]. No other adverse effects on the reproductive performance of the F0 parental females were observed, and the survival indices, reproductive performance of the F1 generation and survival of the F2 offspring were normal.

In a study in juvenile rats, brain weight (absolute and relative to body weight) was reduced in females at base 120 mg/kg/day, and in males and females at 360 mg/kg/day. This remained apparent at 360 mg/kg/day after a recovery period. Mortalities and reductions in body weight and body weight gain were observed at 120 and/or 360 mg/kg/day [Report RD1997/04060]. The general appearance of the affected animals was similar to that of controls. Brain growth can be influenced in rats during the first 3 months of life by factors which restrict body growth. Thus, in studies of 4 to 13 weeks duration normal brain weight may not be achieved [Greaves, 1990]. The histopathologic findings were consistent with reduced brain growth subsequent to malnutrition during the critical period of juvenile development. There was no morphologic evidence of a direct toxic effect of the drug on the developing brain. The pattern of brain and body weight changes was characteristic of under-nutrition, such as might be induced by reduced suckling during the critical period of brain growth [West, 1976; Dobbing, 1979; Greaves, 1992b; Okamura, 1994; Rosso, 1997].

Lamivudine

In a combined peri-/post-natal and juvenile toxicity study in rats, mated females received 3TC at 90, 450 or 2000 mg/kg twice daily from Day 17 of pregnancy until post-natal Day 22. Two male and female offspring from each dam received a single daily dose of 3TC orally at 90, 450 or 2000 mg/kg/day from Litter Day 3 until Litter Day 43. No treatment-related effects were observed on gestation length, gestation index, the number of offspring born, the proportion of male offspring, birth index, viability index or weaning/lactation index [Report WPT/93/165]. Most dams receiving 4000 mg/kg/day showed a swollen/reddened anus/rectum during the lactation period, which correlated with histological inflammatory changes at the ano-rectal junction. An increased incidence of swollen/reddened anus/rectum was also observed in some offspring receiving 2000 mg/kg/day, with similar histological changes to those seen in the dams. These changes, together with slight diffuse epithelial hyperplasia in the cecum of several dams and offspring at the high dose levels, were attributed to the prolonged exposure to large concentrations of unchanged 3TC in the gastrointestinal tract, resulting in typical responses to an irritant material. Similar cecal changes were also recorded in the 6-month oral toxicity study in the rat. Haematological changes consistent with a mild macrocytic anaemia, as seen in the adult repeat dose rat studies, were noted in the juvenile rats treated with up to 2000 mg/kg/day 3TC. A statistically significant reduction in testis weight was observed in juveniles at this dose level. Histological examination of the testes revealed slight to moderate dilatation of the seminiferous tubules in several high dose males (8 out of 25). There was no evidence of morphological abnormality other than slight compression of the germinal epithelium. None of the other toxicity studies conducted with 3TC using adult rats and dogs revealed testicular effects. Similarly, no effects were noted in a fertility study in the rat. The toxicity would therefore appear specific to the developing/immature testis. The no effect level for the testicular effects was considered to be the intermediate dose level of 450 mg/kg/day (around 80 times above human exposure based on Cmax).

2.5.3.2. Immunotoxicity

Dolutegravir

A concern for potential immunotoxicity was theorized for juveniles based on a publication demonstrating that two HIV integrase inhibitor compounds (p8 [5CITEP] and p10 [L-708,906]) have activity on recombination activating gene (RAG1/2) and therefore may affect T and B cell repertoire development [Melek, 2002]. To address the potential effects of DTG on RAG1/2, immunotoxicity endpoints (TDAR, immunophenotyping and TCRVβ usage) were added to the definitive rat juvenile toxicity study. There were no test article-related effects on immunologic competence as measured by TDAR, and no effects on lymphocyte subset counts (T cells, both CD4 and CD8 subsets, and B cells) and CD4 or CD8 T cell receptor Vβ usage in peripheral blood. Histopathology of immunologic organs (spleen, thymus, lymph nodes) and haematology evaluation revealed no effects. The NOAEL for immunotoxicity endpoints was 75 mg/kg/day. These results provided a robust non-clinical assessment of potential development of immune-toxicologic effects and suggested no unusual drug-specific risk of developmental immunotoxicity in paediatric patients.

2.5.4. Ecotoxicity/environmental risk assessment

The main route of HIV infection in paediatric cases is mother-to-child transmission. Based on a review of HIV/AIDS surveillance data for Europe conducted in 2020, the number of new diagnoses in children infected through this route decreased by 35% from 576 cases in 2010 to 373 cases in 2019, representing 1.2% of all new HIV diagnoses in 2010 and 0.8% in 2019 [WHO 2020], but using only one tenth of the normal adult dose. Considering the decreasing trend in cases and paediatric diagnoses at less than 1% of the total diagnoses (approximately between 136000 and 137000 new infections in the WHO European region in 2019 [WHO 2020]), the population of paediatric patients that could potentially be prescribed under the DTG/ABC/3TC paediatric regimen would be insignificant in comparison to adult population numbers in Europe.

Therefore, the increase in predicted environmental concentration (PECs) from the proposed increase in patient population was considered negligible and conclusions of the Triumeq environmental risk assessment (ERA) from 2017 were still considered relevant.

Table 1. Summary of main study results for Dolutegravir

Substance (INN/Invented Name): Dolutegravir			
CAS-number (if available): Not applicable			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log K_{OW}	OECD TG107*	Log Dow (pH 5) =-2.28 Log Dow (pH 7) =-2.45 Log Dow (pH 9) =-3.21	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	-2.45	not B
	BCF		
Persistence	DT50 or ready biodegradability	Not biodegradable	P
Toxicity	NOEC or CMR		***See below****
PBT-statement:	Log Dow is below trigger value. Data taken together does not indicate that the criterion for T is met*.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

$PEC_{surfacewater}$, default or refined (e.g., prevalence, literature)	0.5	µg/L	> 0.01 threshold (Y)
Other concerns (e.g., chemical class)			(N)

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Sorption-activated sludge	OPPTs 835.1110	Kd_{OC} =10609-15367 (Activated sludge) Freundich sorption coefficient 14 407 (Koc=4.16)	Sorps to sludge Instead of OECD TG106.
Ready Biodegradability Test	OECD TG301B	Not biodegradable	28 days
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	Aerobic: $DT_{50,\ whole\ system}$ >1000 days % Shifting to sediment = 82.1-88	Once in sediment the system remained generally unchanged

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG201	NOEC	0.0954	mg/L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD TG211	NOEC	0.834	mg/L	Reproduction and survival
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	0.753	mg/L	*Pimephales promelas* No surviving fry at 11 mg/l, NOEC for hatching success 3.57 mg/l.
Activated Sludge, Respiration Inhibition Test	OECD TG209	EC50	>100	mg/L	No inhibitory effect
Phase IIb Studies					
Bioaccumulation	OECD TG305	BCF	NA		
Aerobic and anaerobic transformation in soil	OECD TG307	DT_{50}	>1000 days		for 3 soils (in South Witham soil not possible to determine)
Soil Microorganisms: Nitrogen Transformation Test	OECD TG216	NOEC	985	mg/kg	EC50 could not be calculated
Water sediment effects	OECD TG218	NOEC	858	mg/kg	*Chironomus riparius*
Terrestrial Plants, Growth Test/*Species a)*	OECD TG208	NOEC EC50	12 79.9 (pea) to >1000 (wheat, onion)	mg/kg	Wheat, onion, dwarf bean, tomato, turnip, pea
Earthworm, Acute Toxicity Tests	OECD TG207	NOEC	1000	mg/kg dry soil	*Eisenia fetida*
Collembola, Reproduction Test	OECD TG232	NOEC	29	mg/kg	*Folsomia candida* (reproduction)

Table 2 Summary of main study results for Abacavir

Substance (INN/Invented Name): Abacavir			
CAS-number (if available): *188062-50-2*			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	OECD TG107	Log Dow (pH 5) = 0.88 Log Dow (pH 7) = 1.18 Log Dow (pH 9) = 1.20	Potential PBT (N)
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{SW}, default	3.0	µg/L	> 0.01 threshold (Y)
Other concerns (e.g., chemical class)			(N)

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-activated sludge	Pagga and Taeger protocol	Kb 154 (3 h), 11169 (24 h)	Not in accordance with recommended protocol
Soil adsorption study	TAD 3.08	Sandy silt loam Koc = 934 Clay loam Koc = 298 Sandy loam Koc = 147	Instead of OECD TG106.
Ready Biodegradability Test	OECD TG301B	Not readily biodegradable DOC = 27 % Primary degradation = 41-94 %	
Inherent Biodegradability	OECD TG302B	Primary degradation (14 days) >99 %	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50,\ water}$ = 6.1-8.7d $DT_{50,\ sediment}$ = 8.3-25d $DT_{50,\ whole\ system}$ = 9.1 -15d % Shifting to sediment > 10%	Not persistent in sediment (DT50, system <120d).

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG201	NOEC	25.62	mg/L	*Selenastrum capricornutum*
Daphnia sp. Acute effects		EC_{50} (48h) NOEC	119 61.60	mg/L	
Ceriodaphnia dubia Chronic effects, Reproduction	EPA 821-R02-013	LOEC (7 d) NOEC (7 d)	8.50 4.80	mg/L	*Ceriodaphnia dubia*
Fish, Acute effects	TAD 4.11	EC_{50} (96h) NOEC (96h)	>103 103		*O. mykiss*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	10	mg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	61	mg/L	*Sludge microorganisms*
Phase IIB Studies					
Sediment dwelling organism	OECD TG218	NOEC $NOEC_{OC10}$	112 933	mg/kg	*C. riparius*

Table 3. Summary of main study results for Lamivudine

Substance (INN/Invented Name): Lamivudine			
CAS-number (if available): 134678-17-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	Log Dow (pH 5) = -1.86 Log Dow (pH 7) = -1.44 Log Dow (pH 9) = -1.17	Potential PBT (N)
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC_{SW}, default or refined (e.g., prevalence, literature)	1.5	µg/L	> 0.01 threshold (Y)
Other concerns (e.g., chemical class)			(N)

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Soil adsorption study	TAD 3.08	Clay loam Koc = 32 Sandy loam Koc = 30.2 Sandy silt loam Koc = 108	Instead of OECD TG106
Ready Biodegradability Test	OECD TG301B	Not readily biodegradable Ultimate biodegradation (DOC) = 1%	
Inherent Biodegradability	OECD TG302B	Not Inherently Biodegradable DOC = 0 % Primary degradation = 4 %	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50,\ water}$ = 14-22d $DT_{50,\ sediment}$ = 15-18d $DT_{50,\ whole\ system}$ = 22-29d % Shifting to sediment > 10%	Not persistent In sediment (DT50, system <120d).

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG201	NOEC	96.9	mg/L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD TG211	NOEC	100.0	mg/L	*D. magna*
Fish, Acute effects	TAD 4.11	NOEC (96 h)	97.9	mg/L	*O. mykiss*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	10	mg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	1000	mg/L	*Sludge microorganisms*
Microbial Growth inhibition Test	TAD 3.02	NOEC EC_{50}	1000 > 1000	mg/L	*Azotobacter beijerinckii* *Aspergillus niger* *Nostoc commune* *Pseudomonas aeruginosa* *Trichoderma harzianum* Not the recommended test
Microbial Inhibition Control Readily Biodegradability Test 5-day Bacterial Inhibition Test	OECD TG301B/301D	NOEC	23.9	mg/L	Not the recommended test
Phase IIB Studies					
Sediment dwelling organism	OECD TG218	NOEC $NOEC_{OC10}$	155 775	mg/kg	*C. riparius*

2.5.5. Discussion on non-clinical aspects

Dolutegravir

Based on the fact that effects on offspring body weights were noted at doses where maternal toxicity was observed, and the presence of considerable safety margins expected at the proposed doses, there

is minimal risk for adverse effects on postnatal development in offspring of mothers receiving dolutegravir. On the other hand, the clinical relevance of the findings in the juvenile toxicity study in rats is unknown.

Dolutegravir was not immunotoxic in adult rats at doses around 1000 mg/kg/day. In juvenile rats, there were no test article-related effects on TDAR, and no effects on lymphocyte subsets (T cells, both CD4 and CD8 subsets, and B cells) and CD4 or CD8 T-cell receptor V-beta usage in peripheral blood.

Abacavir

The effects on juvenile brain growth at 120 mg/kg/day (NOAEL of 40mg/kg) that corresponded to ~0.5 times Cmax-based margin compared to human adult Cmax at 600mg, it is thought that are due to under-nutrition subsequent to reduced suckling resulting from the marked reactions to exposure observed during the early period of treatment. The clinical relevance of these findings is unknown but there are no clinical experience so far that indicates clinical relevance.

Lamivudine

Large safety margins exist for the findings from the pre-/post-natal/juvenile toxicity study in rats (>80 times, based on human Cmax for adult 300mg dose), and thus it is considered that they represent no safety hazard to children receiving 3TC.

Combination considerations

Overall, the present application attempts to extend the previous paediatric weight limit of >40kg to >25kg and >14kg. 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).

The possible outcome of combining these two active pharmaceutical ingredients (APIs) in a juvenile toxicity setting is unclear (e.g., possible combination/mixture developmental toxicity). The individual APIs have previously been approved for the lower weight limit (i.e., 14kg) which tends to correspond to an age range slightly after 2 years of age in humans (roughly corresponding to the immediate post-weaning period in rat which is likely less sensitive than the pre-weaning period). As such, and combined with previous clinical experience, the presently proposed lowest clinical age or weight range (>14kg) is still considered unlikely to result in novel Triumeq-generated toxicity. Based on the existing non-clinical data, any further reduction of these indication (age or body weight) limits would be accompanied with increasingly greater toxicological uncertainty.

Environmental risk assessment

DTG, ABC and 3TC are not persistent, bioaccumulative and toxic (PBT) substances. The increase in patient population for the proposed indication is deemed to generate a negligible increase in PEC for the different APIs.

The overall conclusion for the environmental risk remains the same as in the Triumeq ERA from 2017. None of the risk quotients (RQs) for the three active substances was close to or above the trigger value (i.e., RQ<1).

2.5.6. Conclusion on the non-clinical aspects

The overall existing non-clinical data supports the efficacy and safety for the proposed FDC product in the sought indication.

Based on the available data, the use of Triumeq in the sought indication, is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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**

Study Identifier	Study Objective(s)	Study Design	Healthy Participants or Diagnosis of Patients	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Participants by Group Entered/ Completed[a]	Study Reporting Status (Type of Report) / Location of Report
Study 205860 (IMPAACT 2019) Interim Non-Compartmental PK Report GSK Doc. No 2021N487161_00	Interim Non-Compartmental Pharmacokinetic Analysis of TRIUMEQ in HIV-1 Infected Pediatric Subjects (≥14 kg to <40 kg) in Study 205860 (IMPAACT 2019)	IMPAACT 2019 is an ongoing Phase I/II, multi-center, open-label study that investigates the PK, safety, tolerability and efficacy of Triumeq FDC (Tablets and DT) in a pediatric patients less than 12 years of age living with HIV-1.	Pediatric participants living with HIV-1	WHO Weight band based Fixed Dose Combinations DTG/ABC/3TC FDC 14 to <20 kg: 25/300/150 mg DT 20 to <25 kg: 30/360/180 mg DT 25 to <40 kg: 50/600/300 mg Tablet	21 participants across 3 weight bands (≥14 to <20 kg, ≥20 to <25 kg, and ≥25 kg) included in the analysis	Completed: Interim Clinical Pharmacology Report Current Submission m5.3.3.2

Study Identifier	Study Objective(s)	Study Design	Key Inclusion Criteria of Participants	Treatment Details (Drug/Dose/Form/Route/ Frequency/Duration)	No. of Participants by Group Entered / Completed	Study Status (Type of Report) / Location of Report
RBA Study 205894	To compare the RBA of DTG, ABC, and 3TC administered as Triumeq DTs with the conventional Triumeq Tablet (reference) administered as direct to mouth when: • Pediatric Triumeq DTs are administered as a dispersion and taken immediately • Pediatric Triumeq DTs are administered as direct to mouth	Phase I, 2-part, single dose, open-label, randomized, 3-period, crossover	Healthy participants 18 to 65 years old male / female	Part 1: Treatment A: Triumeq Tablets (DTG 50 mg / ABC 600 mg / 3TC 300 mg, 1 tablet) administered as direct to mouth (reference). Treatment B: Triumeq DTs (DTG 5 mg /ABC 60 mg /3TC 30 mg, 10 DTs) administered as a dispersion and taken immediately (test). Treatment C: Triumeq DTs (DTG 5 mg /ABC 60 mg /3TC 30 mg, 10 DTs) administered as direct to mouth (test). Part 2: Treatment D: DTG (50 mg, 1 tablet) and 3TC (300 mg,1 tablet) administered as direct to mouth (reference). Treatment E: DTG/3TC DTs (DTG 5 mg/3TC 30 mg, 10 DTs) administered as a dispersion and taken immediately (test). Treatment F: DTG/3TC DTs (DTG 5 mg/3TC 30 mg, 10 DTs) administered as direct to mouth (test).	36 total enrolled Part 1: 18 Enrolled; 17 Completed Part 2: 18 Enrolled; 18 Completed	Completed: CPSR Current Submission m5.3.1.2

RBA Study 200402	To evaluate the RBA of DTG, ABC, and 3TC administered as Triumeq DTs as compared to the administration of Epzicom + DTG taken with purified water: • When DTG/ABC/3TC tablet was dispersed in water with high mineral content and taken immediately • When DTG/ABC/3TC tablet was dispersed in water with high mineral content and taken 30 min after dispersion • When DTG/ABC/3TC tablet was dispersed in purified water and taken immediately • When DTG/ABC/3TC tablet was dispersed in purified water and taken 30 min after dispersion	Phase I, single-dose, open-label, randomized, 5-period, crossover	Healthy participants 18 to 65 years old male / female	Treatment A: Epzicom (ABC 600 mg / 3TC 300 mg) plus 4 Tivicay (DTG 10 mg) tablets taken with purified water. Treatment B: 4 Triumeq DTs (ABC 150 mg / DTG 10 mg / 3TC 75 mg) dispersed in a vehicle prepared with high mineral content water plus flavor & sweeteners (stock solution 1) and taken immediately. Treatment C: 4 Triumeq DTs (ABC 150 mg / DTG 10 mg / 3TC 75 mg) dispersed in a vehicle prepared with high mineral content water plus flavor & sweeteners (stock solution 1) and taken after 30 min. Treatment D: 4 Triumeq DTs (ABC 150 mg / DTG 10 mg / 3TC 75 mg) dispersed in a vehicle prepared with purified water plus flavor & sweeteners (stock solution 2) and taken immediately. Treatment E: 4 Triumeq DTs (ABC 150 mg / DTG 10 mg / 3TC 75 mg) dispersed in a vehicle prepared with purified water plus flavor & sweeteners (stock solution 2) and taken after 30 min.	20 Enrolled 20 of 20 Completed Treatments A-D 19 of 20 Completed Treatment E	Completed: CPSR Current Submission m5.3.1.2
216149 (Food Effect)	To assess the effect of food (fasted and high-fat meal) on the PK of Triumeq DTs To assess the effect of food (fasted and high-fat meal) on the PK of Dovato DTs	Phase I, single-dose, open-label, randomized, 2-cohort, 2-period, crossover	Healthy participants 18 to 50 years old male / female	Cohort 1 Treatment A: Triumeq DTs (DTG 5 mg /ABC 60 mg /3TC 30 mg, 6 DTs) administered as a dispersion and taken immediately under fed conditions. Treatment B: Triumeq DTs (DTG 5 mg /ABC 60 mg/ 3TC 30 mg, 6 DTs) administered as a dispersion and taken immediately under fasted conditions. Cohort 2 Treatment C: Dovato DTs (DTG 5 mg/ 3TC 30 mg, 6 DTs) administered as a dispersion and taken immediately under fed conditions. Treatment D: Dovato DTs (DTG 5 mg /3TC 30 mg, 6 DTs) administered as a dispersion and taken immediately under fasted conditions.	33 total enrolled Cohort 1: 16 Enrolled; 16 Completed Cohort 2: 17 Enrolled; 16 Completed	Completed: Interim CPSR (for Cohort 1) Current Submission m5.3.1.2 Amended CPSR (for Cohort 2) pending

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Objective

The objectives of the Population Pharmacokinetic analysis (PopPK) analysis were to evaluate the predictive performance of previously developed single entity models for describing and predicting Triumeq PK of the paediatric participants in the IMPAACT 2019 study.

Methods

Plasma samples were analysed for DTG, ABC and 3TC concentrations using validated liquid chromatography coupled to tandem mass spectroscopy (LC-MS/MS) methods.

Three-individual paediatric PopPK models were fit to the individual IMPAACT 2019 interim data without re-estimation of the population parameters (table below). Goodness of fit and visual predictive checks were used to evaluate if the 3 models were able to describe and predict the interim data sufficiently.

Table 4. Number of Subjects included in PopPK Analysis of IMPAACT 2019 PK Data by Weight Band-Based Triumeq FDC Doses

Weight Band (kg)	Triumeq Dosage Form	Number of Participants		
		Intensive PK	Sparse PK	Overall
≥14 to <20	DT	7	8	15
≥20 to <25	DT	7	3	10
≥25 kg	Tablet	7	4	11

DTG Paediatric PopPK Model

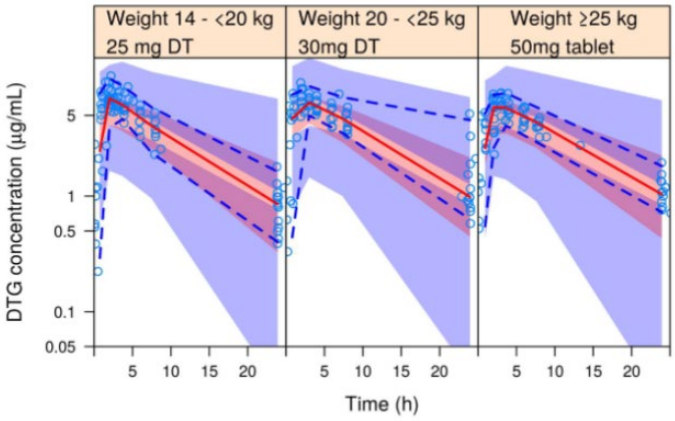
Plasma DTG exposure in paediatric participants (n=239) aged 2 months to 18 years of age was previously well described by a 1-compartment PK model (Table below). The PopPK model accounts for differences in bioavailability across formulations and the impact of food on DTG exposures. The CL/F and V/F were scaled for body weight and a maturation function was also applied to CL/F.

Table 5. 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]*	52.2 FIX	-	-		
Hill*	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 PK sub-studies	0.0123	0.00787, 0.0167	18.4	11.1	16.3
Additive Error (µg/mL), ODYSSEY PK sub-studies	0.090	0.0677, 0.112	12.7	SD=0.300	-
Covariate relationships: • CL/F =1.03 x $(WT/70)^{0.488}$ x FMAT; where FMAT = $(PMA^{HILL}/(PMA^{HILL}+TM50^{HILL})$; and PMA (weeks) =PNA (years)*52 (weeks) + 40 (weeks) • V/F =13.6*$(WT/70)^{0.888}$					
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 * $\sqrt{\quad} - 1$.					
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-participant 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					

The previously developed DTG PopPK model was successfully able to describe the interim IMPAACT 2019 PK data. Visual Predictive Checks (VPC) plots showed that observed DTG PK data in the IMPAACT 2019 study were contained mostly within the 90% prediction interval for each of the weight bands (figure below).

Figure 1. Visual predictive check for the DTG model, stratified by weight band



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% prediction intervals

ABC Paediatric PopPK Model

Plasma ABC exposure in paediatric participants (n=169) aged 5 months to 13 years of age was well described by a 2-compartment PK model. Covariate effects included weight on CL/F and V2/F fixed to the exponent values estimated in the prior 3-study model and a study-specific F1 term for tablet and solution for the ARROW PK Sub-study Part 2 (Table below).

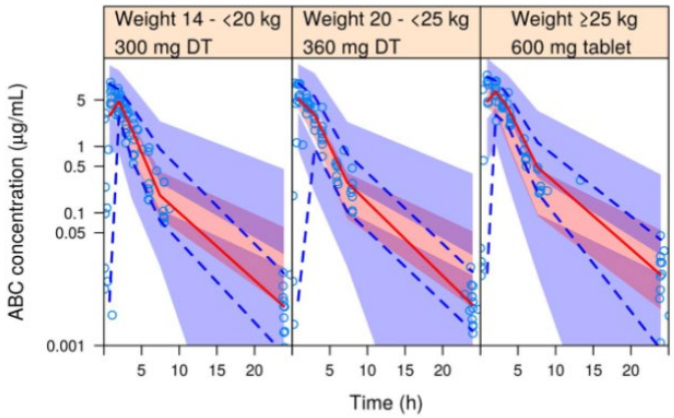
Table 6. ABC Paediatric PopPK Parameter Estimates

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%.

The previously developed ABC PopPK model was successfully able to describe the interim IMPAACT 2019 PK data. The model diagnostics demonstrated adequate model fit to the observed data at the population and individual level. VPC plots showed that observed ABC PK data in the IMPAACT 2019 study fell mostly within the 90% prediction interval for each of the weight bands (figure below).

Figure 2. Visual predictive check for the ABC model, stratified by weight band



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

3TC Paediatric PopPK Model

Plasma 3TC exposure in paediatric participants (n=210) aged 4 months to 19 years of age was well described by a 1-compartment model. A higher bioavailability 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 paediatric participants and accounted for in the PopPK model. The CL/F and V/F were scaled for body weight (Table below).

Table 7. 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.

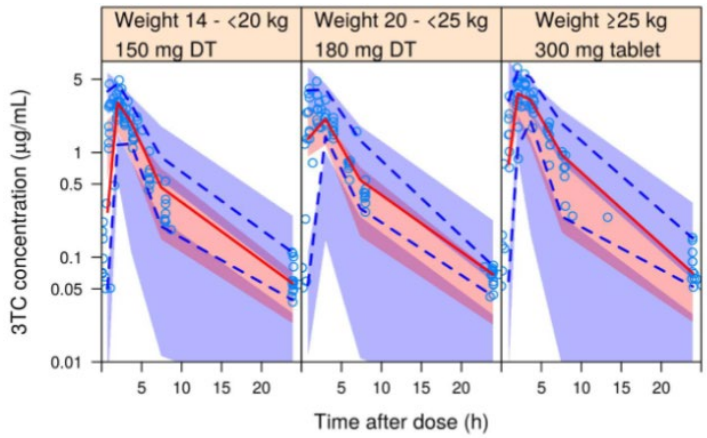
ALAG1 = lag time for absorption; CI = confidence interval; CV = coefficient of variation; OCCCL = interoccasion variability in clearance; OCCKA = interoccasion variability in Ka; OCCV = interoccasion variability in V; RSE = relative standard error; WT = body weight; Θ = PK parameter estimation; η = interindividual 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 interoccasion variability of the PK parameters calculated as the square root of Ω x 100%.

The previously developed 3TC PopPK model was successfully able to describe the interim IMPAACT 2019 PK data. The model diagnostics demonstrated an adequate model fit to the observed data at the population and individual level. VPC plots showed that observed 3TC PK data in the IMPAACT 2019 study fell mostly within the 90% prediction interval for each of the weight bands (figure below).

Figure 3. Visual predictive check for the 3TC model, stratified by weight band



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

Absorption

Relative bioavailability study 205894

This was a single-dose, three-way crossover study conducted in 18 healthy volunteers, comparing Triumeq DT (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) with Triumeq (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. The study was conducted between 26 February 2018 and 28 April 2018.

Table 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for dolutegravir, n=17.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	C_{24h} µg/ml	t_{max} h
Treatment A (Triumeq tablet)	**59.742 ± 16.9453**	**3.147 ± 0.5896**	**0.975 ± 0.3213**	**3.00 (1.50-4.08)**
Treatment B (Triumeq DT)	**99.892 ± 22.5115**	**5.431 ± 0.8175**	**1.580 ± 0.471**	**2.50 (1.00-6.00)**
***Ratio (90% CI)**	**1.7001 (1.5685-1.8428)**	**1.7382 (1.5983-1.8904)**	**1.6503 (1.5131-1.8000)**	**-**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
C_{24h}	plasma concentration at 24 hours
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for abacavir, n=17.

Treatment	AUC_{0-t} µg*h/ml	AUC_{0-24h} µg*h/ml	C_{max} µg/ml	t_{max} h
Treatment A (Triumeq tablet)	**16.947 ± 3.6212**	**16.959 ± 3.6305**	**5.176 ± 1.0877**	**1.50 (0.50-2.57)**
Treatment B (Triumeq DT)	**17.632 ± 3.6004**	**17.634 ± 3.6001**	**5.445 ± 1.0464**	**1.00 (0.25-2.00)**
***Ratio (90% CI)**	**1.0410 (1.0121-1.0708)**	**-**	**1.0533 (0.9885-1.1223)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-24h} area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 10. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for lamivudine, n=17.

Treatment	AUC_{0-t} µg*h/ml	AUC_{0-24h} µg*h/ml	C_{max} µg/ml	t_{max} h
Treatment A (Triumeq tablet)	**13.260 ± 3.5429**	**12.356 ± 3.3308**	**2.281 ± 0.6870**	**2.50 (1.50-5.05)**
Treatment B (Triumeq DT)	**13.182 ± 3.3238**	**12.295 ± 3.2817**	**2.171 ± 0.7640**	**2.50 (1.00-4.00)**
***Ratio (90% CI)**	**0.9994 (0.9525-1.0486)**	**-**	**0.9362 (0.8677-1.0101)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Relative bioavailability study 200402

This was a single-dose, five-way crossover study conducted in 20 healthy volunteers, comparing Epzicom (ABC 600 mg/3TC 300 mg, 1 tablet) + Tivicay (DTG 10 mg, 4 tablets) with Triumeq DT (ABC 150 mg/3TC 75 mg/DTG 10 mg, 4 tablets) dispersed in purified water or high mineral content water, taken immediately or 30 minutes after dispersion. All treatments were given under fasted conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. The study was conducted between 12 September 2016 and 25 November 2016.

Table 11. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for dolutegravir, n=20.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	C_{24h} µg/ml	t_{max} h
Treatment A (Epzicom + Tivicay)	**47.693 ± 11.7495**	**2.611 ± 0.7006**	**0.761 ± 0.2005**	**2.50 (0.51-5.01)**
Treatment B (Triumeq DT, high mineral, immediately)	**73.113 ± 11.1638**	**4.051 ± 0.5314**	**1.131 ± 0.1947**	**2.00 (1.00-4.01)**
Treatment C (Triumeq DT, high mineral, 30 min after)	**71.483 ± 9.9882**	**3.963 ± 0.5586**	**1.113 ± 0.1619**	**2.25 (0.50-4.00)**
Treatment D (Triumeq DT, purified, immediately)	**74.466 ± 14.0761**	**3.975 ± 0.6417**	**1.180 ± 0.2570**	**2.02 (1.50-5.00)**
Treatment E (Triumeq DT, purified, 30 min after) [a]	**73.037 ± 11.8084**	**4.057 ± 0.6769**	**1.160 ± 0.2289**	**2.50 (1.00-4.08)**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{24h} plasma concentration at 24 hours
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
[a] *N=19*

Table 12. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for lamivudine, n=20.

Treatment	AUC_{0-t} µg*h/ml	AUC_{0-24h} µg*h/ml	C_{max} µg/ml	t_{max} h
Treatment A (Epzicom + Tivicay)	**15.175 ± 4.0080**	**14.093 ± 3.8191**	**2.701 ± 0.7860**	**2.04 (1.00-4.05)**
Treatment B (Triumeq DT, high mineral, immediately)	**14.995 ± 4.2532**	**13.782 ± 4.0950**	**2.511 ± 0.7546**	**2.01 (1.00-4.01)**
Treatment C (Triumeq DT, high mineral, 30 min after)	**15.772 ± 4.4349**	**14.536 ± 4.2770**	**2.563 ± 0.6746**	**2.26 (1.50-4.00)**
Treatment D (Triumeq DT, purified, immediately)	**15.227 ± 4.1173**	**13.993 ± 3.8556**	**2.436 ± 0.6844**	**2.00 (0.50-4.00)**
Treatment E (Triumeq DT, purified, 30 min after) [a]	**14.785 ± 4.1475**	**13.595 ± 3.8972**	**2.525 ± 0.7907**	**2.01 (1.00-3.01)**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-24h} area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
[a] *N=19*

Table 13. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for abacavir, n=20.

Treatment	AUC_{0-t} µg*h/ml	AUC_{0-24h} µg*h/ml	C_{max} µg/ml	t_{max} h
Treatment A (Epzicom + Tivicay)	**16.993 ± 3.9340**	**16.999 ± 3.9330**	**5.879 ± 1.7362**	**1.03 (0.50-3.01)**
Treatment B (Triumeq DT, high mineral, immediately)	**16.555 ± 4.2768**	**16.562 ± 4.2747**	**6.039 ± 2.0290**	**1.00 (0.50-2.50)**
Treatment C (Triumeq DT, high mineral, 30 min after)	**16.646 ± 4.0652**	**16.648 ± 4.0652**	**5.577 ± 1.6022**	**1.00 (0.50-4.00)**
Treatment D (Triumeq DT, purified, immediately)	**17.092 ± 4.5211**	**17.095 ± 4.5214**	**5.697 ± 1.4429**	**1.01 (0.50-3.00)**
Treatment E (Triumeq DT, purified, 30 min after) [a]	**17.098 ± 3.7898**	**17.104 ± 3.7875**	**5.946 ± 1.5510**	**1.00 (0.50-2.50)**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-24h} area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
[a]N=19

Food effect study 216149

This was a single-dose, two-way crossover study conducted in 16 healthy volunteers, comparing Triumeq DT (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) under fasting or fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. The study was conducted between 07 May 2021 and 23 July 2021.

Table 14. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for dolutegravir, n=16.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	C_{24h} ng/ml	t_{max} h
Treatment A (fed)	**57210 ± 13173**	**2392 ± 403.39**	**992.8 ± 266.13**	**5.00 (3.00-12.00)**
Treatment B (fasted)	**65310 ± 14801**	**3387 ± 689.51**	**1027 ± 259.07**	**1.25 (0.50-4.00)**
***Ratio (90% CI)**	**0.8744 (0.8293-0.9219)**	**0.7102 (0.6598-0.7643)**	**-**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{24h} plasma concentration at 24 hours
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 15. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for abacavir, n=16.

Treatment	AUC_{0-t} ng*h/ml	AUC_{0-24h} ng*h/ml	C_{max} ng/ml	t_{max} h
Treatment A (fed)	8742 ± 2062.0	8786 ± 2027.9	1873 ± 360.33	2.75 (0.50-4.00)
Treatment B (fasted)	10300 ± 2918.9	10360 ± 2921.9	4268 ± 1286.2	0.50 (0.25-1.50)
*Ratio (90% CI)	0.8567 (0.8159-0.8995)	-	0.4503 (0.3976-0.5100)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-24h} area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 16. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for lamivudine, n=16.

Treatment	AUC_{0-t} ng*h/ml	AUC_{0-24h} ng*h/ml	C_{max} ng/ml	t_{max} h
Treatment A (fed)	6422 ± 1189.0	5905 ± 1058.6	901.8 ± 137.07	3.50 (2.00-4.00)
Treatment B (fasted)	7393 ± 1704.3	6889 ± 1663.8	1491 ± 475.43	1.50 (0.50-3.50)
*Ratio (90% CI)	0.8798 (0.8202-0.9438)	-	0.6373 (0.5594-0.7260)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-24h} area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Distribution

No new data has been presented.

Elimination

The half-life of DTG, ABC and 3TC for Triumeq DTs were about 14-16 hours, 2-2.5 hours and 16-19 hours respectively.

No additional data regarding excretion, metabolism and inter-conversion have been obtained with Triumeq DTs.

Dose proportionality and time dependencies

Dose proportionality and time dependency was not evaluated for Triumeq DTs.

PK in target population – paediatric patients

Target exposure

The target exposure to achieve in paediatric patients for DTG, ABC and 3TC are shown in the tables below.

Table 17. 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 18. 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 19. DTG PK Targets

Table 4 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).

Overall, the estimated PK parameters for DTG, ABC, and 3TC with the Triumeq DT and Triumeq Tablet in the ongoing IMPAACT 2019 study were comparable with the observed exposures with the individual components in adults and pediatrics (m2.7.2 Section 3 & Response to Q10). The PK target ranges were selected based on observed PK of individual components in adults and pediatric participants.

Paediatric exposure from PopPK Simulation

A total of 600,000 virtual subjects were simulated spread equally over the three weight bands. Statistical summaries of the resulting secondary PK parameters are presented here in table and figure format and compared against PK parameters from the post-hoc evaluation and noncompartmental analysis. These clinical trial simulations included uniform weights across the weight bands. Thus, its more generalizable scenario compared to the study population where the small sample size was not uniformly distributed.

The predicted DTG, ABC and 3TC exposures with the proposed doses of Triumeq (DT and Tablet formulations) across different weight bands are provided in tables below.

Table 20. Simulated (N=600000) Steady State DTG PK Parameters in HIV-Infected Children Based on Proposed Triumeq DT and Triumeq Tabled Dosing

Weight Bands	Proposed Daily Dose	AUC0-24 (µg.h/mL)	Cmax (µg/mL)	C24 (ng/mL)
≥14 to <20 kg	25 mg DT	68.59 (31.79 – 147.7)	7.10 (4.05 – 12.47)	816.30 (120.60 – 3714.00)
≥20 to <25 kg	30 mg DT	72.17 (33.43 – 155.5)	7.40 (4.29– 12.96)	886.10 (134.80– 3957.00)
≥25 to <40 kg	50 mg Tablet	66.80 (30.93 – 144.5)	6.23 (3.44 – 11.25)	950.30 (158.80 – 4019.00)

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

Table 21. Simulated (N=600000) Steady State ABC PK Parameters in Children with HIV-1 Infection Based on Proposed Triumeq DT and Triumeq Tabled Dosing

Weight Bands	Proposed Daily Dose	AUC0-24 (µg.h/mL)	Cmax (µg/mL)	C24 (ng/mL)
≥14 to <20 kg	300 mg DT	15.42 (5.99-38.23)	6.39 (2.74 - 14.48)	18.30 (1.25- 168.90)
≥20 to <25 kg	360 mg DT	14.75 (5.75-36.53)	6.26 (2.66 -14.15)	14.21 (1.25 -131.30)
≥25 to <40 kg	600 mg Tablet	18.42 (7.11-46.42)	8.03 (3.37 -18.41)	13.46 (1.25 -129.70)

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

Table 22. Simulated (N=600000) Steady State 3TC PK Parameters in HIV-Infected Children Based on Proposed Triumeq DT and Triumeq Tabled Dosing

Weight Bands	Proposed Daily Dose	AUC0-24 (µg.h/mL)	Cmax (µg/mL)	C24 (ng/mL)
≥14 to <20 kg	150 mg DT	10.68 (5.49 - 20.22)	2.73 (1.40 - 5.20)	83.62 (1.25 – 118.50)
≥20 to <25 kg	180 mg DT	10.37 (5.36 - 19.50)	2.68 (1.38 - 5.09)	81.71 (1.25 - 115 .70)
≥25 to <40 kg	300 mg Tablet	13.08 (6.63 - 25.11)	3.47 (1.76 - 6.72)	84.29 (1.25 – 121.90)

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

NCA vs model predicted exposure – paediatric patients

Dosing for IMPAACT study and dosing approved for individual components are shown in the table below.

Table 23. Triumeq (DTs and Tablets) Dosing and Approved Individual Component Dosing in Children ≥ 14 kg

Drug	Weight Bands	Triumeq Dose in IMPAACT 2019 study	Approved Individual Component Dose (Tablets)
ABC			
	≥14 to <20 kg	300 mg DT	300 mg Tablet
	≥20 to <25 kg	**360 mg DT**	**450 mg Tablet**
	≥25 to <40 kg	600 mg Tablet	600 mg Tablet
3TC			
	≥14 to <20 kg	150 mg DT	150 mg Tablet
	≥20 to <25 kg	**180 mg DT**	**225 mg Tablet**
	≥25 to <40 kg	300 mg Tablet	300 mg Tablet
DTG			
	≥14 to <20 kg	25 mg DT	
	≥20 to <25 kg	30 mg DT	
	≥25 to <40 kg	50 mg Tablets	

Bayes estimation method showed PK parameters were comparable to observed data and were within the variability of the NCA parameter estimates (Tables below).

Table 24. NCA Calculated vs. 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	Analysis Method	PK Parameter GM (95% CI)		
					Cmax (μg/mL)	AUC0-24 (μg*h/mL)	C24 (ng/mL)
≥14 to <20	DT	25 mg	15	PopPK[a]	6.97 (6.13-8.24)	65.1 (56.6-79.3)	746 (560-1350)
			7	NCA[b]	7.04 (6.02 -8.23)	71.45 (57.66 -88.53)	787.31 (532.89-1163.19)
≥20 to <25	DT	30 mg	10	PopPK[a]	6.85 (5.86-8.15)	77.8 (61-102)	1090 (562-2230)
			7	NCA[b]	7.29 (6.26 -8.50)	84.44 (66.49 -107.24)	1346.35 (639.57 -2834.18)
≥25 to <40	Tablets	50mg	11	PopPK[a]	6.17 (5.35-7.26)	64.3 (55.8-75.8)	900 (695-1250)
			7	NCA[b]	6.25 (5.18 -7.55)	71.80 (63.19 -81.58)	976.75 (758.39 -1257.98)

[a]Model based Individual Post-hoc PK Parameters. Source: Appendix Table 6.
[b]NCA PK parameters (GSK Document Number 2021N487161_00, Table 4)

Table 25. NCA Calculated vs. 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	Analysis Method	PK Parameter GM (95% CI)		
					Cmax (μg/mL)	AUC0-24 (μg*h/mL)	C24 (ng/mL)
≥14 to <20	DT	300 mg	15	PopPK[a]	6.02 (5.36-7.07)	15.6 (13.7-19)	11.1 (9.51-31.4)
			7	NCA[b]	6.26 (4.73 -8.28)	15.09 (10.54 – 21.66)	2.84 (1.26 -6.39)
≥20 to <25	DT	360 mg	10	PopPK[a]	6.21 (4.64-8.71)	16.0 (14.0-18.5)	8.83 (5.29-19.2)
			7	NCA[b]	6.65 (5.17 -8.56)	17.33 (14.54 -20.66)	3.61 (1.83 -7.13)
≥25 to <40	Tablets	600 mg	11	PopPK[a]	10.6 (9.00-13.0)	26.1 (23.1-30.1)	15.0 (11.0-36.3)
			7	NCA[b]	9.04 (7.40 -11.04)	25.74 (22.51 -29.44)	10.53 (3.02 -36.77)

[a]Model based Individual Post-hoc PK Parameters. Source: Appendix Table 7.
[b]NCA PK parameters (GSK Document Number 2021N487161_00, Table 5)

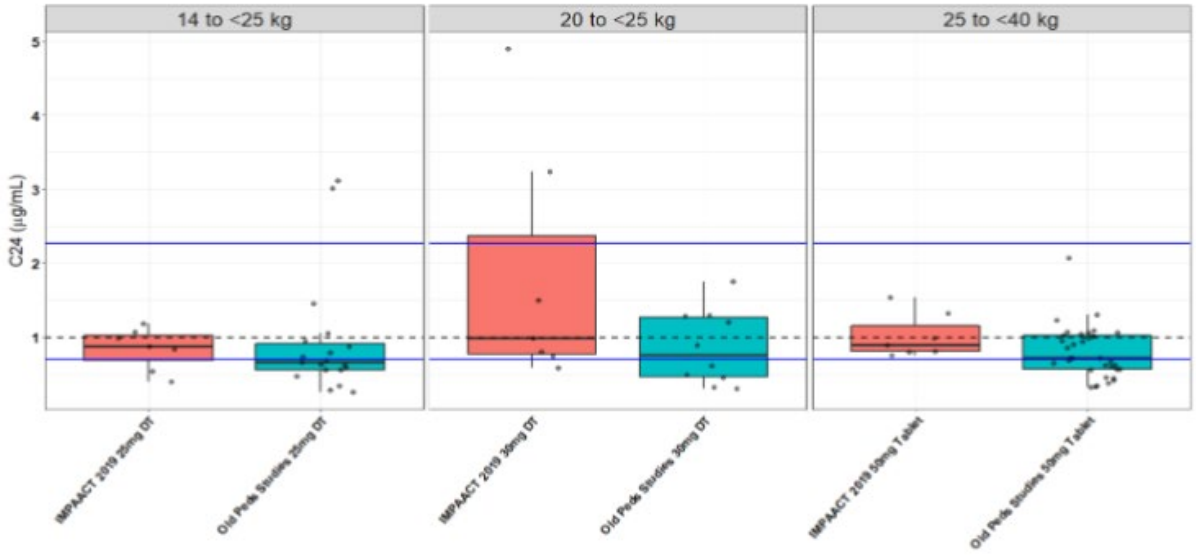
Table 26. NCA Calculated vs. Individual Post-hoc 3TC Steady-State PK parameters Following Once Daily Oral Dosing of Triumeq in IMPAACT 2019 Study

Weight Band (kg)	Triumeq Dosage Form	3TC Dose	N	Analysis Method	PK Parameter GM (%CV)		
					Cmax (μg/mL)	AUC0-24 (μg*h/mL)	C24 (ng/mL)
≥14 to <20	DT	150 mg	15	PopPK[a]	2.77 (2.49-3.22)	12.7 (10.8-16)	20.1 (20.8-83.2)
			7	NCA[b]	2.92 (2.36 -3.60)	13.02 (11.28 -15.02)	58.33 (42.00 -81.01)
≥20 to <25	DT	180 mg	10	PopPK[a]	2.61 (2.03-3.46)	12.1 (10-15)	9.21 (3.21-38.2)
			7	NCA[b]	2.99 (2.24 -3.99)	14.50 (12.47 -16.87)	60.12 (50.86 -71.06)
≥25 to <40	Tablets	300 mg	11	PopPK[a]	3.56 (3.07-4.39)	17.6 (14.6-22.6)	15.5 (9.55-46.6)
			7	NCA[b]	4.15 (3.18 -5.41)	21.73 (17.13 -27.58)	83.88 (61.25 114.88)

[a]Model based Individual Post-hoc PK Parameters. Source: Appendix Table 8.
[b]NCA PK parameters (GSK Document Number 2021N487161_00, Table 6)

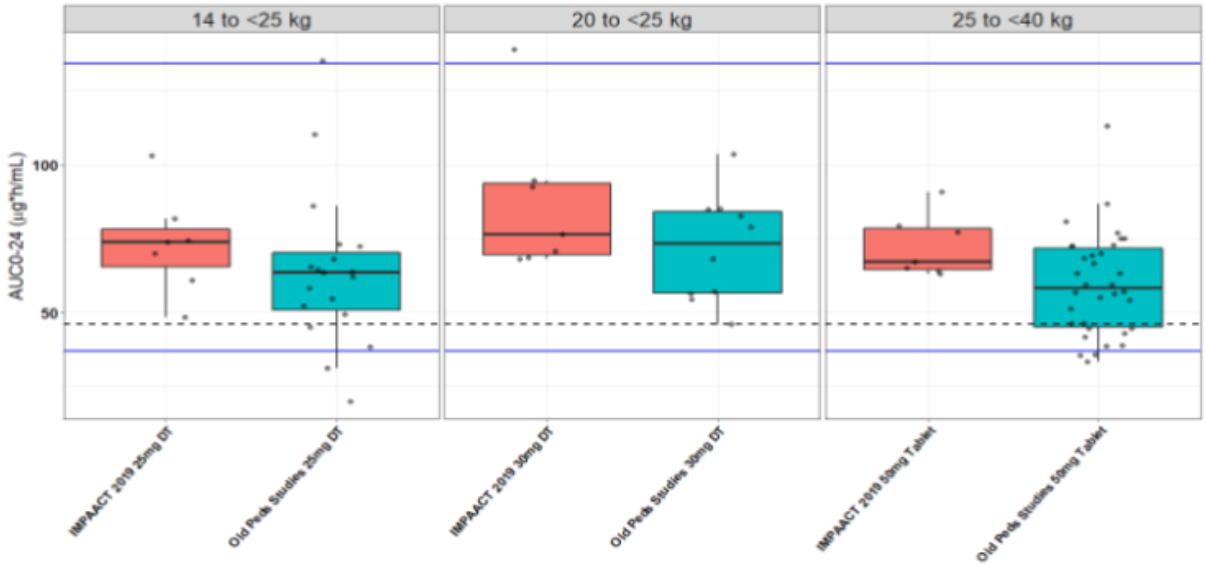
The observed plasma DTG C24h, AUC0-24, and Cmax (Figures below) values following administration of Triumeq FDC in the IMPAACT 2019 (≥14 kg) were consistent with historically observed in adults and paediatrics with single entity QD dosing.

Figure 4. Comparison of observed DTG C24h in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics Subjects



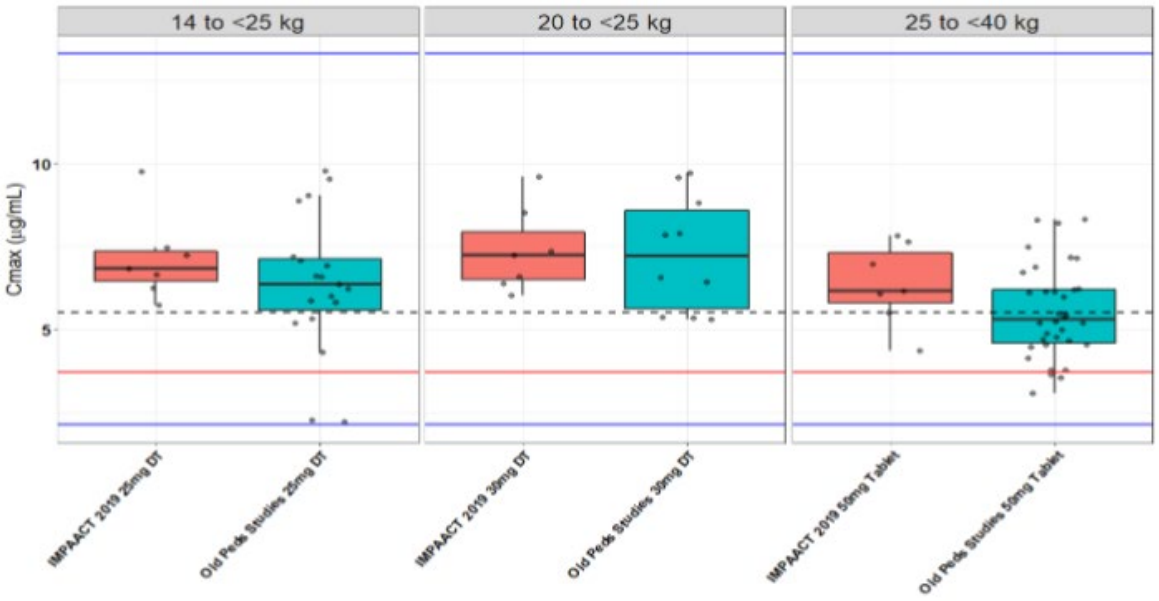
Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line through the middle of the boxes (Whiskers) represent minimum and maximum, Circles represents observed C24h values. Blue solid horizontal line: Geometric mean C24h target range (0.697 to 2.26 µg/mL). 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 Peds Studies= DTG PK data from P1093 & ODDYSSEY studies combined (≥14 to <40 kg) for this analysis.

Figure 5. Comparison of observed DTG AUC0-24 in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics 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 minimum and maximum, Circles represents observed AUC0-24h values. Blue solid horizontal line: Geometric mean AUC0-24h target range (37 to 134 µg*h/mL). Black dashed horizontal line: Target Geometric mean C24h exposure (46 µg*h/mL). IMPAACT 2019= DTG exposures with Triumeq FDC doses. Old Peds Studies= DTG PK data from P1093 & ODDYSSEY studies combined (≥14 to <40 kg) for this analysis.*

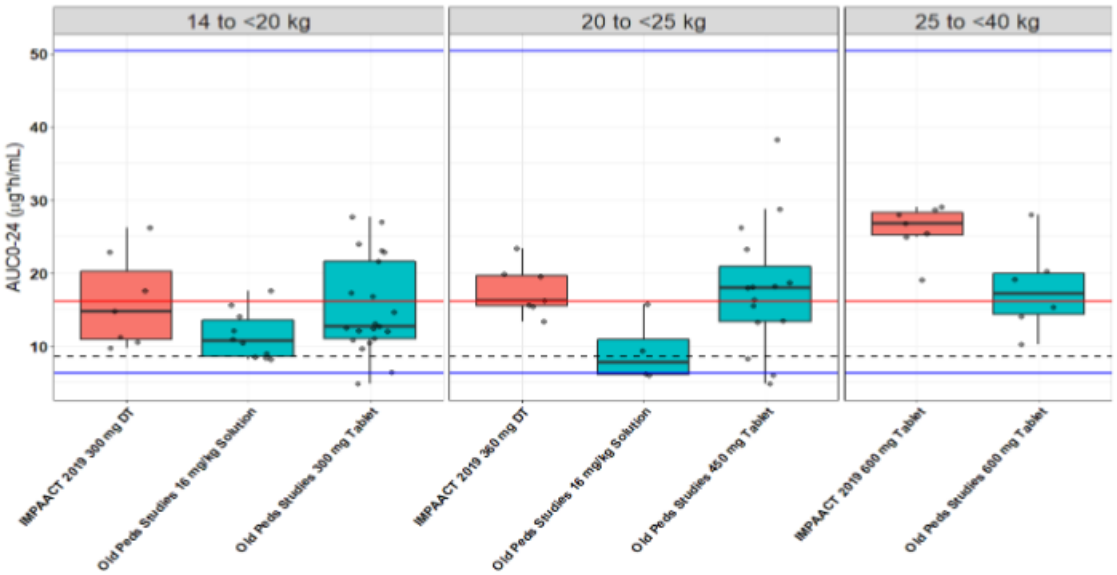
Figure 6. Comparison of observed DTG Cmax in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics Subjects



*Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line through the middle of the boxes (Whiskers) represent minimum and maximum, Circles represents observed Cmax values. Blue solid horizontal line: Geometric mean Cmax target range (2.12 to 13.3 µg/mL). Black dashed horizontal line: Geometric mean Cmax exposure with DT and FCT dosing in pediatrics (5.32 µg/mL), solid horizontal line: Geometric mean observed in adults after 50 mg FCT (3.7 µg*h/mL). IMPAACT 2019= DTG exposures with Triumeq FDC doses. Old Peds Studies= DTG PK data from P1093 & ODDYSSEY studies combined (≥14 to <40 kg) for this analysis.*

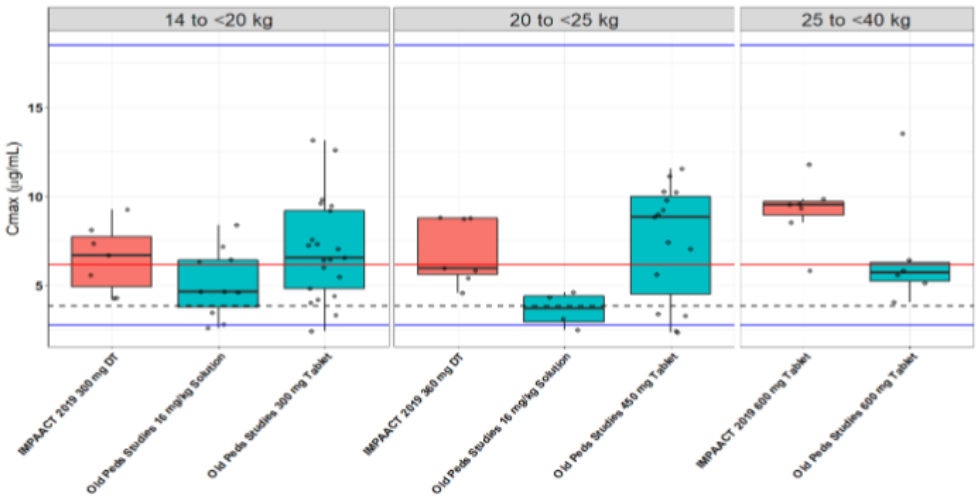
The observed plasma ABC AUC0-24 and Cmax (Figures below) values following administration of Triumeq FDC in the IMPAACT 2019 (≥14 kg) were consistent with historically observed in adults and paediatrics with single entity QD dosing.

Figure 7. Comparison of observed ABC AUC0-24 in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics 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 minimum and maximum, Circles represents observed AUC0-24 values. Blue solid horizontal line: Geometric mean AUC0-24 target range (6.3 to 50.4 µg*h/mL). Black dashed line: 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 (≥14 to <40 kg) for this analysis.*

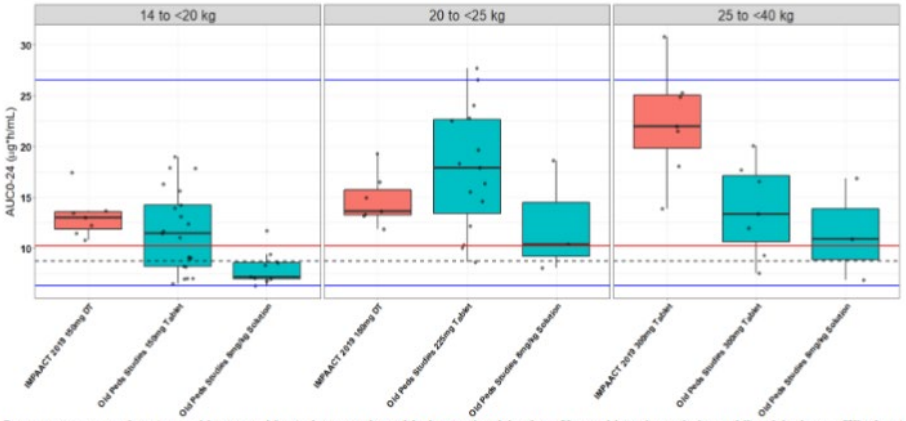
Figure 8. Comparison of observed ABC Cmax in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics Subjects



Boxes represent median (central horizontal line), 1st quartile and 3rd quartile of the data, Vertical line through the middle of the boxes (Whiskers) represent minimum and maximum, Circles represents observed Cmax values. Blue solid line: PopPK based 90% predicted intervals of Cmax with once-daily ABC dosing in pediatrics (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 (≥14 to <40 kg) for this analysis.

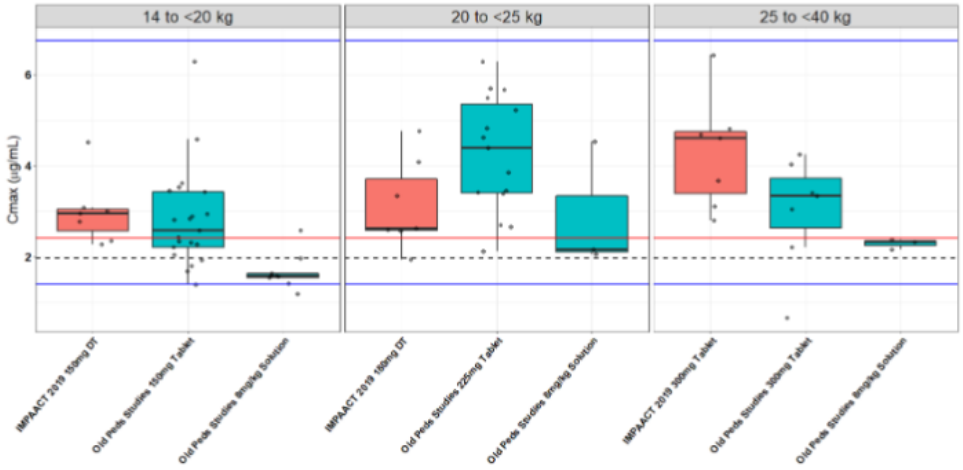
The observed plasma 3TC AUC0-24 and Cmax (Figures below) values following administration of Triumeq FDC in the IMPAACT 2019 (≥14 kg) were consistent with historically observed in adults and paediatrics with single entity QD dosing.

Figure 9. Comparison of observed 3TC AUC0-24 in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics 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 minimum and maximum, Circles represents observed AUC0-24 values. Blue solid line: 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 (≥14 to <40 kg) for this analysis.*

Figure 10. Comparison of observed 3TC Cmax in Paediatrics with Triumeq FDC and Previously Observed Exposures in the Paediatrics 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 minimum and maximum, Circles represents observed Cmax values. Blue solid line: PopPK based 90% predicted intervals of Cmax with once-daily ABC dosing in pediatrics (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.

Interactions

Drug-drug interaction information from single entities (DTG, ABC, 3TC) can be extended to Triumeq Tablet and DT formulations.

Special populations

Renal impairment

No data is available on the use of 3TC in children less than 25 kg with renal impairment.

2.6.2.2. Pharmacodynamics

No new pharmacodynamic studies were performed with Triumeq DTs.

2.6.3. Discussion on clinical pharmacology

Methods

The performance of the analytical methods P1165 and P1170 as well as the method performance during study sample analysis in studies 205894, 216194 and 200402 were satisfactory. The bioanalytical methods for study IMPAACT2019 were adequately validated and the performance of the study sample analysis was satisfactory.

PopPK analysis

The number of paediatric patients in each weight band was considered sufficient to conduct a PK bridge from adults to paediatric patients. With both rich and sparse PK sampling, deriving exposure metrics using a popPK mode is generally preferred over Non-Compartmental Analysis (NCA), provided that the popPK models' predictive ability was satisfactory. Starting from the previous popPK model is considered a good approach. The MAH ran the previous model without re-estimation (maxeval 0).

DTG popPK model: From the VPC, the median appears well captured while the variability is slightly overpredicted. Overall, the DTG model is considered satisfactory to conduct simulations in paediatric patients and compare with adult exposure.

ABC popPK model: From the VPC, the Cmin appears to not be well captured for the DT. For the FCT, Cmax and concentrations for the first 10h are slightly underpredicted while the Cmin is better predicted. The ABC popPK model is not deemed satisfactory for Cmin. For Cmin, the NCA results are preferred.

3TC popPK model: From the VPC, there is some underprediction by the model. This is more prevalent for patients above 25 kg (FCT). Underpredicting the exposure can be considered conservative with regards to efficacy and updating the model at this time is not considered needed.

popPK discussion

The MAH approach to use the previous popPK models is agreed with. The observed data fall within the 90% prediction interval for DTG, ABC and 3TC. No-re estimation of parament estimates was conducted. For ABC and 3TC, updating the models could have been considered but with sufficient NCA data available, this is not further pursued. Therefore, it is preferred that the ABC and 3TC Cmin are derived from NCA at this time even if spare sampling patients are not included.

The AUC for ABC and 3TC from the popPK analysis and the NCA were very similar providing support that AUC satisfactory predicted by the ABC and 3TC models. Due to different intracellular half-life for ABC and 3TC, AUC is the main parameter of interest.

Absorption

Study 205894

After single dose administration of Triumeq DTs, the systemic exposure (AUC, Cmax) of ABC and 3TC was comparable to that obtained from Triumeq conventional tablets. For DTG, about 1.7-fold greater exposure was observed following single oral administration of Triumeq DTs compared to Triumeq tablets. This information is included in the SmPC section 5.2, which is supported.

Of note, similar results were observed when DTG DT was compared with conventional DTG FCT (study 205893, Tivicay, EMEA/H/C/002753/X/0058/G). The suggested DTG dose for patients who weight at least 14 kg to less than 25 kg is the same as already approved Tivicay DT. The ABC and 3TC doses are

lower for the 20-25 kg group compared to approved doses for single entities. As this is a FDC, it is acknowledged that it is not possible to match the dose for all 3 components. However, an issue is raised regarding the adequacy of same DTG dose but lower ABC and 3TC dose.

It is agreed that Triumeq FCT and DTs are not exchangeable. This information is included in the SmPC section 4.2, which is supported.

The proposed volume of 20 ml water was not used in study 205894, where Triumeq DT were taken with a total of 240 ml water according to the study protocol. As difference of volume used in the study and proposed volume was accepted before, and as 20 ml water was used in the ongoing paediatric study, IMPAACT 2019, no issue is raised.

Study 200402

There were no significant differences when the Triumeq DT were taken with purified water or with high mineral content water and when Triumeq DT were taken immediately or after 30 minutes. This information is included in SmPC section 4.2, which is supported. According to the information in the PI, Triumeq DT are supposed to be dispersed in 20 ml of water. This information is included in SmPC section 4.2, which is supported.

Study 216149

The AUC of DTG, ABC and 3TC was within the conventional BE criteria (80.00-125.00%) and thus comparable when Triumeq DT was taken in fasted or fed state. The C_{max} of DTG, ABC and 3TC was 29%, 55% and 36% lower, respectively. The t_{max} of DTG, ABC and 3TC was delayed about 4 hours, 2 hours and 2 hours respectively. However, it is agreed that the differences in C_{max} is not clinically significant. Triumeq DTs can be taken with and without food. This information is included in SmPC section 5.2, which is supported.

Distribution, Elimination and Dose proportionality and time dependencies

No new data being submitted for Triumeq DTs is acceptable. This application is a Line Extension, and PK in adults were established for Triumeq FCT. Further, Triumeq DTs are intended for children weighing at least 14 kg to less than 25 kg.

PK in target population – paediatric patients

Target exposure

The DTG target exposure is based on adult exposure. Adults is the population which efficacy and safety was established and this is considered appropriate.

The target exposure for ABC and 3TC appear to be derived from children according to the provided target exposure table. The MAH provided tables with adult target exposure for AUC and Cmax for ABC and 3TC.

Paediatric dosing

The ABC and 3TC doses are lower for the 20-25 kg group compared to approved doses for mono entities which was discussed by the MAH. It is acknowledged that with the FDC, it is not possible to match the dose for all 3 components. The ABC and 3TC exposures were within the same range as adult exposure. Therefore, the slightly lower dosing compared to individual components is not expected to be clinically relevant.

All the simulations are provided for once daily dosing. The MAH supported the advantage of FDC and everyday dosing with regards to less frequent dosing and decreased pill burden, and by also combining

the single components. The MAHs argumentation is understood, still a BID dosing recommendation where possible may have been useful but this is not further pursued.

The MAH provided the target exposure tables with adult exposure, figures as well as effects table. Exposures are comparable to historical exposures observed in paediatric and adult studies. Further, the 3 individual components of Triumeq FDC (DT and FCT) were already approved for use in paediatric patients weighing at least 14 kg. The proposed doses are same except for 20-25 kg regarding ABC and 3TC but this slightly lower dose was adequately justified and is deemed acceptable.

Special populations

Renal impairment

No new data being submitted for Triumeq DT is acceptable. No data being available on the use of lamivudine in children with renal impairment who weigh less than 25 kg is included in the SmPC section 4.2, which is supported.

Interactions

No new data was presented for Triumeq DT. This is accepted. A different interaction profile for Triumeq DT is not expected compared to Triumeq tablets. In the SmPC section 4.2, dose recommendations are given in children when Triumeq DT is administered concomitantly with strong enzyme inducers. The recommendations are in line with previously approved DTG products and is supported.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of Triumeq DTs are sufficiently characterized. The approval of Triumeq DTs for the proposed indication is acceptable.

2.6.5. Clinical efficacy

2.6.5.1. Main studies

Treatments

Each of the single entities of the DTG/ABC/3TC FDC are already approved for use in paediatric patients weighing at least 14 kg and the proposed doses for the Triumeq formulations (DTs and FCT) are the same or similar to those currently approved. The MAH is seeking approval for the FDC for participants weighing at least 14 kg by relying on previously submitted data along with relative bioavailability (RBA) data, food effect data, modelling and simulations.

Dose:

The sought dose of Triumeq FDC in patient weighing at least 25 kg is one tablet once daily of 50 mg dolutegravir, 600 mg of abacavir and 300 mg of lamivudine.

Table 27. Dispersible Tablet dose recommendations in children weighing at least 14 kg to less than 25 kg

Body Weight (kg)	Daily Dose	Number of Tablets
14 to less than 20	25 mg DTG, 150 mg 3TC, 300 mg ABC once daily	Five
20 to less than 25	30 mg DTG, 180 mg 3TC, 360 mg ABC once daily	Six

Results

The efficacy studies listed in the table below support once daily weight-based dosing of Triumeq in patients weighing at least 14 kg. This list is comprised of solely historical studies that supported both the original Triumeq submission for use in patients weighing at least 40 kg as well as those which supported recommendations of the single entities (DTG, ABC, 3TC) for use in paediatric patients weighing at least 14 kg.

A specific demonstration of antiviral efficacy in paediatric patients is not required. The PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred.

Table 28. Results of Efficacy Studies

Study	Treatment Arm	No. Enrolled/ Completed	Efficacy Variables[a]			Other Comments
			Plasma HIV-1 RNA <400 c/mL	Plasma HIV-1 RNA <50 c/mL	Measures of CD4+	
			n/N (%)	n/N (%)	Median (Q1, Q3)	
Adult Studies						
ING113086 (SPRING-2) GSK Doc. No. 2013N158737_01	DTG 50 mg once daily + 2 NRTI	413 Rand. 349 Completed Rand. Phase 336 Ongoing in Open Label Phase	369/411 (90) - Week 48 338/411 (82) - Week 96	361/411 (88) - Week 48 332/411 (81) - Week 96	229.5 (128.0, 338.0) - Week 48 276.0 (159.0, 402.0) - Week 96	CD4+ measure shown is change from Baseline in CD4+ cell count
	RAL 400 mg BID + 2 NRTI	414 Rand. 332 Completed Rand. Phase	355/411 (86) - Week 48 321/411 (78) - Week 96	350/411 (85) - Week 48 314/411 (76) - Week 96	230.0 (139.0, 354.0) - Week 48 264.0 (155.0, 396.0) - Week 96	
ING114467 (SINGLE) GSK Doc. No. 2014N198290_01	DTG 50 mg + ABC/3TC once daily	414 Rand. 342 Completed Rand. Phase 317 Completed Open Label Phase	Not reported	364/414 (88) - Week 48 332/414 (80) - Week 96[b]	246.0 (150.0, 352.0) - Week 48 298.0 (198.5, 427.5) - Week 96	
	EFV/TDF/FTC once daily	419 Rand. 310 Completed Rand. Phase 278 Completed Open Label Phase	Not reported	338/419 (81) - Week 48 303/419 (72) - Week 96[b]	187.0 (107.0, 304.0) - Week 48 263.0 (159.0, 380.0) - Week 96	
ING111762 (SAILING) GSK Doc. No. 2012N154814_01	DTG 50 mg once daily + BR	360 Rand. 299 Completed Rand. Phase 282 Ongoing in Open Label Phase	278/354 (79) - Week 48	251/354 (71) - Week 48	144.0 (73.0, 242.0) - Week 48	
	RAL 400 mg BID + BR	364 Rand. 283 Completed Rand. Phase 23 Ongoing in Open Label Phase	257/361 (71) - Week 48	230/361 (64) - Week 48	137.0 (67.0, 224.0) - Week 48	

Study	Treatment Arm	No. Enrolled/ Completed	Efficacy Variables[a]			Other Comments
			Plasma HIV-1 RNA <400 c/mL	Plasma HIV-1 RNA <50 c/mL	Measures of CD4+	
			n/N (%)	n/N (%)	Median (Q1, Q3)	
Pediatric Studies						
P1093 (ING112578) GSK Doc. No. 2019N395492_00	DTG ~1 mg/kg to ~1.25 mg/kg (max dose of 50 mg) once daily + optimized background therapy	Efficacy Evaluable: 58 at Week 24 24 at Week 48	50/58 (86.2) – Week 24 18/24 (75) – Week 48	36/58 (62.1) – Week 24[c] 16/24 (66.7) – Week 48[c]	5.1 (1, 9.3) – Week 24[d] 8 (0,11) – Week 48[d]	CD4+ measure shown is change from Baseline in CD4+ percent

Study	Treatment Arm	No. Enrolled/ Completed	Efficacy Variables[a]			Other Comments
			Plasma HIV-1 RNA <400 c/mL	Plasma HIV-1 RNA <50 c/mL	CD4 Measures	
			n/N (%)	n/N (%)	Median (Q1, Q3)	
ARROW Randomization 3 (COL105677) GSK Doc. No. 2013N164513_00	ABC+3TC once daily	336 Rand. 331 in follow-up at trial end	256/330 (78) - Week 48 255/331 (77) - Week 96	236/330 (72) - Week 48[e] 230/331 (69) - Week 96[e]	CD4% mean increase from randomization: Week 48 – 0.9% Week 96 – 1.6%	- Snapshot analysis not performed for viral load analyses (proportions are shown). - The difference in increase in CD4% since randomization between once daily and BID groups was not statistically significant at Week 48 or Week 96.
	ABC+3TC BID	333 Rand. 326 in follow-up at trial end	260/331 (79) - Week 48 254/326 (78) - Week 96	242/331 (73) - Week 48[e] 234/326 (72) - Week 96[e]	CD4% mean increase from randomization: Week 48 – 1.3% Week 96 – 2.5%	

a. For Study P1093, efficacy was a secondary endpoint at Week 24 and Week 48. In all other studies, efficacy was a primary endpoint at Week 48.
b. The Week 96 viral load data was reported in GSK Document Number 2013N167896_00.
c. Results of <200 c/mL from HIV-1 RNA testing using a lower limit of detection of 200 c/mL were censored to >50 c/mL in this analysis.
d. n=57 participants contributing data for Week 24 and n=23 participants for Week 48.
e. Results shown are for <80 c/mL.
Note: Snapshot algorithm was used in the RNA analyses for all studies except ARROW.
Note: Only PK and Safety were evaluated in the ODYSSEY PK sub-studies. Thus, no efficacy data are available.

The following weight bands or age groups were enrolled in the paediatric studies with efficacy data available:

Table 29.P1093: Efficacy data for participants who completed or had the opportunity to complete, at a minimum, the Week 24 study visit (i.e., the PD Efficacy Population n=58)

Weight band	Total n=58
≥35 kgs	24
14 to <20 kg	4
10 to <14 kg	3
6 to <10 kg	17
3 to <6 kg	10

Table 30. ARROW: number of patients randomisation into the once daily versus twice daily ABC + 3TC (after ⩾36 weeks on ART).

Age (years) at last birthday	Twice Daily (total n=333)	Once Daily (total n=336)
0-2	38	36
3-6	180	164
7-12	111	131
13+	4	5

Acceptability of Triumeq film-coated tablets and dispersible tablets

The acceptability and palatability of DTG/ABC/3TC FCTs and DTs among participants in the IMPAACT 2019 study were assessed throughout the study as secondary objectives.

For the FCTs, acceptability was assessed by questions focused on determining if the FCT were swallowed whole. Eleven participants (≥25kg) were originally enrolled onto the FCT. Caregivers for 2 participants reported administration with cut or broken FCT (see table below). No participant discontinued the study or treatment due to the unacceptability of the FCT.

Table 31. Caregiver-reported questionnaire responses for DTG/ABC/3TC FCT and DTs at study Week 4 and Week 48

Question	DTG/ABC/3TC DTs		DTG/ABC/3TC Tablets	
	Total Week 4 N=46	Total Week 48 N=46	Total Week 4 N=11	Total Week 48 N=11
n	44	43	11	11
How easy is it to give DTG/ABC/3TC to the child? n (%)				
The child takes by themselves easily	22 (50.0)	20 (46.5)	9 (81.8)	10 (90.9)
The child takes with help, but you need to bribe them or promise a reward	18 (40.9)	19 (44.2)	2 (18.2)	1 (9.1)
The child takes with help, but you need to force them or threaten them	2 (4.5)	3 (7.0)	0	0
You need to hold the child	2 (4.5)	1 (2.3)	0	0
What does the child's face look like when taking DTG/ABC/3TC? n (%)				
Very good	8 (18.2)	16 (37.2)	5 (45.5)	6 (54.5)
Good	17 (38.6)	15 (34.9)	2 (18.2)	0
Average	13 (29.5)	6 (14.0)	4 (36.4)	5 (45.5)
Bad	4 (9.1)	2 (4.7)	0	0
Very bad	2 (4.5)	4 (9.3)	0	0
What does the child's face look like when taking their favorite food n (%)				
Very good	18 (40.9)	31 (72.1)	8 (72.7)	11 (100.0)
Good	19 (43.2)	12 (27.9)	2 (18.2)	0
Average	7 (15.9)	0	1 (9.1)	0
Bad	0	0	0	0
Very bad	0	0	0	0

2.6.6. Discussion on clinical efficacy

With this submission no new efficacy data has been provided. A specific demonstration of antiviral efficacy in paediatric patients was not required and efficacy could be extrapolated from adult patients given similar exposure.

The acceptability and palatability of the DTs were considered adequate and administration acceptable for most children/caregivers and no major concerns were identified. As for the acceptability testing of the adult FCTs, for 2 of 11 participants the caregiver reported administration with cut or broken FCTs. There is no information on the age distribution of the 11 children who were treated with the FCTs.

The available DTs cannot be administered to patients ≥25 kg as the relative exposures of the separate components of the FDC are not similarly bioavailable compared to the FCTs. DTG is approximately 1.7 times more bioavailable when administered as a DT whereas the bioavailability of 3TC and ABC are nearly the same in either form. The strength of the Triumeq dispersible tablets (5mg DTG/30mg 3TC/60 mg ABC) takes this difference into account to enable approved dose approximation across weight bands up to 25 kg.

It is not an option to match all components in the currently available Triumeq DT to the approved doses in adults and adolescents (50mg DTG/300mg 3TC/600mg ABC) without significantly over- or under- dosing one or more of the components.

Overall, the FCT may be acceptable to some patients but may be too large, particularly for younger children. There is no alternative formulation of this FDC for children who are unable to swallow the

FCT. Thus, there are remaining concerns regarding the acceptability of the FDC in all children 6-11 years weighing ≥25 kg.

2.6.7. Conclusions on the clinical efficacy

Given that exposure to all active substances is comparable to that seen in adults, the efficacy of Triumeq can be bridged and inferred in the treatment of HIV in paediatric patients.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The table below lists the clinical studies which provide safety and efficacy data that support once daily weight-based dosing of Triumeq in patients weighing at least 14 kg. This list is comprised of historical studies previously reviewed in support of the original Triumeq submission for use in patients weighing at least 40 kg as well as those which supported recommendations of the SEs (DTG, ABC, 3TC) for use in paediatric patients weighing at least 14 kg.

Table 32. Adult and Paediatric Studies that Support Triumeq Once Daily Dosing for Patients 14 kg and Above

Protocol Number (Study Identifier)	Date of Submission	Entity(ies) Supported	Submission Identifier
Pediatric Clinical Studies			
COL105677 (ARROW Randomization 3)	Current Submission	ABC and 3TC	m5.3.5.1[a]
ING112578 (P1093)	Current Submission	DTG	m5.3.5.2[a,b]
201296 (ODYSSEY, PENTA-20)	Current Submission	DTG	m5.3.5.2[a,b]
Adult Clinical Studies			
ING113086 (SPRING-2)	28 Oct 2013	DTG, ABC, and 3TC	EMEA/H/C/002754/0000
ING111762 (SAILING)	28 Oct 2013	DTG, ABC, and 3TC	EMEA/H/C/002754/0000
ING114467 (SINGLE)	26 Jun 2015	DTG, ABC, and 3TC	EMEA/H/C/2754/II/xx

a. These reports have also been previously submitted to their respective entity marketing applications.
b. Data from these studies supported the recently approved dosing of DTG in children of at least 4 weeks of age or older and weighing at least 3 kg (approval 11 January 2021). For the P1093 CSR, the safety data cut-off date was 30 April 2019 and the efficacy data cut-off date was 14 February 2019. For the ODYSSEY CSR, the data cut-off date was 28 February 2019.

P1093, ODYSSEY PK sub-studies

P1093 and the ODYSSEY PK sub-studies

Across both studies, a total of 258 unique participants were exposed to at least 1 dose of DTG. Of these, 80/159 (50.3%) from P1093 and 83/99 (83.8%) from the ODYSSEY PK sub-studies weighed at least 14 kg at enrollment.

In the P1093 all treatment (AT) Population, 145/159 (91%) participants were exposed to DTG for at least 24 weeks while 117/159 (74%) were exposed for at least 48 weeks. In the AT Population, the median extent of exposure to DTG was 731 days, ranging from 15 to 1993 days.

Similar exposure was seen in the safety population of the ODYSSEY PK sub-studies where 86/99 (87%) participants were exposed to DTG for at least 24 weeks while 74/99 (75%) were exposed for at least 48 weeks. The median extent of exposure to DTG in the safety population was 466 days, ranging from 26 to 842 days.

All participants in study P1093 and the ODYSSEY PK sub-studies were taking DTG. Across both studies, a total of 83 participants weighing at least 14 kg were also exposed to ABC and 3TC as part of their ARV; 7 participants from P1093 and 76 participants from the ODYSSEY PK sub-studies.

Table 33. Median Days of Exposure to DTG by Analysis Population in Study P1093 and the ODYSSEY PK Sub-studies

Analysis Population	Exposure to DTG Days Median (range)			
P1093	**14 to <20 kg (N=26)**	**20 to <25 kg (N=14)**	**25 to <35 kg[a] (N=12)**	**≥35 kg[a] (N=28)**
AT Population (N=159)	917 (49-1392)	1347.5 (85-1672)	1330 (232-1946)	1306.5 (281-1993)
ODYSSEY PK Sub-studies	**14 to <20kg (N=33)**	**20 to <25kg (N=28)**	**25 to <30kg[a] (N=16)**	**30 to <40kg[a] (N=6)**
Safety Population (N=99)	371.0 (165-594)	508.5 (335-841)	672.5 (505-842)	643.0 (568-841)

Data Source: P1093 CSR Table 1.65, ODYSSEY CSR Table 3.4

a. The highest 2 enrollment weight bands for each study differ as shown.

Table 34. Extent of Exposure to ABC and 3TC in the P1093 and ODYSSEY PK Sub-studies by Enrollment Weight Band

Study	Exposure to DTG + ABC and 3TC				
P1093 (AT Population)	**14 to <20kg (N=26)**	**20 to <25kg (N=14)**	**25 to <35kg[a] (N=12)**	**≥35kg[a] (N=28)**	**Total (N=80)**
Taking ABC/3TC, n	2	0	0	0	2
Days Median (min, max)	334.5 (40-629)	-	-	-	334.5 (40-629)
Participant years Median (min, max)	0.92 (0.1-1.7)	-	-	-	0.92 (0.1-1.7)
Taking ABC/3TC (inc other ARVs[b]), n	2	-	-	3	5
Days Median (min, max)	636.0 (7-1265)	-	-	1344.0 (1100-1358)	1265.0 (7-1358)
Participant years Median (min, max)	1.74 (0.0-3.5)	-	-	3.68 (3.0-3.7)	3.46 (0.0-3.7)
ODYSSEY PK Sub-studies (Safety Population)	**14 to <20kg (N=33)**	**20 to <25kg (N=28)**	**25 to <30kg[a] (N=16)**	**30 to <40kg[a] (N=6)**	**Total (N=83)**
Taking ABC/3TC, n	30	25	16	5	76
Days Median (min, max)	367.0 (165-595)	578.0 (335-841)	672.5 (505-842)	613.0 (568-841)	507.0 (165-842)
Participant years Median (min, max)	1.00 (0.5-1.6)	1.58 (0.9-2.3)	1.84 (1.4-2.3)	1.68 (1.6-2.3)	1.39 (0.5-2.3)

Data Source: P1093 Exposure Table 1, ODYSSEY Exposure Table 1

Note: Duration of exposure in days=(treatment stop date - treatment start date + 1), excluding dose interruptions. Participant exposure years=duration of exposure in days/365.25.

Note: In P1093, ABC and 3TC were administered either as SEs or an ABC/3TC FDC tablet. In addition, only on-treatment (i.e. on study) exposure to ABC/3TC in combination with DTG was considered.

a. The highest 2 enrollment weight bands for each study differ as shown.

b. These participants received other ARVs in addition to DTG + ABC and 3TC.

ARROW Randomization 3

In ARROW Randomization 3 a total of 669 participants were randomized to receive ABC and 3TC either twice daily (n=333) or to change to once daily (n=336).

Table 35. ARROW Randomization 3: Exposure to ABC + 3TC or ABC/3TC FDC (Paediatric Participants Weighing at Least 12 kg)

	12 to <15 kg Solution	12 to <15 kg Tablet	15 to <17 kg Tablet	17 to <20 kg Tablet	20 to <25 kg Tablet	25 to <30 kg Tablet	30 to <35 kg Tablet	35 to <40 kg Tablet
Once Daily ABC + 3TC								
Participants ever on ABC	7	109	138	162	175	107	55	20
Total participant-years on ABC	1.5	105.6	103.6	140.5	191.0	99.1	39.2	10.1
Participants ever on ABC (not Kivexa)	7	109	138	161	172	43	2	1
Total participant-years on ABC (not Kivexa)	1.5	105.6	103.6	140.5	184.8	14.6	0.8	0.5
Participants on Kivexa	0	0	0	1	30	89	53	20
Total participant-years on Kivexa	0	0	0	0.1	6.2	84.5	38.4	9.6
Participants ever on 3TC (not Kivexa)	7	105	134	160	173	43	2	1
Total participant-years on 3TC (not Kivexa)	1.5	100.5	99.5	141.2	185.8	14.6	0.8	0.5
Twice Daily ABC + 3TC								
Participants ever on ABC-containing	16	114	145	167	157	96	45	20
Total participant-years on ABC-containing	3.2	113.3	121.6	143.7	170.1	101.9	32.0	10.2
Participants ever on ABC (not Kivexa)	16	114	145	167	157	96	45	20
Total participant-years on ABC (not Kivexa)	3.2	113.2	121.5	143.7	170.1	100.6	32.0	10.2
Participants on Kivexa	0	0	0	0	0	2	1	0
Total participant-years on Kivexa	0	0	0	0	0	1.4	0	0
Participants ever on 3TC (not Combivir)	16	75	101	125	119	65	21	8
Total participant-years on 3TC (not Combivir)	4.2	77.2	85.8	106.0	136.6	67.2	14.4	2.2

Data Source: ARROW CSR Table 14

IMPAACT 2019 (205860)

IMPAACT 2019 is an ongoing Phase I/II, multi-centre, open-label study that investigates the PK, safety, tolerability, and efficacy of Triumeq FDC (Tablets and DT) in paediatric patients less than 12 years of age living with HIV-1. Paediatric participants were enrolled concurrently in 5 separate weight bands. Available safety data on SAEs from the IMPAACT 2019 study are reviewed.

Table 36. IMPAACT 2019 Enrollment and PK Accountability by Weight Band

Weight Band (kg)	Body weight, kg, median (range)	Triumeq Dosage Form	Number of Participants at Enrollment (11 March 2021)	Number of Participants Providing Evaluable Intensive PK Parameter Data
≥14 to <20	17 (14.4 - 19.6)	DT	15	7
≥20 to <25	21.5 (20 - 24.6)	DT	10	7
≥25 to <40	28.5 (25.6 - 39.3)	Tablet	11	7

Table 37 Triumeq Dosing for Paediatric Patients living with HIV-1 in IMPAACT 2019 Study

Triumeq 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
Triumeq 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

Adult Studies (SPRING-2, SAILING, SINGLE)

Exposure in the adult studies, that supported the safety and efficacy of Triumeq were part of the initial MAA.

2.6.8.2. Adverse events

The collection of adverse events (AEs) differed between studies. AEs of all grades were collected in P1093 while in the ODYSSEY PK sub-studies, Grade 1/2 AEs were only collected if they resulted in a

dose modification or DTG discontinuation. In ARROW, only Grade 3/4 AEs and Serious Adverse Events (SAEs) were collected (including deaths not judged primary HIV-related) were collected.

Table 38. Summary of AEs by Enrollment Weight Band through Week 24 (P1093 AT Safety Population and ODYSSEY PK Sub-study Safety Population)

P1093 Participants, n (%)	3 to <6kg (N=17)	6 to <10kg (N=37)	10 to <14kg (N=25)	14 to <20kg (N=26)	20 to <25kg (N=14)	25 to <35kg[a] (N=12)	≥35kg[a] (N=28)	Total (N=159)
With 1 or more clinical AEs	14 (82.4)	28 (75.7)	18 (72.0)	23 (88.5)	13 (92.9)	9 (75.0)	24 (85.7)	129 (81.1)
With 1 or more serious clinical AEs	4 (23.5)	7 (18.9)	1 (4.0)	1 (3.8)	1 (7.1)	1 (8.3)	0	15 (9.4)
With 1 or more serious drug related[b] clinical AEs	1 (5.9)	2 (5.4)	0	0	0	0	0	3 (1.9)
Who died due to clinical AEs	1 (5.9)	1 (2.7)	0	0	0	0	0	2 (1.3)
With 1 or more ≥Grade 3 clinical AEs	5 (29.4)	7 (18.9)	4 (16.0)	1 (3.8)	1 (7.1)	0	0	18 (11.3)
With 1 or more ≥Grade 3 drug related[b] clinical AEs	1 (5.9)	0	0	0	0	0	0	1 (0.6)
ODYSSEY PK Sub-study Participants, n (%)	**3 to <6 kg (N=1)**	**6 to <10 kg (N=10)**	**10 to <14kg (N=5)**	**14 to <20kg (N=33)**	**20 to <25kg (N=28)**	**25 to <30kg[a] (N=16)**	**30 to <40kg[a] (N=6)**	**Total (N=99)**
With any ≥Grade 3 AE[c]	0	4 (40)	1 (20)	5 (15)	3 (11)	0	1 (17)	14 (14)
With any SAE	0	2 (20)	0	2 (6)	0	0	1 (17)	5 (5)

Data Source: P1093 CSR Table 3.355, Table 3.361; ODYSSEY CSR Table 3.9, Table 3.22
Note: Only clinical AEs are shown for Study P1093.
Note: 145 (91%) P1093 participants and 86 (87%) ODYSSEY PK sub-study participants were exposed to DTG for at least 24 weeks.
Note: There were no drug related AEs or deaths reported in the ODYSSEY PK sub-studies (Data Source: ODYSSEY CSR Table 3.16, Table 3.20, Table 3.21).
a. The highest 2 enrollment weight bands for each study differ as shown.
b. In Study P1093, drug related AEs were determined to be possibly, probably or definitely related to study drug by the protocol team.
c. By design in the ODYSSEY study, AEs included are Grade 1/2 AEs Leading to Dose Modification or Withdrawal, ≥Grade 3 AEs. Note, there were no Grade 1 or 2 AEs leading to dose modification or withdrawal and all SAEs were ≥Grade 3.

Overall, in P1093, SAEs and ≥Grade 3 AEs occurred more frequently in participants enrolled to the <14 kg weight bands. In the ODYSSEY PK sub-studies, despite the small numbers of cases reported up to Week 24, the exposure-adjusted incidence rates (EAIRs) overall were highest in participants <14 kg. The events more frequently reported for ≥Grade 3 clinical AEs included infectious events (gastroenteritis, pneumonia events), gastrointestinal (diarrhoea) and general disorders (pyrexia).

Overall AEs in ARROW Randomization 3

The proportions of participants reporting Grade 3/4 AEs and SAEs were similar in the twice daily versus once daily treatment groups.

Table 39. Adverse Events (Grade 3/4 & SAEs) in the Once Daily versus Twice Daily ABC + 3TC (ARROW Randomization 3)

	Twice Daily (N=333)	Once Daily (N=336)	Total (N=669)
Grade 3/4 AEs			
Participants with at least 1 AE, n (%)	54 (16.2)	57 (17.0)	111 (16.6)
Total AEs	82	95	177
Total person years at risk	727	735	1462
AE rate (per 100 years)	11.3	12.9	12.1
SAEs			
Participants with at least 1 SAE, n (%)	37 (11)	30 (9)	67 (10)
Total SAEs	47	40	87
Total person years at risk	727	735	1462
SAE rate (per 100 years)	6.5	5.4	6.0

Source Data: ARROW CSR Table 48. Table 53

Common Adverse Events

Study P1093 and the ODYSSEY PK Sub-studies

Cough, pyrexia, diarrhoea, rhinorrhoea, vomiting, and nasal congestion were the most common AEs reported based on the entire AT safety population (all enrollment weight bands, P1093). Diarrhoea is a known adverse drug reaction for DTG.

Through 24 weeks in the ODYSSEY PK sub-studies, only neutropenia and anaemia were observed in ≥2 participants across all enrollment weight bands. As only ≥Grade 3 AEs were reported, the profile of common AEs is not directly comparable with that in P1093. Hepatitis A, pneumonia, anaemia, and neutropenia were AEs observed in more than a single participant through the safety data cut-off.

ARROW Randomization 3

The most frequently reported Grade 3/4 AEs in the ARROW Randomization 3 analysis were neutropenia and *P. falciparum malaria*.

Drug-related AEs

P1093

In P1093, through Week 24 in the AT safety population, 33/159 (20.8%) participants developed drug-related clinical or laboratory AEs, which were most commonly reported from the Investigations System Organ Class (SOC). Of these drug-related AEs, the majority were considered possibly related and only 3 were considered definitely related by the protocol team, all of which were cases of immune reconstitution inflammatory syndrome (IRIS) in participants <14 kg at enrollment. Drug related AEs were reported across enrollment weight bands (n=14, <14 kg; n=19, ≥14 kg), excluding the 25 to <35 kg enrollment weight band where no drug-related AEs were reported.

The most commonly reported drug-related AEs through Week 24 in the AT safety population were absolute neutrophil count (ANC) decreased (n=9) and haemoglobin decreased (n=6). All but 1 of drug-related AEs were maximum Grade 1 or Grade 2 severity. There were no Grade 4 or Grade 5 drug-related AEs reported. The majority of drug related AEs were non-serious.

Most drug-related AEs were reported during the first 24 weeks of treatment. Through Week 48, 2 additional participants were reported with drug related AEs and beyond Week 48, an additional 3 participants.

ODYSSEY PK Sub-studies

No AEs were considered drug related.

ARROW Randomization 3

One Grade 3/4 AE was considered definitely/probably or uncertainly related to ABC and/or 3TC and not HIV-1-related. This male participant had a Grade 4 hepatitis (cause unknown) that was considered by the investigator to be uncertainly related to 3TC and ABC. The participant was randomized to once daily dosing. The event did not meet the criteria for being reported as an SAE.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Death was reported for 3 participants enrolled into P1093 as of 30 April 2019, including 2 participants from the 2 lowest enrollment weight bands (3 to <6 kg, 6 to <10 kg) and 1 participant from the heaviest enrollment weight band (≥35 kg). None of the deaths were considered related to the study drug. No participants enrolled into the ODYSSEY PK sub-studies died as of 28 February 2019.

Table 40. Deaths in Study IMPAACT P1093 (AT Population)

DTG Formulation/Study Cohort	Age/Gender	Cause of Death	Days on DTG	Relationship to Study Drug[a]

FCT/IIA	15 years/male	Drowning	1459	Not related
DT/IV-DT	8 months/female	Acute gastroenteritis	57	Probably not related
DR/III-DT	2 years/male	Unknown cause[b]	130	Not related

Site investigator assessments are shown. The assessments of the protocol team concurred with those of the site investigator.
[b]It was initially reported that the participants developed generalized convulsions having previously been clinically well but was found unconscious. Due to lack of witnesses, there was no confirmation that any convulsions had occurred. Formal investigation including postmortem examination into possible causes of death ruled out expected causes including non-accidental injury. The cause of death was considered as unknown.

In total, 5 participants died during ARROW Randomization 3, and included 4 participants in the BID dosing group and 1 participant in the once-daily dosing group. None of the deaths during ARROW Randomization 3 were considered related to ABC + 3TC treatment.

Table 41. Deaths in the ARROW Study (Randomization 3)

Age/Gender	Cause of Death	Weeks post Randomization
Twice Daily ABC and 3TC		
9 years/male	Tuberculosis (pulmonary – smear negative or not done)	51
7 years/female	Uncertain cause	100
11 years/male	Pneumonia (no organism identified, aspiration pneumonia) and HIV-related indeterminate cerebral disease	68
5 years/male	Cor Pulmonale (pulmonary heart disease), bronchiectasis, and lymphoid interstitial pneumonia	51[a]
Once Daily ABC and 3TC		
10 years/male	Lung syndrome	65

[a]The participant had switched to 2nd line (ZDV + didanosine + Aluvia) 59 weeks after randomization and was not taking 3TC or ABC at the time of death.

SAEs in P1093 and the ODYSSEY PK Sub-studies

In the P1093 AT safety population, a small proportion of participants reported at least 1 SAE through Week 24; 15/159 (9%). A small proportion of participants with SAEs was also observed through Week 24 in the ODYSSEY PK sub-studies Safety Population; 5/99 (5%).

In P1093, most of the participants with SAEs (11/15) started study treatment in the 2 lowest enrollment weight bands and SAEs were most frequently from the infections and infestations SOC. Although most participants reported a single SAE in the first 24 weeks, a single participant from the 6 to <10 kg enrollment weight category experienced 7 SAEs in the first 24 weeks.

Data from the ODYSSEY PK sub-studies are consistent with P1093, but the numbers of participants in the lower weight bands are small. Overall, the frequency of SAEs was the same or lower than that reported in the Phase III adult DTG study (SAILING) which was 8% at the 24-week database cut off. In the SAILING study, most SAEs (10/28 participants) were also reported from the infections and infestations SOC.

≥Grade 3 AEs in P1093 and the ODYSSEY PK Sub-studies

The ODYSSEY PK sub-studies only reported ≥Grade 3 AEs. The 18 participants with ≥Grade 3 AEs through Week 24 were reviewed. In 14 of these 18 participants with ≥Grade 3 AEs, at least 1 event was also considered serious.

All participants were <25 kg at enrollment, and 16/18 were <14 kg. These ≥Grade 3 AEs were mainly from infections and infestation SOC (10/18 participants) (mainly pneumonia events and gastroenteritis), general disorders SOC (5/18 participants) (mostly pyrexia), and gastrointestinal disorders SOC (3/18 participants) (all diarrhoea).

3 serious cases of IRIS were considered related to DTG. These participants had a higher proportion of contemporaneous Grade 1 and 2 haemoglobin declines, but no other obvious laboratory abnormalities.

Compared to other weight categories, a higher use of trimethoprim/sulfamethoxazole, zidovudine, and lopinavir/ritonavir was observed in this group. The more frequently reported ≥Grade 3 clinical AEs included infectious events (gastroenteritis, pneumonia events), gastrointestinal (diarrhoea) and general disorders (pyrexia).

According to the MAH, the overall impression was that the pattern of more severe/serious events in the lowest weight categories is due to relevant background factors such as higher use of concomitant medications such as lopinavir/ritonavir, zidovudine, and sulfamethoxazole/trimethoprim at the start of study treatment compared to the heavier participants. In addition, children under 2 years have the highest background risk of morbidity and mortality due to diarrhoea or pneumonia. This pattern was observed in the P1066 study evaluating another INSTI based therapy in paediatric participants in low- and middle-income countries.

In P1093 there were relatively more Grade 3 or 4 AEs, SAEs and Grade 3 or 4 lab events (driven by ANC decreases) reported from participants enrolled into the lowest weight bands. P1093 may have overestimated graded changes to neutrophil counts as Division of AIDS table grading was used which does not account for lower normal neutrophil levels in African populations. Higher EAIRs of ≥Grade 3 AEs were observed in those participants weighing <14 kg in the ODYSSEY PK sub-studies, although numbers were low. EAIRs were available for those participants receiving the DT formulation in the P1093 study, and similar conclusions were drawn. Irrespective of the methods used to calculate EAIRs, both studies demonstrate that higher proportions of participants <14 kg experienced ≥Grade 3 AEs. However, neither study suggests an excess of drug attributable events in lower weight categories.

SAEs in ARROW Randomization 3

All SAEs that occurred during the once daily versus twice daily ABC + 3TC randomization of ARROW were considered unrelated to ABC or 3TC. Overall, a total of 87 SAEs were experienced in 67 participants (67/669 [10.0%]) during the once daily versus twice daily ABC + 3TC randomization of ARROW.

The category with the most SAEs was specific infections (67 events), driven by the number of participants with malaria. The most frequently reported SAEs were *P. falciparum malaria* (59 events), measles (4 events), acute diarrhoea (3 events), pneumonia (3 events), septicaemia/bacteraemia (3 events), trauma (3 events), and clinical anaemia (3 events).

≥Grade 3 AEs in ARROW Randomization 3 by Weight Band

There were no occurrences of Grade 3 and 4 AEs in participants <15 kg taking oral solution formulations once daily. For those taking the tablet formulation, the EAIR of Grade 3 and 4 AEs varied between weight bands. However, no weight-band related pattern was observed. Overall, 16.6% of participants experienced at least one Grade 3/4 AE during the once daily versus twice daily randomization part of the study. For participants receiving once daily ABC + 3TC, the children in the 17 to <20 kg weight band experienced the most Grade 3 and 4 AEs overall (27 of 94 events). The numbers of specific Grade 3 and 4 AEs reported in each weight band varied. However, no weight band-related pattern was observed. The numbers of events by weight band were similar between the once daily and twice daily regimens.

Table 42. Grade 3 and 4 AEs by Weight Band – ABC + 3TC or ABC/3TC FDC Once Daily - in ARROW Randomization 3 (Tablet Formulations)

Events, n	Weight Band (kg)						
	12 to <15	15 to <17	17 to <20	20 to <25	25 to <30	30 to <35	Total
Grand Total Events, n	17	11	27	16	13	10	94
Neutropenia	2	1	6	2	4	8	23
P falciparum malaria	5	2	5	3	1		16
Thrombocytopenia		3	2	4	1	2	12
Anemia with clinical symptoms		1	3	2	1		7
Raised liver enzymes	2	1	1	1			5
Raised AST			1	2	1		4
Anemia with no clinical symptoms		1	1		1		3
Presumed septicemia/ bacteremia - not investigated	1		2				3
Acute diarrhea not investigated			1	1			2
Acute febrile episode - undiagnosed	2						2
Cataract					2		2
Dog bite	1		1				2
Hypoglycemia			2				2
Pneumonia no organism identified		1			1		2
Acute diarrhea no pathogen, idiopathic AIDS enteropathy	1						1
Coma	1						1
Hepatitis cause unknown	1						1
Hyponatremia			1				1
Leucopenia			1				1
Measles				1			1
Paraffin poisoning		1					1
Raised ALT					1		1
Raised bilirubin	1						1

Data Source: ARROW CSR Table 55

Note: No Grade 3 or 4 AEs were reported in participants weighing <15 kg taking once daily oral solution formulations (see ARROW CSR Table 57).

IN-STREAM DATA FROM IMPAACT 2019

The formal safety analysis from this study will be presented in a future submission to support the use of Triumeq in patients weighing 6 to <14 kg. SAEs and pregnancies are reported in real time to the GSK Safety Database. As of 31 August 2021, one SAE of Grade 4 Drug-induced liver injury was reported from IMPAACT 2019. This SAE was reported in a 7-year-old male participant (20 kg), with an elevated total bilirubin at screening, who was receiving DTG/ABC/3TC FDC DT and experienced increased ALT (Grade 4), increased AST (Grade 3), increased total bilirubin and a direct bilirubin that was 50% of total bilirubin at his Week 36 visit. Although asymptomatic, transaminases for this participant increased peaking 2 weeks after study drug was withdrawn. Liver function subsequently improved over the next 3 weeks. This participant was withdrawn from study treatment for suspected drug-induced liver injury (DILI), and no alternative aetiology was identified at the time.

2.6.8.4. Laboratory findings

P1093 and ODYSSEY PK sub-studies

In P1093, the overall profile of ALT, bilirubin, creatinine, haemoglobin, and ANC median levels over time followed the patterns seen in adult studies. No differences were apparent across weight categories.

Laboratory events were typically Grade 1 or 2 (i.e., in 116/151 participants) and the most common laboratory events through Week 24 were blood bicarbonate decreased (n=99) (conclusion that this was artefactual), blood sodium decreased (n=77), ANC decreased (n=61), haemoglobin decreased (n=53), and blood glucose decreased (n=41). Most abnormal laboratory findings occurred during the first 24 weeks of treatment in the AT safety population.

In the ODYSSEY PK sub-studies, the profile of median ALT, bilirubin, creatinine, haemoglobin, and ANC median levels over time followed the patterns seen in adult studies. No differences were apparent across weight categories. The majority of post-baseline emergent laboratory abnormalities were maximum Grade 1 or 2 and there were few ≥Grade 3 laboratory events.

ARROW Randomization 3

In the evaluation of the incidence of Grade 3/4 clinical laboratory events, no significant difference was observed between the once- and twice-daily dosing groups. As with the overall AE profile, the most common Grade 3/4 clinical laboratory AE was neutropenia (34 participants, 5%). The next most common Grade 3/4 clinical laboratory AEs involved abnormalities in haemoglobin values (16 participants, 2%), AST and ALT values (15 participants, 2% each), and platelets (14 participants, 2%). These AEs were not deemed related to ABC or 3TC.

Growth Measures

P1093 and the ODYSSEY PK Sub-studies

Weight

In P1093, the median Z scores for participants weighing ≥35 kg at enrollment remained above the 50th percentile while the medians of participants in the lower enrollment weight band categories remained below the 50th percentile. In the ODYSSEY PK sub-studies some improvement over time in weight Z scores was apparent. As both studies do not have a direct comparator with other ARV classes, no further conclusions can be made on weight gain.

Height

In P1093, the Z scores remained consistent, and no difference was observed between enrollment weight bands while in the ODYSSEY PK sub-studies some improvement over time in height Z scores was apparent.

Body Mass Index (BMI)

In both studies, where data were available, no clear changes in Z scores were apparent over time.

ARROW Randomization 3

Height for Age

No significant differences between the once daily and twice daily ABC + 3TC groups were observed for the mean change from randomization in height for age Z-scores and mean absolute Z-scores for height for age.

Weight for Age

No significant differences between the once daily and twice daily ABC + 3TC groups were observed for the mean change from randomization in weight for age Z-scores and mean absolute Z-scores for weight for age.

BMI for Age

No significant differences between the once daily and twice daily ABC + 3TC groups were observed for the mean change from randomization in BMI for age Z-scores and mean absolute Z scores for BMI for age. BMI Z-scores decreased in both groups as a consequence of stable weight and increasing height-for-age: weight gain was rapid during the first year on ART and then stabilized, whereas improvements in height took longer to achieve.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

No new analyses were undertaken in support of this submission.

In study P1093, pregnancy triggered withdrawal from treatment with DTG, but participants were still followed while on an alternate SOC treatment. 3 female adolescent participants, all in the ≥35 kg enrollment weight band (Cohort I), became pregnant while participating in P1093 as of the data cut-off date of 30 April 2019.

• 1 participant was found to have a positive pregnancy test when being evaluated for a suspected pneumonia nearly 4 years after starting on study drug. Treatment with DTG was discontinued and the participant had an elective termination.

• 1 participant was reported to be pregnant 824 days (over 2 years) after the start of study drug. Treatment with DTG was permanently discontinued. The participant delivered a healthy baby girl.

• 1 participant disclosed the onset of sexual activity at her Week 144 study visit and a urine pregnancy test result at that time was positive. This was reported by the investigator as exposure to DTG in the first trimester. At 39 weeks gestation, the participant gave birth via normal spontaneous vaginal delivery. The neonate weighed 3,270 grams at birth, without apparent congenital anomaly. The participant continued taking DTG throughout the pregnancy.

In ODYSSEY, pregnancy triggered withdrawal from treatment with DTG, but participants were still followed while on an alternate SOC treatment. 1 female adolescent participant from the 30 to <40 kg enrollment weight band became pregnant 606 days after starting treatment with DTG. Treatment with DTG was stopped and the pregnancy resulted in a live birth after the safety cut-off date. No other details on the birth were provided.

2.6.8.7. Immunological events

Three cases of IRIS were reported in study P1093.

2.6.8.8. Safety related to drug-drug interactions and other interactions

There is no new safety information to report for drug interactions from ARROW Randomization 3, P1093, or the ODYSSEY PK sub-studies.

2.6.8.9. Discontinuation due to adverse events

In Study P1093, there were no AEs that resulted in discontinuation of study drug. In the ODYSSEY PK sub-studies, 2 participants withdrew from treatment with DTG due to an AE and were both diagnosed with Hepatitis A. Both participants, who were ≥14 kg at enrollment, met protocol defined liver stopping criteria. These cases of Hepatitis A were not considered related to DTG.

In ARROW Randomization 3, no participant discontinued or had an ART modification due to an AE.

2.6.8.10. Post marketing experience

Patient Exposure data from Marketing Experience

Triumeq, Tivicay, Ziagen, Epivir and Kivexa/Epzicom have well-characterized safety profiles from extensive post-marketing experience. Triumeq and Tivicay post-marketing experience is mainly in adults and there are no reliable estimates for post-marketing exposure specifically in children. The estimated total post-approval exposure to Triumeq, Tivicay, Ziagen, Epivir and Kivexa/Epzicom based on IQVIA sales volume data are as follows:

• 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 2021 was estimated to be 1,097,918 patient years.

• For Tivicay the best estimates of total post-marketing experience assuming all patients take a single tablet of DTG per day, irrespective of tablet strength (DTG 50 mg, 25 mg, 10 mg tablets or 5 mg DTs), from licensure (12 August 2013) to 31 March 2021 was 2,142,583 patient years. The majority of post-marketing exposure was to 50 mg Tablets. The data suggested that exposure to the 25 mg and 10 mg tablets and 5 mg DTs, which support paediatric dosing in children weighing <40 kg, is low (~0.1% of all exposure to DTG).

• For Ziagen the best estimates of total post-marketing experience assuming patients take a standard daily dose of 300 mg twice daily or 15 mL twice daily to 31 March 2021 was 900,615 patient years (882,623 patient years for tablets and 17,993 patient years for oral solution).

• For Epivir the best estimates of total post-marketing experience assuming patients take a standard daily dose of 150 mg twice daily or 300 mg once daily to 31 March 2021 was 2,605,511 patient years (2,551,079 patient years for tablets and 54,432 patient years for oral solution).

• For Kivexa/Epzicom the best estimates of total post-marketing experience assuming patients take one tablet daily to 31 March 2021 was 1,604,715 patient years.

These figures do not include sales through generic companies or licensing partners and therefore do not capture use in some countries where the products are provided through licensing agreements between ViiV Healthcare and generic companies. IQVIA sales data are considered to represent the best available source for estimating exposure for Triumeq, Tivicay, Ziagen, Epivir and Kivexa/Epzicom. However, it should be noted that the data can be up to 6 months in arrears and provide only a gross approximation of exposure.

Post-marketing reports involving Triumeq in children (<12 years of age)

The GSK Safety database was searched on 3 September 2021 for spontaneous and post marketing surveillance reports involving Triumeq as a suspect drug reported through 31 August 2021. A total of 9,368 cases were retrieved cumulatively, 5 of which were identified in children <12 years of age (excluding cases where exposure to Triumeq was *in utero* or via breastmilk). All 5 cases were non-serious. Cases were received between 2016 and 2020. Age was reported in 2 cases in which the patients were 5 years and 8 years old. Specific age was not reported in the remaining 3 cases. Gender was reported in 3 cases and included 2 females and 1 male. 3 of the 5 cases reported medication error terms and are briefly summarized below:

• In the first case (involving a 5-year-old male) a pharmacist reported a hospital prescription of half a Triumeq tablet daily (PTs: Product use issue, Wrong technique in product usage process, and Product prescribing issue). At the time of the report the pharmacist had not dispensed the prescription and it was not reported if the prescription was intentional or non-intentional.

• The second case reported off-label use of Triumeq tablets in an 8-year-old female (PTs: Off label use and Product use issue). The reporter noted it was being checked with the hospital whether the prescribing of Triumeq was intended. Overall, the case was poorly documented, and it was unclear whether the patient received Triumeq or not.

• The third case reported a child of unknown age (weight 12 to 13 kg) receiving half a crushed Triumeq tablet daily due to lack of other alternatives (PTs: Wrong technique in product usage process and Product use issue). It was also reported that the child had been administered one third Genvoya tablet daily (Genvoya reported as co-suspect medication). The case was poorly documented with no information provided on whether the child experienced any AEs.

The fourth case was a consumer report of treatment noncompliance in a female of unknown age. It was reported that the patient sometimes pretended to swallow the tablets. The case was poorly documented, and no information was provided on whether any AEs occurred. The remaining case reported headache in a child of unknown age following a recent switch to Triumeq. The case was poorly documented with no further information provided on date of switch, time to onset, outcome or action taken with drug. Headache is a listed as a known adverse drug reaction for Triumeq.

No new safety concerns are evident from review of the small number of cases identified involving Triumeq use in children.

Post-marketing reports involving Tivicay administered in combination with ABC and 3TC in children (<12 years of age)

The GSK Safety database was searched on 3 September 2021 for spontaneous and post marketing surveillance reports involving Tivicay as a suspect drug reported through 31 August 2021.

Cases were reviewed to identify those reported in children <12 years of age and where both ABC and 3TC (either as SEs or FDC) were reported as co-suspect drugs. A total of 11,164 cases were retrieved cumulatively for Tivicay, 6 of which 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.

Cases were received between 2019 and 2020. Age was reported in all 6 cases (range 4 - 11 years) with a median age of 7.5 years old. Gender was reported in all cases and included 4 males and 2 females. All 6 cases were non-serious. 3 of the 6 cases reported medication error terms and are briefly summarized below:

• The first case involved a 4-year-old year male and reported abnormal behaviour and off-label use of Tivicay in a child less than 6 years old (PTs: off-label use, product use issue, and abnormal behaviour). The patient experienced behavioural issues an unknown time after switching from Kaletra (lopinavir+ritonavir) and Tivicay to Kivexa and Tivicay. Kivexa and Tivicay were interrupted, and the outcome was unknown.

• The second case concerned a 9-year-old male (23 kg) and reported splitting of Ziagen tablets so that the patient could take them more easily. However, this made the tablets taste bitter and the patient started to refuse the drug. It was reported that the antiviral effect of the drug did not work adequately as the patient's adherence was poor. PTs reported included product use issue, product complaint, treatment noncompliance, therapeutic product effect incomplete and off-label use. Ziagen was discontinued and the regimen was changed to Tivicay and Epivir. Based on the available information it does not appear that this patient was treated with all 3 components of Triumeq concurrently.

• The third case involved a 4-year-old male (21 kg) and reported DTG use in an unapproved age group (PTs: off-label use and product quality issue). The child started on DTG, 3TC and ABC at 4 years old because he did not tolerate Kaletra. No side effects were reported, and the patient had less than 20 copies/mL (not further defined) during the treatment.

The remaining 3 cases reported clinical AEs following exposure to Tivicay plus Kivexa.

• In one case abnormal sweat odour (PT: skin odour abnormal) was reported in a 7-year-old female an unknown time after starting Kivexa and Tivicay 25 mg. The action taken with the drugs and the outcome of the event was unknown. Abnormal skin odour is not a known adverse drug reaction for either Tivicay or Kivexa.

• The second case reported obstipation (PT: constipation) in an 8-year-old male patient approximately 10 months after starting Tivicay 25 mg daily and approximately 3 months after starting Kivexa. The dose of Tivicay was increased and Kivexa was unchanged. The outcome of constipation was reported as recovering. Constipation is not a known adverse drug reaction for either Tivicay or Kivexa.

• The third case described headache and sleep problems in an 11-year-old female at unknown time after switching from Kivexa and another product (not further specified) to Kivexa and Tivicay. The action taken with the medicines and the outcome of the events was unknown. Headache is a known adverse drug reaction for Kivexa and Tivicay. Insomnia and abnormal dreams are listed events for Tivicay or Kivexa.

No new safety concerns are evident from review of the small number of cases identified involving DTG administered in combination with ABC and 3TC (where all 3 components are reported as suspect drugs) in children <12 years of age.

Literature

A literature review (through 31 August 2021) was conducted to identify use of Triumeq, or DTG used in combination with both ABC and 3TC, in children <12 years age. Articles were assessed to determine whether the safety profile in the literature was consistent with the established safety profile of Triumeq or its individual components.

Preliminary PK and Week 4 safety results for once-daily dosing of Triumeq Tablets and DTs in children weighing ≥14 kg from IMPAACT 2019 were presented at the 2021 International Workshop on HIV Paediatrics and the 11th IAS Conference on HIV Science. Triumeq Tablets and DTs were well-tolerated and no new safety concerns were identified (Brooks, 2021).

Review of the literature did not identify any other articles containing specific safety information on the use of Triumeq FDC in children <12 years age. A number of conference abstracts, posters and papers were identified that described use of DTG in children. However, the review of these articles identified only a small number of articles which reported use of DTG in combination with both 3TC and ABC.

Monaghan (2021) described a case report of a 5-year-old girl who had a 6-week onset of rapidly deteriorating mobility, progressive proximal muscle weakness and a raised creatinine kinase of 4330 U/L [25-200 U/L] diagnosed with inflammatory myositis. It was reported that she had had a recent switch in medication, from twice daily raltegravir to once daily DTG while continuing on established daily ABC and 3TC. Changing DTG back to raltegravir, in combination with continuing ABC and 3TC, made no difference to her weakness or creatinine kinase levels. These drugs had been well-tolerated over the preceding 7-month period. Her viral load had been undetectable over the preceding 2 years. There was a dramatic improvement when the ART regimen was changed to monotherapy with ritonavir and darunavir, including regained ability to stand and walk within 10 days and reduction in creatinine kinase from 1700 at time of switch to 403 U/L. However, the authors did not report if treatment was

given to the patient. There has been no recurrence of myositis since the patient switched to ritonavir and darunavir. The authors noted that DTG is not cited as a cause of inflammatory myositis and in one study was not associated in the adult population with a risk of significant creatinine kinase level rise. Furthermore, the authors reported that it is known that other ARV medications, such as zidovudine and 3TC, may cause this potential adverse effect. They concluded that this case highlights the potential risk of developing inflammatory myositis from ARV even years into treatment. The authors reported that there were no other medications or confounding factors upon additional follow-up. However, the MAH considers that HIV associated myositis or other aetiologies cannot be ruled out in this case.

Thivalapill (2020) conducted a retrospective observational cohort analysis of BMI measurements 1 year before and after transition to DTG in 460 virally suppressed adolescents (10-19 years of age) living with HIV in Eswatini. 50 (10.9%) patients transitioned to ABC/3TC/DTG and 410 (89.1%) transitioned to TDF/3TC/DTG. At the time of DTG transition, 29% of adolescents were between 10-12 years of age. Across the entire cohort BMI increased at a rate of 0.3 kg/m^2 per year before DTG transition and increased to a rate of 1.2 kg/m^2 per year after DTG transition. The BMI rate of change was 1.1 kg/m^2 in females and 0.6 kg/m^2 per year in males. The authors concluded that further investigation was required to elucidate the mechanism that underlies these observations and to assess how DTG impacts BMI in adolescents following longer durations of treatment. No specific analysis of BMI change was provided by age at time of transition or by DTG companion drugs.

Actions taken for safety reasons

No significant actions were taken for safety reasons by the sponsor or by the competent authorities with respect to the use of Triumeq, Tivicay, Epzicom/Kivexa or Ziagen in children. For Epivir, a number of actions have previously been taken in relation to a drug interaction between 3TC and sorbitol, including a 25% dose increase for paediatric patients (aged at least 3 months) for Epivir Oral Solution.

• The interactions section of the company global data sheet for 3TC HIV was updated in November 2016 following results from a study undertaken to address a US FDA post marketing requirement to evaluate the effect of sorbitol on the PK of 3TC. For 3TC oral solution only, a statement was also added to the special warnings and precautions for use to advise prescribers that an all-tablet regimen should be used where possible and to consider more frequent monitoring of viral load if 3TC oral solution is chronically administered with sorbitol containing medicines. The company global data sheet for 3TC HIV was further updated on 14 May 2018 to include a 25% increase in the recommended total daily dosage for 3TC oral solution from 8 mg/kg/day to 10 mg/kg/day in HIV-1 infected paediatric patients aged 3 months and older. For consistency of information, the dosing recommendations for children with renal impairment aged at least 3 months and weighing less than 25 kg was also updated to reflect the 25% dose increase.

• On 17 February 2017, the MAH submitted a type II variation for 3TC HIV (EMEA/H/C/000107/II/0104) in order to update the product information with the sorbitol interaction data. The product information approved as a result of this variation included a dose increase in the recommended total daily dosage for 3TC oral solution from 8 mg/kg/day to 10 mg/kg/day in HIV-1 infected paediatric patients aged 3 months and older. The CHMP positive opinion was received 25 January 2018 and Commission Decision on 05 March 2018. On 24 September 2018, the MAH submitted a further variation (EMEA/H/C/000107/II/0108) to update the 3TC oral solution product information with similarly revised dosing advice for paediatric patients with renal impairment. The CHMP opinion was received on 13 December 2018 and Commission Decision on 06 February 2019. Of note, the 25% dose increase applied to Epivir oral solution only and did not impact dosing recommendations for 3TC containing tablet formulations including FDC, such as Triumeq. Information on the interaction between 3TC and sorbitol is already described in the current Triumeq PI and advises that, when possible, to avoid chronic coadministration of Triumeq with medicinal products containing

sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols. The PI also advises to consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided. No further updates with respect to this interaction are proposed as part of the current submission.

2.6.9. Discussion on clinical safety

Since the safety data from IMPAACT 2019 study is limited, the safety assessment mainly relied on historical studies previously reviewed in support of the original Triumeq submission for use in patients weighing at least 40 kg as well as those which supported recommendations of the single entities (DTG, ABC and 3TC) for use in paediatric patients weighing at least 14 kg. This approach is considered acceptable since the safety profile of Triumeq is expected to be consistent with the safety profile of the individual components used in children at these licensed doses. The safety of ABC and 3TC use in children is well established based on many years of post-marketing experience. These safety conclusions are supported by the fact that predicted exposures in this FDC (Tablet and DT formulations) are comparable to predicted paediatric exposures of the individual components at approved doses and are also comparable to observed data in adults. The safety profiles of the individual components and FDCs are already described in the approved product information and no additional safety concerns are proposed for inclusion in the revised Triumeq PI.

The safety data reported from three key paediatric clinical studies using the individual components of Triumeq uncovered no additional safety concerns compared to observed adult safety data.

One SAE of Grade 4 DILI was reported from the ongoing study IMPAACT 2019. Causality is possible. ALT and/or AST elevations are listed as common and hepatitis as uncommon adverse reactions in the Triumeq SmPC Section 4.8.

Regarding the case of myositis reported by Monaghan (2021) causality is possible. It is known that other ARV medications, such as zidovudine and 3TC, may cause this potential adverse effect. The authors reported that there were no other medications or confounding factors upon additional follow-up. Myalgia, rarely myolysis, arthralgia and elevated creatine phosphokinase are listed in the SmPC Section 4.8 as signs of ABC hypersensitivity.

No new safety signals were identified from the review of post-marketing safety data in children (<12 years) with Triumeq or Tivicay administered with both ABC and 3TC, or ABC/3TC. As Triumeq is not yet authorized for use in children the lack of data in this population is not unexpected.

2.6.10. Conclusions on the clinical safety

There are no new or specific safety issues making Triumeq non-suitable in paediatric patients weighing $\geqslant$14 kg.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of 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

Discussion on safety specification

A parallel procedure to address the removal of three important risks (Dolutegravir Hypersensitivity reactions, Hepatobiliary reactions and Serious rash) from all four dolutegravir-containing product EU-RMPs was approved within the procedure EMEA/H/C/WS2210, following finalisation of procedure EMEA/H/C/WS1810 concerning submission of EuroSIDA (category 3 PASS) study. In addition, the MAH took the opportunity to harmonise the risks across all four dolutegravir-containing product EU-RMPs. In this context, also "depression" was deleted as important potential risk from the Triumeq RMP v. 18.0.

Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

2.7.2. Pharmacovigilance plan

Summary of planned additional PhV activities from RMP

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 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.	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
			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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Expected Final Report	October 2023

Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

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

Safety concern (risk/ missing information)	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reactions (identified risk for ABC)	**Routine risk minimisation 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 minimisation 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 (potential risk for DTG)	**Routine risk minimisation measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:**	**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

Safety concern (risk/ missing information)	Risk minimisation measures	Pharmacovigilance activities
	Direct health care professional communication completed in 2018	**Additional pharmacovigilance activities:** Review of the APR Study 208613 – DOLOMITE EPPICC Study 208759 – DOLOMITE NEAT ID Network Study (208759)
Pregnant/ breastfeeding women (missing information)	**Routine risk minimisation measures:** Section 4.6. of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Review of the APR **Additional pharmacovigilance activities:** Study 208613 – DOLOMITE EPPICC Study 208759 – DOLOMITE NEAT ID Network Study

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7.4. Conclusion

The Triumeq RMP was updated into a single version to consolidate versions 19.0 and 20.0 (that already included the approved changes from version 18.0).

The CHMP considered that the risk management plan version 21.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to to Triumeq 50 mg/600 mg/300 mg film-coated tablets and Tivicay 5 mg dispersible tablets respectively. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HIV infection remains a major public health concern with approximately 38 million people infected worldwide, including an estimated 1.7 million children under 15 years of age. There were an estimated 1.7 million new HIV infection worldwide in 2019, of which 150,000 (9% of the total) were in children under 15 years of age, principally (84%) in sub-Saharan Africa. Of all global deaths in 2019, 95,000 [61,000–150,000] were in children less than 15 years of age.

The HIV targets the immune system and weakens people's defence. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. The most advanced stage of HIV infection is AIDS, defined by the development of certain cancers, infections or other severe long-term clinical manifestations.

3.1.2. Available therapies and unmet medical need

The recommended initial treatment of HIV-1 infection for paediatric patients is therapy with two NRTIs in combination with an INSTI or an NNRTI (≥3 years of age) or a boosted protease inhibitors (<3 years of age). The choice of HIV-1 therapy depends on various factors including the availability of age-appropriate formulation, ease of use, age/developmental stage of the patient, prior exposure (maternal or prevention), adherence, and in adolescent girls, the risk of pregnancy.

The goal of combination ART in paediatric patients is to achieve and sustain HIV-1 virologic suppression, preserve/restore immune function, minimize drug toxicity, prevent drug resistance, and ultimately lead to normal growth and neurocognitive development.

People living with HIV-1 who are aware of their status, take ART as prescribed, and get and keep an undetectable viral load can live healthy lives.

3.1.3. Main clinical studies

Triumeq FCT and DTs are both currently being evaluated in a Phase I/II study (IMPAACT 2019 - study 205860) for paediatric patients <12 years of age. However, each active component is already approved for use in paediatric patients weighing at least 14 kg.

The MAH is utilizing previously submitted PK, safety, and efficacy data for the active components (DTG, ABC and 3TC). In addition, the MAH submitted relative bioavailability and food effect data for Triumeq DTs, modelling and simulation, and interim intensive PK data from IMPAACT 2019 to support dosing recommendations for Triumeq FCT and Triumeq DTs in paediatric patients weighing ≥14 kg. The MAH studied 36 patients weighing at least 14 kg (21 with rich PK sampling and 15 with sparse PK sampling).

Historical paediatric safety and efficacy data comes from the studies ARROW (ABC+3TC, twice daily n=333 or once daily n=336), ODYSSEY (safety only DTG, N=99) and P1093 (DTG, n=159).

3.2. Favourable effects

The efficacy of Triumeq was established in adult and adolescent patients ≥40 kg. The efficacy demonstration in children is based on a PK bridge, inferred through similar exposure as in adults.

Treatment of HIV requires the use of combination antiretroviral therapy, and the options are more limited for paediatric patients compared to adults. A fixed dose combination could facilitate dosing and may enhance compliance.

The acceptability and palatability of the DTs (for children under 25 kg) were considered adequate.

3.3. Uncertainties and limitations about favourable effects

There is slightly lower dosing of ABC and 3TC in paediatric patients weighing 20-25 kg compared to individual components. However, the exposure is within the same range as the adult exposure and therefore is not expected to be of concern.

The PK data from 36 patients (21 rich PK sampling and 15 sparse PK sampling) was considered sufficient. The provided interim popPK analysis as well as the observed PK data generally supported the PK bridge.

There is limited data on the acceptability of the FCTs in children ≥25 and <40 kg. The available DTs cannot be administered to patients ≥25 kg as the relative doses (adjusted for bioavailability) of the separate components of the FDC are not the same in the DT form compared to the FCT form. Thus, there is no alternative formulation of this FDC for children who are unable to swallow the FCTs and there is a risk that some children may need to use monocomponents instead. Current guidelines for the management of HIV consider it a priority to make DTs available for young children living with HIV.

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 the licensed doses. The safety profiles of the individual components and FDC are already described in approved PIs and no additional safety concerns are proposed for inclusion in the revised Triumeq PI.

One SAE of Grade 4 DILI was reported from the ongoing study IMPAACT 2019 in a 7-year-old male participant (20 kg), with an elevated total bilirubin at screening, who was receiving DTG/ABC/3TC FDC DT and experienced increased ALT (Grade 4), increased AST (Grade 3), increased total bilirubin and a direct bilirubin that was 50% of total bilirubin at his Week 36 visit. The participant was withdrawn from study treatment for suspected DILI, and no alternative aetiology was identified at the time. Causality was possible. ALT and/or AST elevations are listed as common and hepatitis as uncommon adverse reactions in the Triumeq SmPC Section 4.8.

One case of myositis was reported by Monaghan (2021). It is known that other ARV medications, such as zidovudine and 3TC, may cause this potential adverse effect. Myalgia, rarely myolysis, arthralgia and elevated creatine phosphokinase are listed in the SmPC Section 4.8 as signs of ABC hypersensitivity.

3.5. Uncertainties and limitations about unfavourable effects

Since new safety data submitted in this application from the ongoing IMPAACT 2019 study is limited, the safety assessment mainly relies on historical studies that were previously reviewed in support of the original Triumeq submission for use in patients weighing at least 40 kg as well as those which supported recommendations of the SEs (DTG, ABC and 3TC) for use in pediatric patients weighing at least 14 kg. However, predicted exposures in this FDC (FCT and DT formulations) appears comparable to predicted paediatric exposures of the individual components at approved doses and were also comparable to observed data in adults.

3.6. Effects Table

Table 43. Triumeq favourable effects table in paediatric patients

Geometric mean exposure in paedaitric patients compared to adult exposure

Favourable effects Triumeq DTG/ABC/3TC									
		Geometric mean (%CV)				%GMR (90% CI)			
		Paediatric Subjects ≥14< 20 kg (n=15)[a]	Paediatric Subjects ≥ 20 < 25 kg (n=10)[a]	Paediatric ≥25<40 kg (n=11)[a]	Adult Target exposure[b]	Paediatric vs Adult[c]			
Analyte	PK Parameter					≥14< 20 kg	≥ 20 < 25 kg	≥25< 40 kg	Uncertainties / Strength of evidence Model predicted
ABC	AUC_{tau} (h*µg /mL)	15.6 (33)	16.00 (19)	26.1 (21)	8.52 (43)	183	188	306	Robust pediatric 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=169 subjects from 6 studies)) accurately able to describe and predict the observed data (≥14 kg to <40 kg) in the IMPAACT 2019 study
	C_{max} (µg /mL)	6.02 (28)	6.21 (41)	10.6 (29)	3.85 (37)	156	161	275	
3TC	AUC_{tau} (h*µg /mL)	12.7 (36)	12.1 (27)	17.6 (38)	8.7 (21)	146	139	202	
	C_{max} (µg /mL)	2.77 (28)	2.61 (34)	3.56 (37)	1.96 (26)	141	133	182	
DTG	AUC_{tau} (h*µg/mL)	65.1 (32)	77.8 (33)	64.3 (23)	53.6 (27)	121	145	120	
	C_{max} (µg /mL)	6.97 (26)	6.85 (22)	6.17(23)	3.67 (20)	190	187	168	
	C_{tau} (µg /mL)	0.746 (83)	0.900 (44)	0.977 (28)	1.11 (46)	67	81	88	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The extrapolation of efficacy and safety from adults to paediatric patients is in accordance with regulatory practice in the field of HIV. The PD target is expected to respond in the same manner to similar plasma concentrations of the HIV antivirals in both adult and paediatric patients.

There is slightly lower dosing of ABC and 3TC in paediatric patients weighing 20-25 kg compared to the individual components. However, the exposures are within in the same range as adult exposure and therefore not expected to be of concern.

The safety profile is well established in patients weighing at least 40 kg as well as the safety profile for each SEs (DTG, ABC, 3TC) for use in pediatric patients weighing at least 14 kg.

3.7.2. Balance of benefits and risks

The overall non-clinical and clinical data presented supports the efficacy and safety for the proposed FDC product in the sought indication. The proposed doses of the combination of DTG/ABC/3TC in paediatric subjects are comparable to that seen in adults. There are still concerns regarding the acceptability of the FCT in children 6-11 years weighing ≥25 kg.

Regarding safety, since the data from IMPAACT 2019 study is limited, the safety assessment mainly relied on historical studies (part of the original Triumeq submission) for use in patients weighing at least 40 kg as well as those which supported recommendations of the single entities (DTG, ABC and 3TC) for use in paediatric patients weighing at least 14 kg. As Triumeq is not yet authorized for use in children the lack of safety data in this population is not unexpected. The safety profiles of the individual components and FDCs are already described in the approved product information. No additional safety concerns are proposed for inclusion in the revised Triumeq PI.

3.7.3. Additional considerations on the benefit-risk balance

Extrapolation of efficacy from adults to paediatric patients is in line with other HIV antivirals including the mono entities DTG, ABC and 3TC.

3.8. Conclusions

The overall benefit/risk balance of Triumeq is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Triumeq 5 mg / 60 mg / 30 mg dispersible tablets is favourable in the following indication(s):

- Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected children weighing at least 14 kg to less than 25 kg.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Triumeq subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0116/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variations approved		**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, IIIA and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, II, IIIA, IIIB and A
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extension	I, II, IIIA, IIIB and A

Extension application to introduce a new pharmaceutical form associated with new strength (5 mg/60 mg/30 mg dispersible tablet). The new presentation is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected children weighing at least 14 kg to less than 25 kg.
This extension application is grouped with a type II variation (C.I.6.a) to include treatment of children

weighing at least 25kg for the already approved film-coated tablets for Triumeq (EU/1/14/940/001-002); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.
The RMP (version 21.0) is updated in accordance.
Furthermore, the PI is brought in line with the latest QRD template version 10.3.