12 November 2020
EMA/CHMP/540603/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tivicay

International non-proprietary name: dolutegravir

Procedure No. EMEA/H/C/002753/X/0058/G

Note

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

Table of contents

List of abbreviations

3TC	Lamivudine
ABC	Abacavir
ABC/3TC	Abacavir/lamivudine
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AT	All-Treated (Population)
ATV	Atazanavir
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve within time span 0 to infinity
AUC_{0-24h}	Area under the plasma concentration-time curve within time span 0 to 24 hours
BID	Two times per day
BMI	Body mass index
c/mL	Copies per milliliter
C24h	Drug plasma concentration at the end of the 24-hour dosing interval
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CD8+	Cytotoxic T-lymphocyte having surface antigen CD8 (cluster of differentiation 8)
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
Cmax	Maximal observed drug concentration during a dosing interval
CRF	Case Report Form
CSR	Clinical Study Report
CTU	Clinical Trial Unit
CV	Coefficient of variation
DAIDS	Division of AIDS (United States)
DRV	Darunavir
DRV/r	Darunavir/ritonavir
DT	Dispersible tablet
DTG	Dolutegravir, GSK1349572 (Tivicay)
EAIR	Exposure Adjusted Incidence Rate
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERC	Endpoint Review Committee
EU	European Union
F	Female
FCT	Film-coated tablet
FDA	Food and Drug Administration (United States of America)
FDC	Fixed-dose combination
FTC	Emtricitabine
GDS/RSI	Global Datasheet/Reference Safety Information
GI	Gastrointestinal
GM	Geometric mean
GSK	GlaxoSmithKline
Hb	Hemoglobin
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
ICH	International Conference on Harmonisation
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group

INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
IQVIA	Formerly Quintiles and IMS Health, Inc.
IRIS	Immune Reconstitution Inflammatory Syndrome
kg	Kilogram
LDL	Low density lipoprotein
LLOD	Lower limit of detection
LLQ	Lower limit of quantification
LMIC	Low and middle-income countries
Log	Logarithmic
LPV/r	Lopinavir/ritonavir (Kaletra)
M	Male
m	Meter
MCV	Mean corpuscular value
mos	Months
MRC	Medical Research Council
MUAC	Mid-upper arm circumference
NCA	Non-compartmental PK analysis
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NOAEL	No observed adverse effect level
NTD	Neural tube defect
OBT	Optimized Background Therapy
PD	Proposed Dose (Population)
PK/PD	Pharmacokinetics/pharmacodynamics
PENTA	Paediatric European Network for Treatment of AIDS
PI	Protease inhibitor
PID	Participant ID
PK	Pharmacokinetics
PT	Preferred term
PY	Person years
Q1	1st Quartile
Q3	3rd Quartile
RAL	Raltegravir, MK-0518 (Isentress)
RNA	Ribonucleic acid
RAP	Reporting and analysis plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TQT	Thorough QT/QTc
UGT1A1	Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1
URTI	Upper respiratory tract infection
USA	United States of America
VF	Virologic failure
WB-PK	Weight Band Pharmacokinetics (Sub-study)
WHO	World Health Organization
Wk	Week
yrs	Years
zBMI	BMI for age z score
ZDV	Zidovudine (Retrovir)
ZDV/3TC	Zidovudine/lamivudine (Combivir)

1. Background information on the procedure

1.1. Submission of the dossier

ViiV Healthcare B.V. submitted on 11 December 2019 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

- Extension application to add a new pharmaceutical form associated with new strength (5mg dispersible tablet). The new presentation is indicated for the treatment of HIV infected children from 4 weeks of life and weighing at least 3 kilograms.

- Type II variation (C.I.4) to update the currently approved Product Information, Labelling and Package Leaflet for the existing film -coated tablets (10mg, 25mg and 50mg) for children 6 years and older and weighing at least 15 kg. The application comprises PK, safety, and efficacy data from the Phase I/II study (P1093) and PK and safety data from relevant sub-studies nested within the Phase II/III Study ODYSSEY (PENTA 20).

In addition, the applicant took the opportunity to amend section 4.1 of SmPC, the indication for the approved Tivicay film-coated tablets to clarify that children should be "aged at least 6 years" as the current approved indication is inclusive of those aged 6 years.
The RMP (version 16.2) is updated in accordance.

The legal basis for this application refers to:

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0017/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0017/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson

The application was received by the EMA on	11 December 2019
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	22 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	28 May 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	22 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 April 2020
The CHMP agreed on a list of outstanding issues in writing and to be sent to the MAH on	15 October 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	29 October 2020
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 Tivicay on	12 November 2020

2. Scientific discussion

2.1. Problem statement

Combination antiviral therapy with human immunodeficiency virus type-1 (HIV-1) protease and reverse transcriptase inhibitors has significantly reduced acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality. However, emerging multi-class drug-resistant human immunodeficiency virus (HIV) strains as well as potential long-term toxicities warrant development of new antiretroviral therapies without or with limited cross-resistance to available drugs. INSTIs are a newer class of ARV drugs designed to block the action of the IN viral enzyme, which catalyzes 2 key steps in the HIV life cycle and is responsible for insertion of the viral genome into the DNA of the host cell.

2.1.1. Disease or condition

Treatment of patients (adults, adolescents and children from 4 weeks of age) infected with HIV-1 in combination with other anti-retroviral medicinal products.

2.1.2. Epidemiology

Worldwide, at the end of 2017, an estimated 36.9 million (range: 31.1 million–43.9 million) people were living with HIV infection, comprising an estimated 0.8% of adults aged 15-49 years [UNAIDS, 2018a]. However, the global burden of HIV varies by country and region. In Eastern Europe and Central Asia, a reported 1.4 million people (1.3 million-1.6 million) were living with HIV at the end of 2017, compared to 2.2 million people (1.9 million-2.4 million) living in Western and Central Europe and North America.

The incidence of HIV infection in the Middle East, North Africa, and Eastern Europe and Central Asia has doubled in less than 20 years following years of stability [UNAIDS, 2018b].

In 2017, an estimated 130,000 (120,000-150,000) new infections occurred in Eastern Europe and Central Asia.

In 2018, 160,000 (110,000–260,000) children aged 0-14 acquired HIV infection globally. The estimated number of children aged 0-14 living with HIV was 1.7 million (1.3–2.2 million) globally in 2018, more than 90% of whom were living in sub-Saharan Africa [UNAIDS20UNAIDS19]. By contrast, in the Western and Central Europe and North America region, the estimated number of children living with HIV in 2013 was 2,800 (2,300–3,600), and it is estimated that over 95% of these children were receiving antiretroviral therapy [UNAIDS, 2014].

Globally, deaths among children younger than 15 years of age are reported to be declining. At the end of 2018, an estimated 100,000 (64,000–160,000) children aged 0-14 years had died from AIDS- related causes, representing 52% fewer deaths in this age group than in 2012 [UNAIDS, 2019]. In North America, Western and Central Europe, fewer than 200 children died from AIDS-related illnesses in 2012 [UNAIDS, 2013].

2.1.3. Clinical presentation and diagnosis

The clinical presentation and diagnosis of HIV is well-known and not further discussed in this assessment report.

2.1.4. Management

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

Treatment options in children are more limited compared to adults.

About the product

Tivicay (Dolutegravir, DTG) was first authorised in the US on 12 August 2013 and in the EU on 16 Jan 2014. DTG is an integrase strand transfer inhibitor (INI), currently indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) in patients above 6 years of age.

INIs are a newer class of antiretroviral (ARV) drugs designed to block the action of the integrase (IN) viral enzyme, which catalyses two key steps in the HIV life cycle and is responsible for insertion of the viral genome into the deoxyribonucleic acid (DNA) of the host cell. Since genome integration is a vital step in retroviral replication, it is an attractive target for HIV therapy.

Type of Application and aspects on development

Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, Extensions of marketing authorisations

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

Accelerated assessment

Not Applicable.

Conditional marketing authorisation

Not Applicable.

Biosimilarity

Not Applicable.

Additional data exclusivity/ marketing protection

Not Applicable.

New active substance status

Not Applicable.

Orphan designation

Not Applicable.

The assessment reports were shared with WHO at every stage of the procedure for comments.

2.2. Quality aspects

2.2.1. Introduction

This application is a line extension to the already approved Tivicay 10 mg, 25 mg and 50 mg film-coated tablets. This line extension involves the addition of a 5 mg strength dispersible tablets and an extension of indication to HIV infected children from 4 weeks of life and weighing at least 3 kilograms.

The finished product is presented as dispersible tablets containing 5 mg dolutegravir as active substance.

Other ingredients are:

Tablet core: mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, crospovidone, sodium stearyl fumarate, calcium sulfate dihydrate, sucralose, strawberry cream flavour.

Tablet coating: titanium dioxide (E171), hypromellose, macrogol.

The product is available in HDPE (high density polyethylene) bottles closed with child resistant polypropylene screw closures, with a polyethylene faced induction heat seal liner as described in section 6.5 of the SmPC.

2.2.2. Active Substance

This application is a line extension and contains the same active substance, dolutegravir, used to manufacture the already approved film-coated tablets. The information presented by the Applicant in the dossier as was already assessed in the original submission and includes updates from any subsequent variations. No new information on the active substance has been provided within this application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Tivicay 5 mg dispersible tablets are round (6 mm diameter), biconvex, white, fil- coated tablets, debossed "SV H7S" on one face and "5" on the other face. The composition of Tivicay Dispersible Tablets includes dolutegravir (as sodium salt), mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycolate, crospovidone, sodium stearyl fumarate, calcium sulfate dihydrate, sucralose and strawberry cream flavour. The film coating includes titanium dioxide (E171), hypromellose, and macrogol.

The aim of the development was to identify an immediate release oral dosage form for use in paediatric patients (children ≥4 weeks old, weighing at least 3 kilograms (kg)), which can be swallowed easily, that meets compendial and other relevant quality standards, and is packaged protected from moisture. Development was based on knowledge of the physicochemical and functional properties of the active substance and excipients used in the formulation design. Prior knowledge of the existing products Tivicay film-coated tablets, was also used throughout the design and development.

As indicated above, the active substance is the same as the one used in the approved film-coated tablets. Dolutegravir is very slightly soluble in Simulated Intestinal Fluids and practically insoluble in Simulated Gastric Fluid. Solubility increases to a maximum between the pH values of 8 to 10. Based on the solubility data along with its high permeability, dolutegravir sodium is considered to be a Class II compound in the Biopharmaceutical Classification System.

A clinical study was conducted investigating the PK when dispersed in water with low and high ionic content. Comparable PK performance was demonstrated.

Excipients with appropriate compatibility and functionality were assessed for the finished product based on scientific and prior knowledge to meet the requirement of the QTPP for dolutegravir dispersible tablets, 5 mg. As indicated above, the same granulation process is used to manufacture the existing film-coated tablets and the dispersible tablets. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The discriminatory power of the dissolution method has been demonstrated.

To assess whether the proposed commercial formulation, as described in the description and composition of the Finished Product, gives equivalent exposure when dosed as a dispersion or direct to mouth, a Relative Bioavailability was conducted in adults which compared 5 Dolutegravir dispersible tablets, 5 mg, given as a dispersion compared with 5 dolutegravir dispersible tablets, 5 mg given direct to mouth. Comparable exposure results were seen.

The manufacturing process for the 5 mg dispersible tablets was developed and optimized at the proposed manufacturing site. A systematic, science and risk-based approach has been applied in defining the manufacturing process and the associated control strategy. This began with an overview of the proposed manufacturing process, which, together with prior knowledge, were used to identify risks (failure modes) and process variables that could impact quality using a Failure Mode and Effects Analysis (FMEA) risk assessment tool. The results were then prioritised and used to inform development activities which included univariate and multi-factorial studies in order to understand and control the risks to acceptable levels.

Risk assessments were continually updated throughout development as additional knowledge was gained, and then used to further develop the control strategy proposed for the commercial finished product to minimise residual risk.

This approach is aligned with ICH Q8, Q9 and Q10 for the development and manufacture of finished products applying QbD elements. Also Established Conditions (ECs) have been identified in line with draft ICH Q12. A Design Space has been developed for the unit operations of dolutegravir granulation based on prior knowledge of the marketed tablets regarding the active substance, granules, particle size and excipient compatibility. This design space was also explored for dolutegravir 5 mg dispersible tablets to confirm these CPPs are applicable for the proposed manufacturing process. The manufacturing process is described as target values and ranges for a Design Space, PARs and set points.

The manufacturing process consists of mixing intra-granular excipients with the active substance, wet granulation, milling drying. As indicated above, this granule manufacture is identical to the granule manufacture used for commercial Tivicay film-coated tablets.

The formulation used during clinical studies is the same as that intended for marketing. The primary packaging is HDPE bottle closed with child resistant polypropylene screw closures, with a polyethylene faced induction heat seal liner. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of several main steps: mixing and wet Granulation, milling, drying, blending, compression, film-coating and packaging.

In the original submission, the applicant identified Established Conditions (EC) for the finished product, and proposed regulatory reporting categories for post-approval changes to those ECs, in line with the ICH Q12 guideline on Lifecycle Management. As the definition of Established Conditions and their reporting categories must follow the requirements laid down in the current EU Variations Regulation and associated EU Variations Guidelines, the applicant was asked to confirm that all future changes to the content of module 3.2.P.3.3 will be handled in line with the EU Variation Classification Guideline and the respective variations will be filed. Once the legal framework is updated to allow implementation of ICH Q12, all future changes to the identified ECs will be handled according to that EU legislation.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for the manufacturing process of the dispersible tablets.

The design space has been developed at commercial scale.

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

Proven acceptable ranges (PARs) have been identified in the process description. The available development data, the proposed control strategy and batch data from commercial scale batches fuly support the proposed PARs.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, UV), dolutegravir content (HPLC), uniformity of dosage units (HPLC), finesses of dispersion (Ph. Eur.), dissolution (UV or HPLC), disintegration, and microbiological quality of the finished product (Ph. Eur.).

The potential presence of class 1, 2A and selected class 3 *elemental impurities* in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the information presented it is concluded that the material specifications, in combination with adherence to the overall control strategy is appropriate to control elemental impurities in the product to within safe levels below 30% of the respective PDE limits defined in ICH Q3D therefore, elemental impurities are not included in the finished product specification.

The information on the control of elemental impurities is satisfactory.

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.

The finished product is released onto the market based on release specifications, through traditional final product release testing.

A risk assessment concerning the presence of nitrosamine impurities was performed for the finished product based on the combined recommendations from health authorities, including EMA communication EMA/189634/2019. The nitrosamine impurities risk assessment of the finished product included evaluating contributions from dolutegravir, excipients, finished product manufacturing facilities, and packaging components. It was concluded that there is no risk related to the presence of nitrosamine impurities in the product. Therefore, no changes to the control strategy for Tivicay are necessary to mitigate potential contamination by nitrosamines.

Batch analysis results are provided for four production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 24 months under long term conditions (25 ºC/ 60% RH), three production 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) according to the ICH guidelines were provided. The batches of Tivicay 5 mg dispersible tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, data have been generated at stress and simulated patient in-use conditions.

Based on available stability data, the proposed shelf-life of 36 months under the following conditions: Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant. Do not swallow the desiccant. This medicinal product does not require any special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information on development, manufacture and control of the finished product has been presented in a satisfactory manner. No new information was presented on the active substance. 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 QbD principles in the development of the finished product and its manufacturing process. Design space has been proposed for the initial step of the manufacturing process of the finished product.

2.2.5. 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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

An overview of the non-clinical properties of dolutegravir (DTG) is derived from the EPAR of the Tivicay procedure EMEA/H/C/002753/X/0018/G with a more extensive discussion on those developmental toxicity aspects of dolutegravir (DTG) that are relevant for the extension of indication to children aged between ≥4w and <6 years. No new non-clinical studies have been submitted for this procedure.

2.3.2. Pharmacology

Primary pharmacodynamics

Dolutegravir (DTG) is referred to as a second-generation integrase inhibitor, with activity against raltegravir resistant viruses. DTG binds to the HIV integrase active site blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. The IC50 of DTG against the purified enzyme HIV-1 integrase ranged from 2.7nM to 12.6nM.

Secondary pharmacodynamics

In vitro, DTG inhibited the binding of radiolabelled α-melanocyte-stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) receptor by 64% at a concentration equal to the clinical Cmax. The

MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in the MC4R is associated with monogenic obesity. There were no findings associated with MC4R in toxicity studies, and no clinically significant patterns of changes in vital signs across the clinical studies.

Safety pharmacology

Results from safety pharmacology studies indicated that single oral doses of DTG up to 500 (rat) and 1000 (monkey) mg/kg have a low likelihood to induce acute effects on major organ function in the central nervous, respiratory and cardiovascular systems.

Conclusions

In summary, the non-clinical pharmacology of DTG was thoroughly evaluated during the original marketing authorisation application for Tivicay. No new studies have been submitted in support of the present application. This is considered acceptable.

2.3.3. Pharmacokinetics

Absorption

Bioavailability of DTG in rat and monkey ranged from 25 to 34% and increased to levels of 76 to 87% after fasting. With increasing doses systemic exposure levels increased although less than dose-proportionally. Systemic exposure levels were overall similar at similar doses in animals given intramuscular or subcutaneous doses. After repeated doses there was a trend for increased exposure in female animals compared with males although this gender difference was not consistently observed.

Distribution

Distribution studies in rats indicated highest levels of radiolabel at 6 hours post dose and tissues with highest radioactivity included liver, adrenal medulla, myocardium, pigmented skin, renal cortex and renal medulla, lung and lymph nodes. Levels in the brain were low, but quantifiable. Studies in pregnant rats showed that DTG crossed the placenta and that foetal radioactivity was highest in blood, myocardium and muscle. In addition, lacteal transfer of DTG was evident. At postnatal day 10 (PND10), total DTG related concentrations in milk were up to 2x greater than those in maternal blood.

Metabolism

In vitro studies in rat and human liver microsomes showed that a metabolite of DTG, consistent with addition of glutathione through oxidative defluorination, was formed. Data indicated that DTG induced a formation of an electrophilic metabolite in rat and human microsomes. The significance of the formation of this metabolite is likely limited at doses relevant for the clinical setting. Metabolic profiling in mouse and rat showed that DTG was the major radiolabelled compound in plasma, liver and faeces. In monkey, DTG was the major radiolabelled compound in plasma. In bile major components were glucuronide and hexose conjugates.

Excretion

In mouse, rat and monkey the major part of the radioactivity was eliminated in faeces.

Conclusions

In summary, the non-clinical pharmacokinetics of DTG was thoroughly evaluated during the original marketing authorisation application for Tivicay. No new studies have been submitted in support of the present application. This is considered acceptable.

2.3.4. Toxicology

Repeat dose toxicity

The toxicity of DTG was investigated in repeat-dose studies in adult animals: in rat up to 26 weeks (w), in monkey up to 38w, and in mouse up to 13w. Adverse effects of DTG were evident in the stomach, cecum, colon and rectum in both rat and monkey, but based on systemic exposure as well as dose, monkeys were considerably more sensitive to these effects than rats. Concerning the gastrointestinal targets, comparisons based on mg/m^2 may be more relevant than systemic exposure levels and at the NOAEL multiples were in the range of 2-3x the expected human values.

There were indications of a potential of DTG to disturb liver functional activity in the mouse 3-month study, and in the monkey liver effects were reported at doses from 300 mg/kg in the 2w study with more pronounced reactions, including single cell necrosis and hypertrophy at a dose of 1000 mg/kg. The mechanism of liver injury in the monkey is not known. An electrophilic metabolite of DTG appears to be formed but it is unclear whether this is involved in mechanisms of toxicity identified in non-clinical studies. Some clinical data have indicated a potential for liver reactions to DTG.

Genotoxicity

Negative results were reported except for a weakly positive result in the mouse lymphoma assay at high cytotoxicity. A previous non-GLP mouse lymphoma test was positive at high dose, but cytotoxicity may have confounded results. The in vivo rat micronucleus test was negative. Taken together the data did not indicate any relevant genotoxic potential of DTG.

Carcinogenicity

Long term carcinogenicity studies were conducted in mouse and rat. Overall DTG did not exhibit any significant neoplastic activity in either study.

Reproductive and developmental toxicity

Fertility and early embryonic development: There were no noteworthy findings with respect to sperm functional parameters and morphology in male rats (Sprague-Dawley) treated with doses of DTG up to 1000mg/kg. Male and female fertility did not appear to be affected at doses up to 1000mg/kg providing exposure multiples of approximately 27x the expected clinical value at a dose of 50mg BID.

Embryo-foetal development: Teratological assessment for DTG was conducted using rat and rabbit animal models. In rat (Sprague-Dawley), an oral exposure between gestational day (GD) 6 and GD17 with doses

between 100 and 1000mg/kg per day led to a slight increase in preimplantation loss at 1000mg/kg but without clearly affecting litter parameters. The NOAEL of the study was set to 1000mg/kg.

In rabbit (Japanese White), an oral exposure between GD6 and GD18 with doses between 40 and 1000mg/kg per day resulted in a reduction of maternal body weight gain and food intake plus scant or no faeces/urine at the middle dose (≥200mg/kg). No adverse effects on the embryos/foetuses were observed.

Prenatal and postnatal development, including maternal function: The perinatal toxicity profile of DTG was characterized in rats (Sprague-Dawley). The exposure duration was between GD6 (maternal-in utero exposure of offspring) and postnatal day 20 (PND20; maternal-lactation exposure of offspring) at doses of 5, 50 and 1000mg/kg per day. The study included an assessment of the F1-offspring generation (e.g. endpoints for gross pathology, sexual development and behaviour) and pre-implantation and viability of F2-generation embryos.

The dams (F0) demonstrated some reduction in body weight gain at the maximum dose (1000mg/kg; maternal NOAEL 50mg/kg). In the F1-generation, one new-born had external malformations (meningocele and eye bulge aplasia) at 1000mg/kg. Due to overall low incidence of developmental anomalies in the study, this defect was not considered DTG related. Statistically significant female F1-offspring body weight decreases were noted at 1000mg/kg between PND11 and PND42 as compared to the control animals.

Juvenile toxicity*:* Three juvenile toxicity studies in rat (Sprague-Dawley) were performed: two dose-range finding (DRF) studies and one pivotal study which were submitted in the original procedure that lead to market authorization (EMEA/H/C/002753, market authorization from 2014). The most recent assessment of the juvenile toxicity studies was conducted in procedure EMEA/H/C/002753/X/0018/G which extended the indication to children aged six years and older. Overall, the juvenile toxicity studies in general and the pivotal study in particular (oral gavage exposure between PND4 and PND66 with no recovery period; doses 0.5, 2 and 75mg/kg per day) identified mainly two outcomes of interest/concern:

- *Mortality*: DTG-linked mortality in the pre-weaning period (PND4 to PND21) was observed at the max doses in all juvenile toxicity studies (shifting the max dose from 1000mg/kg and 300mg/kg in the DRF-studies to 75mg/kg in the pivotal study). In the pivotal study, two pre-weaning male pup deaths occurred on PND12 and PND17 in the 75 mg/kg/day dose group.
- *Body weight gain*: For the 75 mg/kg/day dose, an body weight reduction induced during pre-weaning occurred in both sexes but was transient in male offspring (having recovered compared to controls between PND28 and PND42) while females did not recover before the termination of the experiment (mean female body weight on PND66 was 257g compared to a control mean value of 282g). During the pre-weaning period, the body weight gain of the exposed animals was 0.74x to 0.86x compared to controls.
- *Other effects*: Nasal degeneration was observed at all dose levels, being ascribed to a local irritant effect but considered clinically relevant. Among other endpoints it can be noted that there were no observed effects on spermatogenesis (reproductive toxicity) or immunological competence or on lymphocyte subsets counts (immunotoxicity).

The overall NOAEL and LOAEL for the pivotal study was set to 2mg/kg/day (PND13 Cmax 15.8 ug/mL and $AUC_{0\text{-}24h}$ 309.5ug x h/mL; PND32 Cmax 7.59ug/mL and $AUC_{0\text{-}24h}$ 89.5ug x h/mL) and 75mg/kg/day (PND13 Cmax 86.7 ug/mL and $AUC_{0\text{-}24h}$ 1544.5ug x h/mL; PND32 Cmax 73.7ug/mL and $AUC_{0\text{-}24h}$ 980.5ug x h/mL) respectively. Based on that the stated human target exposure (AUC for ≥4w and <18 years) of the applicant is 46 (37-134) ug x h/mL (in the Clinical Overview of the dossier, and from ongoing clinical trials

P1093/ING112578 and ODYSSEY/201296), this gives the following systemic exposure margins (animal/human AUC):

- Rat PND13
    - NOAEL : 6.7x margin (range 2.3x – 8.4x)
    - LOAEL : 33.6x margin (range 11.3x – 41.7x)
- Rat PND32
    - NOAEL : 2.0x margin (range 0.7x – 2.4x)
    - LOAEL : 21.3x margin (range 7.2x – 24.1x)

2.3.5. Ecotoxicity/environmental risk assessment

Dolutegravir (DTG or experimental name GSK1349572A) is a monosodium salt which, in aqueous solution, dissociates into its active moiety, the free base (experimental name GSK1349572B) and the counter sodium ion. DTG has the formula of C20H18F2N3NaO5 and a molecular weight of Mw = 441.36 g/mol as a salt and Mw = 419.38g/ml as a free base. The solubility in water is 3.176mg/mL (at 21°C) and the pKa for DTG is 8.2. Regarding the clinical pharmacokinetics properties of DTG, 53% of the total oral dose is excreted unchanged in the faeces. Furthermore, 31% of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

DTG is a non-lipophilic slightly water-soluble compound that binds sludge solids and that will distribute to both the aquatic and terrestrial environments and has the potential to accumulate both in STP sludge (sludge adsorption Kdoc =10609-15367) and sediment (not degradable, sediment-water system DT50 > 1000d). DTG is able to generate toxicity in organisms from both aquatic ecosystems (algae toxicity with a NOEC 0.0954mg/L followed by fish larval survival at a NOEC of 0.22mg/L) and terrestrial ecosystems (phytotoxicity in pea; NOEC 12mg/kg) but, based on the predicated environmental concentrations, not to a degree that is expected to pose an environmental concern. While not remarked upon in the original submission ERA for Tivicay, a potent and clear deviation in soil micro-organism nitrate formation was also detected subsequent to DTG exposure. The biological significance of this effect is unclear but as this effect was stimulatory rather than inhibitory, this finding will not influence the present ERA.

Overall, while very persistent in sediment, all environmental compartment risk quotients were < 0.1 and DTG is therefore not considered to pose a risk to the environment. DTG is also not classified as a PBT or vPvB compound.

2.3.6. Discussion on non-clinical aspects

During the EMEA/H/C/002753/X/0018/G assessment, the possible reasons for the pre-weaning effects were discussed more in depth by the MAH. Based on toxicokinetic measurements on PND13 and PND32, the systemic exposure of DTG was higher on PND13 in the younger pre-weanling pups compared to the more mature juvenile pups on PND32 (at NOAEL 48% less at Cmax and 29% at AUC; at LOAEL 85% less at Cmax and 64% less at AUC). The toxicokinetic-time profiles on PND13 indicate a longer half-life in pre-weaning rats compared to post-weaning PND32 rats, possibly due to immaturity of clearance pathways. The biliary excretion in animals accounts for the major portion of the absorbed dose and represented the predominant

excretion route for DTG glucuronide. The predominant biotransformation pathway for DTG in humans is glucuronidation by orthologous UDP glucuronosyltransferase 1A1 (UGT1A1) with a notable oxidative contribution from CYP3A4. In rats, UGT1A1 gene expression has a surge immediately after birth, but then is low until ~PND14 when it begins to rise to near adult levels by PND28 [1] while CYP3A expression seems to slowly increase towards adult level at PND42 [2], roughly correlating with the developing capability in rat to eliminate via bile route after the first ~14 days. It seems therefore likely that at least some aspect of the increased pre-weaning rat sensitivity (expressed as mortality and reduced growth) to DTG is due to higher early systemic exposure due to ADME differences.

For the previous indication extension down to 6 years of age, this was considered an argument against DTG toxicity in children considering that the end of the rat-weaning period (~PND21) is generally stipulated to correspond to a human age around 20-24 months. In the present procedure, which aims at a lower human age limit of 4w, the extrapolation and risk assessment is more uncertain. As noted by the MAH in the previous procedure, in humans, UGT1A1 expression is triggered at birth and its activity reaches adult levels by 3 to 6-months of age[3], while hepatic CYP3A4 expression begins to dramatically increase at about 1w of age, reaching 30% of adult levels by 1 month of age[4]. Based on the ADME-argument, at a minimum, this would indicate an increased likelihood of higher systemic exposure of DTG in the younger infants (e.g. 1-6 months of age).

No data or persuasive arguments (the MAH mainly argues that ~3x to ~6x margin provides sufficient safety multiples for infants 4-weeks of age or older and focuses on LOAEL based exposure margins as a basis for safety) have been provided that shed light on the clinical relevance of the likely higher DTG exposure in paediatric populations aged at least 4 weeks and weighing at least 3kg. The MAH has provided additional AUC and NOAEL-based mean exposure margin estimates (based on non-clinical PND13 AUC values) which are similar to those previously calculated:

- Human weight 3 to <6kg (5mg DTG): 6.3x
- Human weight 6 to <10kg (10mg DTG), age <6 months: 3.6x
- Human weight 6 to <10kg (15mg DTG), age >6 months: 5.4x

2.3.7. Conclusion on the non-clinical aspects

The CHMP considered that there is no objection for the approval of Tivicay from a non-clinical point of view.

1 Kishi M. et al. (2008), "Ontogenic isoform switching of UDP-glucuronosyltransferase family 1 in rat liver", Biochemical and Biophysical Research Communications. 2008; 377(3), pp 815-819.

2 de Zwart L. et al (2008), "The ontogeny of drug metabolizing enzymes and transporters in the rat", Reproductive Toxicology. 2008; 26(3-4), pp 220-230.

3 McCarver D.G. & Hines R.N. (2002), "The ontogeny of human drug-metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms." Journal of Pharmacology and Experimental Therapeutics. 2002; 300(2), pp 361-366.

4 Hines R.N. & McCarver D.G. (2002), "The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes." Journal of Pharmacology and Experimental Therapeutics. 2002; 300(2), pp 355-360

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

Table 1: Tabular overview of clinical studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed[a]	Study Reporting Status (Type of Report); Location
Biopharmaceutical Studies						
ING114556	To evaluate the bioavailability of DTG Granules for Oral Suspension relative to DTG FCT, 50 mg To evaluate the impact of different types of water and infant formula on the bioavailability of DTG Granules for Oral Suspension	Phase 1, randomized, open-label, 5-period, 10-sequence crossover	Healthy adult subjects	Treatment A: DTG FCT 50 mg strength; 50 mg; PO; single dose Treatment B: DTG Granules for Oral Suspension; 50 mg (direct to mouth); PO; single dose Treatment C: DTG Granules for Oral Suspension; 50 mg (reconstituted with purified water); PO; single dose Treatment D: DTG Granules for Oral Suspension; 50 mg (reconstituted with Contrex mineral water; PO; single dose Treatment E: DTG Granules for Oral Suspension; 50 mg (reconstituted with milk-based infant formula; PO; single dose **Note:** Contrex water contains calcium + magnesium of approximately 524 mg/L. **Note:** Treatments A, C, D, E were administered with a total of 240 mL	20 Enrolled 20 Completed	Completed: CPSR m5.3.1.1
200401	To evaluate the bioavailability of DTG DTs, 5 mg relative to DTG Granules for Oral Suspension	Phase I, randomized, open-label, 5-period, 5-sequence crossover	Healthy adult subjects	Treatment A: DTG Granules for Oral Suspension; 20 mg (reconstituted with purified water); PO; single dose Treatment B: DTG DT 5 mg strength; 20 mg (dispersed in low mineral content water); PO; single dose Treatment C: DTG DT 5 mg strength; 20 mg (dispersed in Contrex mineral water); PO; single dose	15 Entered 15 Completed	Completed: CPSR m5.3.1.1

	To evaluate the impact of different types of water on the bioavailability of DTG DTs			Treatment D: DTG DT 5 mg strength; 20 mg (dispersed in low mineral content water); PO; single dose, held for 30 minutes, re-dispersed, and then taken by subject Treatment E: DTG DT 5 mg strength; 20 mg (dispersed in Contrex mineral water); PO; single dose; held for 30 minutes, re-dispersed, and then taken by subject **Note:** Contrex water contains calcium + magnesium of approximately 524 mg/L.		
205893	Part 1: To evaluate the bioavailability of DTG FCTs, 10 mg relative to DTG FCTs, 50 mg Part 2: To evaluate the bioavailability of DTG DTs, 5 mg relative to DTG FCTs, 25 mg	Part 1: Phase 1, randomized, open-label, 2-period, 2-sequence crossover Part 2: Phase 1, randomized, open-label, 3-period, 6-sequence crossover	Healthy adult subjects	Part 1 Treatment A (test) DTG FCT 10 mg strength; 50 mg; PO; single dose Treatment B (reference): DTG FCT 50 mg strength, 50 mg; PO; single dose Part 2: Treatment C (test): DTG DT 5 mg strength; 25 mg (dispersed in water); PO; single dose Treatment D (test): DTG DT 5 mg strength; 25 mg (direct to mouth); PO; single dose Treatment E (reference): DTG FCT 25 mg strength; 25 mg; PO, single dose	Part 1: 14 enrolled and completed Part 2: 24 enrolled and completed	Completed CPSR m5.3.1.1
Human Pharmacokinetic Studies						
Pooled NCA Report (2019N422597_00)	To summarize plasma DTG PK across pediatric HIV studies.	Plasma DTG PK data from pediatric HIV-1 infected participants in P1093 and ODYSSEY were combined for summary.	HIV-infected infants, children and adolescent participants	DTG DTs, 5 mg strength DTG Granules for Oral Suspension DTG FCTs, 10, 25, and 50 mg strengths Dose were administered PO once daily for up to 48 weeks; PK was collected up to Week 24. Doses were according to weight band and a variety of doses were administered	119 were included in the analyses	PK Report m5.3.3.2
PopPK & Safety E-R Report (2019N424147_00)	PopPK: To characterize the PK of DTG, identify and quantify covariates that explain variability, and support DTG dosing recommendations for the pediatric population	PopPK Analysis Methods: Plasma DTG concentration data from pediatric HIV-1 infected participants in P1093 and ODYSSEY were	HIV-infected infants, children and adolescent participants	DTG DTs, 5 mg strength DTG Granules for Oral Suspension DTG FCTs, 10, 25, and 50 mg strengths Dose were administered PO once daily for up to 48 weeks; PK was collected up to Week 24. Doses were according to weight band and a variety of doses were administered	239 were included in the analyses	PopPK Report m5.3.3.5

	Safety E-R: To explore relationships between plasma DTG concentrations and safety parameters (clinical labs and AEs)	combined for PopPK analysis using nonlinear mixed effect modelling. Safety E-R Methods: Relationships were eva-luated by linear regression (clinical labs) and logistic regression (AEs)				
Efficacy E-R Report (2019N424148_00)	To evaluate the relationship between plasma DTG exposure (C24h, AUC0-24h, Cavg) and antiviral response (proportions <50 c/mL and <400 c/mL at Weeks 4, 24, and 48) and to characterize the effects of covariates	Efficacy E-R Methods: Plasma DTG exposure metrics from pediatric HIV-1 infected participants in P1093 were evaluated for relationships with antiviral response using nonlinear mixed-effect modelling. Parallel logistic regression analyses were performed to select the most appropriate exposure metric for inclusion in all subsequent models. BVL (continuous and categorical as	HIV-infected infants, children and adolescent participants	DTG DTs, 5 mg strength DTG Granules for Oral Suspension DTG FCTs, 10, 25, and 50 mg strengths Dose were administered PO once daily for up to 48 weeks; PK was collected up to Week 24. Doses were according to weight band and a variety of doses were administered	146 were included in the analyses	PK-PD Report m5.3.4.2

		<100,000 c/mL vs. ≥100,000 c/mL), baseline CD4+ count, and HIV disease status were tested as covariates.				
Efficacy and Safety Studies						
ING112578 (P1093)	To select a DTG dose for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG once daily adult dose. To determine the safety and tolerability of DTG in HIV-1 infected infants, children, and adolescents at 24 and 48 weeks. To evaluate steady-state PK of DTG in combination with other ARVs that achieves a targeted C24h and AUC0-24h in this population.	Phase I/II, multicenter, open-label, non-comparative intensive PK and safety study	HIV-infected infants, children and adolescent participants	DTG; target dose (~1 mg/kg to ~1.25 mg/kg) up to a maximum dose of 50 mg FCT or 30mg DT, or granules for oral suspension; once daily; 48 weeks	PD population: Enrollment Weight Band 3 to <6 kg 15 enrolled 6 to <10 kg 20 enrolled 10 to <14 kg 10 enrolled 14 to <20 kg 6 enrolled ≥35 kg 24 enrolled	Ongoing; 161 enrolled to date of which ~75 are considered evaluable; overall target is ~120 evaluable CSR m5.3.5.2
ODYSSEY (PENTA 20, GSK 201296) WB-PK1 WB-PK2 Lower WB-PK1	WB-PK sub-studies; To provide PK data for participants in the first 3 WHO weight bands (Lower WB-PK1, ongoing) To provide PK data with	The main study is a Phase I/II, multicenter open-label, randomised (1:1), non-inferiority, 2-arm clinical trial comparing DTG+2NRTIs with	HIV-infected ARTnaïve or ARTexperienced infants, children and adolescent participants	WB- PK sub-study dosing; DTG; once daily; dosed according to weight band: 3 to <6 kg: one or two 5 mg DT 6 to <10 kg: three 5 mg DT 10 to <14 kg: four 5 mg DT 14 to <20 kg: five 5 mg DT 20 to <25: one 50 mg FCT or six 5mg DT 25 to <35: one 50 mg FCT ≥35 kg: one 50 mg FCT	Safety Population Enrollment Weight Band 3 to <6 kg 1 enrolled 6 to <10 kg 10 enrolled 10 to <14 kg	Both PK substudies are ongoing; enrollment: 99 participants; target enrollment: ≥8 participants with evaluable PK curves per weight band

	DTG 25 mg FCTs in participants from 14 to <25 kg (WB-PK1, Part I, completed) To provide PK data in participants from 14 to <20 kg on DTG administered as DTs and in participants from 20 to <25 kg on DTG administered as DTs or 50 mg FCTs once daily (WB-PK1 Part II, completed) To provide PK data with DTG 50 mg in participants from 25 to <40 kg (WB-PK2, completed) To provide safety data for new dosing	SOC. The study has integrated PK substudies: WB-PK1 Parts I and II, WBPK2 and Lower WBPK1.			5 enrolled 14 to <20 kg 33 enrolled 20 to <25 kg 28 enrolled 25 to <30 kg 16 enrolled 30 to <40 kg 6 enrolled	PK sub-studies and full CSR m5.3.5.2

a. For ongoing studies, the number of ongoing participants are reported as of data cut-off date 30 April 2019 for P1093 and 28 February 2019 for ODYSSEY.

AIDS = acquired immunodeficiency syndrome
ART = antiretroviral therapy
ARV = antiretroviral
AE = adverse event
AUC0-24h = area under the plasma concentration-time curve within time span 0 to 24 hours
BVL = baseline viral load
C24h = Drug plasma concentration at the end of the 24-hour dosing interval
CD4+ = Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CPSR = clinical pharmacology study report
CSR = clinical study report
DT = dispersible tablet
DTG = dolutegravir
E-R = exposure-response
FCT = film-coated tablet
GSK = GlaxoSmithKline
HIV = human immunodeficiency virus
HIV-1 = human immunodeficiency virus type 1
NCA = noncompartmental analysis
NRTI = nucleoside reverse transcriptase inhibitor
PD = Proposed Dose (population)
PENTA = Paediatric European Network for Treatment of AIDS
PK = pharmacokinetics
PK-PD = pharmacokinetics-pharmacodynamics
PO = oral administration
PopPK = population pharmacokinetics
SOC = standard of care
WB-PK = Weight Band Pharmacokinetics (sub-study)
WHO = World Health Organization

2.4.2. Pharmacokinetics

Bioanalytical method

Study 200401 and 205893 was analysed according to the method validation report 2012N147635_00 including supplemental 1-9, study ING114556 was analysed according to method validation report 2011N112453 including supplemental 1-3, study P1093 was analysed according to the method validation report 2019N420285_00 and study Odyssey was analysed according to the method validation report 2019N420284_00. Overall, these appears acceptable.

Relative bioavailability study 200401

This study was conducted to evaluate the pharmacokinetic and relative bioavailability of a dispersible tablet formulation compared to a paediatric granule formulation in healthy subjects, as well as the effect of mineral content in dispersible water and holding time of the dispersion before consumption of the dispersible tablet formulation. Note that the dispersible 5 mg tablet, evaluated in this study, was an earlier formulation of the dispersible tablet and is not the intended formulation for marketing.

The study was an open label, randomised, five-treatment, five-period, five-sequence single-dose crossover study. 15 healthy volunteers were enrolled and received a sequence of five treatments. Study drug administration was performed after an overnight fast period of 8 hours. Blood-samples were collected pre-dose and up to 48 hours after drug administration. The study periods were separated by a wash-out period of 7 days. The results from this study are presented in the table below.

Table 2: Results from study 200401

Geometric LSMean					Comparison			CVw (%)
TX A	TX B	TX C	TX D	TX E	Test/Ref.	Ratio	90% Confidence Interval	
AUC(0-∞) (hr*ug/mL)								
30.7	32.7	30.9	33.6	32.3	B vs A	1.07	(1.01, 1.13)	9.2
					C vs B	0.944	(0.893, 0.999)	
					D vs B	1.03	(0.971, 1.09)	
					E vs C	1.05	(0.988, 1.11)	
AUC(0-tau) (hr*ug/mL)								
27.7	29.5	28.0	30.2	29.0	B vs A	1.07	(1.01, 1.12)	8.9
					C vs B	0.947	(0.897, 1.00)	
					D vs B	1.02	(0.969, 1.08)	
					E vs C	1.04	(0.984, 1.10)	
Cmax (ug/mL)								
1.77	1.99	1.82	1.96	1.91	B vs A	1.13	(1.06, 1.20)	10.1
					C vs B	0.918	(0.863, 0.976)	
					D vs B	0.987	(0.928, 1.05)	
					E vs C	1.05	(0.986, 1.12)	
C24 (ug/mL)								
0.455	0.468	0.448	0.499	0.454	B vs A	1.03	(0.944, 1.12)	14.3
					C vs B	0.958	(0.878, 1.05)	
					D vs B	1.07	(0.977, 1.16)	
					E vs C	1.01	(0.928, 1.10)	
CL/F (L/hr)								
0.651	0.611	0.647	0.595	0.620	B vs A	0.939	(0.888, 0.993)	9.2
					C vs B	1.06	(1.00, 1.12)	
					D vs B	0.974	(0.921, 1.03)	
					E vs C	0.957	(0.905, 1.01)	

Geometric LSMean					Comparison			CVw (%)
TX A	TX B	TX C	TX D	TX E	Test/Ref.	Ratio	90% Confidence Interval	
t1/2 (hr)								
14.1	14.2	14.0	14.5	14.3	B vs A	1.00	(0.963, 1.05)	6.8
					C vs B	0.986	(0.946, 1.03)	
					D vs B	1.02	(0.983, 1.07)	
					E vs C	1.02	(0.983, 1.07)	

Source Data: Table 11.5

Treatment A : DTG 20 mg Pediatric Granule

Treatment B : DTG 20 mg Dispersible Tab dispersed in low mineral content (LMC) water

Treatment C : DTG 20 mg Dispersible Tab dispersed in Contrex mineral water

Treatment D : DTG 20 mg Dispersible Tab dispersed in LMC water, stand 30 minutes before consumption

Treatment E : DTG 20 mg Dispersible Tab dispersed in Contrex mineral water, stand 30 minutes before consumption

DTG: Dolutegravir

ANOVA: Analysis of variance, TX: Treatment

Relative bioavailability study ING114556

This study was conducted to evaluate the single-dose relative bioavailability of an oral dolutegravir granule formulation given as single 50 mg dose in the fasted state administered with and without various liquids (purified water, Contrex mineral water, and a milk-based infant formula) compared to the tablet formulation administered with tap water in the fasted state. The direct to mouth treatment was included to simulate real-world conditions where potable water is not available. The applicant states that the two water arms represented the best case and worst-case scenarios for the potential effect of metal cations in drinking water on dolutegravir absorption.

The study was an open label, randomised, five-treatment, five-period, ten-sequence single-dose crossover study conducted in 20 healthy volunteers to evaluate the bioavailability of dolutegravir granules for oral suspension administrated with and without various liquids (purified water, Contrex mineral water and a milk-based infant formula) compared to dolutegravir 50 tablets administrated with tap water. Study drug administration was performed after an overnight fast period of at least 6 hours. Blood-samples were collected pre-dose and up to 48-hours post- dose. The study periods were separated by a wash-out period of 5 days. The results from this study is presented in the table below.

Table 3: Results from the relative bioavailability study ING114556

Comparison	Ratio of GLS Means (90% CI)			
	Plasma DTG PK Parameter			
	AUC(0-∞)	AUC(0-t)	Cmax	C24
B vs A	1.58 [1.46, 1.71]	1.58 [1.46, 1.71]	1.62 [1.49, 1.77]	1.61 [1.47, 1.75]
C vs A	1.57 [1.45, 1.70]	1.58 [1.46, 1.71]	1.66 [1.52, 1.81]	1.58 [1.45, 1.72]
D vs A	1.55 [1.43, 1.67]	1.56 [1.44, 1.69]	1.65 [1.51, 1.79]	1.52 [1.40, 1.66]
E vs A	1.83 [1.69, 1.98]	1.84 [1.70, 1.99]	2.02 [1.86, 2.20]	1.88 [1.72, 2.04]
B vs C	1.01 [0.933, 1.09]	1.00 [0.928, 1.09]	0.978 [0.899, 1.07]	1.02 [0.933, 1.11]
D vs C	0.986 [0.912, 1.07]	0.990 [0.915, 1.07]	0.993 [0.912, 1.08]	0.965 [0.886, 1.05]
E vs C	1.17 [1.08, 1.26]	1.17 [1.08, 1.26]	1.22 [1.12, 1.33]	1.19 [1.09, 1.29]

Source Data: Table 11.5
Treatment A = DTG 50 mg using the current Phase 3 formulation 50 mg tablet given with 240 mL tap water
Treatment B = DTG 50 mg using the granule formulation given directly to mouth (no liquid)
Treatment C =DTG 50 mg using the granule formulation given with 30 mL purified water
Treatment D =DTG 50 mg using the granule formulation given with 30 mL Contrex mineral water
Treatment E =DTG 50 mg using the granule formulation given with 30 mL milk-based infant formula
GLS = Geometric Least-Squares

Relative bioavailability study 205893

This was a Phase I, single-dose, crossover, relative bioavailability study comparing TIVICAY dispersible tablets and direct-to-mouth paediatric tablets to conventional TIVICAY tablets. This study was conducted in 2 separate parts with separate groups of fasted healthy adult subjects to investigate both 10-mg conventional tablets (Part 1) and 5-mg dispersible tablets (Part 2). Subjects participated in only one part of the study. Parts 1 and 2 of the study were conducted concurrently.

Part 1 was an open label, randomised two-treatment, two-period, two-sequence single-dose crossover study conducted in 14 healthy volunteers to evaluate the bioavailability of dolutegravir 10 mg tablets (5 tablets) compared with DTG 50 mg tablet. Both treatments were administrated direct to mouth with 240 ml water.

Part 2 was an open label, randomized, three period, six-sequence cross-over study conducted in 24 healthy volunteers to evaluate the relative bioavailability of five, 5mg dispersible tablets administrated as "disperse and immediately taken" and of five dispersible 5-mg tablets to be administered as "direct to mouth" with 240 ml of water, compared to a 25-mg conventional tablet (reference) administered direct to mouth with 240 ml of water.

Both parts: Study drug administration was performed after an overnight fast period of at least 10 hours. Blood-samples were collected pre-dose and up to 72 hours after drug administration. The study periods were separated by a wash-out period of 7 days (i.e. 7 days minus 4 hours). The study results are presented in the two tables below:

Table 4: Statistical Analysis of Dolutegravir Plasma Pharmacokinetic Parameters - Part 1

Parameter Treatment	N	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
AUC(0-t) (h•ng/mL)						
A	14	14	55800	A/B	1.0121	(0.8648, 1.1845)
B	14	14	55200			
AUC(0-∞) (h•ng/mL)						
A	14	14	58900	A/B	1.0084	(0.8626, 1.1789)
B	14	14	58400			
Cmax (ng/mL)						
A	14	14	2780	A/B	1.0329	(0.8623, 1.2373)
B	14	14	2700			

Source Data: Post-text Table 3.4.
CI = confidence interval; DTG = dolutegravir; LS = least squares; N = number of subjects in the treatment; n = number of subjects with evaluable data
Note: An analysis of variance with treatment and period as a fixed effects and subject as a random effect was performed on the natural ln-transformed parameters AUC(0-t), AUC(0-∞), and Cmax.
Treatment A = Conventional 10-mg DTG tablet (5 tablets) administered direct to mouth (test).
Treatment B = Conventional 50-mg DTG tablet administered direct to mouth (reference).

Table 5: Statistical Analysis of Dolutegravir Plasma Pharmacokinetic Parameters - Part 2

Parameter Treatment	N	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
AUC(0-t) (h•ng/mL)						
C	24	24	49000	C/E	1.6292	(1.5030, 1.7661)
D	24	24	46700	D/E	1.5519	(1.4317, 1.6822)
E	24	24	30100			
AUC(0-∞) (h•ng/mL)						
C	24	24	51300	C/E	1.6242	(1.4986, 1.7604)
D	24	24	48800	D/E	1.5448	(1.4253, 1.6743)
E	24	24	31600			
Cmax (ng/mL)						
C	24	24	2690	C/E	1.7933	(1.6226, 1.9819)
D	24	24	2700	D/E	1.7974	(1.6263, 1.9865)
E	24	24	1500			

Source Data: Post-text Table 3.5.
CI = confidence interval; DTG = dolutegravir; LS = least squares; N = number of subjects in the treatment; n = number of subjects with evaluable data.
Note: An analysis of variance with treatment and period as a fixed effects and subject as a random effect was performed on the natural ln-transformed parameters AUC(0-t), AUC(0-∞), and Cmax.
Treatment C = 5-mg dispersible DTG tablet (5 tablets) administered as a dispersion and immediately taken (test 1).
Treatment D = 5-mg dispersible DTG tablet (5 tablets) administered as direct to mouth (test 2).
Treatment E = Conventional 25-mg DTG tablet administered as direct to mouth (reference).

Influence of food

No food effect study has been submitted with this application. In the SmPC it is stated that dolutegravir may be taken with or without food, which is found acceptable.

Population pharmacokinetic model

A population PK model for DTG was previously developed in paediatric subjects using the available partial data (388 concentration records from 41 subjects with 90% data from FCT and only 10% from granules) from P1093. The predictive performance of this interim model was evaluated by using the additional data from P1093 and the available data from ODYSSEY studies as an external validation dataset and performing simulation using a prediction-corrected visual predictive check (pcVPC) method. The existing population PK

model was then updated with all the available data from P1093 (1751 concentration records from 152 subjects) and ODYSSEY (963 concentration records from 88 subjects). The additional data included both intensively and sparsely sampled data from various weight bands following FCT, granules and DT formulations, both in fasted and without regards to food conditions. The full model with backward deletion approach was utilized for covariate modelling. The model was then refined by estimating the allometric scaling coefficients, estimating separate bioavailability in fasted versus without regard to food conditions and estimating maturation function to CL/F. Once the final population PK model was developed, the ability of the model to describe the observed data was investigated using pcVPCs.

Software

NONMEM® program version 7.3.0 was used for the population PK analysis (ICON, Ellicott City, Maryland, USA).

Dataset

Previous dataset: A total of 2714 plasma concentrations (1751 from P1093 and 963 from ODYSSEY) were available from 240 subjects (152 from P1093 and 88 from ODYSSEY). Out of 2714, 21 plasma concentrations were BLQ and were excluded from the PK analysis. Further a total of 43 quantifiable plasma concentrations (24 from P1093 and 19 from ODYSSEY) were excluded from population PK analysis (reasons for exclusion were: outlier (very low concentration), sample thought to be flipped , subject had multiples comorbidities, sample haemolysis, non adherence to trial medication). A total of 239 subjects (2650 plasma concentrations), 151 from Study P1093 (1711 concentrations) and 88 from Study ODYSSEY (939 concentrations) were included in the current population PK analysis.

Updated dataset: New data are only available from study P1093 and the PopPK model has been updated with inclusion of these new data. The Applicant has updated the model included with the submission. After a cut-off date of 30 April 2019, an additional 183 concentrations (~6%) were available from 26 paediatric participants.

Model development

The previous population PK model was updated with the additional data from P1093 and ODYSSEY studies. The structural PK model remained the same as the interim model and the PK of DTG following oral administration were adequately described by a one-compartment model with first-order absorption and elimination; absorption rate constant (KA) was formulation specific and relative bioavailability (F) was both formulation and diet-specific. Allometric coefficients of the weight effect on CL/F and V/F were previously fixed but are now estimated to be lower than the theoretical values of 0.75 and 1, respectively. A maturation function from literature (Andersson et al.) was also applied to CL/F to account for the CL/F in infants. Random effects included inter-individual variability (IIV) on all parameters as well as inter-occasion variability (IOV) on both the apparent clearance (CL/F) and KA. Separate residual errors were estimated for the two studies. See tables below for parameter estimates for the current final model and comparison to the previous (interim model) and the adult model.

Table 6: Parameter Estimates of Fixed and Random Effects for the Final Population PK Model (Run 2019z)

Parameter [Units]	NONMEM Estimates				
	Point Estimate	95% CI	%RSE		
CL/F [L/hr]	1.03	0.980-1.07	2.31		
V/F [L]	13.6	13.0-14.3	2.42		
KA, FCT [hr^{-1}]	0.854	0.686-1.06	11.2		
KA~DT and Granules [hr^{-1}]	2.04	1.41-2.67	15.7		
F, Fasted FCT	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		
TM_{50} [week][a]	52.2 FIX	-	-		
Hill[a]	3.43 FIX	-	-		
Inter-individual variability		**Etabar (SE)**	**p val**	**CV%**	**Shr%**
ω^2_{CL}	0.0863	0.00139	0.925	29.4	21.5
Covar η_{CL}, η_V	0.0499	-	-	R=0.643	-
ω^2_V	0.0698	0.000651	0.961	26.4	22.2
Covar η_{CL}, η_{KA}	0.0953	-	-	R=0.372	-
Covar η_V, η_{KA}	0.138	-	-	R=0.598	-
ω^2_{KA}	0.762	-0.00170	0.964	107	33.2
$\omega^2_{IOV,CL}$	0.115	0.0220	0.171	33.9	26.6
$\omega^2_{IOV,CL}$	0.115	0.0314	0.0409	-	29.8
$\omega^2_{IOV,CL}$	0.115	-0.0213	0.0835	-	43.8
$\omega^2_{IOV,CL}$	0.115	-0.0306	0.0183	-	40.7
$\omega^2_{IOV,KA}$	0.610	0.0868	0.00415	91.7	39.9
$\omega^2_{IOV,KA}$	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 (ug/mL), P1093	0.00164	-0.00142-0.00470	95.1	SD=0.0405	-
Proportional Error, ODYSSEY	0.0123	0.00787-0.0167	18.4	11.1	16.3
Additive Error (ug/mL), ODYSSEY	0.0900	0.0677-0.112	12.7	SD=0.300	-

Abbreviations: %RSE: percent relative standard error of the estimate = SE*100; CL/F = apparent clearance, V/F = apparent volume, KA= absorption rate constant, Q/F = apparent inter-compartmental clearance, ω^2_{CL}, ω^2_V, ω^2_{KA} = variance of random effect of CL/F, V/F and KA and Q/F, respectively, DT=Dispersible tablet, FCT=Film coated tablet, F=Relative bioavailability, TM_{50} [week] =maturation half-time and Hill=Hill coefficient related to the slope of this maturation process.
Etabar is the arithmetic mean of the η estimates and the p-value for the null hypothesis that the true mean is 0, Shr=shrinkage. [a] SD

For IIV, if $\omega^2 > 0.15$, CV% = $100 * \sqrt{e^{\omega^2} - 1}$.
The reference population is a 70 kg subject.

[a]Parameters were taken from Anderson [14] and were used in the model with maturation function.
Covariate relationships:
CL/F =1.03* [(Weight /70)$^{0.455}$
V/F =13.6*(Weight /70)$^{0.556}$
KA (DT and 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)
F, without regard to food, DT/Granules =1.68 (1.47-.91), calculated as 1.10*1.53 (95% CI: 1.03*1.43-1.17*1.63)

Source: 2019z.res, Table 8.3-7

Table 7: Comparison of the Parameter Estimates of the Adult (Run 304), Paediatric Interim (Run 023) and the Current Paediatric Final (Run 2019z) Population PK Models

	NONMEM estimates Point estimate (95% CI)		
Parameter	**Adult Population PK model in Treatment Naïve patients (Run 304.res)***	**Interim Pediatric Population PK model (Run 023.res)*)**	**Current Pediatric Final Population PK model (Run 2019z.res)**
CL/F [L/hr]	0.901 (0.864-0.938)	1.02 (0.853-1.19)	1.03 (0.980-1.07)
V/F [L]	17.4 (16.5-18.3)	18.1 (15.7-20.5)	13.6 (13.0-14.3)
KA [hr^{-1}]	2.24 (1.56-2.92)	-	-
KA [hr^{-1}], FCT	-	0.694 (0.216-1.17)	0.854 (0.686-1.06)
KA [hr^{-1}], DT/Granules	-	1.42 (1.08-1.76)	1.74 (1.20-2.28)
F, FCT	-	1 FIX	-
F, DT/Granules	-	1.45 (1.22-1.68)	-
F, Fasted FCT	-	-	1 FIX
F, without regards to food, FCT	-	-	1.10 (1.03-1.17)
F, Fasted, DT/Granules	-	-	1.53 (1.43-1.63)
F, without regards to food, DT/Granules	-	-	1.68 (1.47-.91)
ALAG [hr]	0.263 (0.0942-0.432)	-	-
ALAG [hr], FCT	-	0.567 (0.0692-1.06)	-
ALAG [hr], Granule	-	0 FIX	-
CL/F~WT	0.438 (0.293-0.583)	0.750 FIX	0.455 (0.418-0.492)
V/F~WT	0.768 (0.605-0.931)	1.00 FIX	0.556 (0.514-0.598)
TM50 [week][a]	-	-	52.2 FIX
Hill[a]	-	-	3.43 FIX
CL~smoking	1.16 (1.10-1.22)	-	-
CL~Age	0.193 (0.103-0.283)	-	-
CL~Bilirubin	-0.211 (-0.269- -0.153)	-	-
F~Gender	1.21 (1.13-1.29)	-	-

popPK analysis with updated dataset: Model estimated PK parameters were compared for final model 2019z and model 2020y with the updated dataset. The Applicant also evaluated a model with fixed allometric exponents (0.75 and 1 for CL and V) and estimated only maturation half time (TM50) with both the current (2019z3) and updated (2020z2) data. A comparison of the model. The fixed and random effect parameters estimated in model 2019z and 2019z3 were comparable, showing no significant difference between the 2 models. However, when estimating TM50 (model 2019z3 or 2020z2), both fixed and random effect parameters were less precise. The applicant concludes that based on the model parameters, pcVPC and similar estimated TM50, the current model with the previous dataset is considered adequate. The popPK model submitted previously (2019z) was updated with new data (~6%). The parameter estimates and the OFV are included in Table 8 and Table 9 below.

Table 8: Parameter Estimates of Fixed and Random Effects for the PopPK Models

Parameter [Units]	2019z Estimate [%RSE]	2019z3 Estimate [%RSE]	2020y Estimate [%RSE]	2020z2 Estimate [%RSE]
CL/F [L/hr]	1.03 (2.31)	1.40 (8.4)	1.20 (25.3)	1.41 (10.6%)
V/F [L]	13.6 (2.42)	23.81 (0.9)	12.94 (1.5)	24.1 (0.8)
KA, FCT [hr^{-1}]	0.854 (11.2)	1.07 (168.6)	0.82 (58.8)	1.04 (275.3)
KA~DT and Granules [hr^{-1}]	2.04 (15.7)	1.44 (13.8)	2.44 (12.7)	1.45 (11.9)
F, Fasted FCT	1.00	1.00	1.00	1.00
F, without regard to food, FCT	1.10 (3.03)	1.12 (3.1)	1.12 (6.2)	1.12 (4.7)
F, Fasted DT/Granules	1.53 (3.26)	1.28 (2.3)	1.46 (8.2)	1.27 (2.2)
CL/F~WT	0.455 (4.15)	0.75 FIX	0.57 (5.9)	0.75 FIX
V/F~WT	0.556 (3.87)	1 FIX	0.53 (12.3)	1 FIX
TM_{50} [week][a]	52.2 FIX	51.2 (8.3)	52.2 FIX	48 (9.5%)
Hill[a]	3.43 FIX	3.43 FIX	3.43 FIX	3.43 FIX
Inter-individual variability %CV (%RSE)				
ω^2_{CL}	29.4 (8.5)	31.2 (9.3)	32.7 (8.8)	35.6 (8.9)
ω^2_{V}	26.4 (8.9)	34.9 (8.4)	32.2 (6.9)	35.4 (6.3)
ω^2_{KA}	87.3 (11.7)	72.5 (16.6)	103.9 (13.2)	65.5 (14.1)
$\omega^2_{IOV,CL}$	33.9 (4.6)	35.2 (5.1)	42.8 (3.9)	41.6 (4.2)
$\omega^2_{IOV,CL}$	-	-	-	-
$\omega^2_{IOV,CL}$	-	-	-	-
$\omega^2_{IOV,CL}$	-	-	-	-
$\omega^2_{IOV,KA}$	78.1 (11.1)	77.5 (13.2)	89.4 (8.6)	91.5 (8.2)
$\omega^2_{IOV,KA}$	-	-	-	-
Residual variability				
Proportional Error, P1093	0.0818 (7.67)	0.0829 (7.1)	0.0822 (17.9)	0.0842 (7.3)
Additive Error (ug/mL), P1093	0.00164 (95.1)	0.0012 (100.8)	0.0 (249.1)	0.00 (172.6)
Proportional Error, ODYSSEY	0.0123 (18.4)	0.0114 (17.7)	0.0066 (68.5)	0.0075 (32.8)
Additive Error (ug/mL), ODYSSEY	0.0900 (12.7)	0.0946 (12.4)	0.116 (18.8)	0.112 (14.6)

Abbreviations: %RSE:percent relative standard error of the estimate = SE*100; CL/F = apparent clearance, V/F = apparent volume, KA= absorption rate constant, Q/F = apparent inter-compartmental clearance, ω^2_{CL}, ω^2_{V}, ω^2_{KA} = variance of random effect of CL/F, V/F and KA and Q/F, respectively, DT=Dispersible tablet, FCT=Film coated tablet, F=Relative bioavailability, TM_{50} [week] =maturation half-time and Hill=Hill coefficient related to the slope of this maturation process.
Note: The reference population is a 70 kg participant.
a. Parameters were taken from Anderson and Holford [Anderson, 2009] and were used in the model with maturation function.

Table 9: Summary of Population PK Model with Objective Function Values

Run	OFV	Data	Details
500_2020	3435.8	NM_PKDATA_V7_updated.csv	Base Model updated with new data
2020y15	1496.0	NM_PKDATA_V7_updated.csv	Final model updated with new data Allometric exponent for CL and V estimated; Maturation function fixed
2020y20	1670.4	NM_PKDATA_V7_updated.csv	Final model updated with new data Allometric exponent Fixed CL~1 and V~0.75; Maturation function (TM50 estimated)

Model Evaluation

The final model was evaluated by performing pcVPCs. The median, 5th and 95th percentiles for the predicted DTG concentrations are overlaid with the observed data. Note that this is the model using the previous dataset, not the updated dataset. The plots stratified by weight band indicated an overall good prediction of the observed concentrations (see figures below).

Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations; Left plot: linear; Right plot: log-linear

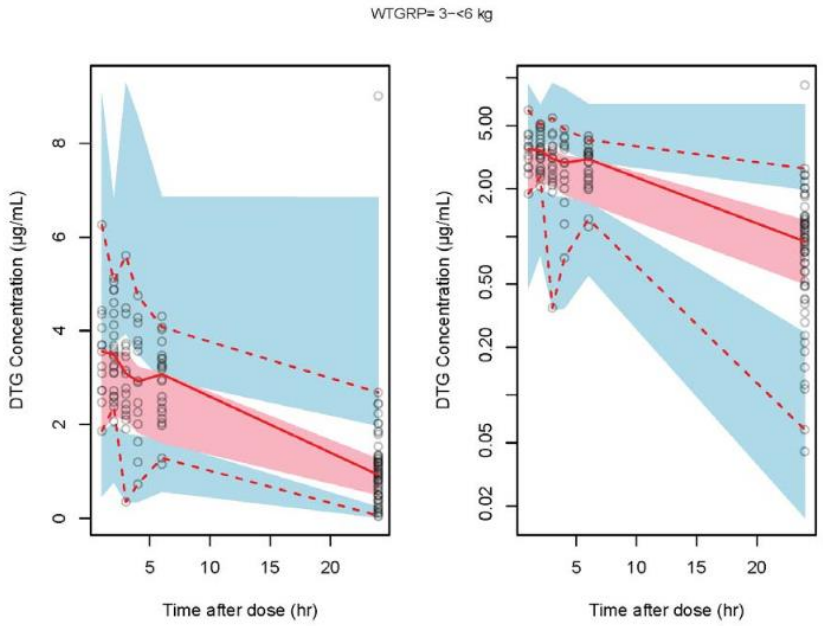


Figure 1: Prediction-Corrected Visual Predictive Check for Final Population PK Model (Run 2019z), Stratified by WHO Weight Band

Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations; Left plot: linear; Right plot: log-linear

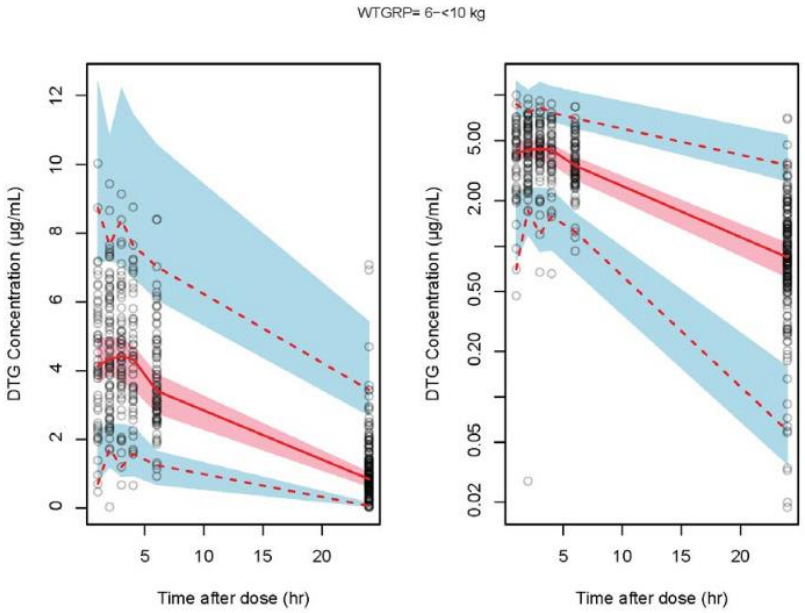


Figure 2: Prediction-Corrected Visual Predictive Check for Final Population PK Model (Run 2019z), Stratified by WHO Weight Band

Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations; Left plot: linear; Right plot: log-linear

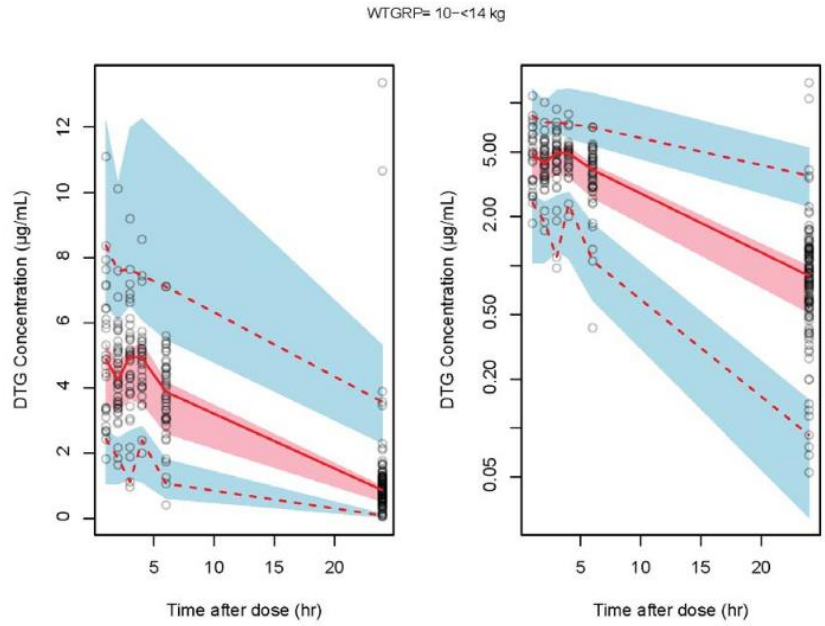


Figure 3: Prediction-Corrected Visual Predictive Check for Final Population PK Model (Run 2019z), Stratified by WHO Weight Band

Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations; Left plot: linear; Right plot: log-linear

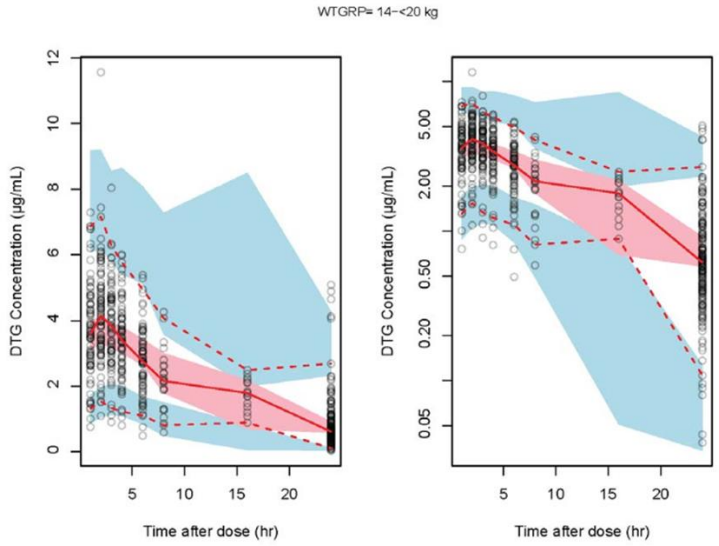


Figure 4: Prediction-Corrected Visual Predictive Check for Final Population PK Model (Run 2019z), Stratified by WHO Weight Band

Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations; Left plot: linear; Right plot: log-linear

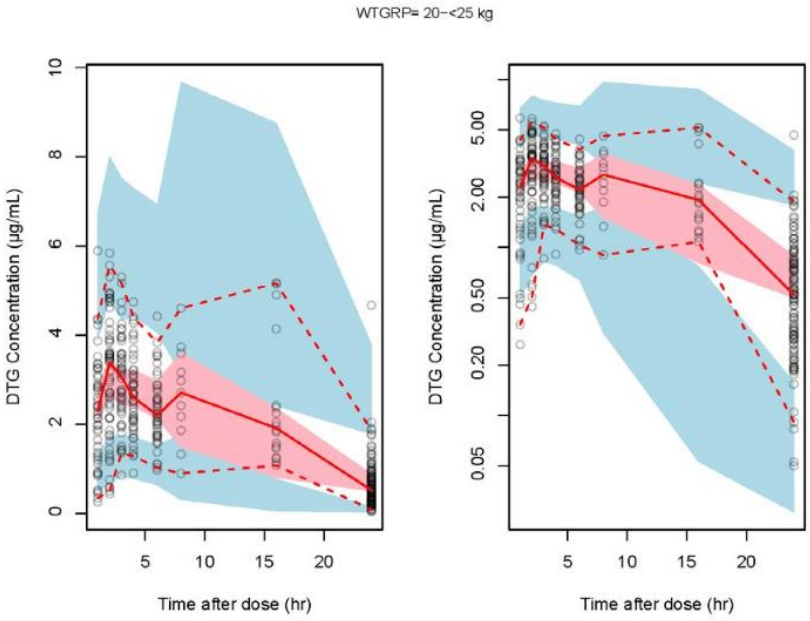


Figure 5: Prediction-Corrected Visual Predictive Check for Final Population PK Model (Run 2019z), Stratified by WHO Weight Band

Target PK parameters

The goal of the DTG paediatric clinical program is to determine optimal paediatric dosing that achieves plasma DTG AUC0-24h and C24h values associated with efficacy in adults. The target PK parameters and range are shown in the table below. The upper range target is the 95th percentile observed in adults in Study ING112961 in which DTG was dosed twice daily in adults with documented INSTI resistance.

Table 10: Target PK Parameters and Ranges for DTG Exposure

Parameters	Parameters PK Targets
C24h	
Target GM (range)	995 (697 – 2260) ng/mL
AUC0-24h	
Target GM (range)	46 (37 – 134) µg*hr/mL

The applicant has now provided PK target exposure for Cmax. The GM target of 3.67 µg/mL represents a post hoc GM estimate in treatment naïve participants following 50 mg FCT QD DTG dosing. The lower limit (2.94 µg/mL) is selected as 80% of the GM Cmax (3.67 µg/mL). The upper limit (6.7 ug/mL) represents the 95th percentile of post hoc estimates in treatment experienced participants following 50 mg FCT BID dosing. The upper limit for individual participants was selected based on a supratherapeutic dose of 250mg once daily as an oral suspension in 41 adult participants in thorough QT/QTc (TQT) Study (ING111856) where GM Cmax [min-max] was 12.4 [5.3 – 20.5] µg/mL.

Table 11: Target for Steady State Cmax

Parameter	PK Target
Cmax	
Target for GM	3.7 µg/mL
Range for GM	2.9 – 6.7 µg/mL
Max for individual	12.4 µg/mL

DTG exposure in paediatric patients

The proposed weight band-based DTG dosing is designed to align dosing recommendations with WHO-defined weight bands [WHO, 2016] and supported by regulatory guidance. The proposed weight band based DTG doses simplify dosing by minimizing the number of different doses, dosage forms, and dosage form strengths required across paediatric and adult patients. For example, DTG 50mg FCT is currently approved for use in adult and paediatric patients >40 kg. The proposal to extend the 50mg FCT dose to children weighing at least 20 kg is supported by the similar plasma DTG C24h observed among the three weight bands in ODYSSEY (20to <25 kg, 25to <30 kg, and 30to <40 kg) compared with data for >40 kg in P1093 and historical data in adults following 50 mg once daily. See first table below for summary of simulated DTG exposure in paediatric patients. The 2nd table below shows observed exposure for the 50 mg FCT dose in paediatric patients and adults. Simulated Cmax for the BID dosing (same daily dose as QD) is also shown in figure below. Note that Cmax in paediatric cohorts is higher than Cmax for twice daily 50 mg dose in adults.

Table 12: Summary of Simulated DTG PK Parameters for Proposed Doses for Paediatric Patients

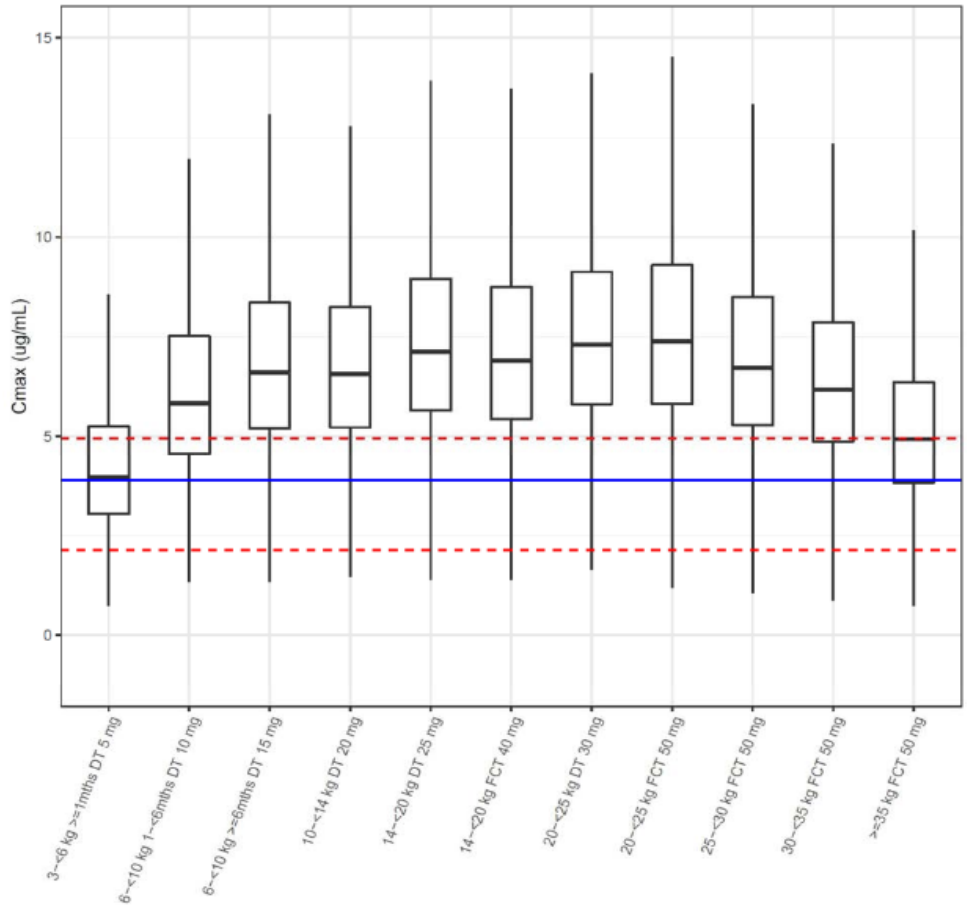
Weight Band (kg)	DTG Dosage Form	Once Daily Dose (mg)	PK Parameter GM (90% CI)		
			Cmax (µg/mL)	AUC0-24h (µg*h/mL)	C24h (ng/mL)
3 to <6	DT	5	4.02 (2.44, 6.78)	49.4 (25.4, 95.4)	1070 (357, 3010)
6 to <10 & <6 months	DT	10	5.90 (3.67, 9.57)	67.4 (35.9, 127)	1240 (392, 3630)
6 to <10 & ≥6 months	DT	15	6.67 (4.24, 10.6)	68.4 (36.4, 128)	964 (262, 3210)
10 to <14	DT	20	6.61 (4.30, 10.2)	63.1 (34.3, 115)	719 (184, 2560)
14 to <20	DT	25	7.17 (4.63, 11.2)	69.5 (37.8, 127)	824 (212, 2870)
14 to <20	FCT	40	6.96 (4.38, 11.0)	72.6 (39.6, 132)	972 (254, 3250)
20 to <25	DT	30	7.37 (4.77, 11.4)	72.0 (39.3, 133)	881 (227, 3020)
20 to <25	FCT	50	7.43 (4.73, 11.8)	78.6 (43.2, 145)	1080 (289, 3620)
25 to <30	FCT	50	6.74 (4.26, 10.6)	71.4 (39.3, 131)	997 (272, 3320)
30 to <35	FCT	50	6.20 (3.94, 9.78)	66.6 (36.5, 121)	944 (256, 3100)
≥35	FCT	50	4.93 (3.07, 7.93)	54.0 (29.2, 99.1)	814 (233, 2590)

Data Source: GlaxoSmithKline Document Number 2019N424147_00 Table 5.10-1

Table 13: Summary of Plasma DTG PK Parameters for FCT 50 mg by Weight Band vs. Historical Adult Data

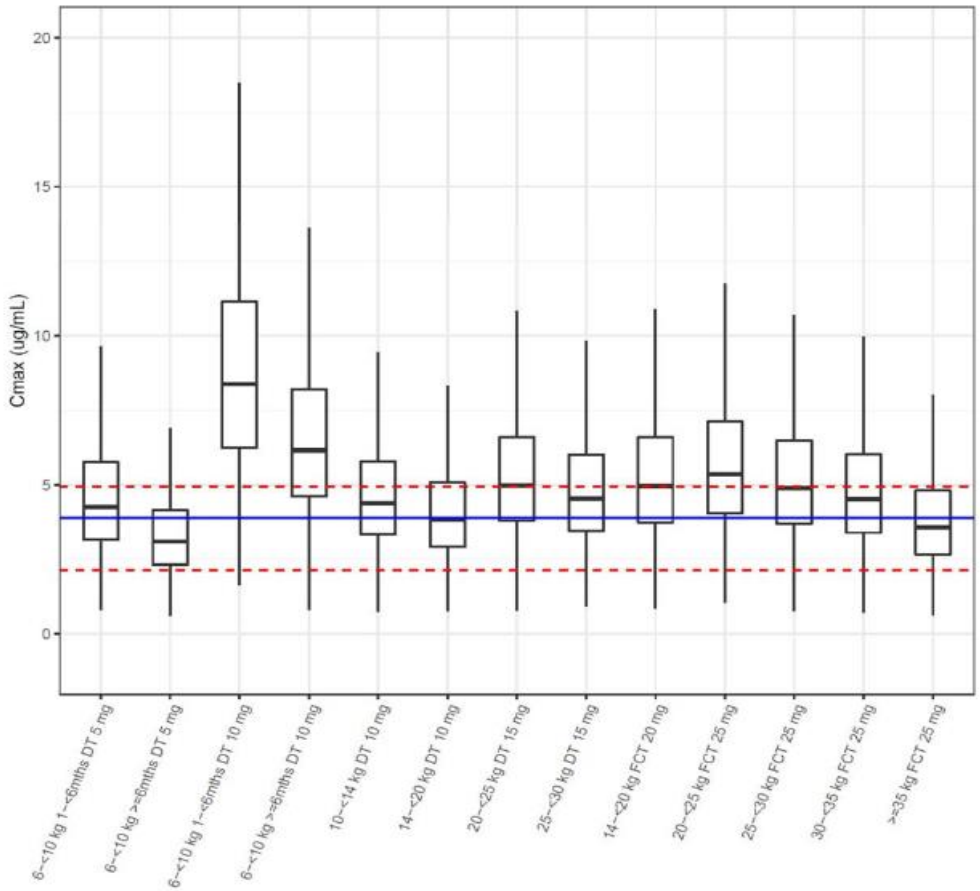
Study	Weight Band (kg)	DTG Dosage Form[a]	Once Daily Dose (mg)	N	PK Parameter GM (%CVb)		
					Cmax (µg/mL)	AUC0-24h (µg*h/mL)	C24h (ng/mL)
ODYSSEY	20 to <25	FCT	50	7	6.07 (29)	62.82 (30)	770 (51)
	25 to <30	FCT	50	15	5.36 (26)	57.16 (30)	706 (46)
	30 to <40	FCT	50	13	5.10 (23)	54.30 (28)	692 (47)
P1093	≥40	FCT	50	14	3.89 (58)	49.92 (70)	965 (95)
ING111521 & ING112276	Adults	FCT	50	25	3.38 (23)	46.14 (33)	956 (57)
PopPK	Adults	FCT	50 mg Twice Daily	-	4.15 (29)	75.1 (35)	2120 (47)

Data Source: ODYSSEY Table 5.3; P1093 Table 5.28; P1093 Protocol Version 4 Table 8; Tivicay, current labeling



Note: Boxes represent median (black horizontal line in the middle), 1st quartile, and 3rd quartile of the data, Vertical black line through the middle of the boxes (Whiskers) represent minimum and maximum, Blue line: Geometric mean Cmax (3.89 μg/mL) in treatment experienced participants. Red dotted lines: 5th and 95th percentile (2.14 μg/mL and 4.95 μg/mL) Cmax in treatment experienced participants.

Figure 6: Simulated Cmax by WHO weight bands after QD Dosing of DTG



Note: Boxes represent median (black horizontal line in the middle), 1st quartile, and 3rd quartile of the data, Vertical black line through the middle of the boxes (Whiskers) represent minimum and maximum, Blue line: Geometric mean Cmax (3.89 μg/mL) in treatment experienced participants. Red dotted lines: 5th and 95th percentile (2.14 μg/mL and 4.95 μg/mL) Cmax in treatment experienced participants.

Figure 7: Simulated Cmax by WHO weight bands after BID dosing of DTG

2.4.3. Pharmacodynamics

There are no new PD data within this application.

2.4.4. Discussion on clinical pharmacology

Three relative bioavailability studies (study 200401, ING114556 and 205893) were submitted by the applicant in order to bridge the different types of formulation (dispersible tablet, tablet and granules of oral suspension) to each other in fasting state. A bridge to either the 25 mg tablet, as reference in study 205893, or to the 50 mg tablet, as reference, in study ING114556 is found acceptable, since the composition of the commercial 25 mg tablet is proportional to the commercial 50 mg tablet and the in vitro dissolution profiles are generally considered similar to the 50 mg tablet.

An earlier 5 mg dispersible tablet formulation was used in study 200401 which is not the same as the one intended for marketing. The applicant has not discussed the differences in composition between the earlier 5

mg dispersible tablet used in study 200401 and the intended 5 mg dispersible tablet for marketing. However, the two relative bioavailability studies (205893 and ING114556), are assessed as sufficient to bridge the different types of formulation (dispersible tablet, tablet and granules of oral suspension) to each other in this case.

In study 200401, bioequivalence was shown between four, 5 mg dispersible tablet (earlier formulation and not the formulation intended for marketing) dispersed in low mineral content water compared with the 20 mg paediatric granule, since the 90% confidence interval fell within the conventional acceptance range of 80.00-125.00% for AUC0-t and Cmax. In this study it could also be concluded that the dispersible tablet seems not be affected by different types of water (low mineral content water or Contrex water). If the dispersible tablet is first dispersed and then stands for 30 minutes in low mineral water or Contrex water before consumption seems not to have any affect either.

In study ING114556 bioequivalence was not established for the granule for oral suspension compared with the 50 mg tablet, since the 90 % confidence interval fell outside the conventional acceptance range of 80.00-125.00%. In this study the granules for oral suspension, administrated direct to mouth without liquid or reconstituted with various liquids (purified water, Contrex mineral water or milk-based infant formula), showed higher bioavailability compared with the 50 mg tablet; geometric dolutegravir mean plasma AUC0-∞ values were 1.55- to 1.83-fold higher, AUC0-t was 1.56- to 1.84 fold higher and Cmax was 1,62- to 2.02-fold higher.

The oral bioavailability for the granule for oral suspension was not affected if given direct to mouth or with different types of water (purified water or HMC water). The oral bioavailability was affected to a small extent when given with milk-based infant formula compared with purified water; geometric mean AUC0-∞, AUC0-t were both 1.17-fold higher and Cmax was 1.22-fold higher.

Study 205893 was divided in two parts. In part 1, bioequivalence was shown between the conventional 10 mg tablet (administrated as 5 tablets) and the commercial 50 mg tablets since the 90% confidence interval for AUC0-t and Cmax fell within the conventional acceptance range of 80.00-125.00%.

In the previously approved SmPC of Tivicay it is stated in section 4.2 that the 50 mg once daily dose should not be given as five, 10 mg tablets. In section 5.2 it is further stated that bioequivalence has not been unequivocally shown for 1x50 mg tablet compared to 5x10 mg tablets and therefore, the 50 mg once daily dose should not be given as five, 10 mg tablets. In this application this text has been removed from the SmPC. This is assessed acceptable based on that bioequivalence is shown between five commercial 10 mg tablets and the commercial 50 mg tablet.

In part 2 of the same study, bioequivalence was not established for dispersible tablet compared to the conventional 25 mg tablet. AUC0-t, AUC0-∞ were both increased about 1.5- to 1.6- fold and Cmax was increased about 1.8-fold following administration of five dispersible, 5mg tablets, administrated as a dispersion or administrated direct to mouth with 240 ml of water compared with one conventional 25 mg tablet.

From the relative bioavailability data, it can be concluded that the dolutegravir dispersible tablet deliver higher plasma exposure than dolutegravir tablets. Thus, the two dosage forms are not substitutable on a mg-per-mg basis and a dose adjustment is necessary when switching between the two dosage forms. It can also be concluded that the dolutegravir dispersible tablet seems not to be affected by different types of water (low mineral content water or Contrex water).

No food effect study has been submitted with the new dispersible tablet. However, based on the formulation of the new dispersible tablet it is not considered likely that the new dispersible tablet has higher food effect than the conventional tablet. This is supported by the fact that the dispersible tablet and the granule for oral suspension is based on the same granules, and for the granules for oral suspension the oral bioavailability was affected to a small extent when given with milk based infant formula compared with purified water; geometric mean AUC0-∞, AUC0-t were both 1.17-fold higher and Cmax was 1.22-fold higher. Thus, the food effect for the tablet can be considered as a worst-case scenario for the dispersible tablet.

The Cmax geometric mean observed in the 20 to <25 kg weight band (the weight cohort with the highest Cmax) and assuming a worst-case scenario with a high fat meal would be ~11.95 ug/mL (67% higher [7.16 x 1.67 = 11.95 ug/mL]). While high, this GM Cmax is in line with 250 mg single dose observed in adults.

It is however agreed that the worst-case scenario food effect is unlikely. Overall, the applicant has mitigated some of the concern regarding food effect on Cmax but a quantitative information on the food effect is still lacking.

Thus, information regarding food effect of the dispersible tablet cannot be included in the SmPC, but information in the SmPC that the dispersible tablet can be taken both under fasting and fed condition is agreed.

The SmPC has been updated accordingly to reflect that no formal food effect studies were conducted for dispersible tablets. However, based on the available data a higher a food effect is not expected for the dispersible tablet compared to the film coated tablets.

The applicant has clarified that long- term stability data cover the time from first sample collection to analysis in the two studies (study P1093 and Odyssey).

Regarding popPK

There were very few BQL data, thus not using M3 method or other appropriate method for handling BQL data is acceptable. Removing 43 plasma concentrations and providing reason for exclusion is considered adequate.

The date for the data cut-off was 30 Apr 2019 for P1093 and 28 Feb 2019 for ODYSSEY, this is considered to be too long ago. The applicant has now updated the dataset with more recent data.

The approach to start with the previous popPK model is supported. From the run record, when estimating the maturation function parameters, the OFV increased. This means that the model ended up in a local minimum. Further, estimating both allometric exponents and maturation function is likely not possible as the model will be over parameterized. The estimated allometric exponents are now likely accounting for some of the maturation. The applicant should estimate a model with fixed allometric exponents (0.75 and 1 for CL and Vd) and estimate parameters for the maturation function (using the updated dataset). The hill factor may be difficult to estimate, and the applicant can also try estimating only TM50. The updated model should be compared to the current final model (both using the updated dataset). The applicant should provide weight stratified pcVPC for the updated models. The applicant has developed updated models using an updated dataset with more data but still concludes that the previous model with the previous data set is adequate and thus the final model. This is not agreed with. A model with the updated dataset is considered more correct since it uses all the available data. In addition, no OFVs were presented. It is unclear if the model with fixed allometric scaling and estimated maturation may be in a local minimum. The applicant should present OFV compared to base model (using updated dataset only). The applicant should try different initial estimates if there are indication of local minimum.

The applicant has now provided run record including OFV for models with the updated dataset. The run record support a model with estimated allometric exponent and fixed maturation function. The parameter estimates and the provided VPCs for the updated model are similar to the previous model. Since the updated model and the previous model are similar the simulations from the previous model are accepted. The simulations support the proposed posology.

The applicant has not adequately motivated the proposed PK target parameters and ranges. Cmax is missing and needs to be included. The applicant has now provided a table with target range for Cmax. Cmax and safety are discussed in clinical safety section.

The applicant has changed the proposed dosing in already approved paediatric weight/age groups to simplify dosing by minimizing the number of different doses, dosage forms, and dosage form strengths required across paediatric population. In the new proposed dosing, children weighing ≥20 kg will receive same dose as adults. Cmax in several paediatric cohorts including children 20-25 kg are higher than Cmax for twice daily (100 mg/day) dosing in adults. Cmax and safety are discussed in clinical safety section.

2.4.5. Conclusions on clinical pharmacology

Extrapolating efficacy and safety from adults to children based on exposure similarity is supported. The issues regarding the popPK analysis have now been solved. The popPK model with the updated dataset has same model structure and similar parameter estimates as the previous model with the previous dataset and thus the simulations and conclusions from the previous model are accepted. The simulations support the proposed posology.

The applicant has mitigated some of the concern regarding the food effect. The food effect for the tablet can be considered as a worst-case scenario for the dispersible tablet but the food effect is likely less. Thus, information regarding food effect of the dispersible tablet cannot be included in the SmPC, but information in the SmPC that the dispersible tablet can be taken both under fasting and fed condition is agreed. .

The applicant agreed with the remaining SmPC comments and updates as requested by CHMP.

The SmPC has been updated with the remaining comments on food effect.

2.5. Clinical efficacy

2.5.1. Dose response studies

The current application is based on data from the ongoing paediatric study P1093 and PK sub-studies in the ODYSSEY study (PENTA 20, 201296);

- to support the 5 mg DTG DT for approval with dosing recommendations in children ≥3 kg and ≥4 weeks of age and to
- update current dosing recommendation for paediatric patients to align with the WHO-defined weight bands
- to support new paediatric dosing recommendations in children ≥14 kg in film-coated tablets (10 mg, 25 mg and 50 mg)

The assessment of efficacy in this variation is based on P1093 data only, while safety is based also on the ODYSSEY study. There are no dose-response studies in this application.

The previous paediatric line extension (TIVICAY X/0018G), included an assessment of PK, safety and efficacy data from two sub-cohorts in the study P1093: Cohort IIA containing children 6-12 years (scope of application), and Cohort I containing adolescents 12-18 years (supportive data) for a line extension to register two new tablet strengths; 10 mg and 25 mg tablets and a type II variation to extend the therapeutic indication for TIVICAY to children from 6 to 12 years of age.

In the current application, the MAH includes interim data on PK, safety and efficacy of TIVICAY in Cohorts I-V (≥4 weeks old to >18 years) from the P1093 study and interim data on PK and safety from the ODYSSEY study (patients aged ≥28 days and <18 years).

2.5.2. Main studies

Study P1093 (ING112578), *Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir (GSK1349572), a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents: Cohorts I-V, Interim Report*

P1093 is an ongoing Phase I/II multi-center, open-label non-comparative, dose-finding study of at least 120 HIV-1 infected infants, children, and adolescents ages ≥4 weeks to <18 years to evaluate the PK parameters, safety, tolerability, and antiviral activity of DTG when administered both prior to starting and in combination with optimized background therapy (OBT). This study enrolled children in age-defined cohorts sequentially from oldest to youngest.

Study ODYSSEY (201296), *ODYSSEY (PENTA 20): A Randomized Trial of Dolutegravir-based Antiretroviral Therapy vs. Standard of Care in Children with HIV Infection Starting First-line or Switching to Second-line ART: Interim Results from 2 Pharmacokinetic Sub-studies*

ODYSSEY is an ongoing, open-label, multi-center, randomized (1:1), non-inferiority, Phase II/III, 96-week, 2-arm clinical trial to compare the efficacy and safety of DTG plus 2 NRTI vs. SoC in ~700 HIV-infected children aged less than 18 years who are starting first-line ART or switching to second-line ART.

- ODYSSEY A: paediatric participants starting first-line ART
- ODYSSEY B: paediatric participants starting second-line ART.

The trial incorporates several sub-studies, including 2 weight band-based DTG dosing PK sub-studies, WB-PK1 and WB-PK2 (described below); intensive PK and safety data from these PK sub-studies are assessed in this report.

The objectives of the ODYSSEY PK sub-studies are to generate complementary DTG PK data, using dosing according to WHO weight bands in younger children receiving the 5 mg DT, to provide DTG PK data in older children receiving simplified dosing with the 50 mg FCT, and to provide safety data to support new proposed dosing.

Details of the PK sub-studies (WB-PK1 and crossover WB-PK2) were as follows:

WB-PK1: This sub-study evaluated DTG PK in participants <25 kg and was divided into 3 components. WB-PK1 part I evaluated the steady-state PK of DTG dosed as one 25 mg FCT once daily in participants weighing 14 to <20 kg and 20 to <25 kg. Participants were recruited to the sub-study until at least 16 participants (8

participants per weight band) had a single evaluable steady-state 24-hour intense PK profile. Subsequently in WB-PK1 part II, participants were enrolled at doses of 25 mg DT and 30 mg DT or 50 mg FCT in the 14 to <20 kg and 20 to <25 kg weight bands, respectively.

WB-PK2: In this crossover sub-study, the PK of 2 different DTG doses were assessed in participants weighing ≥25 kg in a sequential design within the same child. Participants weighing from 25 to <40 kg and taking DTG as described in the protocol (25 mg FCT for 25 to <30 kg weight band and 35 mg FCT for 30 to <40 kg weight band) were enrolled in the sub-study until at least 16 participants (at least 8 per weight band) had evaluable 24-hour PK profiles on their current dose. Thereafter, the DTG dose was changed to 50 mg FCT and a second 24-hour PK profile was obtained at least 1 week after crossing over to the 50 mg FCT dose.

Methods

Both P1093 and ODYSSEY include patients between 4 weeks and 18 years of age. The original enrolment in P1093 was based on age but data has post hoc been regrouped based on weight. In the ODYSSEY study patients are grouped according to weight bands.

Study Participants

P1093

Key inclusion criteria include ART-experienced or naïve infants, children, and adolescents age ≥4 weeks to <18 years at study entry, with confirmed HIV-1 infection, and an OBT that contains at least 1 fully active drug for ART-experienced participants.

Key exclusion criteria include; known resistance to an integrase inhibitor, presence of any active AIDS-defining opportunistic infections, evidence of pancreatitis, liver toxicity, known exposure to an integrase inhibitor, use of chronic systemic immunosuppressive agents or systemic interferon, any known Grade 4 laboratory toxicities or specified Grade 3 laboratory toxicities 30 days prior to study entry (Note: ≥Grade 3 bilirubin was allowed if the participant was on ATV).

Participants initially began sequential enrolment in age-specific cohorts to assess different formulations as shown below:

Cohort I: Adolescents ≥12 to <18 years of age (FCT);

Cohort IIA: Children ≥6 to <12 years of age (FCT);

Cohort IIB: Children ≥6 to <12 years of age (granules for suspension);

Cohorts III: Children ≥2 to <6 years of age (granules for suspension);

Cohort III-DT: Children ≥2 to <6 years of age (DT);

Cohort IV: Children ≥6 months to <2 years (granules for suspension);

Cohort IV-DT: Children ≥6 months to <2 years of age (DT);

Cohort V-DT: Infants ≥4 weeks to <6 months (DT).

Due to increasing international recommendations for paediatric dosing according to weight, independent of age, enrolment of sufficient participants to analyse by weight band was also incorporated into the protocol (v5.0) as shown below:

- 3 to <6 kg;
- 6 to <10 kg;
- 10 to <14 kg;
- 14 to <20 kg.

Participants are enrolled into the study first into Stage 1, during which intensive PK samples are collected at steady state. Target enrolment for Stage 1 is 10 evaluable participants for each age cohort, after which exposure and 4-week safety data are reviewed by the protocol team. Within each age cohort participants were dosed by weight. With the latest protocol amendment, enrolment into Stage 1 continued until at least 8 evaluable participants were enrolled into each of the WHO-defined weight bands. Stage 2 opens to enrolment if data from Stage 1 are considered acceptable. Target enrolment for Stage 2, during which only sparse PK samples are collected, is 12. Participants are followed through Week 48 and then for another 3 years as part of long-term safety follow-up.

AT Population (n=159) includes all participants exposed to DTG at any dose.

AT Safety Population (n=159) includes all participants who took at least one dose of DTG and deemed safety evaluable per the protocol.

PD Safety Population (n=75) is a subset of participants from the AT Population that started DTG at the proposed doses.

PD Efficacy Population (n=58) is a subset of participants from the AT Population that started DTG at the proposed doses shown and who were enrolled at least 24 weeks prior to an agreed upon efficacy cut-off date.

Data presented in this submission include Stage 1 (intensive PK) and longer term follow up data (including Stage 2) as available. Safety and efficacy data from Cohorts I and II (using the FCT) have been previously submitted and are included. Enrolment into Cohorts III and IV continues as outlined in the protocol. Enrolment into Cohort V is complete.

ODYSSEY

Key inclusion criteria for the ODYSSEY study included paediatric participants aged between ≥28 days and <18 years of age and weighing ≥3 kg with confirmed HIV-1 infection. Participants in ODYSSEY A must have been planning to start first-line ART. Participants in ODYSSEY B must have been planning to start second-line ART defined as either: (i) switch of at least 2 ART drugs due to treatment failure; or (ii) switch of only the third agent due to treatment failure where drug sensitivity tests showed no mutations conferring NRTI resistance. In addition, participants in ODYSSEY B:

- Must have been treated with only 1 previous ART regimen. Single-drug substitutions in their previous ART regimen for toxicity, simplification, changes in national guidelines, or drug availability were allowed. ODYSSEY B participants must have had at least 1 NRTI with predicted preserved activity available for a background regimen.
- In countries where resistance tests are routinely performed, at least 1 active NRTI from TDF/TAF, ABC or ZDV should be chosen based on all resistance test results in the child (historic and recent). The interpretation of the mutations should be based on the up-to-date version of the Stanford HIV Drug Resistance Database.

- In countries where resistance tests are not routinely performed, clinicians should follow national/WHO Guidelines. At least 1 new NRTI with presumed preserved activity (from ABC, TDF or ZDV) should be chosen (Section 5.1 of the protocol).
- Viral load ≥500 c/mL at Screening Visit or within 4 weeks prior to Screening. (Note: Prior to Version 3.0, the viral load requirement was ≥1000 c/mL.)

Key exclusion criteria included history or presence of known allergy or contraindications to DTG, proposed available NRTI backbone, or proposed available standard of care third agent, hepatic impairment, anticipated need for hepatitis C virus therapy, pregnancy or breastfeeding, and evidence of lack of susceptibility to INSTIs or more than a 2-week exposure to ARVs of this class.

Inclusion/Exclusion Criteria: PK Sub-studies

Participants should have met the inclusion criteria for the main study (ODYSSEY A or ODYSSEY B), should have been randomized to DTG, and should have met the following additional inclusion criteria for the PK sub-studies:

- Weight 3 to <25 kg for the WB-PK1 sub-study
- Weight 25 to <40 kg for the WB-PK2 sub-study
- Parents/caregivers and paediatric participants, where applicable, gave informed written consent.

In addition to the exclusion criteria for the ODYSSEY study, the following participants were excluded from the PK sub-studies:

- Children who suffered from illnesses that could have influenced drug PK; i.e., severe diarrhoea, vomiting, renal disease, or liver disease
- Children treated with concomitant medications known to have interactions with DTG
- Children with current severe acute malnutrition.

Interim Analyses

The planned interim analyses for ODYSSEY only include evaluation of the populations participating in the 2 PK sub-studies (WB-PK1 and WB-PK2) nested within the ODYSSEY study to support Tivicay paediatric global regulatory submissions.

Final Analyses

The MRC CTU have produced an analysis plan for the ODYSSEY study and PK sub-studies that they will conduct after completion of the ODYSSEY study, to evaluate the efficacy and safety of once daily DTG-based ART compared with standard of care in children and adolescents starting first- or second-line ART in resource-limited and well-resourced settings.

Table 14: Population Analysis in ODYSSEY

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprised all participants who consented to enter either of the PK sub-studies and received at least 1 dose of DTG formulations • This population was based on the treatment the participant actually received	• Safety • Study Population
Safety Intended DTG Dose	• Comprised all participants who consented to enter either of the PK sub-studies and received at least 1 dose of the intended DTG formulations and doses. Only intended doses were included in summaries using the Safety Intended DTG dose • Intended DTG doses included DT (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg) and FCT (50 mg) used according to the weight bands defined dosing in Table 7.	• Safety • Study Population
Safety from First Intended DTG Dose	• Comprised all participants who enrolled into either of the PK sub-studies and received at least 1 dose of the intended DTG formulations and doses • Participants were grouped according to their first intended dose; i.e., if a participant started on 5 mg DT and then subsequently took 10 mg DT, all events were presented in the 5 mg DT group	• Safety • Study Population
Intensive PK Concentration	• All enrolled participant doses who underwent intensive PK sampling while the participant was receiving that dose, where samples were collected according to the intensive sampling schedule and were analyzed. Participants could have therefore been assigned to the Pharmacokinetic Concentration Population for more than 1 DTG dose level • Participants were included in the weight band according to the DTG dose they received; i.e., if a participant weighed 29.4 kg and received 35 mg FCT, they were included in the 30 to <40 kg weight band. For safety and study population analyses, participants were included in their actual weight band	• PK
Intensive PK Parameter	• All participant doses in the Intensive Pharmacokinetic Concentration Population who provided at least 1 evaluable PK parameter	• PK

Safety Population, n=99; Safety Intended DTG Dose, n=97; Safety from First Intended DTG Dose, n=97; Intensive PK Concentration, n=88; Intensive PK Parameters, n=88

Treatments

P1093

Dolutegravir Film-Coated Tablet Dosing

For Cohort I and Cohort IIA, the initial starting dose of DTG FCT was approximately 1 mg/kg once daily, with a maximum daily dose of 50 mg.

Table 15: P1093 Cohort I and IIA DTG FCT Dosing

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

Dolutegravir Granule Dosing

For Cohort IIB, Cohort III, and Cohort IV, the initial starting dose of DTG granules for suspension was ~0.64 mg/kg once daily for mini-cohort IIB and ~0.8 mg/kg once daily for Cohorts III and IV. Doses were revised to ~0.8mg/kg in Cohort IIB and ~1.25mg/kg in Cohort IV. The maximum daily dose was 32 mg.

The development of granules for suspension is no longer being pursued by the MAH; dispersible tablets will be the commercially available paediatric formulation.

Dolutegravir Dispersible Tablet Dosing

According to the revised proposed SmPC, dispersible tablets are recommended for:

- adults
- adolescents, children and infants aged at least 4 weeks and weighing at least 3 kg

For Cohort III-DT, the initial starting DTG DT dose was designed to target approximately 0.8 mg/kg with a maximum dose of 30 mg but was subsequently increased. For Cohort IV-DT the initial starting DTG DT dose was designed to target 1.25 mg/kg with a maximum dose of 30 mg but was subsequently increased. For Cohort V, the initial DTG DT dose was designed to target 1.25 mg/kg and was accepted. When participants in Cohort V-DT grew to reach ages above 6 months, they were instructed to follow the dosing for the cohort that matched their age.

Table 16: P1093 Cohort III-DT (2 to <6 years) DTG DT Dosing (~0.80 mg/kg)

Weight Band (kg)	Initial DTG DT Dose (mg)	Revised DTG DT Dose (mg)
3 to <6	5	10
6 to <10	10	15
10 to <14	15	20
14 to <20	15	25
20 - <25	20	30
≥25	30	30

Table 17: P1093 Cohort IV-DT (6 months to <2 years) DT Dosing (~1.25 mg/kg)

Weight Band (kg)	Initial DTG DT Dose (mg)	Revised DTG DT Dose (mg)
3 to <6	5	10
6 to <10	10	15
10 to <14	15	20
14 to <20	25	25
≥20	30	30

Table 18: P1093 Cohort V-DT DTG (4 weeks to <6 months) DT Dosing

Age	Weight Range (kg)	Initial DTG DT Dose (mg)
≥4 weeks to <6 months	3 to <6	5
	6 to <10	10
≥6 months	3 to <6	10
	6 to <10	15
	10 to <14	20
	14 to <20	25
	≥20	30

In all cohorts, for participants receiving concomitant rifampin, EFV, FPV/r, or TPV/r after the intensive PK was performed, it was recommended that the dose of DTG be increased to BID administration.

ODYSSEY

Table 19: ODYSSEY PK Sub-studies and DTG Doses (FCT and DT)

WHO Weight Band (kg)	WB-PK1 Sub-study Dose	WB-PK2 Sub-study Initial Dose	WB-PK2 Sub-study Second Dose
3 to <6[a]	5 mg (<6months) or 10 mg (≥6months) DT[b]		
6 to <10	15 mg DT[b]		
10 to <14	20 mg DT[b]		
14 to <20	25 mg FCT[c]/25 mg DT[d]	--	--
20 to <25	25 mg FCT[c]/30 mg DT[d]/ 50 mg FCT[d]	--	--
25 to <30	--	25 mg FCT	50 mg FCT
30 to <40	--	35 mg FCT	50 mg FCT

a. No PK data will be provided for participants in the 3 to <6 kg weight band because PK data were not available in time for the PK cut-off.
b. Lower WB-PK1
c. WB-PK1 part I
d. WB-PK1 part II

Objectives

According to the 2013 EMA draft guidelines on the clinical development of medicinal products for the treatment of HIV infection, a specific demonstration of antiviral efficacy in paediatric patients is not required. As it is assumed that 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.

The objectives are in line with the overall approach to bridge both efficacy and safety from the adult to the paediatric population, as such, the studies are not powered to allow a precise estimation of neither efficacy nor safety. The endpoints are well-established in the field of HIV clinical trials.

For the ODYSSEY study, the evaluation of the efficacy and safety of TIVICAY compared with standard of care will be presented at study completion.

P1093

Primary Objectives

- To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily adult dose.
- To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.
- To evaluate the steady-state PK of DTG in combination with optimized background therapy? (OBT) in treatment experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C24h and AUC0-24h PK parameters in this population. (Note: Under Version 5.0 of the protocol, C24h became the primary PK endpoint and

AUC0-24h became secondary.)

Secondary Objectives

- To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks.
- To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.
- To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in participants experiencing virologic failure.
- To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and Pop PK analysis.
- To determine the extended long term (≥48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents.
- To explore the relationship between DTG exposure and the antiviral activity.
- To evaluate PK, safety and tolerability profile of DTG when dosed by weight bands.

ODYSSEY

The primary objective of the ODYSSEY study is to evaluate the efficacy and safety of once daily DTG-based ART compared with standard of care in children and adolescents starting first- or second-line ART in resource-limited and well-resourced settings.

The objectives for the PK sub-studies are to provide PK and safety data in support of dosing recommendations for DTG in paediatric patients. This report details PK and safety data from the sub-population of the ODYSSEY study who participated in the WB-PK1 and WB-PK2 sub-studies through the cut-off on 28 February 2019.

Outcomes/endpoints

P1093

Safety assessments

Safety assessments included monitoring and recording all AEs and SAEs, laboratory parameters including haematology, fasting lipid profile, and blood chemistry. Toxicity through Week 24 was a primary endpoint and through Week 48 and beyond was a secondary endpoint and included all AEs or laboratory toxicities of ≥Grade 3 severity, AEs or laboratory toxicities of ≥Grade 3 judged to be at least possibly attributable to the study medication, termination from treatment due to a drug-related AE or death. Laboratory samples were analysed using certified local laboratories, and sites were notified of participants with abnormal results.

Efficacy assessments

Key secondary efficacy analyses include virologic outcomes based on HIV-1 RNA (c/mL) through Week 24 and Week 48. At both of these time points, the primary definition of virologic outcome was calculated

according the Snapshot algorithm. Participants were classified as virologic failures if they had missing HIV-1 RNA data throughout the window surrounding the time point of interest.

Participants included in the efficacy and the safety analysis are comprised of those who completed, or had the opportunity to complete, the Week 48 visit by 12 December 2019.

ODYSSEY

Safety Assessments

All participants in the PK sub-studies were reviewed at 4 and 12 weeks after their initial dose of DTG in the ODYSSEY study and every 12 weeks thereafter. In addition, participants <14 kg or those changing to a higher dose of DTG were reviewed at Week 2. Where scheduled visits for the ODYSSEY study did not coincide with PK visits, participants attended additional visits. The safety assessments at these visits included: clinical assessment, collection of blood to assess haematology and biochemistry safety parameters, and acceptability, sleep and mood questionnaires. Additional safety blood tests or investigations may have been performed if clinically indicated to investigate symptoms or monitor emergent laboratory test abnormalities.

Sample size

P1093

For Cohorts I, IIA, and IIB, the selection of a sample size of 10 participants in Stage I for each age cohort was based on feasibility and historical paediatric recruitment experience of GSK and IMPAACT, as well as justification to target a 95% CI within 60% and 140% of the point estimate for the GM estimates of CL/F and V/F for DTG with an at least 80% power.

Under Protocol Version 5.0, for Cohorts III-V-DT, Stage 1 included enrolment of the full age cohorts (N=10 per Cohort) followed by additional enrolments to ensure at least 8 participants per weight band were included.

ODYSSEY

At least 8 participants per weight band with evaluable PK curves on the investigated doses were planned to be enrolled. If any large difference in PK parameters within a weight band was observed in either sub-study, then recruitment of additional participants in the relevant weight band was considered. Recruitment into the lower weight band PK sub-study was ongoing; therefore, there were less than 8 participants per weight band (3 to <14 kg weight bands) at the point of the data cut.

Randomisation and blinding (masking)

P1093 and ODYSSEY are open-label studies.

P1093

P1093 was a single-arm study.

ODYSSEY

In ODYSSEY participants were enrolled in 2 different strata depending on their previous ART experience:

- ODYSSEY A: paediatric participants starting first-line ART
- ODYSSEY B: paediatric participants starting second-line ART.

Within each stratum, participants were randomized 1:1 to either DTG-based ART (DTG Arm) or standard of care (bPI-, or NNRTI-, or INSTI-based ART; Standard of Care Arm). ARVs were dosed according to WHO weight band-based dosing recommendations and/or national dosing recommendations. DTG in the PK sub-studies was dosed using WHO weight bands. The safety assessment is based on data from the two PK sub-studies.

Treatment was open-label and dispensed at randomization for 4 weeks and then at maximum 12-week intervals.

Statistical methods

P1093

Safety Analyses

The AT Safety Population includes all participants who took at least one dose of DTG and deemed safety evaluable per the protocol.

PD Safety Population is a subset of participants from the AT Population that started DTG at the proposed doses.

The following AEs were summarized overall and by cohort, enrolment weight band and formulation: all AEs, AEs by grade, Grade 3 or greater drug-related AEs, fatal and non-fatal Grade 3 or greater SAEs, and AEs leading to withdrawal. SAEs were summarized on-therapy. Mean values and changes from Baseline for laboratory values and vital signs (including height and weight) were also summarized.

AEs were also summarized by the weight band at the time of AE onset. These analyses were only performed for participants taking the DT formulation, and include multiple events if participants reported a new AE when within a higher weight band. Exposure adjusted incidence rates and 95% CIs were only calculated for these analyses of weight band at time of AE onset for participants taking DT formulation.

Efficacy Analyses

AT Population includes all participants exposed to DTG at any dose.

PD Efficacy Population is a subset of participants from the AT Population that started DTG at the proposed doses shown and who were enrolled at least 24 weeks prior to an agreed upon efficacy cut-off date.

Key secondary analyses included virologic outcomes, based on HIV-1 RNA (c/mL), assessed through Weeks 24 and 48. At both of these time points, the primary definition of virologic outcome will be calculated according to the Snapshot algorithm. Participants will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest.

ODYSSEY

Safety Analyses

In the ODYSSEY study and the sub-population included in the PK sub-studies, all ≥Grade 3 AEs, all SAEs, and all Grade 1/2 AEs leading to dose modification or DTG discontinuation were collected. AE analyses including the analysis of SAEs, ≥Grade 3 AEs, deaths, and other significant AEs were performed based on GSK Core Data Standards where applicable. Grade 1 or 2 AEs of TB which were treated with rifampin (and hence resulted in a doubling of the DTG dose to overcome the induction effect of rifampin on DTG and maintain PK) were not considered as Grade 1 or 2 AEs leading to dose modification. Exposure-adjusted incidence rate summaries and corresponding 95% CIs were produced for all AEs by SOC and PT. The 95% CIs were Poisson CIs.

Results

The initial submission included in the efficacy analysis are comprised of those who completed, or had the opportunity to complete, the Week 24 visit by the efficacy data cut-off date of 14 February 2019. For PK and safety, the data cut-off date is 30 April 2019.

The P1093 study analyses have been updated with a data cut-off date of 12 December 2019. Revised efficacy analyses include a total of 66 participants with 48 weeks of follow up. The remaining 9 participants completed Week 48 after the revised data cut and key outcome data for these 9 participants are summarized separately.

Participant flow

Table 20: P1093 Summary of Participant Disposition (as of 12 December 2019)

Participant Status	AT Population N=159 n (%)	PD Population N=75 n (%)
Ongoing at time of report[a]	**72 (45.3)**	**48 (64)**
Participants Completed Week 24	157 (98.7)	74 (98.7)
Participants Completed Week 48	141 (88.7)	64 (85.3)
Participants Completed Week 96	101 (63.5)	30 (40)
Participants Completed Week 144	74 (46.5)	16 (21.3)
Participants Completed Week 192	52 (32.7)	11 (14.7)
Off Study (Off Study-drug)	**87 (54.7)**	**27 (36)**
Completed protocol: No follow-up	52 (32.7)	12 (16)
Completed protocol: On extension meds & safety follow-up	2 (1.3)	0
Met study requirements: No further follow-up[b]	9 (5.7)[c]	3 (4)
Death	3 (1.9)	2 (2.7)
Severe debilitation, unable to continue	1 (0.6)	0
Participant/parent not able to get to clinic	2 (1.3)	1 (1.3)
Site is closing	4 (2.5)	1 (1.3)
Participant/parent withdrew consent prior completion	3 (1.9)	2 (2.7)
Participant/parent not willing to adhere to requirements	6 (3.8)	4 (5.3)
Clinic site unable to contact participant/parent	5 (3.1)	2 (2.7)

Data Source: Table 1.3, Table 1.4

a A participant "completed" Weeks 24, 48, 96, 144, and 192 if participant was on study treatment to at least Relative Day 127, 295, 631, 967, and 1303, respectively

b Met a requirement for study discontinuation or treatment discontinuation as described in Section 6.8 and Section 6.9 of the P1093 protocol.

c Of these 9 participants, 2 ended participation because of pregnancy while 7 ended participation due to virologic failure.

Table 21: ODYSSEY Summary of Participant Disposition as of 28 February 2019 (Safety Population)

	Total Unique Participants (N=99) n (%)
Participant Status	
Ongoing[a]	94 (95)
Changed DTG dose	87 (88)
Stopped DTG[b]	5 (5)
Withdrawn from study[c]	1 (1)
Primary Reason / Subreason for Study Withdrawal	
Informed consent withdrawn	1 (1)
Social Problems	1 (1)
Outcome of AEs Which Led to Study Withdrawal	
Non-fatal	0
Fatal	0

Data Source: Table 1.1
Note: Participants may be summarized under more than 1 status category.
a. Participants were categorized as ongoing if they were still receiving DTG.

a. 5 participants discontinued study treatment because of pregnancy, acute hepatitis, raised liver enzymes, unable/failed to attend clinic and defaulted visits.

b. Participants who stopped DTG and then withdrew were included for the last DTG dose/formulation. Only 1 participant withdrew (withdrew consent because of social problems)

Recruitment

Judging by the distribution of site locations in relation to cohort, it appears that the younger cohorts overall have been studied in more challenging resource settings compared to the older.

P1093

This study is a multicenter study conducted at 34 Clinical Research Sites in 9 countries: Botswana (2 centers, n=), Brazil (5 centers), Kenya (1 center), South Africa (3 centers), Tanzania (1 center), Thailand (3 centers), US (17 centers), Uganda (1 center), and Zimbabwe (1 center). The first participant enrolled in Cohort I on 20 April 2011; the study is ongoing.

Table 22: P1093 Number of Participants Entered by Country and Formulation (AT Population). All Available Data as of April 30, 2019

Country	Cohorts I and IIA (Film-Coated Tablet) (N=46) n	Cohorts IIB, III and IV (Oral Granules) (N=39) n	Cohorts III-DT, IV-DT and V-DT (Dispersible Tablet) (N=74) n	Total (N=159) n
Botswana	0	1	3	4
Brazil	0	8	8	16
Kenya	0	0	8	8
South Africa	4	12	9	25
Tanzania	0	1	8	9
Thailand	6	7	7	20
USA	36	10	4	50
Uganda	0	0	2	2
Zimbabwe	0	0	25	25

N = Number of participants in each formulation.
n = Number of participants in each subcategory

Note: One participant got enrolled on the day of the data freeze with not CRFs into the database. Participant was excluded from all analyses.

Table 23: P1093 Number of Participants Entered by Country and Formulation (PD Population). All Available Data as of April 30, 2019

Country	Cohorts I and IIA (Film-Coated Tablet) (N=24) n	Cohorts III-DT, IV-DT and V-DT (Dispersible Tablet) (N=51) n	Total (N=75) n
Botswana	0	2	2
Brazil	0	7	7
Kenya	0	8	8
South Africa	0	3	3
Tanzania	0	4	4
Thailand	1	6	7
USA	23	2	25
Uganda	0	2	2
Zimbabwe	0	17	17

N = Number of participants in each formulation.
n = Number of participants in each subcategory

Note: One participant got enrolled on the day of the data freeze with not CRFs into the database. Participant was excluded from all analyses.

ODYSSEY

This study is being conducted in the following countries:

Uganda, Zimbabwe, South Africa, Thailand, UK, Portugal, Spain, and Germany. Overall, the majority of participants were enrolled in Uganda (59 [60%] participants), followed by Zimbabwe (37 [37%] participants) and South Africa (3 [3%] participants). The first participant was recruited in Zimbabwe on 20 September 2016.

Conduct of the study

P1093

The original protocol has been amended 4 times and the original enrolment was based on age but under protocol Version 5.0 stratification by weight bands was introduced. In addition, C24h has been elevated to the primary PK target with AUC0-24h secondary.

Participants receiving the FCT formulation were initially enrolled sequentially into Cohorts I and IIA. Version 3.0 (16 January 2013) introduced granules for suspension. When it subsequently became clear that DT would be the commercially available paediatric formulation, new cohorts for DT were opened in Protocol Version 4.0 (13 April 2016). Under protocol Version 5.0 (12 July 2018), the target enrolment in Stage I was increased to allow for additional examination of PK, safety, and tolerability by weight bands, including participants from all of Cohorts III-DT, IVDT, and V-DT. Additional cohorts and weight-band groups may be opened or reopened to investigate data gaps or new modifications to dosing, for example, regarding fasting requirements or background regimens. The fundamental procedure for evaluation of DTG doses remained unchanged through all protocol versions.

With regard to PK parameters, in protocol versions 1-4, AUC0-24h was considered the primary target parameter and C24h was the secondary target parameter. Under protocol Version 5.0, based upon the request of the US FDA, C24h has been elevated to the primary PK target with AUC0-24h secondary.

ODYSSEY

The ODYSSEY protocol has been amended 3 times.

Version 3.0 (18 January 2017) clarified non-DTG INSTIs could be included as a standard of care third agent option, clarified secondary outcomes (from ≥50 and ≥400 copies/mL to <50 and <400 copies/mL), added the WBPK1 and WB-PK2 sub-studies.

Version 4.0 (22 December 2017) added that up to 60 additional participants from 3 to <14 kg would be enrolled. The formulation and dosing information was added to Version 4.0 for the WB-PK1 sub-study. Clarification was added to explain that all participants, the original 700 planned for recruitment and the additional participants in the 3 lower weight bands would be followed up for a minimum of 96 weeks.

Version 5.0 (01 March 2019) included recommendation to switch female participants on DTG-based regimen identified to be pregnant within the first 8 weeks after the last menstrual period to a non-DTG ART regimen if there are other good options available, update to the virological response component of primary outcome measure, addition of folate sub-study, updated safety information, collection of information on babies born to female participants, and an additional interview within the Qualitative sub-study.

Note: As of the data cut-off date of 28 February 2019, no data were collected under Version 5.0 of the protocol (the cut-off for enrolment was 07 December 2018).

Baseline data

Over 90% of participants in both the AT and PD Populations had prior ARV treatment experience. NRTI use was most common at 91% and 88% for the AT and PD population, respectively, followed by PI use (74 and 76%) and NNRTI use (50 and 44%).

P1093

Table 24: P1093 Participant Baseline Characteristics by Cohort All Treated Population All Available Data as of December 12, 2019

	Cohort I (N=23)	Cohort IIA (N=23)	Cohort IIB (N=15)	Cohort III (N=17)	Cohort IV (N=7)	Cohort III-DT (N=26)	Cohort IV-DT (N=25)	Cohort V-DT (N=23)	Total (N=159)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender									
Male	5 (21.7)	16 (69.6)	12 (80.0)	9 (52.9)	2 (28.6)	15 (57.7)	9 (36.0)	12 (52.2)	80 (50.3)
Female	18 (78.3)	7 (30.4)	3 (20.0)	8 (47.1)	5 (71.4)	11 (42.3)	16 (64.0)	11 (47.8)	79 (49.7)
Race									
Asian	3 (13.0)	3 (13.0)	3 (20.0)	2 (11.8)	3 (42.9)	4 (15.4)	1 (4.0)	2 (8.7)	21 (13.2)
Native Hawaiian or other Pacific Islander	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)
Black or African American	12 (52.2)	12 (52.2)	10 (66.7)	11 (64.7)	3 (42.9)	18 (69.2)	21 (84.0)	19 (82.6)	106 (66.7)
White	7 (30.4)	4 (17.4)	0 (0)	2 (11.8)	0 (0)	1 (3.8)	1 (4.0)	0 (0)	15 (9.4)
Other*	1 (4.3)	3 (13.0)	2 (13.3)	2 (11.8)	1 (14.3)	3 (11.5)	2 (8.0)	2 (8.7)	16 (10.1)
Ethnicity									
Hispanic or Latino	6 (26.1)	6 (26.1)	4 (26.7)	8 (47.1)	1 (14.3)	4 (15.4)	3 (12.0)	2 (8.7)	34 (21.4)
Not Hispanic or Latino	16 (69.6)	13 (56.5)	6 (40.0)	6 (35.3)	6 (85.7)	20 (76.9)	22 (88.0)	21 (91.3)	110 (69.2)
Unknown	1 (4.3)	4 (17.4)	5 (33.3)	3 (17.6)	0 (0)	2 (7.7)	0 (0)	0 (0)	15 (9.4)
Baseline Plasma HIV RNA (copies/mL)									
<400	0 (0)	0 (0)	1 (6.7)	0 (0)	1 (14.3)	1 (3.8)	1 (4.0)	1 (4.3)	5 (3.1)
400 - <1,000	0 (0)	1 (4.3)	0 (0)	0 (0)	1 (14.3)	3 (11.5)	1 (4.0)	0 (0)	6 (3.8)
1,000 - <5,000	2 (8.7)	3 (13.0)	1 (6.7)	2 (11.8)	0 (0)	3 (11.5)	5 (20.0)	7 (30.4)	23 (14.5)
5,000 - <10,000	4 (17.4)	1 (4.3)	1 (6.7)	1 (5.9)	0 (0)	1 (3.8)	1 (4.0)	3 (13.0)	12 (7.5)
10,000 - <25,000	8 (34.8)	0 (0)	3 (20.0)	0 (0)	0 (0)	3 (11.5)	1 (4.0)	2 (8.7)	17 (10.7)
25,000 - <50,000	5 (21.7)	4 (17.4)	1 (6.7)	2 (11.8)	1 (14.3)	4 (15.4)	2 (8.0)	1 (4.3)	20 (12.6)
50,000 - <100,000	2 (8.7)	3 (13.0)	6 (40.0)	5 (29.4)	1 (14.3)	3 (11.5)	1 (4.0)	0 (0)	21 (13.2)
>=100,000	2 (8.7)	11 (47.8)	2 (13.3)	7 (41.2)	3 (42.9)	8 (30.8)	13 (52.0)	9 (39.1)	55 (34.6)
Baseline CD4 Cell Count (cells/mm)									
<50	1 (4.3)	2 (8.7)	0 (0)	1 (5.9)	0 (0)	1 (3.8)	0 (0)	0 (0)	5 (3.1)
>=50 - <200	1 (4.3)	2 (8.7)	1 (6.7)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	5 (3.1)
>=200 - <350	6 (26.1)	1 (4.3)	3 (20.0)	2 (11.8)	0 (0)	0 (0)	0 (0)	0 (0)	12 (7.5)
>=350 - <500	4 (17.4)	1 (4.3)	2 (13.3)	1 (5.9)	0 (0)	4 (15.4)	0 (0)	0 (0)	12 (7.5)
>=500	11 (47.8)	17 (73.9)	9 (60.0)	13 (76.5)	5 (71.4)	21 (80.8)	25 (100)	23 (100)	124 (78)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	1 (0.6)
Baseline CD4 Percent									
<=14	3 (13.0)	5 (21.7)	1 (6.7)	2 (11.8)	1 (14.3)	5 (19.2)	1 (4.0)	1 (4.3)	19 (11.9)
>14 - <25	11 (47.8)	7 (30.4)	6 (40.0)	5 (29.4)	3 (42.9)	8 (30.8)	9 (36.0)	13 (56.5)	62 (39)
>=25	9 (39.1)	11 (47.8)	8 (53.3)	10 (58.8)	2 (28.6)	13 (50.0)	15 (60.0)	9 (39.1)	77 (48.4)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	1 (0.6)
Baseline HIV Subtype									
A1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (11.5)	2 (8.0)	2 (8.7)	7 (4.4)
A1,D	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.0)	0 (0)	1 (0.6)
B	20 (87.0)	11 (47.8)	5 (33.3)	9 (52.9)	1 (14.3)	4 (15.4)	3 (12.0)	3 (13.0)	56 (35.2)
C	0 (0)	5 (21.7)	7 (46.7)	5 (29.4)	3 (42.9)	12 (46.2)	12 (48.0)	16 (69.6)	60 (37.7)
CRF01_AE	1 (4.3)	3 (13.0)	2 (13.3)	2 (11.8)	3 (42.9)	3 (11.5)	1 (4.0)	2 (8.7)	17 (10.7)
CRF02_AG	0 (0)	1 (4.3)	1 (6.7)	0 (0)	0 (0)	1 (3.8)	0 (0)	0 (0)	3 (1.9)
CU	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.0)	0 (0)	1 (0.6)
D	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	0 (0)	2 (1.3)
G	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	0 (0)	2 (1.3)

H	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.0)	0 (0)	1 (0.6)
Missing	2 (8.7)	1 (4.3)	0 (0)	1 (5.9)	0 (0)	1 (3.8)	4 (16.0)	0 (0)	9 (5.7)

N = Number of participants in each cohort.
n (%) = Number (percent) of participants in each subcategory.
* This category is a combination of More than one race, Other and Unknown.

Table 25: P1093 Participant Baseline Characteristics by Cohort PD Population All Available Data as of December 12, 2019

	Cohort I (N=19) n (%)	Cohort IIA (N=5) n (%)	Cohort III-DT (N=16) n (%)	Cohort IV-DT (N=12) n (%)	Cohort V-DT (N=23) n (%)	Total (N=75) n (%)
Gender						
Male	5 (26.3)	3 (60.0)	8 (50.0)	3 (25.0)	12 (52.2)	31 (41.3)
Female	14 (73.7)	2 (40.0)	8 (50.0)	9 (75.0)	11 (47.8)	44 (58.7)
Race						
Asian	0 (0)	1 (20.0)	4 (25.0)	0 (0)	2 (8.7)	7 (9.3)
Black or African American	11 (57.9)	2 (40.0)	9 (56.3)	10 (83.3)	19 (82.6)	51 (68)
White	7 (36.8)	2 (40.0)	1 (6.3)	0 (0)	0 (0)	10 (13.3)
Other*	1 (5.3)	0 (0)	2 (12.5)	2 (16.7)	2 (8.7)	7 (9.3)
Ethnicity						
Hispanic or Latino	6 (31.6)	2 (40.0)	3 (18.8)	2 (16.7)	2 (8.7)	15 (20)
Not Hispanic or Latino	12 (63.2)	3 (60.0)	13 (81.3)	10 (83.3)	21 (91.3)	59 (78.7)
Unknown	1 (5.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
Baseline Plasma HIV RNA (copies/mL)						
<400	0 (0)	0 (0)	1 (6.3)	1 (8.3)	1 (4.3)	3 (4)
400 - <1,000	0 (0)	1 (20.0)	2 (12.5)	1 (8.3)	0 (0)	4 (5.3)
1,000 - <5,000	1 (5.3)	2 (40.0)	2 (12.5)	4 (33.3)	7 (30.4)	16 (21.3)
5,000 - <10,000	4 (21.1)	0 (0)	0 (0)	0 (0)	3 (13.0)	7 (9.3)
10,000 - <25,000	7 (36.8)	0 (0)	2 (12.5)	0 (0)	2 (8.7)	11 (14.7)
25,000 - <50,000	5 (26.3)	0 (0)	3 (18.8)	0 (0)	1 (4.3)	9 (12)
50,000 - <100,000	1 (5.3)	1 (20.0)	1 (6.3)	1 (8.3)	0 (0)	4 (5.3)

>=100,000	1 (5.3)	1 (20.0)	5 (31.3)	5 (41.7)	9 (39.1)	21 (28)
Baseline CD4 Cell Count (cells/mm)						
<50	1 (5.3)	0 (0)	1 (6.3)	0 (0)	0 (0)	2 (2.7)
>=50 - <200	1 (5.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
>=200 - <350	5 (26.3)	1 (20.0)	0 (0)	0 (0)	0 (0)	6 (8)
>=350 - <500	4 (21.1)	0 (0)	4 (25.0)	0 (0)	0 (0)	8 (10.7)
>=500	8 (42.1)	4 (80.0)	11 (68.8)	12 (100)	23 (100)	58 (77.3)
Baseline CD4 Percent						
<=14	2 (10.5)	1 (20.0)	3 (18.8)	0 (0)	1 (4.3)	7 (9.3)
>14 - <25	10 (52.6)	2 (40.0)	7 (43.8)	3 (25.0)	13 (56.5)	35 (46.7)
>=25	7 (36.8)	2 (40.0)	6 (37.5)	9 (75.0)	9 (39.1)	33 (44)
Baseline HIV Subtype						
A1	0 (0)	0 (0)	3 (18.8)	1 (8.3)	2 (8.7)	6 (8)
A1,D	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (1.3)
B	19 (100)	4 (80.0)	3 (18.8)	2 (16.7)	3 (13.0)	31 (41.3)
C	0 (0)	0 (0)	4 (25.0)	5 (41.7)	16 (69.6)	25 (33.3)
CRF01_AE	0 (0)	1 (20.0)	3 (18.8)	0 (0)	2 (8.7)	6 (8)
CRF02_AG	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)	1 (1.3)
D	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)	1 (1.3)
G	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)	1 (1.3)
Missing	0 (0)	0 (0)	0 (0)	3 (25.0)	0 (0)	3 (4)

N = Number of participants in each cohort.
n (%) = Number (percent) of participants in each subcategory.
* This category is a combination of More than one race, Other and Unknown.

Table 26: P1093 Summary of Prior ARV for Treatment or Prophylaxis

	AT Population N=159 n (%)	PD Population N=75 n (%)
Number of Participants with any Prior ART Taken	149 (93.7)	68 (90.7)
NRTI	145 (91.2)	66 (88)
1 drug	29 (18.2)	24 (32)
2 drugs	64 (40.3)	16 (21.3)
3 drugs	26 (16.4)	10 (13.3)
4 drugs	14 (8.8)	7 (9.3)
5 drugs	7 (4.4)	4 (5.3)
6 drugs	4 (2.5)	4 (5.3)
7 drugs	1 (0.6)	1 (1.3)
NNRTI	80 (50.3)	33 (44)
1 drug	74 (46.5)	32 (42.7)
2 drugs	6 (3.8)	1 (1.3)
PI	118 (74.2)	57 (76)
1 drug	89 (56)	38 (50.7)
2 drugs	20 (12.6)	13 (17.3)
3 drugs	7 (4.4)	4 (5.3)
4 drugs	1 (0.6)	1 (1.3)
5 drugs	1 (0.6)	1 (1.3)
Fusion Inhibitor	2 (1.3)	2 (2.7)
Median (range) Time on Prior ART (days)	858 (1 – 6024)	433 (11 – 6024)

Data Source: Table 1.117, Table 1.118, Table 1.99, Table 1.100

Table 27: P1093 ARV Treatment History of the AT and PD Efficacy Populations

	AT Efficacy Population (N=142)	PD Efficacy Population (N=58)
ARV-experienced	129	51
ARV-treatment naïve	13	7

Data Source: Table 2.48, Table 2.50

More than 90% of participants recruited into P1093 were ARV experienced. A subsequent review of prior ART by drug class for the N=159 showed >90% exposed to prior NRTI use, >70% exposed to prior PI use, and ≥50% to prior NNRTI use. As for specific agents used in prior ART, >50% of participants were exposed to the following; 3TC, LPV/r, and AZT while >40% were exposed to ABC and NVP. Collectively, this data characterizes the P1093 population as mostly ARV experienced, and nearly half of the patients experienced in 2 or more regimens.

ODYSSEY

The demographic characteristics of the Safety Population are shown below. All participants were Black-African and approximately half (52%) the participants were female. Median age was 7.6 years and ranged from 0 to 18 years of age; over half the participants (61%) were between 6 and 12 years of age. 48% of participants were treatment-naïve (starting first-line ART) and 52% of participants were treatment experienced (switching to second-line ART).

Table 28: ODYSSEY Baseline Demographic Characteristics at Starting DTG Dose by Weight Band (Safety Population)

Parameter[a]		3 to <6 kg (N=1)	6 to <10 kg (N=10)	10 to <14 kg (N=8)	14 to <20 kg (N=34)	20 to <25 kg (N=44)	25 to <30 kg (N=41)	30 to <40 kg (N=26)	Total Unique Participants (N=99)
Starting in Weight Band, n		1	10	5	33	28	16	6	99
Age Years[b]	n	1	10	5	33	28	16	6	99
	median (range)	0.345 (0.34-0.34)	1.305 (0.57-2.92)	2.031 (1.85-3.30)	6.168 (3.44-10.76)	9.240 (6.88-12.14)	10.375 (8.76-17.02)	12.092 (9.90-17.51)	7.578 (0.34-17.51)
Age Group[b] n (%)	4 wks to <6 mos	1 (100)	0	0	0	0	0	0	1 (1)
	6 mos to <2 yrs	0	9 (90)	2 (40)	0	0	0	0	11 (11)
	2 yrs to <6 yrs	0	1 (10)	3 (60)	15 (45)	0	0	0	19 (19)
	6 yrs to <12 yrs	0	0	0	18 (55)	27 (96)	13 (81)	2 (33)	60 (61)
	12 yrs to <18 yrs	0	0	0	0	1 (4)	3 (19)	4 (67)	8 (8)
Sex n (%)	n	1	10	5	33	28	16	6	99
	Female, n (%)	1 (100)	8 (80)	4 (80)	17 (52)	13 (46)	4 (25)	4 (67)	51 (52)
	Male, n (%)	0	2 (20)	1 (20)	16 (48)	15 (54)	12 (75)	2 (33)	48 (48)
Weight[c] (kg)	n	1	10	5	33	28	16	6	99
	median (range)	4.10 (4.1-4.1)	8.25 (6.5-9.9)	11.40 (10.1-12.0)	17.40 (14.0-19.6)	22.20 (20.2-24.6)	27.00 (25.3-29.8)	30.70 (30.0-36.7)	20.20 (4.1-36.7)
Height (cm)	n	1	10	5	33	28	16	6	99
	median (range)	55.60 (55.6-55.6)	72.25 (57.8-86.2)	84.60 (77.0-93.8)	106.10 (89.0-117.0)	123.80 (116.4-135.0)	131.50 (125.7-135.5)	141.25 (138.0-155.2)	117.00 (55.6-155.2)
MUAC (cm)	n	0	10	5	33	28	16	6	98
	median (range)	--[d]	12.90 (11.0-15.5)	15.00 (13.0-15.4)	15.90 (13.5-18.7)	16.40 (14.7-19.0)	17.95 (16.4-20.5)	19.00 (15.9-20.3)	16.30 (11.0-20.5)
BMI-for-age Z-score	n	1	10	5	33	28	16	6	99
	median (range)	-2.530 (-2.53 to 2.53)	-0.500 (-3.11 to 1.54)	-0.480 (-1.95 to 1.85)	-0.650 (-1.70 to 3.00)	-1.060 (-3.82 to 0.44)	-0.585 (-3.67 to 0.62)	-0.610 (-4.18 to 0.25)	-0.800 (-4.18 to 3.00)

Data Source: Table 1.9

Note: Characteristics presented in this table were Baseline characteristics at the time of entry into the ODYSSEY study.

a. n = number of participants in weight band at the time of enrollment to the ODYSSEY study; N = number of participants in a weight band at any time
b. Age at randomization.
c. Weight at time of first DTG dose.
d. MUAC scores are not available for participants <6 months of age.

Table 29: ODYSSEY Additional Baseline Characteristics by Enrolment Weight Band (Safety Population)

	3 to <6 kg (N=1)	6 to <10 kg (N=10)	10 to <14 kg (N=8)	14 to <20 kg (N=34)	20 to <25 kg (N=44)	25 to <30 kg (N=41)	30 to <40 kg (N=26)	Total Unique Participants (N=99)
Starting DTG Dose, n	1	10	5	33	28	16	6	99
Baseline CD4+ Count (cells/mm³)								
n	1	10	5	33	28	16	6	99
median (range)	1168.0 (1168-1168)	1648.0 (580-3582)	1498.0 (281-3079)	806.0 (2-2362)	561.5 (8-1708)	422.5 (71-1055)	138.0 (19-957)	664.0 (2-3582)
Baseline CD4+ Percent[a]								
n	1	10	5	33	28	16	6	99
median (range)	23.00 (23.0-23.0)	27.00 (13.0-76.8)	26.00 (9.0-29.3)	32.00 (0.0-59.0)	21.50 (1.0-61.0)	20.50 (6.0-45.0)	9.50 (2.0-38.0)	25.00 (0.0-76.8)
Baseline HIV-1 RNA Log10 c/mL[b]								
n	1	10	5	33	28	16	6	99
median (range)	4.432 (4.43-4.43)	5.277 (2.86-6.08)	4.041 (3.75-6.58)	4.786 (2.80-6.32)	4.529 (1.28-5.83)	4.012 (1.28-5.09)	4.868 (3.17-5.76)	4.604 (1.28-6.58)
mean (SD)	4.432	5.093 (0.9486)	4.519 (1.1642)	4.703 (0.7332)	4.521 (0.9359)	3.948 (0.9656)	4.781 (0.9222)	4.561 (0.9174)
WHO Classification of HIV Infection								
n	1	10	5	33	28	16	6	99
Stage 1, n (%)	0	5 (50)	3 (60)	16 (48)	12 (43)	4 (25)	3 (50)	43 (43)
Stage 2, n (%)	1 (100)	2 (20)	2 (40)	12 (36)	12 (43)	10 (63)	0	39 (39)
Stage 3, n (%)	0	1 (10)	0	5 (15)	1 (4)	2 (13)	2 (33)	11 (11)
Stage 4, n (%)	0	2 (20)	0	0	3 (11)	0	1 (17)	6 (6)

Data Source: Table 1.15, Table 1.19, Table 1.23

Note: n = number of participants in weight band at the time of enrollment to the ODYSSEY study (before initiation of DTG); N = number of participants in a weight band at any time

a. 1 participant had a CD4+ cell count of 2 cells/mm³ with a total lymphocyte count of 2,231 cells/mm³. Therefore, the CD4+% appears as 0.0.
b. Undetectable levels of HIV-1 RNA default to a value of 19 c/mL, or a log10 value of 1.28.

Table 30: Summary of Prior ART by Enrolment Weight Band (Safety Population – ODYSSEY B)

	6 to <10 kg (N=1) n (%)	10 to <14 kg (N=3) n (%)	14 to <20 kg (N=18) n (%)	20 to <25 kg (N=29) n (%)	25 to <30 kg (N=24) n (%)	30 to <40 kg (N=10) n (%)	Total Unique Participants (N=51) n (%)
Starting in Weight Band, n[a]	1	2	18	20	8	2	51
Number of Participants with any Prior ART Taken	1 (100)	2 (100)	18 (100)	20 (100)	8 (100)	2 (100)	51 (100)
3 drugs	1 (100)	2 (100)	16 (89)	18 (90)	6 (75)	1 (50)	44 (86)
4 drugs	0	0	2 (11)	1 (5)	2 (25)	1 (50)	6 (12)
5 drugs	0	0	0	1 (5)	0	0	1 (2)
Any NRTI	1 (100)	2 (100)	18 (100)	20 (100)	8 (100)	2 (100)	51 (100)
2 drugs	1 (100)	2 (100)	17 (94)	18 (90)	6 (75)	1 (50)	45 (88)
3 drugs	0	0	1 (6)	2 (10)	2 (25)	1 (50)	6 (12)
NRTI by Ingredient							
ABC	1 (100)	1 (50)	5 (28)	4 (20)	1 (13)	1 (50)	13 (25)
3TC	1 (100)	2 (100)	18 (100)	20 (100)	8 (100)	2 (100)	51 (100)
d4T	0	0	0	0	1 (13)	1 (50)	2 (4)
TDF	0	0	0	1 (5)	0	0	1 (2)
ZDV	0	1 (50)	14 (78)	17 (85)	8 (100)	1 (50)	41 (80)
Any NNRTI	1 (100)	2 (100)	18 (100)	20 (100)	8 (100)	2 (100)	51 (100)
1 drug	1 (100)	2 (100)	17 (94)	19 (95)	8 (100)	2 (100)	49 (96)
2 drugs	0	0	1 (6)	1 (5)	0	0	2 (4)
NNRTI by Ingredient							
EFV	0	0	4 (22)	4 (20)	1 (13)	0	9 (18)
NVP	1 (100)	2 (100)	15 (83)	17 (85)	7 (88)	2 (100)	44 (86)

Data Source: Table 1.301, Table 1.303

a. n = number of participants in weight band at the time of enrollment to the ODYSSEY study (before initiation of DTG); N = number of participants in a weight band at any time

Numbers analysed

P1093

Table 31: P1093 Study Populations

Population	Total (N)
AT Population	159
AT Safety Population	159
AT Efficacy Population	142
PD Population[a]	75
PD Safety Population[a]	75
PD Efficacy Population[a]	58
PK Populations	
Intensive	114
Sparse	146

Data Source: Table 1.50, Table 1.51, Table 2.18, Table 2.19, Table 3.213, Table 3.366, and GlaxoSmithKline Document Number 2019N422597_00.

a. The PD Population includes 1 participant (PID 3046078) ≥6 months of age, weighing 5.5 kg that received a 10 mg dose of DTG DT. (Data Source: Listing Table 1.138, Listing Table 3.320).

ODYSSEY

Note that, since participants could have moved from 1 weight band to another and from 1 dose/formulation to another, participants can appear in more than 1 dose/formulation and weight band. All participants were included in the Safety Population (all ODYSSEY participants who also consented to enter either of the PK sub-studies and received at least 1 dose of DTG).

Table 32: ODYSSEY Study Populations by Weight Band (Safety Population)

Population	3 to <6 kg (N=1) n (%)	6 to <10 kg (N=10) n (%)	10 to <14 kg (N=8) n (%)	14 to <20 kg (N=34) n (%)	20 to <25 kg (N=44) n (%)	25 to <30 kg (N=41) n (%)	30 to <40 kg (N=26) n (%)	≥40 kg (N=4) n (%)	Total Unique Participants (N=99) n (%)
Safety	1 (100)	10 (100)	8 (100)	34 (100)	44 (100)	41 (100)	26 (100)	4 (100)	99 (100)
Safety Intended DTG Dose[a]	1 (100)	10 (100)	8 (100)	22 (65)	22 (50)	32 (78)	26 (100)	4 (100)	97 (98)
Safety from First Intended DTG Dose[b]	1 (100)	10 (100)	5 (63)	22 (65)	16 (36)	30 (73)	13 (50)	0	97 (98)
Intensive PK Concentration[c,d]	0	5	5	27	29	18	13	0	88[e]
Intensive PK Parameter[c,d]	0	5	5	27	29	18	13	0	88[e]

Data Source: Table 1.6

Note: Participants may appear in more than 1 weight band.

a. Safety Intended DTG Dose Population comprises all participants who received at least 1 dose of the intended DTG formulations and doses (5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg DT, and 50 mg FCT) according to the weight bands.

b. Safety from First Intended DTG Dose Population is defined as all participants who received at least 1 dose of DTG using the intended formulation(s)/dose(s) and are grouped according to their first intended dose.

c. Percentages are not shown for either PK population because participants for PK analysis were grouped according to the weight band dosing they received. For example, if a participant weighed 13.5 kg and received 25 mg DT they will be included in the 14 to <20 kg weight band as this was the planned weight band for the 25 mg DT dose. This is further explained in Section 6.1.

d. Participants included in the Intensive PK populations are grouped according to the weight band for the dose they received rather than according to their actual weight.

e. 88 participants provided PK curves, some at more than 1 dose/time point (139 total PK curves). After accounting for exclusions (10 PK curves), 86 participants provided at least 1 PK curve included in summary of PK parameters.

Outcomes and estimation

In the original dataset the rate of virologic success at 24 weeks is relatively low in relation to the <50 c/mL cut-off, but many patients are in between 50-400 c/mL. Most likely, this reflects both the greater virological challenge in younger patients that often have high viral load at baseline, as well as compliance issues. In the youngest Cohort (V-DT) the virologic response is slower and rate of virologic success at 24 weeks is 41.2% when defined as <50 c/mL and 88.2% when defined as <400 c/mL. The number of patients that had reached week 48 were limited.

In the updated dataset, the proportion of patients reaching below 50 and 400 c/mL is more or less unchanged compared to the earlier data cut off at week 48. One additional case of virologic failure has been identified, but this patient has regained virologic control without any change in ART.

Table 33: P1093 Antiviral and Immunologic Activity Through Week 24 and Week 48 (P1093 PD Efficacy Population through 30 April 2019)

	Through Week 24 (N=58)		Through Week 48 (N=24)	
	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of participants with HIV RNA <50 c/mL[a]	36/58	62.1 (48.4 – 74.5)	16/24	66.7 (44.7 - 84.4)
Proportion of participants with HIV RNA <400 c/mL[a]	50/58	86.2 (74.6-93.9)	18/24	75 (53.3 – 90.2)
	Median (n)	(Q1, Q3)	Median (n)	(Q1, Q3)
Change from baseline in CD4+ cell count (cells/mm3)	105 (57)	(-93, 338)	149 (23)	(-17, 291)
Change from baseline in CD4 percent	5.1 (57)	(1, 9.3)	8 (23)	(0,11)

Data Source: P1093 Table 2.16, Table 2.19

a. Snapshot analysis. Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis

Table 34: P1093 Antiviral and Immunological Activity Through Week 24 and Week 48 (PD Efficacy Population through 12 December 2019)

	Week 24 N=75		Week 48 N=66	
	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of participants with HIV RNA <50 c/mL[a, b]	42/75	56 (44.1, 67.5)	43/66	65.2 (52.4, 76.5)
Proportion of participants with HIV RNA <400 c/mL[b]	62/75	82.7 (72.2, 90.4)	53/66	80.3 (68.7, 89.1)
	Median (n)	(Q1, Q3)	Median (n)	(Q1, Q3)
Change from baseline in CD4+ cell count (cells/mm)	145 (72)	(-64, 489)	184 (62)	(-179, 665)
Change from baseline in CD4+ percent	6 (72)	(2.5, 10)	8 (62)	(0.4, 11)

Q1, Q3= First and third quartiles, respectively.

[a] Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis

[b] Snapshot algorithm was used in the analyses

Results for the additional 9 participants who reached Week 48 after the December 2019 data cut are similar to those with the earlier data cut-off. The proportions of these participants with HIV RNA <50 and <400 c/mL at Week 48 were 67% (6 of 9) and 89% (8 of 9), respectively.

Table 35: P1093 Efficacy Analysis by Cohort (Cohorts I, IIA) Proposed Dose Efficacy Population Week 24 (through 30 April 2019)

	Cohort I (N=19)		Cohort IIA (N=5)	
	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of participants with >=1 log10 drop from baseline or HIV RNA <400 copies/mL	17/19	89.5 (66.9, 98.7)	5/5	100 (47.8, 100)
Proportion of participants with HIV RNA <50 copies/mL*	14/19	73.7 (48.8, 90.9)	4/5	80 (28.4, 99.5)
Proportion of participants with HIV RNA <400 copies/mL	16/19	84.2 (60.4, 96.6)	5/5	100 (47.8, 100)
Proportion of participants with HIV RNA below the limit of quantification	13/19	68.4 (43.4, 87.4)	4/5	80 (28.4, 99.5)
	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)
Change from baseline in CD4 cell count (cells/mm)	63 [19]	(-19, 180)	105 [5]	(14, 209)
Change from baseline in CD4 percent	5.6 [19]	(1, 10)	8 [5]	(6.2, 10)
Change from baseline in CD8 cell count (cells/mm)	-117 [19]	(-371, 20)	-313 [5]	(-936, -264)
Change from baseline in CD8 percent	-5 [19]	(-10, -2.3)	-10 [5]	(-15.5, -8)

N = Number of participants in each cohort.
n* = Number of participants contributing data.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of participants.
For continuous endpoints: median changes with the first and third quartiles were reported. Normal distributions were assumed for continuous endpoints.
Missing, Switch, or Discontinuation = Failure (MSDF) approach, as codified by the FDA's Snapshot algorithm, was used in the RNA analyses.
Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the Team, and discontinuation for non-treatment related reasons with the last HIV RNA>=400/50/LLQ copies/mL.
*Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis.

Table 36: P1093 Efficacy Analysis by Cohort (Cohorts III-DT, IV-DT, V-DT) Proposed Dose Efficacy Population Week 24 (through 30 April 2019)

	Cohort III-DT (N=8)		Cohort IV-DT (N=9)		Cohort V-DT (N=17)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of participants with >=1 log10 drop from baseline or HIV RNA <400 copies/mL	8/8	100 (63.1, 100)	9/9	100 (66.4, 100)	16/17	94.1 (71.3, 99.9)
Proportion of participants with HIV RNA <50 copies/mL*	5/8	62.5 (24.5, 91.5)	6/9	66.7 (29.9, 92.5)	7/17	41.2 (18.4, 67.1)
Proportion of participants with HIV RNA <400 copies/mL	6/8	75 (34.9, 96.8)	8/9	88.9 (51.8, 99.7)	15/17	88.2 (63.6, 98.5)
Proportion of participants with HIV RNA below the limit of quantification	4/8	50 (15.7, 84.3)	6/9	66.7 (29.9, 92.5)	6/17	35.3 (14.2, 61.7)
	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)
Change from baseline in CD4 cell count (cells/mm)	75.5 [8]	(-173, 458)	-221 [9]	(-962, 150)	351.5 [16]	(-189, 925.5)
Change from baseline in CD4 percent	4.5 [8]	(-2.3, 8.8)	3 [9]	(-10.2, 7.4)	4.9 [16]	(2.5, 8.7)
Change from baseline in CD8 cell count (cells/mm)	-447.5 [8]	(-485, 83)	-1170 [9]	(-1479, 46)	-225 [16]	(-1140, 503.5)
Change from baseline in CD8 percent	-4.8 [8]	(-9, -1.6)	-8 [9]	(-9.5, -1.4)	-4 [16]	(-9.3, 1.9)

N = Number of participants in each cohort.
n* = Number of participants contributing data.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of participants.
For continuous endpoints: median changes with the first and third quartiles were reported. Normal distributions were assumed for continuous endpoints.
Missing, Switch, or Discontinuation = Failure (MSDF) approach, as codified by the FDA's Snapshot algorithm, was used in the RNA analyses.
Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the Team, and discontinuation for non-treatment related reasons with the last HIV RNA>=400/50/LLQ copies/mL.
*Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis.

Table 37: Efficacy Analysis by Cohort Proposed Dose Population Week 48 (through 12 December 2019)

	Cohort I (N=19)		Cohort IIA (N=5)		Cohort III-DT (N=11)		Cohort IV-DT (N=11)		Cohort V-DT (N=20)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of participants with >=1 log10 drop from baseline or HIV RNA <400 copies/mL	14/19	73.7 (48.8, 90.9)	5/5	100 (47.8, 100)	8/11	72.7 (39, 94)	10/11	90.9 (58.7, 99.8)	18/20	90 (68.3, 98.8)
Proportion of participants with HIV RNA <50 copies/mL*	12/19	63.2 (38.4, 83.7)	4/5	80 (28.4, 99.5)	8/11	72.7 (39, 94)	10/11	90.9 (58.7, 99.8)	9/20	45 (23.1, 68.5)
Proportion of participants with HIV RNA <400 copies/mL	14/19	73.7 (48.8, 90.9)	4/5	80 (28.4, 99.5)	8/11	72.7 (39, 94)	10/11	90.9 (58.7, 99.8)	17/20	85 (62.1, 96.8)
Proportion of participants with HIV RNA below the limit of quantification	12/19	63.2 (38.4, 83.7)	4/5	80 (28.4, 99.5)	8/11	72.7 (39, 94)	9/11	81.8 (48.2, 97.7)	9/20	45 (23.1, 68.5)
	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)	Median [n*]	(Q1,Q3)
Change from baseline in CD4 cell count (cells/mm)	84 [18]	(-23, 225)	373 [5]	(167, 387)	295 [11]	(-58, 813)	-341 [10]	(-449, -1)	721 [18]	(-179, 972)
Change from baseline in CD4 percent	6 [18]	(0, 11)	9 [5]	(8.2, 11)	9.4 [11]	(3.8, 15.2)	-0.1 [10]	(-5.7, 6.9)	8.7 [18]	(2.7, 10.8)
Change from baseline in CD8 cell count (cells/mm)	-52.5 [18]	(-246, 105)	-117 [5]	(-723, 84)	-301 [11]	(-1075, 312)	-1059.5 [10]	(-2509, -223)	-337 [18]	(-1350, 870)
Change from baseline in CD8 percent	-6 [18]	(-13, -1.2)	-9 [5]	(-22, -7)	-6.5 [11]	(-10, -2)	-9.9 [10]	(-15.2, -6.4)	-3.5 [18]	(-11.5, 1.7)

N = Number of participants in each cohort.
n* = Number of participants contributing data.
For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N=number of responders/number of participants.
For continuous endpoints: median changes with the first and third quartiles were reported. Normal distributions were assumed for continuous endpoints.
Missing, Switch, or Discontinuation = Failure (MSDF) approach, as codified by the FDA's Snapshot algorithm, was used in the RNA analyses.
Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the Team, and discontinuation for non-treatment related reasons with the last HIV RNA>=400/50/LLQ copies/mL.
Included in the analysis are participants who reached or had the potential to reach Week 48. PID 3046078, who enrolled on 22Feb2019 and died 8 weeks later, is also included in the analysis.
*Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis.

Table 38: P1093 Study Outcomes Based on Plasma HIV-1 RNA <50 c/mL in Study P1093– PD Efficacy Population (Snapshot Analysis)

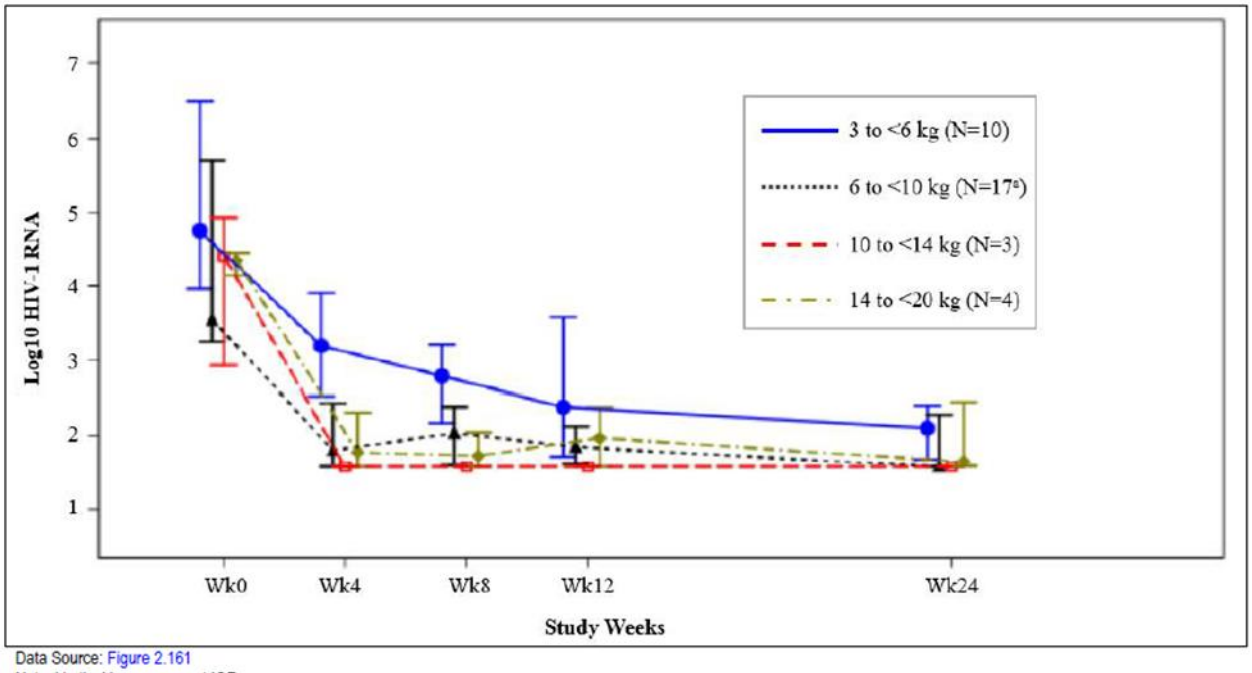
	Week 24 N=58 n (%)	Week 48 N=24 n (%)
Virologic Success[a]	36 (62.1)	16 (66.7)
Virological Failure[b]	22 (37.9)	8 (33.3)
Data in window not below threshold	22 (37.9)	6 (25)
Discontinued while not below threshold	0	2 (8.3)
No Virologic Data	0	0

Data Source: Table 2.114, Table 2.115
Note: n (%) = Number (percent) of participants in each subcategory.
Note: Results of <200 c/mL from HIV-1 RNA testing using an LLOD of 200 c/mL were censored to >50 c/mL in this analysis.

a. Virologic success was defined as plasma HIV-1 RNA <50 c/mL; Snapshot algorithm was used in HIV-1 RNA analysis
b. Failures include participants with missing data due to discontinuation of study for lack of efficacy, change in the background regimen, change in ART without the consent of the protocol team, and discontinuation for non-treatment related reasons with the last HIV RNA ≥50 c/mL.

Table 39: P1093 Summary of Efficacy at Week 24 and Week 48 by the Key Analysis Variables of Cohort, Enrolment Weight Band, Formulation and ARV Treatment History in Study P1093 (PD Efficacy Population through 30 April 2019)

Variables	Week 24				Week 48	
	N	<50 c/mL % (95%CI)	<400 c/mL % (95%CI)	N	<50 c/mL % (95%CI)	<400 c/mL % (95%CI)
Total	58	62.1 (48.4, 74.5)	86.2 (74.6, 93.9)	24	66.7 (44.7, 84.4)	75 (53.3, 90.2)
Cohort I	19	73.7 (48.8, 90.9)	84.2 (60.4, 96.6)	19	63.2 (38.4, 83.7)	73.7 (48.8, 90.9)
Cohort IIA	5	80 (28.4, 99.5)	100 (47.8, 100)	5	80 (28.4, 99.5)	80 (28.4, 99.5)
Cohort III DT	8	62.5 (24.5, 91.5)	75 (34.9, 96.8)	0	NA	NA
Cohort IV DT	9	66.7 (29.9, 92.5)	88.9 (51.8, 99.7)	0	NA	NA
Cohort V DT	17	41.2 (18.4, 67.1)	88.2 (63.6, 98.5)	0	NA	NA
≥35 kgs	24	75 (53.3, 90.2)	87.5 (67.6, 97.3)	24	66.7 (44.7, 84.4)	75 (53.3, 90.2)
14 to <20 kg	4	50 (6.8, 93.2)	75 (19.4, 99.4)	0	NA	NA
10 to <14 kg	3	100 (29.2, 100)	100 (29.2, 100)	0	NA	NA
6 to <10 kg	17	58.8 (32.9, 81.6)	88.2 (63.6, 98.5)	0	NA	NA
3 to <6 kg	10	30 (6.7, 65.2)	80 (44.4, 97.5)	0	NA	NA
FCT	24	75 (53.3, 90.2)	87.5 (67.6, 97.3)	24	66.7 (44.7, 84.4)	75 (53.3, 90.2)
DT	34	52.9 (35.1, 70.2)	85.3 (68.9, 95)	0	NA	NA
ARV-experienced	51	64.7 (50.1, 77.6)	86.3 (73.7, 94.3)	24	66.7 (44.7, 84.4)	75 (53.3, 90.2)
ARV-naïve	7	42.9 (9.9, 81.6)	85.7 (42.1, 99.6)	0	NA	NA



Data Source: Figure 2.161
Note: Vertical bars represent IQR
a. At Week 8, for the 6 to <10 kg enrollment weight band, only 16 of the 17 participants had available data

Figure 8: P1093 Median Log10 HIV-1 RNA Response Through Week 24 in Participants Weighing <20 kg in Study P1093 (PD Efficacy Population through 30 April 2019)

Protocol defined virologic failure (PDVF)

PDVF was defined as a confirmed decrease in plasma HIV-1 RNA of <1.0 log10 c/mL at or after Week 12 unless the HIV RNA is <400 c/mL or a confirmed HIV-1 RNA >400 c/mL starting at Week 24 or beyond on 2 consecutive measurements at least 1 week but no more than 4 weeks apart. Virologic rebound in this study was defined as confirmed HIV-1 RNA >400 c/mL (on 2 consecutive measurements at least 1 week apart) after an initial confirmed response (on 2 consecutive measurements at least 1 week apart) of HIV-1 RNA <400 c/mL or a confirmed >1.0 log10 c/mL increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart). For the purposes of this study, nadir is defined as the lowest HIV-1 RNA while on study drug that is >400 c/mL.

PDVF was observed across all age cohorts, weight bands and formulations. For the 36 cases of virologic failure observed in the April dataset, 18/36 (50%) occurred in children and adolescents ≥6 years, 6/36 (17%) in children 2 to <6 years and 12/36 (33%) cases in children <2 years in age.

Table 40: P1093 Protocol-defined Virologic Failure Over Time (through 30 April 2019)

	Through Week 24 N=142 n (%)	Post Week 24 Through Week 48 N=142 n (%)	Post Week 48 N=142 n (%)	Total N=142 n (%)
PDVF	20 (14)	8 (6)	8 (6)	36 (25)

Data Source: Table 4.2

Through 12 December 2019, only 1 additional case of virologic failure has been identified: One participant in Cohort V experienced virologic failure at Week 24 (HIV-1 RNA >400 c/mL). The participant is still in the study, and has remained on ABC/3TC with DTG since randomization, and has subsequently suppressed through Week 60 with viral load declines from Week 24 at 402 c/mL at Week 32, 258 c/mL at Week 48 and 183 c/mL at Week 60.

Treatment-emergent Resistance

Evidence of treatment-emergent resistance to a PI, NRTI, or NNRTI was seen in 8 participants at virologic failure. Of these 8 participants, 4 had virus with emergence of only secondary ARV resistance-associated substitutions that alone have little to no impact on drug susceptibility as compared to that of wildtype virus. The remaining 4 participants had virus with emergence of primary ARV resistance-associated substitutions at RT positions 184, 190, 215, and 230. In 7 of 8 cases, the OBT consisted of at least 1 agent seen in the prior ARV history. Emergent resistance detected for all 7 participants was associated with agents used in the prior ARV history. 1 participant had an OBT that introduced 2 new agents. Virus from this participant developed NNRTI substitution K238R and PI substitution L10I. This participant had previously been exposed to a PI agent but had no reported NNRTI history. Given the participants age of 2 years, a prior use of an NNRTI for PMTCT cannot be ruled out. Two participants had additional resistance testing conducted post the PDVF visit and results from both showed evidence of secondary ARV resistance only. Evidence of treatment-emergent resistance-associated IN substitutions was observed in 8/36 (22%) participants at PDVF.

Of the 8 subjects with de novo INSTI resistance, only 3 had previous regimens without a core agent with a high barrier of resistance (i.e. PIs). Hence, it cannot be concluded that the cases with INSTI de novo

resistance are related to HIV quasispecies with occult NRTI resistance caused by previous regimens with a low barrier of resistance.

Table 41: P1093 Treatment-emergent IN Resistance

IN Substitution	# of Participants
Any	8/36 (22%)
T66I	1
L74M, L74I	2
E92E/Q	1
G118R, G118G/R	5
E138E/K	1
R263K/R	1
E157Q	1

Data Source: Table 4.6

Table 42: Prior ARV Treatment for Participants with INSTI Resistance in P1093

Cohort	Number of Prior ARV's	Duration of Prior ART (months)	ARV Agents in Prior ART	ARV Classes in Prior ART	INSTI Resistance Detected on Study
Cohort I	8	152	3TC, ZDV, D4T, DDI, RTV, ATV, FTC, TDF	NRTI, PI	L74M, G118R
Cohort I	6	144	ZDV, D4T, 3TC, NFV, ABC, LPV/r	NRTI, PI	R263K
Cohort IIB	5	85	ZDV, ABC, 3TC, NVP, LPV/r	NRTI, NNRTI, PI	G118R, E138EK
Cohort III	3	13	3TC, ZDV, LPV/r	NRTI, PI	E92EQ, G118GR
Cohort III-DT	3	28	ABC,3TC, LPV/r	NRTI, PI	G118R
Cohort IV	4	9	D4T,3TC, NVP, LPV/r	NRTI, NNRTI, PI	T66I, G118R
Cohort IIA	8	132	ZDV,3TC, D4T, DDI, EFV, NFV, ABC, LPV/r	NRTI, NNRTI, PI	E157Q
Cohort III-DT	3	69	3TC, ZDV, LPV/r	NRTI, PI	L74I

Data Source: P1093 CSR Table 2.182, P1093 CSR Table 4.1 [GSK Document Number 2019N395492_00]

Table 43: Baseline and On Study Characteristics for Participants with INSTI Associated Resistance in P1093

Cohort	DTG Form.	DTG Exposure C_{min} (ng/mL) | AUC_{0-24h} (ug*h/mL) Intense PK Day 5-10	Sparse PK Week 4	Sparse PK Week 24	Non-Adherence reported[a]	HIV-1 RNA at BL	HIV-1 Subtype at BL	ARV Resistance at BL	Prior ARV Agents	Prior ARV Classes	OBT	On Study INSTI Resistance Observed
I	FCT	720 | 36	787 | 46	2599 | 93	Yes	17996	B	RT - M41L	3TC,ZDV,D4T, DDI,RTV,ATV, FTC,TDF	NRTI, PI	EFV, FTC, TDF	L74M, G118R
I	FCT	N/A	803 | 46	262 | 27	Yes	7739	B	IN- L74L/M PR-I84I/V	ZDV,D4T,3TC, NFV,ABC,LPV/r	NRTI, PI	FTC, TDF	R263K
IIB	OG	61 | 18	283 | 30	343 | 42	Yes	96369	B	IN- V151I RT - K103S, V106I/V, V179I/V, M184I/M/V, G190A, Y318F	ZDV,ABC,3TC, NVP,LPV/r	NRTI, NNRTI, PI	3TC, ZDV	G118R, E138EK
III	OG	N/A	405 | 28	499 | 44	Yes	1605957	B	RT - T69ADNT	3TC,ZDV,LPV/r	NRTI, PI	3TC, ZDV	E92EQ, G118GR
III-DT	DT	766 | 67	890 | 74	875 | 73	Yes	30531	C	IN - L74I, RT – M184V, H221Y	ABC,3TC,LPV/r	NRTI, PI	3TC, ZDV	G118R
IV	OG	354 | 29	324 | 31	772 | 56	Yes	594	CRF01_AE	IN- L74I PR - K20R RT - V179I, M184V, K238R	D4T,3TC,NVP, LPV/r	NRTI, NNRTI, PI	D4T, 3TC	T66I, G118R
IIA	FCT	1096 | 31	2556 | 86	2464 | 83	Yes	890	B	V179I	ZDV,3TC,D4T, DDI,EFV,NFV, ABC,LPV/r	NRTI, NNRTI, PI	FTC, TDF, RTV, ATV	E157Q
III-DT	DT	N/A	N/A	N/A	Yes	846872	CRF01_AE	PR - L10I/L, K20K/R, L33F, M46I, I50V, I54V, T74P, V82A RT -M41L, D67N, T69N/T, K70R, L74I, A98G, M184V, T215F, K219Q, K238R	3TC,ZDV,LPV/r	NRTI, PI	3TC, EFV, RTV, DRV	L74I

Data Source: Listing Table 4.2, Listing Table 4.3, Listing Table 4.5, and Appendix 15.3 from the P1093 CSR [GSK Document Number 2019N395492_00]
a. Adherence reporting summarized from three sources, Adherence Questionnaire, Reason for Study Discontinuation, and communication with site PI

Update of De Novo Resistance as of 12 December 2019

There have been no additional occurrences of de novo integrase strand transfer inhibitor (INSTI) resistance other than the already described 8 cases. Through December 2019, 1 additional case of virologic failure in a participant in Cohort V has been identified as described above. Paired resistance testing for this participant could not be performed due to a low HIV-1 RNA at the virologic failure testing visit (HIV-1 RNA 402 c/mL).

Discontinued Participants with Missing Paired Resistance Analysis

The Applicant has investigated the number of participants who have discontinued from the study due to/with ongoing treatment failure, for whom paired resistance analysis is missing (due to viral load issues etc.). The table below provides a listing of the 5 participants identified. All 5 participants were missing integrase (IN) resistance testing at Baseline. Reasons for missed testing include insufficient sample volume and samples not identified for testing. Three participants had no or partial resistance test results at virologic failure. Reasons for missed testing include insufficient HIV-1 RNA for testing, insufficient sample volume for testing or no sample identified for testing.

Table 44: Participants with Missing Paired Resistance Assessments in P1093

Virologic Failure Timepoint (Week)	Missing Baseline Resistance Data	Reason for Missed Baseline Testing Data	Missing Virologic Failure Resistance Data	Reason for missed Virologic Failure Testing Data
192	Integrase	No sample available for testing	-	-
204	Integrase	No sample available for testing	Integrase, Protease, Reverse Transcriptase	No samples collected for testing at confirmation of virologic failure
24	Integrase	No sample available for testing	-	-
32	Integrase	No sample available for testing	Integrase	Insufficient sample volume for testing
32	Integrase	No sample available for testing	Integrase, Protease, Reverse Transcriptase	Insufficient HIV-1 RNA for testing at VF testing visit (257 c/mL)

: P1093 CSR Table 4.6 [GSK Document Number 2019N395492_00]

Of the treatment emergent RAVs, only a few are expected to affect DTG susceptibility single-handedly. E92Q and R263K confers FCs of approximately 1.5 and 2, respectively.

G118R, also known to be selected by DTG in vitro (subtypes C and CRF AE_02, not subtype B, and not studied for all HIV subtypes), is the most common and relevant RAV with a fold-change of 5. This was not seen in the previous paediatric submission and has been a rare finding in large scale studies in adult patients. To see this key DTG mutation, which confers cross-resistance to the other agents in the INI class, in 5/36 patients with PDVF is a sad finding. It may be that the mutation is present in a higher proportion of the children with unsuppressed viral loads, than detected so far in the PDVF-population of P1093.

These 5 case narratives were further reviewed. Patients were of subtype B (N=2, Cohort I FCT and Cohort III granules for suspension), CRF28_BF (N=1, Cohort IIB granules for suspension), CRF01_AE (N=1, Cohort IV granules for suspension) and C (N=1, Cohort III dispersible tablets). Having prior treatment histories and resistance in mind, the de novo development of G118R seems related to sub-optimal selection of OBR in addition to DTG, emphasizing the importance that patients with previous drug resistance are managed in a specialist setting. It also shows that, although the resistance barrier of DTG is high, the risk of key resistance is higher than it is for boosted PIs, where this is hardly seen (even as part of a suboptimal regimen). The DTG-containing regimens given to these patients in practice concern functional monotherapy, or dual therapy (DTG + 1 potentially active NRTI) in combination with poor compliance. Concomitant NRTI resistance with both M184V and TAM RAVs were seen at failure, resistance that could have been present but not captured at baseline, given the prior treatment failures in many of the patients.

As requested, the MAH has provided an update of de novo INSTI resistance in relation to prior regimens, baseline resistance, optimized background (OBT), HIV subtype and type of DTG formulation. INSTI resistance development appears related to several factors including baseline resistance, sub-optimal choice of OBT and adherence issues. It is acknowledged that INST resistance has been observed both in the SAILING and DAWNING trials, as well as in bibliographic data. However, none of these describe a rate of de novo INSTI development compared to the P1093 study, illustrating the particular challenges in treating HIV-infected children.

Palatability and Acceptability of the DT Formulation in P1093

The palatability and acceptability of the DT formulation was assessed in age-based Cohort III-DT, Cohort IV-DT and Cohort V-DT at Day 10, Week 4, and Week 24. The overall assessment is shown below. The DT formulation taste was acceptable to the majority of respondents (>98%) and there were very few problems with preparation or administration.

Table 45: Summary of Palatability and Acceptability Responses for DTG DT – AT Population

	Cohort n (%)[a]		
	III-DT (N=26)	IV-DT (N=25)	V-DT (N=23)
Number of Respondents	25 (96.2)	25 (100)	22 (95.7)
Overall taste assessment			
Very Good	6 (23.1)	8 (32.0)	1 (4.3)
Good	16 (61.5)	10 (40.0)	19 (82.6)
Average	2 (7.7)	6 (24.0)	2 (8.7)
Bad	1 (3.8)	0	0
Very Bad	0	1 (4.0)	0
Most Frequent Preparation Problem(s)[b]			
No problems reported	24 (92.3)	24 (96.0)	22 (95.7)
Fully dispersing tablets	1 (3.8)	0	0
Cleaning and drying dosing cup	0	1 (4.0)	0
Most Frequent Administration Problem(s)[c]			
No problems reported	25 (96.2)	24 (96.0)	22 (95.7)
Vomiting	0	1 (4.0)	0

Data Source: Table 1.130
Note: Some participants/caregivers provided more than 1 taste assessment; however only the most recent assessment is displayed.
a. Number (percent) of participants in each subcategory with at least 1 taste assessment
b. Most Frequent Preparation Problem(s) are problems that occurred Often.
c. Most Frequent Administration Problem(s) are problems that occurred for Most or Approximately Half of All Doses.

Summary of main efficacy results

The Applicant has provided an updated dataset from the P1093 study as requested, allowing evaluation of 66 (previously 24) patients at 48 weeks. The proportion of patients reaching below 50 and 400 c/mL is more or less unchanged. One additional case of virologic failure has been identified, but this patient has regained virologic control without any change in ART.

The Applicant has committed to provide the ODYSSEY manuscript which will contain efficacy and long term safety results to 96 weeks as a Post Approval Measure, currently planned to be available by the end of 2021.

From the available data, it can be concluded that the proportion of subjects with HIV RNA below 50 c/mL at week 24 decreases with younger age, but many patients are in the interval between 50-400 c/mL. This is likely related to adherence but could also be partly related to that infants and young children may be slower to reach virologic control due to higher baseline viral load. In the updated dataset the proportion of patients reaching below 50 and 400 c/mL at week 48 is more or less unchanged compared to the earlier data cut off.

Among the patients with protocol-defined virologic failure there are 5 patients with treatment-emergent integrase RAVs (G118R) that are clinically relevant (FC 5). The MAH has proposed a wording for SmPC section 5.1 that is acceptable. Given that there were no additional cases of de novo ART resistance in the updated dataset, it is agreed with the MAH that a specific warning in SmPC section 4.4 is not warranted.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive studies

Not applicable.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The P1093 study is not powered for a precise estimate of efficacy and no control arm is available for comparison. Rather, given that exposure is comparable, efficacy will be estimated through a PK/PD-bridge which is in line with EMA guidance.

Efficacy data and additional analyses

The known challenges in treating HIV positive children are clear in the study estimates of efficacy, with relatively low proportions of patients reaching below 50 c/mL but about 83% reaching below 400 c/mL. When looking at patients fulfilling criteria for protocol-defined virological failure, there are 5 patients with treatment-emergent integrase RAVs (G118R) that are clinically relevant. Although this is likely related both to poor optimization of the NRTI background and sub-optimal treatment compliance, this de novo DTG resistance development is now adequately described in SmPC section 5.1.

It is clear that treatment emergent DTG resistance is a much larger problem when treating paediatric patients compared to adults, a difference that has not been seen to the same extent for protease inhibitors. The implications for patients failing second-line regimens containing DTG are potentially severe, as only one widely available ART class (PIs) remain and that even in cases where the future ART management is state-of-the-art, there would be limited room to adjust for tolerability issues and contraindications.

The SmPC section 5.1 updates regarding resistance development proposed by the MAH are acceptable.

The Applicant has committed to provide the ODYSSEY manuscript which will contain efficacy and long term safety results to 96 weeks as a Post Approval Measure (REC), currently planned to be available by the end of 2021.

2.5.4. Conclusions on the clinical efficacy

Given that exposure is comparable, dolutegravir is effective in the treatment of HIV in paediatric patients.

Recommendations

- The ODYSSEY manuscript with efficacy and long term safety results to 96 weeks should be submitted by the end of 2021.

2.6. Clinical safety

This application includes safety data from the P1093 study with data cut-off on 12 December 2019, the safety assessment includes data from all participants exposed to DTG at any dose (AT Safety Population). Safety data from the ODYSSEY PK sub-studies are also included with data cut-off on 28 February 2019, the safety assessment includes all participants who received at least one dose of DTG (the Safety Population).

Patient exposure

For study P1093 through the cut-off date of 12 December 2019, 156/159 (98.1%) participants in the AT Population had >24 weeks of exposure. Most participants, 150/159 (94%), in the AT Population had either reached the Week 48 visit or were off-study by this date. In the Safety Population of the ODYSSEY PK sub-studies 86 (87%) participants were exposed to DTG for at least 24 weeks while 74 (75%) were exposed for at least 48 weeks.

P1093

As of 30 April 2019, a total of 159 participants were enrolled to the P1093 study, had taken at least 1 dose of DTG and are included in the AT Safety Population. The safety data of these 159 participants are captured through a data cut-off date of 12 December 2019. The median extent of exposure to DTG in the AT Population was 918 days (range 60 to 1993 days).

Table 46: Summary of Exposure to DTG by Enrolment Weight Band – AT Population (through 12 December 2019)

Minimum Exposure	3 to <6kg (N=17) n	6 to <10kg (N=37) n	10 to <14kg (N=25) n	14 to <20kg (N=26) n	20 to <25kg (N=14) n	25 to <35kg (N=12) n	≥35kg (N=28) n	Total (N=159) n
>0 day	17	37	25	26	14	12	28	159
>4 weeks	17	37	25	26	14	12	28	159
>12 weeks	16	37	25	26	14	12	28	158
>24 weeks	16	36	25	26	13	12	28	156
>48 weeks	13	31	19	23	13	11	25	135
>72 weeks	10	24	16	20	13	11	25	119
>96 weeks	6	14	14	18	12	9	23	96
>120 weeks	4	13	13	18	12	9	22	91
>144 weeks	1	6	12	13	12	8	19	71
>168 weeks	1	2	8	12	11	8	17	59
>192 weeks	1	1	3	9	9	4	11	38
>216 weeks	0	0	0	0	2	1	2	5
>240 weeks	0	0	0	0	0	1	1	2

Table 47: P1093 Days of exposure by Cohort (AT Population), all available data as of December 12, 2019

	Cohort I (N=23)	Cohort IIA (N=23)	Cohort IIB (N=15)	Cohort III (N=17)	Cohort IV (N=7)	Cohort III-DT (N=26)	Cohort IV-DT (N=25)	Cohort V-DT (N=23)	Total (N=159)
Mean (SD)	1068 (469)	1178 (422)	1292 (222)	1200 (315)	985 (454)	588 (318)	657 (298)	565 (223)	900 (442)
Median	1199	1352	1345	1332	1061	510	617	563	918
Range	281 - 1993	85 - 1672	491 - 1384	243 - 1371	267 - 1366	130 - 1156	60 - 1122	169 - 918	60 - 1993
Q1, Q3	714, 1348	1008, 1392	1341, 1362	1244, 1345	442, 1356	280, 918	456, 914	396, 774	498, 1344

N = Number of participants in each cohort.
Mean (SD) = Mean (Standard Deviation) Q1,Q3 = 25th percentile, 75th percentile.

ODYSSEY

As of 28 February 2019, a total of 99 participants were enrolled into the weight band-based PK sub-studies in ODYSSEY and represent the Safety Population. Of these 99 participants. The median duration of exposure to DTG in the ODYSSEY Safety Population was 466 days (26 to 842).

Table 48: ODYSSEY Summary of Extent of Exposure to DTG by Weight Band (Safety Population)

	3 to <6 kg (N=1) n (%)	6 to <10 kg (N=10) n (%)	10 to <14 kg (N=8) n (%)	14 to <20 kg (N=34) n (%)	20 to <25 kg (N=44) n (%)	25 to <30 kg (N=41) n (%)	30 to <40 kg (N=26) n (%)	≥40 kg (N=4) n (%)	Total Unique Participants (N=99) n (%)
Exposure (weeks)									
<2	0	1 (10)	0	0	0	0	2 (8)	1 (25)	0
2 to <4	0	0	1 (13)	1 (3)	2 (5)	1 (2)	0	0	1 (1)
4 to <8	0	0	0	3 (9)	5 (11)	0	0	0	0
8 to <12	0	1 (10)	0	0	1 (2)	2 (5)	0	0	0
12 to <16	1 (100)	5 (50)	5 (63)	3 (9)	5 (11)	2 (5)	3 (12)	0	8 (8)
16 to <20	0	1 (10)	0	1 (3)	0	1 (2)	0	0	1 (1)
20 to <24	0	0	1 (13)	1 (3)	2 (5)	2 (5)	0	1 (25)	3 (3)
24 to <28	0	2 (20)	1 (13)	2 (6)	3 (7)	4 (10)	2 (8)	0	4 (4)
28 to <32	0	0	0	2 (6)	0	2 (5)	1 (4)	0	0
32 to <36	0	0	0	1 (3)	4 (9)	0	0	0	1 (1)
36 to <40	0	0	0	2 (6)	4 (9)	8 (20)	2 (8)	0	3 (3)
40 to <48	0	0	0	1 (3)	5 (11)	0	1 (4)	0	4 (4)
48 to <60	0	0	0	11 (32)	6 (14)	5 (12)	1 (4)	1 (25)	15 (15)
60 to <72	0	0	0	3 (9)	4 (9)	7 (17)	6 (23)	1 (25)	10 (10)
72 to <84	0	0	0	3 (9)	2 (5)	4 (10)	3 (12)	0	16 (16)
84 to <96	0	0	0	0	1 (2)	2 (5)	4 (15)	0	12 (12)
≥96	0	0	0	0	0	1 (2)	1 (4)	0	21 (21)
Days Exposed									
Mean (SD)	84.0	98.0 (46.49)	98.1 (44.54)	273.7 (151.49)	243.4 (156.71)	315.0 (175.44)	358.5 (206.32)	250.5 (212.44)	455.6 (215.43)
Median (range)	84.0 (84-84)	85.0 (13-169)	86.0 (26-169)	335.5 (16-587)	251.5 (14-588)	254.0 (14-673)	426.5 (1-694)	278.0 (1-445)	466.0 (26-842)

Data Source: Table 3.1
Note: Participants may appear in more than 1 weight band.
Note: All weight bands are included. Duration of exposure in days = (treatment stop date - treatment start date + 1) summed over all dosing periods for a particular weight band, where dose interruptions are not taken into account. When IP stop date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is earlier.

Adverse events

The most common clinical AEs observed through Week 48 in the AT Safety Population in the December data cut were cough, rhinorrhoea, pyrexia, diarrhoea, nasal congestion, and vomiting. Frequencies of common AEs varied across weight categories without clear patterns. The majority of reported AEs are expected for this population since childhood infections are common, and frequently include URTIs, respiratory infections and diarrheal illnesses for children <5 years. Further, diarrhoea is a known adverse drug reaction for DTG.

In the ODYSSEY PK sub-studies, the most commonly reported ≥Grade 3 AEs reported by the Week 24 timepoint in 2 or more participants included neutropenia (4 cases) and anaemia (2 cases). In the ODYSSEY study only ≥Grade 3 AEs, all SAEs, and all Grade 1/2 AEs leading to dose modification or DTG discontinuation were collected, hence, the profile of common AEs differ from that in P1093.

Table 49: Cumulative Overall AEs in P1093 AT Safety Population through 12 December 2019

	Through Week 24 (N=159) n (%)	Through Week 48 (N=159) n (%)	Through Data Cut-off (N=159) n (%)
With one or more clinical AEs	133 (83.6)	141 (88.7)	145 (91.2)
With one or more serious clinical AEs	15 (9.4)	17 (10.7)	31 (19.5)[a]
With one or more serious drug related[b] clinical AEs	3 (1.9)	3 (1.9)	3 (1.9)
Who died due to clinical AEs	2 (1.3)	2 (1.3)	3 (1.9)
With one or more ≥Grade 3 clinical AEs	18 (11.3)	22 (13.8)	36 (22.6)
With one or more ≥Grade 3 drug related[b] clinical AEs	1 (0.6)	1 (0.6)	1 (0.6)

Data Source: Table 3.63, Table 3.65, and Table 3.67

a The late onset SAEs were more often from the Infections and infestations SOC and occurred most often in participants from Cohorts I and IIA who have been on study drug for the longest period (see Section 7.3.3.2 of the P1093 CSR [GSK Document. Number. 2019N395492_00]). This is consistent with observations from the April dataset.

b Drug related AEs were determined to be possibly, probably or definitely related to study drug by the protocol team.

Table 50: Cumulative Overall AEs in ODYSSEY PK Sub-study Safety Population through 28 February 2019

ODYSSEY PK Sub-study Participants, n (%)	Through Week 24 (N=99)	Through Week 48 (N=99)	Through Data Cut-off (N=99)
With any SAE	5 (5)	8 (8)	8 (8)
With any ≥Grade 3 AE	14 (14)	20 (20)	21 (21)

Note: In the ODYSSY PK sub-studies, 86 (87%) were exposed to DTG for at least 24 weeks while 74 (75%) were exposed for at least 48 weeks. There were no Grade 1 or 2 SAEs leading to dose modification or withdrawal. Further, there were no AEs considered drug-related following ERC adjudication and no fatal reports. ≥Grade 3

events are inclusive of SAEs.

P1093

Table 51: Most Commonly Reported AEs by Enrolment Weight Band Through Week 48 Through 12 December 2019 (Incidence ≥10 Participants Total) – P1093 AT Safety Population

PT	3 to <6 kg (N=17) n (%)	6 to <10 kg (N=37) n (%)	10 to <14 kg (N=25) n (%)	14 to <20 kg (N=26) n (%)	20 to <25 kg (N=14) n (%)	25 to <35 kg (N=12) n (%)	≥35 kg (N=28) n (%)	Total (N=159) n (%)
Cough	9 (52.9)	24 (64.9)	15 (60.0)	17 (65.4)	7 (50.0)	7 (58.3)	11 (39.3)	90 (56.6)
Rhinorrhoea	5 (29.4)	13 (35.1)	9 (36.0)	11 (42.3)	5 (35.7)	2 (16.7)	3 (10.7)	48 (30.2)
Pyrexia	6 (35.3)	15 (40.5)	7 (28.0)	8 (30.8)	5 (35.7)	1 (8.3)	5 (17.9)	47 (29.6)
Diarrheal	6 (35.3)	14 (37.8)	7 (28.0)	4 (15.4)	3 (21.4)	2 (16.7)	6 (21.4)	42 (26.4)
Nasal congestion	3 (17.6)	8 (21.6)	6 (24.0)	7 (26.9)	4 (28.6)	2 (16.7)	6 (21.4)	36 (22.6)
Vomiting	5 (29.4)	11 (29.7)	9 (36.0)	4 (15.4)	2 (14.3)	1 (8.3)	2 (7.1)	34 (21.4)
Rash	5 (29.4)	5 (13.5)	5 (20.0)	7 (26.9)	4 (28.6)	1 (8.3)	4 (14.3)	31 (19.5)
Decreased appetite	2 (11.8)	6 (16.2)	2 (8.0)	2 (7.7)	4 (28.6)	0	4 (14.3)	20 (12.6)
Gastroenteritis	4 (23.5)	5 (13.5)	5 (20.0)	0	1 (7.1)	1 (8.3)	1 (3.6)	17 (10.7)
Lymphadenopathy	2 (11.8)	2 (5.4)	0	1 (3.8)	3 (21.4)	3 (25.0)	5 (17.9)	16 (10.1)
Papule	2 (1.8)	1 (2.7)	6 (24.0)	3 (11.5)	1 (7.1)	2 (16.7)	0	15 (9.4)
Otitis media	1 (5.9)	4 (10.8)	4 (16.0)	2 (7.7)	1 (7.1)	0	2 (7.1)	14 (8.8)
Pharyngitis	1 (5.9)	3 (8.1)	1 (4.0)	3 (11.5)	2 (14.3)	2 (16.7)	2 (7.1)	14 (8.8)
Pharyngeal inflammation	1 (5.9)	9 (24.3)	1 (4.0)	3 (11.5)	0	0	0	14 (8.8)
Pruritus	0	3 (8.1)	1 (4.0)	5 (19.2)	2 (14.3)	1 (8.3)	1 (3.6)	13 (8.2)
Rales	0	3 (8.1)	4 (16.0)	1 (3.8)	3 (21.4)	1 (8.3)	0	12 (7.5)
Headache	0	0	1 (4.0)	3 (11.5)	1 (7.1)	0	6 (21.4)	11 (6.9)
Rhonchi	0	5 (13.5)	3 (12.0)	0	2 (14.3)	1 (8.3)	0	11 (6.9)
Wheezing	1 (5.9)	3 (8.1)	0	2 (7.7)	1 (7.1)	2 (16.7)	2 (7.1)	11 (6.9)
Upper respiratory tract infection	1 (5.9)	6 (16.2)	2 (8.0)	1 (3.8)	0	0	0	10 (6.3)

Data Source: Table 3.3, Table 3.7, Table 3.11

ODYSSEY

Table 52: Most Commonly Reported ≥Grade 3 AEs by Enrolment Weight Band Through Week 24 (Incidence ≥1 Participant Total) ODYSSEY PK Sub-studies Safety Population

PT	3 to <6 kg (N=1) n (%)	6 to <10 kg (N=10) n (%)	10 to <14 kg (N=5) n (%)	14 to <20 kg (N=33) n (%)	20 to <25 kg (N=28) n (%)	25 to <30 kg (N=16) n (%)	30 to <40 kg (N=6) n (%)	Total (N=99) n (%)
Anemia	0	1 (10)	1 (20)	0	0	0	0	2 (2)
Neutropenia	0	0	1 (20)	1 (3)	2 (7)	0	0	4 (4)
Thrombocytopenia	0	0	0	0	1 (4)	0	0	1 (1)
Hepatitis A	0	0	0	1 (3)	0	0	0	1 (1)
Lower respiratory tract infection	0	1 (10)	0	0	0	0	0	1 (1)
Malaria	0	0	0	1 (3)	0	0	0	1 (1)
Meningitis cryptococcal	0	0	0	0	0	0	1 (17)	1 (1)
Otitis media	0	1 (10)	0	0	0	0	0	1 (1)
Pneumonia	0	1 (10)	0	0	0	0	0	1 (1)
Diarrhea	0	1 (10)	0	0	0	0	0	1 (1)
Pyrexia	0	0	0	1 (3)	0	0	0	1 (1)
Hepatic enzyme increased	0	0	0	0	1 (4)	0	0	1 (1)
Malnutrition	0	1 (10)	0	0	0	0	0	1 (1)
Seizure	0	0	0	1 (3)	0	0	0	1 (1)

Data Source: ODYSSEY Table 3.9
Note: There were no Grade 1 or 2 AEs leading to dose modification or withdrawal.
Note: N = number of participants at enrollment per weight band.

To account for the potential differences in the duration of exposure of participants across weight band, formulations and dose, the rate of AEs per period of exposure was calculated in each study.

P1093

In P1093 EAIRs were evaluated by weight band at the time of AE occurrence. This 'safety weight' presentation of data was confined to participants receiving the DT formulation (i.e. weight bands <25 kg).

Table 53: P1093 Exposure-adjusted Incidence Rates for Most Commonly Reported AEs by Weight Band Through Week 24 – Participants on DT Dosing in AT Safety Population (through 30 April 2019)

PT[a]	3 to <6 kg (N=17)			6 to <10 kg (N=54)			10 to <14 kg (N=55)			14 to <20 kg (N=47)		
	n (%)	Rate/100 PY	95% CI	n (%)	Rate/100 PY	95% CI	n (%)	Rate/100 PY	95% CI	n (%)	Rate/100 PY	95% CI
n	16			48			43			30		
Cough	2 (13)	61.2	(15.3,244.8)	15 (31)	75.5	(45.5,125.2)	6 (14)	67.2	(30.2,149.7)	9 (30)	120.2	(62.6,231.1)
Diarrhea	3 (19)	91.8	(29.6,284.8)	9 (19)	45.3	(23.6,87.0)	2 (5)	22.4	(5.6,89.6)	1 (3)	13.4	(1.9,94.8)
Nasal congestion	2 (13)	61.2	(15.3,244.8)	5 (10)	25.2	(10.5,60.4)	3 (7)	33.6	(10.8,104.2)	2 (7)	26.7	(6.7,106.8)
Pyrexia	1 (6)	30.6	(4.3,217.3)	12 (25)	60.4	(34.3,106.3)	5 (12)	56	(23.3,134.6)	0	0	0
Gastroenteritis	3 (19)	91.8	(29.6,284.8)	3 (6)	15.1	(4.9,46.8)	1 (2)	11.2	(1.6,79.6)	0	0	0
Rhinorrhea	0	0	0	8 (17)	40.2	(20.1,80.5)	3 (7)	33.6	(10.8,104.2)	2 (7)	26.7	(6.7,106.8)
Vomiting	1 (6)	30.6	(4.3,217.3)	10 (21)	50.3	(27.1,93.5)	2 (5)	22.4	(5.6,89.6)	1 (3)	13.4	(1.9,94.8)
Rash	1 (6)	30.6	(4.3,217.3)	3 (6)	15.1	(4.9,46.8)	1 (2)	11.2	(1.6,79.6)	2 (7)	26.7	(6.7,106.8)
Decreased appetite	0	0	0	5 (10)	25.2	(10.5,60.4)	1 (2)	11.2	(1.6,79.6)	1 (3)	13.4	(1.9,94.8)
Lymphadenopathy	0	0	0	2 (4)	10.1	(2.5,40.2)	0	0	0	0	0	0
Pharyngitis	0	0	0	1 (2)	5.0	(0.7,35.7)	0	0	0	0	0	0

Data Source: Table 3.40, Table 3.54, Table 3.66, Table 3.78, Table 3.90

a. The PTs shown are those that were also observed as the most common AEs by enrollment weight band from Table 35.

Notes:

- CI is based on Wald Estimate.
- The calculation for the number of participants with AE per 100 person-years is described in the RAP.
- For participants taking DTs, there were no clinical AEs reported in the 25 to <35 kg enrollment weight band. Thus, this group is not shown above.
- The N values are the number of participants in each weight band at any time on study. The n values are the number of participants that received the DT formulation in each weight band. Participants may appear in more than 1 weight band..

ODYSSEY

In the ODYSSEY PK sub-studies, EAIRs based on weight at the time of event were calculated and presented for each AE PT, formulation, and dose. The presentation includes participants on both formulations (DT and FCT).

Table 54: Exposure-adjusted Incidence Rates for Most Commonly Reported AEs by Weight Band Through 28 February 2019 (Incidence ≥1 Participant Total) – ODYSSEY PK Sub-studies Safety Population

	n (%) Rate/100 PY, 95% CI								
PT	3 to <6 kg (N=1)	6 to <10 kg (N=10)	10 to <14kg (N=8)	14 to <20kg (N=34)	20 to <25 kg (N=44)	25 to <30 kg (N=41)	30 to <40 kg (N=26)	≥ 40 kg (N=4)	Total (N=99) n (%)
Neutropenia	0	0	1 (13) 46.5 (6.6, 330.3)	1 (3) 4.0 (0.6, 28.2)	2 (5) 7.0 (1.8, 28.1)	1 (2) 2.9 (0.4, 20.3)	0	0	5 (5) 4.2 (1.8, 10.1)
Anemia	0	1 (10) 41.7 (5.9, 296.3)	1 (13) 51.3 (7.2, 364.2)	0	0	0	1 (4) 4.1 (0.6, 29.5)	0	3 (3) 2.5 (0.8, 7.7)
Pneumonia	0	1 (10) 40.1 (5.6, 284.6)	0	1 (3) 3.9 (0.6, 27.9)	0	0	0	0	2 (2) 1.6 (0.4, 6.5)
Acute sinusitis	0	0	0	0	1 (2) 3.5 (0.5, 24.7)	0	0	0	1 (1) 0.8 (0.1, 5.8)
Hepatitis A	0	0	0	1 (3) 3.9 (0.6, 27.9)	1 (2) 3.4 (0.5, 24.2)	0	0	0	2 (2) 1.6 (0.4, 6.5)
Lower respiratory tract infection	0	1 (10) 37.8 (5.3, 268.1)	0	0	0	0	0	0	1 (1) 0.8 (0.1, 5.8)
Malaria	0	0	0	1 (3) 4.1 (0.6, 29.1)	0	0	0	0	1 (1) 0.8 (0.1, 5.8)
Measles	0	0	0	0	1 (2) 3.5 (0.5, 24.8)	0	0	0	1 (1) 0.8 (0.1, 5.8)
Meningitis cryptococcal	0	0	0	0	0	0	1 (4) 4.1 (0.6, 29.2)	0	1 (1) 0.8 (0.1, 5.8)
Otitis media	0	1 (10) 40.1 (5.6, 284.6)	0	0	0	0	0	0	1 (1) 0.8 (0.1, 5.8)
Thrombocytopenia	0	0	0	0	1 (2) 3.5 (0.5, 25.2)	0	0	0	1 (1) 0.8 (0.1, 5.8)
Diarrhea	0	1 (10) 40.2 (5.7, 285.3)	0	0	0	0	0	0	1 (1) 0.8 (0.1, 5.8)
Pyrexia	0	0	0	0	1 (2) 3.5 (0.5, 24.8)	0	0	0	1 (1) 0.8 (0.1, 5.8)
Fracture	0	0	0	0	0	0	0	1 (25) 36.5 (5.1, 258.8)	1 (1) 0.8 (0.1, 5.7)
Hepatic enzyme increased	0	0	0	0	1 (2) 3.5 (0.5, 25.2)	0	0	0	1 (1) 0.8 (0.1, 5.8)
Malnutrition	0	1 (10) 37.8 (5.3, 268.1)	0	0	0	0	0	0	1 (1) 0.8 (0.1, 5.8)
Seizure	0	0	0	1 (3) 4.0 (0.6, 28.6)	0	0	0	0	1 (1) 0.8 (0.1, 5.8)
Nephropathy toxic	0	0	0	0	0	0	1 (4) 4.0 (0.6, 28.4)	0	1 (1) 0.8 (0.1, 5.8)

Data Source: ODYSSEY Table 3.6

Notes: EAIRs and corresponding 95% CIs are estimated from a poisson model with loge(exposure time) included in the model as an offset, by fitting this model separately to each distinct weight band.

Growth Measures

Changes in weight, height, BMI were followed in both P1093 and the ODYSSEY PK sub-studies. Median Z-scores for weight, height, and BMI were reviewed at Baseline and over time by enrolment weight band up to Week 48 in Study P1093 and up to Week 96 in the ODYSSEY PK sub-studies. Brief summaries of the observations are presented below for the AT Safety Population (P1093 through 30 April 2019) and the Safety Population (ODYSSEY PK sub-studies through 28 February 2019).

Weight

In P1093, the median Z scores for participants weighing ≥35 kg at enrolment remained above the 50th percentile while the medians of participants in the lower enrolment weight band categories remained below the 50th percentile. In the ODYSSEY PK sub-studies some improvement over time in weight Z scores was apparent.

Height

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

BMI

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

Adverse Events of Special Interest (AESIs)

AESIs that have been determined for DTG are discussed in this section. These AESIs have been identified based on non-clinical and/or clinical safety data for DTG (e.g., GI disorders, renal disorders, hepatobiliary disorders), labelling and/or regulatory authority interest for INSTIs and/or the INSTI class (e.g., psychiatric disorders, rhabdomyolysis and myositis, serious rash and/or hypersensitivity), increased incidence of IRIS; and/or regulatory requirements.

New AESIs in the December dataset were identified based on a review of AE onset dates (i.e., AEs with onset later than 30 April 2019) identified in the December listings.

Immune Reconstitution Inflammatory Syndrome Events:

This is discussed in the section on immunological events.

Hypersensitivity and Rash:

This is discussed in the section on immunological events.

Hepatobiliary Disorders:

Liver chemistry data and relevant clinical event data are discussed in the section on laboratory findings.

P1093

Seven participants (4.4%) experienced a clinical event from the Hepatobiliary disorders SOC. All events were Grade 1 (6 of Hepatomegaly and 1 of Ocular icterus) and none were considered related to study treatment. There were no serious clinical AEs reported from the Hepatobiliary disorders SOC.

ODYSSEY

There were no AEs reported in the Hepatobiliary disorders SOC, however, there were 2 participants who experienced Grade 4 Hepatitis A (1 serious). Both participants met liver stopping criteria and stopped treatment with DTG, although neither were considered related to treatment.

There was also 1 participant who experienced non-serious, Grade 3 hepatic enzyme increased including ALT and AST increased. The participant had slightly raised AST/ALT at Screening and Grade 1 AST at Day 1. Grade 3 AST and ALT elevations occurred at Week 24 and were isolated elevations which resolved 15 days later with no interruption to study treatment. In addition, at Week 24, the participant reported a nonserious AE of thrombocytopenia (Grade 3), which also resolved in parallel with the liver enzyme elevations.

Psychiatric Disorders Including Suicidality

Psychiatric AEs reports are dominated by patients with pre-existing conditions, similar to what is seen in adults. None of the other AESIs reported raise any issues of a different safety profile compared to adults.

P1093

Through 30 April 2019 fifteen participants reported 1 or more AEs (mainly Grade 1 or 2) from the Psychiatric disorders SOC. Of the 15 participants reporting a psychiatric event, 9 were from the oldest age cohorts (Cohort I [6 participants] and Cohort IIA [3 participants]). The remaining 6 participants were from younger enrolment cohorts (Cohort III [4 participants] and Cohort IV-DT [2 participants]).

Between 30 April 2019 and 12 December 2019, there were no additional SAEs or ≥Grade 3 AEs from the Psychiatric disorder SOC. Further, there were no new treatment related AEs observed in the Psychiatric disorder SOC. As previously reported, only the AE of Initial insomnia was considered possibly related to study treatment. The Initial insomnia was experienced by one participant at Week 40 (Grade 1) and Week 168 (Grade 2). An additional 3 participants reported 1 AE each from the Psychiatric disorders SOC for the first time. These AEs were irritability (Grade 1, unrelated) in the 6 to <10 kg enrolment weight band at Week 48, anxiety (Grade 2, unrelated) in the 10 to <14 kg enrolment weight band at Week 108, and ADHD (Grade 2, unrelated) in the 14 to <20 kg weight band at Week 144. The nature of the new psychiatric events AEs in the December dataset are similar to those reported in the April dataset.

Overall, of the 18 participants with 1 or more AEs from the Psychiatric disorders SOC, 9 participants were part of the PD population and all but 2 of these 9 participants were ≥35 kg at enrolment weight band.

Table 55: P1093 Serious Adverse Events

Enrolment weight Band	Baseline (formulation)	AE PT(s)	AE Grade	RWO	Serious	Other relevant AEs / Relevant Medical History
20 to <25 kg 1 participant	IIA (FCTs)	Abnormal behaviour	3	Week 108	Yes	Additional relevant PTs: PTSD (Grade 2) at Week 156. After Week 108, events of Abnormal behaviour (Grade 2 and 3) were

		Affective disorder	2	Week 108	No	reported at each study visit up to Week 180. This participant had a history of ADHD. None of these clinical AEs were considered related to the study treatment.
		Major depression	2	Week 144	No	
20 to <25 kg 1 participant	IIA (FCTs)	Suicidal ideation	4	Week 168	Yes	The event of Initial insomnia was considered possibly related to the study treatment. All other clinical AEs were not considered related to study treatment.
		Initial insomnia	1	Week 40	No	
			2	Week 168	No	
≥35 kg 1 participant	I (FCTs)	Suicide attempt	4	Week 120	Yes	This participant had a long-standing history of mild intermittent situational depression. None of these clinical AEs were considered related to the study treatment.
		Intentional overdose	4	Week 120	No	
		Depression	4	Week 120	No	

Depression Events:

P1093

The following terms were reported: Depressed mood (1), Depression (3), Depressive symptoms (1), Major depression (2). Across weight categories, there was only 1 depression event reported in the first 48 weeks (Grade 2 Depression). The remaining events of depression were reported post Week 48.

ODYSSEY

There were no AEs reported in the SOC of Psychiatric disorders.

Gastrointestinal Disorders:

P1093

Over half of participants (83/159, 52%) reported one or more event from the GI disorders SOC through the cut-off date of 30 April 2019. GI AEs were commonly reported, with Abdominal pain, Diarrhoea, Nausea, Decreased appetite, Gastroenteritis and Vomiting being the most common. GI events were reported across all enrolment weight bands and were mainly Grade 1 or 2 events.

Serious Adverse Events:

Through Week 24, there was 1 SAE of Grade 3 diarrhoea (with concurrent Grade 2 IRIS) in a participant enrolled in the 6 to <10 kg weight band. In addition, while formally captured under the Infections SOC, there were 4 SAE reports of Gastroenteritis through Week 24. After Week 24, only 1 further GI SAE was reported, and this occurred between Week 48 and the data cut-off. None of these SAEs were considered related to the study treatment.

≥Grade 3 Events:

In the P1093 AT Safety population, 6 participants experienced 1 or more Grade 3 GI AEs and none of these were considered related to study treatment.

Between 30 April 2019 and 12 December 2019, there were no additional SAEs or ≥Grade 3 AEs from the GI disorders SOC. There was 1 new treatment related AEs of vomiting (Grade 1) observed in a participant from the 10 to <14 kg enrolment weight band.

By 48 weeks of treatment gastrointestinal events including diarrhoea (26.4%), vomiting (21.4%), and gastroenteritis (12.6%) were among the most common to be reported in this study. There were no clear patterns in the updated December dataset in terms of proportions of clinical AEs reported across weight band categories through 48 weeks of treatment.

Overall, no differences in the GI safety profile were apparent between the April and December datasets for both the AT and PD Safety populations.

ODYSSEY

There was 1 participant in the 6 to <10 kg weight band receiving 15 mg DT who reported Grade 3 diarrhoea (non-serious) 14 days after start of treatment. Dehydration (Grade 3) was also reported by the investigator at the same time. The diarrhoea was reported to resolve after 3 days and was not considered related to treatment.

Musculoskeletal Disorders:

P1093

A total of 26 participants reported 1 or more AE from the Musculoskeletal and connective tissue disorders SOC many (15/26) of which were ≥35 kg at enrolment. In the AT safety population, the most common musculoskeletal AEs were Arthralgia, Back pain, Musculoskeletal chest pain, Musculoskeletal pain, Neck pain and Pain in extremity. All (with the exception of the Grade 3 AE of Pain in extremity described below) were Grade 1 or 2. There was a pattern of more musculoskeletal AEs in participants enrolled in the higher weight band categories (>14 kg). There were no serious musculoskeletal AEs through the final data cut-off.

≥Grade 3 or Severe Adverse Events

There was a single Grade 3 AE from the Musculoskeletal SOC of 'Pain in extremity' (≥35 kg enrolment weight band [Cohort IIA, FCT]), which was not considered related to study treatment.

ODYSSEY

There were no AEs reported in the SOC of Musculoskeletal disorders

Renal Disorders:

P1093

There were no participants with clinical renal AEs which were serious or of ≥Grade 3 severity. 1 participant with persistent proteinuria and raised urinary ACR required follow up with a nephrologist.

There was one additional clinical renal AE reported through 12 December 2019 (Grade 1 dysuria reported at Week 96).

ODYSSEY

There were no study treatment related renal AEs. 1 participant experienced nephropathy (PT: nephropathy toxic) (SAE, Grade 4) 406 days after starting treatment with DTG. Nephrotoxicity was considered unrelated to study drug.

Renal laboratory data and relevant clinical event data are discussed in the section on laboratory

Serious adverse event/deaths/other significant events

Deaths

P1093

Death was reported for 3 participants enrolled into the P1093 study as of 12 December 2019.

Table 56: Listing of Deaths in Study P1093 (AT Population)

Cohort/ DTG formula	Cause of Death	Days on DTG	Relationship to Study Drug[a]
Cohort IIA FCT	Drowning	1459	Not related
Cohort IV-DT DT	Acute gastroenteritis	61	Probably not related
Cohort III-DT DT	Unknown cause[b]	130	Not related

a. The assessments of the protocol team concurred with those of the site investigator.

b. It was initially reported that the participant developed generalized convulsions at home 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 post-mortem examination into possible causes of death ruled out expected causes including non-accidental injury. The cause of death was considered as unknown.

ODYSSEY

In the ODYSSEY study no participants enrolled have died during the PK sub-studies as of 28 February 2019.

Serious adverse events

P1093

Three participants experienced drug-related SAEs, all of which were cases of IRIS, see more details below in section Immunological Events.

Table 57: Summary of SAEs Meeting ICH Seriousness Criteria through Week 24 by Enrolment Weight Band (AT Safety Population through 30 April 2019) – Presented by SOC and PT with an Overall Incidence of ≥1

SOC PT	3 to <6kg (N=17) n (%)	6 to <10kg (N=37) n (%)	10 to <14kg (N=25) n (%)	14 to <20kg (N=26) n (%)	20 to <25kg (N=14) n (%)	25 to <35kg (N=12) n (%)	≥35kg (N=28) n (%)	Total (N=159) n (%)
Number of participants with 1 or more SAEs	**4 (23.5)**	**7 (18.9)**	**1 (4)**	**1 (3.8)**	**1 (7.1)**	**1 (8.3)**	**0**	**15 (9.43)**
Infections and infestations	**3 (17.6)**	**5 (13.5)**	**0**	**1 (3.8)**	**1 (7.1)**	**0**	**0**	**10 (6.29)**
Gastroenteritis	3 (17.6)	1 (2.7)	0	0	0	0	0	4 (2.52)
Pneumonia	0	1 (2.7)	0	0	1 (7.1)	0	0	2 (1.26)
Atypical mycobacterial lymphadenitis[a]	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Bacterial sepsis	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Herpes zoster	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Mycobacterium avium complex infection[a]	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Pneumonia adenoviral[a]	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Pneumonia bacterial	0	0	0	1 (3.8)	0	0	0	1 (0.63)
Pneumonia parainfluenza viral[a]	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Pneumonia respiratory syncytial viral[a]	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Immune system disorders	**1 (5.9)**	**2 (5.4)**	**0**	**0**	**0**	**0**	**0**	**3 (1.89)**
IRIS[a]	1 (5.9)	2 (5.4)	0	0	0	0	0	3 (1.89)
General disorders and administration site conditions	**0**	**2 (5.4)**	**0**	**0**	**0**	**0**	**0**	**2 (1.26)**
Death	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Pyrexia	0	1 (2.7)	0	0	0	0	0	1 (0.63)
GI disorders	**0**	**1 (2.7)**	**0**	**0**	**0**	**0**	**0**	**1 (0.63)**
Diarrhea[a]	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Metabolism and nutrition disorders	**1 (5.9)**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (0.63)**
Malnutrition	1 (5.9)	0	0	0	0	0	0	1 (0.63)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (4)**	**0**	**0**	**0**	**0**	**1 (0.63)**
Retinoblastoma	0	0	1 (4)	0	0	0	0	1 (0.63)
Nervous system disorders	**0**	**1 (2.7)**	**0**	**0**	**0**	**0**	**0**	**1**

SOC PT	3 to <6kg (N=17) n (%)	6 to <10kg (N=37) n (%)	10 to <14kg (N=25) n (%)	14 to <20kg (N=26) n (%)	20 to <25kg (N=14) n (%)	25 to <35kg (N=12) n (%)	≥35kg (N=28) n (%)	Total (N=159) n (%)
								(0.63)
Hemiparesis	0	1 (2.7)	0	0	0	0	0	1 (0.63)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**0**	**0**	**1 (8.3)**	**0**	**1 (0.63)**
Respiratory distress	0	0	0	0	0	1 (8.3)		1 (0.63)

Data Source: Table 3.171, Table 3.165, and Case Narratives (Section 15.1)

a. As noted in Listing Table 3.344, these 7 SAEs were experienced by 1 subject.

From Week 24 through Week 48, there were only 2 additional participants in the AT Safety Population who experienced SAEs by 12 December 2019.

- Cellulitis (Grade 3, not related) which occurred at Week 40 in a participant from the 10 to <14 kg enrolment weight band who was not included in the PD population. This SAE was previously reported in the April dataset.
- Plasmodium falciparum infection (Grade 3, not related) at Week 48 in a participant from the 6 to <10 kg enrolment weight band from the PD population. This SAE is new to the December dataset.

Beyond Week 48, an additional 14 participants (total 30/159 [18.9%]), in the AT Safety Population reported an SAE. Seven of these participants were from the ≥35 kg enrolment weight band (i.e. the older age cohort) and the late onset SAEs in these participants were more often from the Infections and infestations SOC. There were 2 female participants who reported deep vein thrombosis, not related to study drug, at Weeks 108 and 144, respectively. One had been casted and immobilised post orthopaedic surgery and the other presented with large-B-cell lymphoma in the groin on the same side. In the updated December dataset one participant with numerous previous SAEs reported 2 new SAEs; pneumonia (Grade 3, not related) and pneumonia adenoviral (Grade 3, not related).

Most of the participants with SAEs started study treatment in the 2 lowest enrolment weight bands and SAEs were most frequently from the Infections and infestations SOC. The most commonly reported SAEs through Week 24 included IRIS (n=3) and Gastroenteritis (n=4).

In-stream safety data was reviewed for 9 participants who had not reached Week 48 for the efficacy analyses by the 12 December 2019 cut-off date. This did not identify any significant new information, and notably no new SAEs or ≥Grade 3 AEs were reported for these 9 participants between 12 December 2019 through their respective Week 48 visits.

ODYSSEY

Eight (8%) participants in the Safety Population reported SAEs through the data cut-off. The majority of SAEs were from the Infections and infestations SOCs and typically resolved with continued DTG treatment. None of the SAEs, reported in 8 participants in total, were considered related to treatment.

Table 58: ODYSSEY SAEs (Safety Population)

Enrollment Weight Band[b]	Weight Band at AE Start	AE PT(s)[c]	Duration	Maximum Severity Grade	Days Since 1st Dose	DTG Withdrawn?
6 to <10 kg	6 to <10 kg	Lower respiratory tract infection	15 days	3	63	No
		Malnutrition	15 days	4	63	No
6 to <10 kg	6 to <10 kg	Otitis media	13 days	3	16	No
		Pneumonia	13 days	3	16	No
20 to <25 kg	20 to <25 kg	Acute sinusitis	6 days	3	227	No
14 to <20 kg	20 to <25 kg	Hepatitis A	62 days	4	253	Yes[e]
14 to <20 kg	14 to <20 kg	Malaria	ongoing	3	96	No
14 to <20 kg	20 to <25 kg	Measles	4 days	3	352	No
30 to <40 kg	30 to <40 kg	Nephropathy toxic	ongoing	4	406	No
		Meningitis cryptococcal	20 days	4	152	No
		Meningitis cryptococcal	65 days	4	394	No
14 to <20 kg	20 to <25 kg	Pyrexia	ongoing	3	134	No

Data Source: Listing 4, Listing 10
Note: DAIDS version 2.0 was used for severity grade.
a. Age at randomization.
b. Weight band at time of enrollment in the ODYSSEY study.
c. SAEs as recorded on Form 30 (Blinded ERC).

d. One participant also had an SAE bacteraemia which started 15 October 2018. However, this event is not included since this participant stopped DTG treatment (25mg FCT) on August 2018 (listing 5).This SAE is not included in the summary tables unless stated otherwise.

e. No action is stated with regard to DTG withdrawal per Form 30. However, drug withdrawal is noted per Form 21 (Data Source: Listing 6). Hepatitis A was not specifically reported as an AE leading to withdrawal, but blood bilirubin increased and hepatic enzyme increased were reported as AEs leading to withdrawal by the site investigator (Data Source: Listing 12). These events were subsequently subsumed under the term Hepatitis A by the ERC (see Table 50).

Global safety database search

In order to provide up to date safety data from both P1093 and the ODYSSEY PK sub-studies, the Applicant has searched their global safety database to identify new SAEs/pregnancy cases and existing SAEs/pregnancy cases with significant follow up information received through 30 June 2020.

For P1093, 11 new SAEs in 7 participants were identified through 30 June 2020, and this includes newly enrolled participants. In 9 of these SAEs, the event was from the infections and infestations SOC. Of these infectious events, 5 were respiratory, 1 was hepatic, 1 was gastrointestinal, and 2 were other infectious events (1 event of plasmodium falciparum infection and 1 event of cellulitis mentioned above). The remaining included 1 event of ALT increased (follow up is ongoing) and an event of a respiratory disorder. For the ODYSSEY PK sub-study participants (limited to the N=99 participants included in the ODYSSEY CSR), 4 new SAEs in 4 participants were identified through 30 June 2020. For 3 of these participants, the event was an infection, and the remaining event was status epilepticus/epilepsy in the context of a previous seizure and acute bacterial meningitis. Four participants from P1093 and 3 participants from the ODYSSEY PK sub-studies had new medically significant follow up information during the period through 30 June 2020. In summary, a review of this in-stream SAE and pregnancy data from the Applicant's global safety database does not reveal any significant new findings and is in line with previous observations.

Laboratory findings

In both P1093 and ODYSSEY most ≥Grade 3 laboratory events were ANC decrease and the younger / lower body weight participants had common baseline factors including black African race (where natural levels of ANC are overall lower). For study P1093 a consideration is the use of DAIDS toxicity reference tables rather

than WHO references for ANC. In the ODYSSEY study neutrophil grading is based on WHO 2010 guidelines recognizing the lower normal levels in African populations.

Overall, the laboratory findings do not indicate a different safety profile compare to adults.

P1093

Clinical chemistry analyses were carried out on the AT and PD Safety Populations. Fasting was not required for these analyses. However, if triglycerides were Grade 2 or higher (using DAIDS toxicity table for fasting triglycerides), a complete fasting lipid profile (triglycerides, cholesterol, HDL, and LDL) was to be drawn.

For the December dataset through Week 48, laboratory events were typically Grade 1 or Grade 2 (113/155). The most common laboratory events through Week 48 were Blood bicarbonate decreased (114), Blood sodium decreased (82), ANC decreased (70), Haemoglobin decreased (58), Blood glucose decreased (50). This pattern in most common laboratory events was similar to that reported through Week 48 in the April 2019 datasets.

Through Week 48 in the December analysis, there was a higher frequency of ≥Grade 3 laboratory AEs in the lower weight categories, although most participants in each weight category had at least 1 laboratory event including all participants enrolled to weight bands <14 kg. There was 1 serious laboratory AE (ALT increased) which occurred in the 6 to <10 kg enrolment weight band.

Consistent with the analysis of the April dataset, the December dataset showed that most abnormal laboratory findings occurred during the first 24 weeks of treatment. Beyond Week 48 (in the December analysis), there were no new serious laboratory AE and 2 additional ≥Grade 3 laboratory AEs reported. This pattern was also observed in the PD Safety Population.

Table 59: Incidence Rates for Most Commonly Reported Laboratory AEs by Weight Band Through Week 24 – Participants on DT Dosing in AT Safety Population (through 30 April 2019)

PT	3 to <6 kg (N=17)			6 to <10 kg (N=54)			10 to <14 kg (N=55)			14 to <20 kg (N=47)		
	n (%)	Rate/100 PY	95% CI	n (%)	Rate/100 PY	95% CI	n (%)	Rate/100 PY	95% CI	n (%)	Rate/100 PY	95% CI
n	16			48			43			30		
Blood bicarbonate ↓	12 (75)	367.4	(208.6,646.9)	39 (81)	196.2	(143.3,268.5)	17 (40)	190.5	(118.4,306.5)	10 (33)	133.6	(71.9,248.3)
Hemoglobin ↓	14 (88)	428.6	(253.9,723.7)	24 (50)	120.7	(80.9,180.1)	8 (19)	89.7	(44.8,179.3)	4 (13)	53.4	(20.1,142.4)
Blood sodium ↓	10 (63)	306.2	(164.7,569.0)	23 (48)	115.7	(76.9,174.1)	11 (26)	123.3	(68.3,222.6)	8 (27)	106.9	(53.4,213.7)
ANC ↓	9 (56)	275.5	(143.4,529.6)	24 (50)	120.7	(80.9,180.1)	5 (12)	56	(23.3,134.6)	7 (23)	93.5	(44.6,196.2)
Blood albumin ↓	8 (50)	244.9	(122.5,489.8)	11 (23)	55.3	(30.6,99.9)	2 (5)	22.4	(5.6,89.6)	3 (10)	40.1	(12.9,124.3)
Blood potassium ↑	5 (31)	153.1	(63.7,367.8)	12 (25)	60.4	(34.3,106.3)	4 (9)	44.8	(16.8,119.4)	4 (13)	53.4	(20.1,142.4)
ALT ↑	3 (19)	91.8	(29.6,284.8)	4 (8)	20.1	(7.6,53.6)	1 (2)	11.2	(1.6,79.6)	3 (10)	40.1	(12.9,124.3)
Blood glucose ↓	1 (6)	30.6	(4.3,217.3)	5 (10)	25.2	(10.5,60.4)	4 (9)	44.8	(16.8,119.4)	3 (10)	40.1	(12.9,124.3)
Blood glucose ↑	1 (6)	30.6	(4.3,217.3)	8 (17)	40.2	(20.1,80.5)	2 (5)	22.4	(5.6,89.6)	3 (10)	40.1	(12.9,124.3)
Blood ALP ↑	1 (6)	30.6	(4.3,217.3)	3 (6)	15.1	(4.9,46.8)	5 (12)	56	(23.3,134.6)	1 (3)	13.4	(1.9,94.8)
Lipase ↑	1 (6)	30.6	(4.3,217.3)	10 (21)	50.3	(27.1,93.5)	1 (2)	11.2	(1.6,79.6)	0	0	0
AST ↑	1 (6)	30.6	(4.3,217.3)	4 (8)	20.1	(7.6,53.6)	1 (2)	11.2	(1.6,79.6)	2 (7)	26.7	(6.7,106.8)

Data Source: Table 3.548, Table 3.560, Table 3.572, Table 3.584, Table 3.596
Note: CI is based on Wald Estimate.
Note: The calculation for the number of participants with AE per 100 person years is described in the RAP.
Note: For participants taking DTs, there were no laboratory AEs in the 25 to <35 kg enrollment weight band and thus, this group is not shown above.
Note: The N values are the number of participants in each weight band at any time on study. The n values are the number of participants that received the DT formulation in each weight band. Participants may appear in more than 1 weight band..

Serious Laboratory Events

Only 2 participants reported serious laboratory AEs meeting ICH seriousness criteria through the data cut-off of 30 April 2019. There were no new serious laboratory AEs reported through 12 December 2019.

- In one participant (6 to <10 kg at enrolment), Grade 3 serious ALT increases were reported at Weeks 2 and 4. These were considered unrelated to study drug on both occasions.
- In one participant (≥35 kg at enrolment), two Grade 4 serious events of ANC decreased were reported at Weeks 96 and Week 144, the initial occurrence was considered probably not related and the second considered not related.

≥Grade 3 Laboratory Events

Most Grade 3 or 4 laboratory events were reported in the first 24 weeks of study treatment. Compared to heavier participants at enrolment, there was a pattern of higher frequency of ≥Grade 3 laboratory AEs in the lowest enrolment weight bands (ranging from 3 to <20 kg). The most common ≥Grade 3 laboratory event was ANC decrease.

Table 60: P1093 ≥Grade 3 Laboratory Adverse Events through Week 48 by Enrolment Weight Band through 12 December 2019 (AT Safety Population)

PT	3 to <6kg (N=17) n (%)		6 to <10kg (N=37) n (%)		10 to <14kg (N=25) n (%)		14 to <20kg (N=26) n (%)		20 to <25kg (N=14) n (%)		≥35kg (N=28) n (%)		Total (N=159) n (%)	
	Grade		Grade		Grade		Grade		Grade		Grade		Grade	
	3	4	3	4	3	4	3	4	3	4	3	4	3	4
# of participants with 1 or more ≥Grade 3 laboratory AE	7 (41.2)	3 (17.6)	10 (27.0)	5 (13.5)	7 (28.0)	3 (12.0)	1 (3.8)	1 (3.8)	2 (14.3)	0	3 (10.7)	0	30 (18.9)	12 (7.5)
ALT ↑	0	0	2 (5.4)	0	0	0	0	0	1 (7.1)	0	0	0	3 (1.9)	0
AST ↑	0	0	0	0	0	0	0	0	1 (7.1)	0	0	0	1 (0.6)	0
Blood ALP ↑	0	0	1 (2.7)	0	1 (4.0)	1 (4.0)	0	0	0	0	0	0	2 (1.3)	1 (0.6)
Blood bicarb ↓	0	2 (11.8)	4 (10.8)	1 (2.7)	3 (12.0)	0	0	0	0	0	0	0	7 (4.4)	3 (1.9)
Blood bilirubin ↑	0	0	0	0	0	0	0	0	1 (7.1)	0	2 (7.1)	0	3 (1.9)	0
Blood creatinine ↑	1 (5.9)	1 (5.9)	0	0	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Blood glucose ↓	1 (5.9)	0	0	1 (2.7)	1 (4.0)	1 (4.0)	0	1 (3.8)	0	0	0	0	2 (1.3)	3 (1.9)
Blood phosphorus ↓	1 (5.9)	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Blood potassium ↑	0	0	1 (2.7)	1 (2.7)	0	0	0	0	0	0	0	0	1 (0.6)	1 (0.6)
Blood sodium ↑	1 (5.9)	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0
Haemoglobin ↓	2 (11.8)	0	0	0	1 (4.0)	0	0	0	0	0	0	0	3 (1.9)	0
Lipase ↑	0	0	0	1 (2.7)	2 (8.0)	0	0	0	0	0	1 (3.6)	0	3 (1.9)	1 (0.6)
ANC ↓	6 (35.3)	1 (5.9)	5 (13.5)	1 (2.7)	2 (8.0)	1 (4.0)	1 (3.8)	1 (3.8)	0	0	0	0	14 (8.8)	4 (2.5)
Platelet count ↓	1 (5.9)	0	0	0	0	0	0	0	0	0	0	0	1 (0.6)	0

Data Source: Table 3.29, Table 3.33, Table 3.37

Note: There were no ≥Grade 3 laboratory AEs in the 25 to <35 kg enrollment weight band and thus, this group is not shown above.

ODYSSEY

Only ≥Grade 3 events were reported in the study, along with Grade 1 or 2 events leading to either withdrawal from study treatment or a dose modification. However, there were no Grade 1 or 2 events meeting these criteria. 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. The commonest AE reported was neutropenia, and this was reported in 5 participants, see details below. Most ≥Grade 3 laboratory events occurred during the first 24 weeks of study treatment.

Liver Chemistries/Hepatobiliary Findings

P1093

Through Week 24 in the AT Safety Population, there were 6 participants with Grade 3 hepatobiliary laboratory AEs. Through Week 48, there were 7 participants that experienced Grade 3 hepatobiliary laboratory AEs. No additional participants experienced hepatobiliary Grade 3 laboratory AE through the end of the data cut-off. There were no Grade 4 increases in liver enzymes observed through the end of the 12 December 2019 data cut-off.

Serious Laboratory Events (Increased ALT)

One 10-month old participant in the 6 to <10 kg enrolment weight band experienced 2 serious laboratory AEs and 1 non-serious laboratory AE of Grade 3 increased ALT at Week 2, Week 4, and Week 16. This participant had raised liver enzymes at Baseline (Day 0) but which on re-testing showed sufficient improvement to allow participation in the study. This participant had required treatment with multiple courses of antimicrobials because of 3 episodes of pneumonia over the 2-month period prior to enrolment in the study. None of these raised ALT levels were considered related to study treatment.

≥Grade 3 Severe Laboratory Events

There were 3 participants that experienced Grade 3 increases in ALT through the data cut-off; all events occurred during the initial 24 weeks of treatment. None of these were considered related to study treatment.

There were no Hy's Law cases (ALT>3xULN and bilirubin>2xULN).

There was 1 participant from the 10 to <14 kg enrolment weight band from the PD population that experienced Grade 3 blood ALP increase, which occurred at Week 32, not considered related to study treatment. This event was resolved to Grade 2 Blood ALP increase 1 week later and then to Grade 1 after an additional 3 weeks.

ODYSSEY

There were 3 participants with ALT ≥5xULN, and 2 of these participants had ALT ≥10xULN (but <20xULN). Two of these participants met the protocol-defined liver stopping criteria and withdrew from DTG treatment.

In addition, one participant (in the 20 to <25 kg weight band, 25 mg FCT DTG once daily) experienced ALT ≥5xULN (but <10xULN). This participant had non-serious AEs of ALT increased (Grade 3), AST increased (Grade 3) and hepatic enzyme increased (Grade 3) that were considered not related to study drug. These were isolated elevations, which occurred at Week 24 and resulted in no interruption in study treatment. There were no contemporaneous clinical AEs reported. The AEs were reported resolved 15 days later. Overall, the mean time from first dose to first ALT elevation ≥3xULN was 194 days (ranging from 161 to 253 days).

1 participant had a combination of ALT ≥3xULN and bilirubin ≥2xULN at any postbaseline visit. This participant also experienced an SAE of Hepatitis A infection and an SAE of bacteremia both considered not related to study treatment.

Bilirubin

P1093

Median blood bilirubin varied over time, with no clear increases or decreases observed across weight categories. In total, 15 participants reported increased blood bilirubin all of which were reported in participants ≥14 kg at and many in the heaviest participants (≥35 kg) at enrolment (8/15).

≥Grade 3 Severe Laboratory Events (Increased Bilirubin)

Most increased bilirubin findings (12/15) were Grade 1 or 2 events. There were 3 participants that experienced Grade 3 increases in total bilirubin through the data cut-off, in all 3 participants ATV was

reported as part their concomitant ARV. In 2 participants this occurred during the initial 24 weeks of treatment and in the third through 48 weeks. None of these Grade 3 increases were considered related to study treatment.

ODYSSEY

Median bilirubin values for the Safety Population appeared to increase at post-baseline timepoints. The change from baseline showed that there was little change in median bilirubin at Week 24 and 48 for the Safety Population.

There were no ≥Grade 3 increases in bilirubin through the data cut-off.

Renal Findings

P1093

Small increases in creatinine were noted across weight groups by Week 4 and remained between Week 4 and Week 48. There were very few Grade 1 increases in creatinine reported. Through Week 24, there were 3 participants who reported Grade 1 increases in creatinine (2 participants of 14 to <20 kg at enrolment and 1 participant of ≥35 kg at enrolment). No additional Grade 1 or 2 increases were seen after Week 24. There were 2 participants, both from the 3 to <6 kg enrolment weight band, with ≥Grade 3 Creatinine increase by Week 24. Neither of these were considered related to study treatment. One additional clinical renal AE was reported through 12 December 2019 (Grade 1 dysuria reported at Week 96).

Table 61: P1093 Summary of 'Blood Creatinine Increased' by Enrolment Weight Band through 30 April 2019 (AT Safety Population)

Weight Band	Through Week 24				Through Week 48				Through Data Cut-off			
	Grade				Grade				Grade			
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
3 to <6 kg (N=17)	0	0	1 (5.9)	1 (5.9)	0	0	1 (5.9)	1 (5.9)	0	0	1 (5.9)	1 (5.9)
6 to <10 kg (N=37)	0	0	0	0	0	0	0	0	0	0	0	0
10 to <14 kg (N=25)	0	0	0	0	0	0	0	0	0	0	0	0
14 to <20 kg (N=26)	2 (7.7)	0	0	0	2 (7.7)	0	0	0	2 (7.7)	0	0	0
20 to <25 kg (N=14)	0	0	0	0	0	0	0	0	0	0	0	0
25 to <35 kg (N=12)	0	0	0	0	0	0	0	0	0	0	0	0
≥35 kg (N=28)	1 (3.6)	0	0	0	1 (3.6)	0	0	0	1 (3.6)	0	0	0

Data Source: Table 3.509, Table 3.511, Table 3.513. Table 3.515, Table 3.517, Table 3.519
Note: The worst grade for each participant on each subcategory was reported.

ODYSSEY

Participants with raised Creatinine: 2 participants had abnormal creatinine levels (maximum Grade 1 or 2). The first individual appeared to recover. The second had a matching abnormal eGFR at the same time as the abnormal Creatinine. There were no clinical AEs reported and no evidence of renal toxicity.

GFR was estimated in participants using the creatinine based "Bedside Schwartz" equation (eGFR in mL/min/1.73m2 = (0.413 × Height in cm) / Creatinine in mg/dL).

At Week 48, there appeared to be a small decrease in median eGFR in the Safety Population.

Bicarbonate Findings

P1093

The most common laboratory event reported in the P1093 study through the most updated December data cut-off, of any severity, was decrease in bicarbonate.

Decreased blood bicarbonate was reported in 114 participants after the start of treatment by the Week 48 time point. Overall, there were a total of 118 participants with this lab abnormality at the most recent data cut at any time (including before the start of treatment). These 118 participants include 4 who had low bicarbonate reported pre-dose but not at any later time point, and therefore a total of 114 participants were reported in the lab abnormality summary tables. There were 10 participants who had a maximum Grade 3 (n=7) or Grade 4 decrease reported (n=3) at any point on study (pre and post Baseline).

Considering baseline or screening samples, >50% (73/118) participants had an abnormal bicarbonate level before study treatment started i.e. at screening, or baseline, or both. These abnormal levels were either Grade 1 or 2.

There were no clear patterns for individual participants with observed Grade 1 or 2 bicarbonate abnormalities: these were either isolated events, or a fluctuating sequence of low bicarbonate events, without apparent clinical impact. Individual participants with Grade 3 or 4 low bicarbonate appeared to have low bicarbonate results in every, or almost every sample taken, including baseline.

Demographic Factors

Reports of decreased blood bicarbonate at any time were received from all 9 countries with the highest number of reports from Zimbabwe (n=25), South Africa (n=21), US (n=22), Thailand (n=16) and Brazil (n=12). As noted in the Table below, decreased bicarbonate was observed at least once in 100% of participants from Zimbabwe, Kenya, Botswana and Uganda, and in 75% or more of participants from the remaining countries. In the US, however, only 44% of participants had decreased bicarbonate reported.

Table 62: Participants with Decreased Bicarbonate by Country

Country	Total Participants Enrolled N	Participants with Low Bicarbonate n (%)
Zimbabwe	25	25 (100)
South Africa	25	21 (84)
US	50	22 (44)
Thailand	20	16 (80)
Brazil	16	12 (75)
Kenya	8	8 (100)
Tanzania	9	8 (89)
Botswana	4	4 (100)
Uganda	2	2 (100)

Data Source: P1093 CSR Table 1.36, Bicarb Table 2 (see included attachment)
a. Participants with low bicarbonate reported at any time

Most reports involved Black or African American participants (n=83), followed by Asian (n=17) and White (n=9). Ethnicity was reported as other (n=6), unknown (n=2) or multiple (n=1) in the remaining participants. There were slightly more reports in females (n=63) compared to males (n=55).

Grade 3 or 4 Cases of Decreased Bicarbonate

Of the 10 individual cases of (maximum severity) Grade 3 or 4 low bicarbonate all were in participants <14 kg and from 3 sites in Zimbabwe, Tanzania, and Kenya. Three of ten participants with a Grade 3 or 4 low bicarbonate had ZDV use reported during study treatment.

Review of all 10 participants with Grade 3 or 4 low bicarbonate showed that in 8 participants, a low baseline or screening level was observed pre-study drug (either Grade 1 or Grade 2), and levels fluctuated over time in all participants without clear pattern. For 7/10 participants, bicarbonate was observed to be below the lower limit of normal at all, or nearly all time points, including before first dose of study drug. Time to the observation of the most severe grade of bicarbonate varied in these 8 participants but was observed by Week 24 in 7/8 of these participants.

There was no apparent temporal association with study drug, nor any obvious alternative aetiology. Generally, levels fluctuated before and after the Grade 3 or 4 event was reported. These Grade 3 / 4 low bicarbonate levels all improved upon re-testing.

Grade 2 or 1 Cases of Decreased Bicarbonate

Review of the 50 participants with maximum severity Grade 2 low bicarbonate cases shows that 41/50 (82%) had abnormal bicarbonate (Grade 1 or 2 severity) at baseline or screening. Of the remaining 9 participants, times to onset varied. Review of the lab results for these participants varied between Grades 0, 1 and 2, and showed no particular pattern, with some fluctuating, some just occasionally abnormal, and others reported almost continuously or continuously. There were no participants with Grade 2 low bicarbonate who were ≥25 kg at enrolment.

Fifty-eight participants had maximum Grade 1 low bicarbonate and of those 24/58 (41%) already had a Grade 1 bicarbonate abnormality at baseline / screening. In those with normal baselines, times to onset varied across the first 24 weeks in 26 participants but was reported only after 24 weeks in 8 participants. Grade 1 low bicarbonates were observed across weight bands/age cohorts and spread across weight bands: <20 kg (35/58 [60%]), and 23/58 (40%) ≥20 kg. There were no clear patterns with Grade 1 low bicarbonate reports, although the slight majority were in younger/lower weight participants.

Analysis of Zidovudine Use in Relation to Low Bicarbonates

The applicant has provided an analysis of zidovudine (ZDV) use and 44/159 (28%) participants had ZDV use at baseline and 74/159 (47%) participants had ZDV use at any time during the study in the AT population. The analysis shows that regardless of use either at baseline or at any time, ZDV use is not associated with observations of low bicarbonate in the P1093 study.

Table 63: Grade 3 or 4 Cases of Decreased Bicarbonate

Race	Site	Weight Band[a]	Week 0[b]	Worst Grade[c]	Worst Grade Sample Window	Next Sample Result	Last Sample	Pattern of Low Bicarbonate	ZDV Use	AEs or SAEs Reported?
Black or African American	31890	10 to <14 kg	Grade 2	Grade 3	Week 2	Grade 1	Grade 1	All low	No	No SAEs, Multiple G1 and G2 AEs reported from Week 12: Week 12 septic rash (G1) Week 16: cough (G2), Rales (G2), Bacterial Pneumonia (G2) Week 24: Body Tinea (G1) Week 32: Cough (G1)
Black or African American	31890	6 to <10 kg	Grade 2	Grade 3	Week 4	Grade 1	Normal	Continuously low up to week 40	Yes - 4 weeks at start only	No SAEs. No clinical AEs reported.
Black or African American	31890	3 to <6 kg	Grade 1	Grade 4	Week 40	Grade 3	Grade 2	All low	No	Week 24: SAE - diarrhoea (G3), SAE Gastroenteritis (G3), Malnutrition (G3), Poor infant feeding (G1) Week 48: Pneumonia (G2), Wheezing (G1)
Black or African American	31890	6 to <10 kg	Grade 2	Grade 4	Week 32	Grade 2	Grade 2	All low	Yes	No SAEs. No clinical AEs reported.
Black or African American	31890	3 to <6 kg	Grade 2	Grade 4	Week 24	Grade 1	Grade 1	All low except first week 0 sample	No	No Clinical AEs / SAEs reported
Black or African American	31890	10 to <14 kg	Grade 2	Grade 3	Week 2	Grade 1	Grade 1	All low	No	No SAEs. Week 40: diarrhoea (G1), gastroenteritis (G2)
Black or African American	5118	6 to <10 kg	Normal	Grade 3	Week 32	Grade 2	Grade 2	Majority of samples low (8/13)	No	No SAEs. Week 24: rash (G1), rash papular (G1). Week 32: otitis media (G1), otorrhea (G1) Week 40: cough (G1) Week 48: lymphadenopathy (G1)
Black or African American	5118	6 to <10 kg	Grade 2	Grade 3	Week 24	Normal	Grade 2	5/9 samples low	Yes	Week 2: SAE Bacterial Sepsis (G3), pyrexia (G3), diarrhoea (G1), Malnutrition (G2), urinary tract infection (G1), Vomiting (G1) Week 4: haemolytic anaemia (G1) Week 12: SAE hemiparesis (G3) Week 24: bacterial sepsis (G3), Pyrexia (G3), cough (G1), rash (G1)
Black or African American	5121	6 to <10 kg	Normal	Grade 3	Week 4	Normal	Grade 2	5/12 samples low	No	No Clinical AEs / SAEs.
Black or African American	5121	10 to <14 kg	Grade 2	Grade 3	Week 4	Grade 2	Grade 1	All low	No	No SAEs reported. Week 4: Breath sounds abnormal (G1) Week 12: Vomiting (G1) Week 32: Cough (G1)

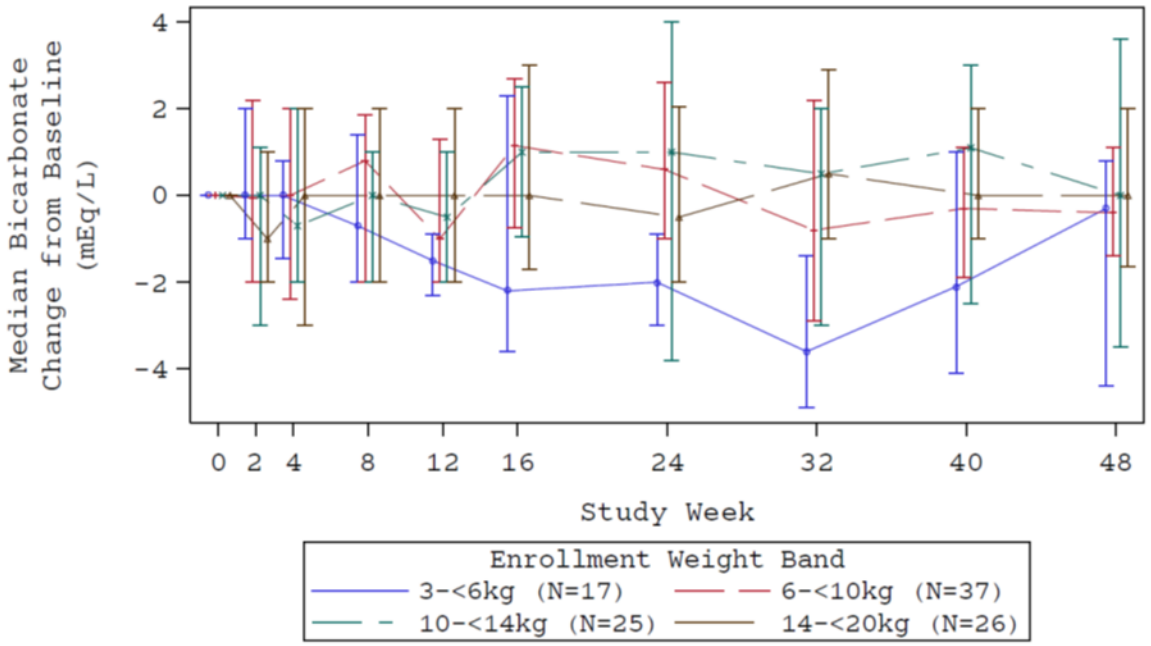
Data Source: Listing Table 3.43, Listing Table 3.49, Listing Table 3.48, Bicarb Table 2 (see included attachment)

a. Enrollment weight band.

b. Screening or baseline worst bicarbonate result.

c. Worst grade of decreased bicarbonate.

Table 64: Median Bicarbonate Change from Baseline Over Time by Enrollment Weight Band (Data through 30 April 2019)



MAH discussion of findings of decreased bicarbonate

The findings of Bicarbonate decrease were assessed by the protocol team and an external consultant (NIH nephrologist). It was concluded that the pattern of low bicarbonate in the smaller participants, the clustering at 2 sites, and the disparity between bicarbonate levels in the single paired blood gas and metabolic panel sample suggested that artefact was the most likely aetiology. This phenomenon has been explored by other groups who report that vacutainer tubes are not practical when taking blood samples from babies and small children. Thus, screw top blood tubes tend to be used instead of vacuum tubes. With screw top blood tubes there is a risk that blood samples get exposed to air for longer, potentially leading to the artificial decreases in bicarbonate.

Conclusion on findings of decreased bicarbonate

The clustering of Grade 3 or 4 low bicarbonate events in younger/lower weight participants at certain sites could indicate an issue with blood sampling in these smaller paediatric patients as suggested by the Applicant. The majority of these participants had low bicarbonates pre-study drug. Overall, the reports of low bicarbonates events pre-study drug were reported in 73/118 (62%) participants and do not indicate an association with DTG-treatment and no association with ZDV use was observed.

ODYSSEY

No reports of bicarbonate decrease (only ≥Grade 3 AEs, all SAEs, and all Grade 1/2 AEs leading to dose modification or DTG discontinuation were collected).

Lipase Findings

P1093

Most increases in lipases in the AT Safety Population were Grade 1 or Grade 2, and most occurred by Week 24. In general, there was a higher number of events in the lower weight bands (3 to <6 kg and 6 to <10 kg).

Most participants who reported increases in lipase through 30 April 2019, were enrolled into cohorts receiving DT (12/21) and oral granules (6/21) with fewer participants in FCT cohorts (3/21). There were 2 participants with ≥Grade 3 lipase increases through the Week 24 data cut-off, and 1 additional participant by Week 48. These cases were not considered related to study treatment. None of these 3 participants, nor any participant, had increased amylase at any point through the data cut-off. There was no clinical suspicion of pancreatitis in these participants. No participant discontinued study treatment due to lipase elevations.

In the December dataset one grade 2 lipase increased was reported as drug-related. Two reports of grade 3 lipase increase (on consecutive days, not related) was reported at Week 48 in a participant (participant had a previous report of a grade 4 ANC decrease at Week 8).

ODYSSEY

No reports of lipase increase (only ≥Grade 3 AEs, all SAEs, and all Grade 1/2 AEs leading to dose modification or DTG discontinuation were collected).

Haematology findings

P1093

Most occurrences of Haemoglobin decreased occurred in the first 24 weeks of treatment. There were 3 participants (2 from the 3 to <6 kg and 1 from the 10 to <14 kg enrolment weight bands) with Grade 3 Haemoglobin decreased through Week 24. All 3 were receiving cotrimoxazole from the start of treatment with DTG, and all 3 had low haemoglobin values (Grade 1 or 2) at Baseline. All 3 participants continued in the study. These Grade 3 events were not considered related to study treatment.

Table 65: Summary of 'Haemoglobin Decreased' by Enrolment Weight Band through 30 April 2019 (AT Safety Population)

Weight Band	Through Week 24				Through Week 48				Through Data Cut-off			
	Grade				Grade				Grade			
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
3 to <6 kg (N=17)	13 (76.5)	0	2 (11.8)	0	13 (76.5)	0	2 (11.8)	0	13 (76.5)	0	2 (11.8)	0
6 to <10 kg (N=37)	14 (37.8)	4 (10.8)	0	0	14 (37.8)	6 (16.2)	0	0	14 (37.8)	6 (16.2)	0	0
10 to <14 kg (N=25)	8 (32.0)	2 (8.0)	1 (4.0)	0	8 (32.0)	2 (8.0)	1 (4.0)	0	8 (32.0)	2 (8.0)	1 (4.0)	0
14 to <20 kg (N=26)	6 (23.1)	0	0	0	6 (23.1)	1 (3.8)	0	0	6 (23.1)	1 (3.8)	0	0
20 to <25 kg (N=14)	2 (14.3)	1 (7.1)	0	0	2 (14.3)	1 (7.1)	0	0	3 (21.4)	1 (7.1)	0	0
25 to <35 kg (N=12)	0	0	0	0	0	0	0	0	0	0	0	0
≥35 kg (N=28)	0	0	0	0	1 (3.6)	0	0	0	2 (7.1)	0	0	0

Data Source: Table 3.509, Table 3.511, Table 3.513, Table 3.515, Table 3.517, Table 3.519
Note: The worst grade for each participant on each subcategory was reported.

ODYSSEY

The majority of decreased in haemoglobin were maximum Grade 1 or 2 and mostly occurred in the first 24 weeks of treatment. Three (3%) participants had emergent Grade 3 decreases in haemoglobin through the data cut-off. Concurrent clinical events of anaemia (all Grade 3, nonserious, which resolved with continued DTG treatment), were reported in all 3 cases. All 3 participants had decreased haemoglobin at enrolment; 2 of the participants had Grade 1 decrease in haemoglobin at Baseline and 1 participant had Grade 2 haemoglobin decreased at Baseline. 3TC (in addition to ABC) was reported as concomitant ARV for all 3 participants. No participants had emergent Grade 4 haemoglobin decrease through the data cut-off.

Table 66: Summary of 'Haemoglobin low' by Enrolment Weight Band (Safety Population)

Weight Band	Through Week 24				Through Week 48			
	Grade				Grade			
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
3 to <6 kg (N=1)	0	0	0	0	0	0	0	0
6 to <10 kg (N=10)	0	1 (10)	1 (10)	0	0	1 (10)	1 (10)	0
10 to <14 kg (N=5)	1 (20)	0	1 (20)	0	1 (20)	0	1 (20)	0
14 to <20 kg (N=33)	3 (9)	3 (9)	0	0	4 (12)	3 (9)	0	0
20 to <25 kg (N=28)	3 (11)	1 (4)	0	0	4 (14)	1 (4)	0	0
25 to <30 kg (N=16)	3 (19)	0	0	0	3 (19)	0	1 (6)	0
30 to <40 kg (N=6)	1 (17)	1 (17)	0	0	1 (17)	1 (17)	0	0

Data Source: Table 3.50, Table 3.84
Note: Maximum emergent post-baseline toxicity derived for enrollment DTG dose/formulation until the end of the Week 24 window (Day 210) or Week 48 window (Day 378).

Neutrophil Count Decrease

P1093

In the April dataset through Week 24, there were 16 participants, all from the <20 kg enrolment weight bands, with ≥Grade 3 ANC decreases. Through Week 48, an additional 2 participants from the 10 to <14 kg enrolment weight band experienced Grade 3 ANC decreases. At the end of the data cut-off, an additional 3 participants experienced ≥Grade 3 ANC decreased. Four of the 5 participants with Grade 4 ANC decreased were from the <20 kg enrolment weight bands.

Table 67: Summary of 'ANC Decreased' by Enrolment Weight Band through 30 April 2019 (AT Safety Population)

Weight Band	Through Week 24				Through Week 48				Through Data Cut-off			
	Grade				Grade				Grade			
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
3 to <6 kg (N=17)	4 (23.5)	2 (11.8)	6 (35.3)	1 (5.9)	3 (17.6)	3 (17.6)	6 (35.3)	1 (5.9)	3 (17.6)	3 (17.6)	6 (35.3)	1 (5.9)
6 to <10 kg (N=37)	6 (16.2)	4 (10.8)	5 (13.5)	1 (2.7)	5 (13.5)	5 (13.5)	5 (13.5)	1 (2.7)	5 (13.5)	5 (13.5)	5 (13.5)	1 (2.7)
10 to <14 kg (N=25)	6 (24.0)	4 (16.0)	0	1 (4.0)	5 (20.0)	4 (16.0)	2 (8.0)	1 (4.0)	5 (20.0)	4 (16.0)	2 (8.0)	1 (4.0)
14 to <20 kg (N=26)	5 (19.2)	3 (11.5)	1 (3.8)	1 (3.8)	5 (19.2)	5 (19.2)	1 (3.8)	1 (3.8)	5 (19.2)	5 (19.2)	1 (3.8)	1 (3.8)
20 to <25 kg (N=14)	2 (14.3)	2 (14.3)	0	0	4 (28.6)	2 (14.3)	0	0	4 (28.6)	1 (7.1)	1 (7.1)	0
25 to <35 kg (N=12)	3 (25.0)	0	0	0	3 (25.0)	0	0	0	3 (25.0)	0	0	0
≥35 kg (N=28)	1 (3.6)	3 (10.7)	0	0	1 (3.6)	3 (10.7)	0	0	1 (3.6)	2 (7.1)	1 (3.6)	1 (3.6)

Data Source: Table 3.509, Table 3.511, Table 3.513, Table 3.515, Table 3.517, Table 3.519
Note: The worst grade for each participant on each subcategory was reported.

ODYSSEY

Five (5%) participants had emergent ≥Grade 3 decreases in neutrophil counts through the data cut-off, including 1 participant who had a maximum Grade 4 event. Most ≥Grade 3 decreases occurred in the first 12 weeks of treatment, excluding 1 participant who had Grade 3 neutrophil count decrease at Weeks 48, 72 and 84. Concurrent clinical events of neutropenia were reported in all 5 participants. All clinical events of neutropenia were non-serious, not drug related and resolved with continued DTG treatment. 3TC/ABC was reported as concomitant ARV in 4 participants and 3TC/ZDV in 1 participant.

All 5 participants reported concomitant use of sulfamethoxazole/trimethoprim at the time of PK sampling, for 2 participants this was reported at a similar time to the neutropenia.

Table 68: Summary of 'Neutrophils low' by Enrolment Weight Band (Safety Population)

Weight Band	Through Week 24				Through Week 48			
	Grade				Grade			
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
3 to <6 kg (N=1)	1 (100)	0	0	0	1 (100)	0	0	0
6 to <10 kg (N=10)	0	0	0	0	0	0	0	0
10 to <14 kg (N=5)	1 (20)	0	0	1 (20)	1 (20)	0	0	1 (20)
14 to <20 kg (N=33)	3 (9)	0	1 (3)	0	5 (15)	0	1 (3)	0
20 to <25 kg (N=28)	1 (4)	1 (4)	2 (7)	0	6 (21)	2 (7)	2 (7)	0
25 to <30 kg (N=16)	2 (13)	1 (6)	0	0	2 (13)	1 (6)	1 (6)	0
30 to <40 kg (N=6)	0	1 (17)	0	0	1 (17)	1 (17)	0	0

Data Source: Table 3.50, Table 3.84
Note: Maximum emergent post-baseline toxicity derived for enrollment DTG dose/formulation until the end of the Week 24 window (Day 210) or Week 48 window (Day 378).

Safety in special populations

Not applicable

Immunological events

Immune Reconstitution Inflammatory Syndrome Events:

In the P1093 AT Safety Population, there were 4 cases of IRIS (3 serious and 1 non-serious) reported through the cut-off of 12 December 2019.

One participant from the 3 to <6 kg enrolment weight band, (Cohort IV), suffered from IRIS (serious, Grade 3) which was considered related to the study treatment. This event occurred on Day 14 (Week 2 Visit). Another participant from the 3 to <6 kg enrolment weight band (Cohort IV-DT) reported IRIS (non-serious, Grade 2) on Day 34 (Week 4 Visit). This IRIS event was not considered related to the study treatment. Two participants from the 6 to <10 kg enrolment weight (Cohort III-DT, Cohort IV-DT) suffered from IRIS (both serious, Grade 2). Both events were considered related to the study treatment. These events occurred on Day 34 (Week 4 Visit) and Day 36 (Week 4 Visit), respectively.

In ODYSSEY there were no reports of IRIS.

Hypersensitivity and Rash:

In the P1093 AT Safety Population and ODYSSEY studies, there were no cases of hypersensitivity, no ≥Grade 3 rashes, and no serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, or Erythema multiforme reported.

P1093

Serious events from the Skin and subcutaneous tissue disorder SOC were reported in 2 participants (Angioedema and Urticaria); both were Grade 3 events (considered unrelated to study treatment).

≥Grade 3 Events:

Through 30 April 2019, most participants (72/75) reported Grade 1 or 2 Skin and subcutaneous tissue disorder events except 3 participants with Grade 3 events (Angioedema, Urticaria and Alopecia [all considered unrelated to study treatment].) One Grade 2 event of Rash in one participant was considered possibly related to study drug.

Between 30 April 2019 and 12 December 2019, there were no additional SAEs or ≥Grade 3 AEs or treatment related AEs from the Skin and subcutaneous tissue disorder SOC.

ODYSSEY

One participant experienced a Grade 2 rash (initially reported by the investigator as hypersensitivity reaction) 25 days after the first dose of DTG and ABC, and unknown time after the first dose of 3TC. The rash resolved following a short course of prednisolone. There was no interruption to study treatment.

Safety related to drug-drug interactions and other interactions

From a clinical perspective, this application raises no new safety issues regarding interactions.

Discontinuation due to adverse events

Adverse Events Leading to Withdrawal

P1093

No adverse events resulted in permanent discontinuation of DTG.

ODYSSEY

Two participants withdrew from DTG due to AEs in the ODYSSEY PK sub-studies. These participants met liver stopping criteria and were subsequently diagnosed with Hepatitis A. The cases of Hepatitis A were not considered related to DTG by the MAH.

Table 69: Participant Withdrawals from DTG Due to AEs

Weight Band at AE onset	PT	Serious/ severity	Days since 1st dose
20 to <25 kg	Hepatitis A[a]	Yes/ Grade 4	253
14 to <20 kg	Hepatitis A	No/ Grade 4	161

Data Source: Listing 6, Listing 12

a. Blood bilirubin increased and hepatic enzyme increased were reported as AEs leading to withdrawal by the site investigator. These events were subsequently subsumed under the term Hepatitis A by the ERC.

Post marketing experience

The GSK Global Clinical Safety database was searched for spontaneous or post-marketing cases reporting use of DTG single entity through 30 April 2019. A total of 7442 spontaneous and post-marketing cases were retrieved. Of these, 51 unique cases were identified in patients <18 years of age (excluding paediatrics cases where exposure to DTG was in utero or via breastmilk). Paediatric cases were identified through review of patient age (in years), ICH age groups, sub-population flags (children and adolescents) and free text narratives searches for relevant terms such as baby, juvenile, toddler and teenager. The majority of paediatrics cases identified (37/51) involved adolescents ≥12 years of age with few cases reported in younger children <12 years (14/51).

The post-marketing data from children below 12 years of age are very limited. The non-solicited post marketing reports are compatible with the known safety profile of DTG. The two fatal cases both appear related to underlying disease (pulmonary hypertension and chronic lung disease).

Children <12 years of age (N=14)

A total of 14 spontaneous cases were identified in children <12 years of age. Cases were received between 2014-2019 and were derived from Sweden (n=4), Germany (n=3), France (n=2), Israel (n=2), Argentina (n=1), Mexico (n=1) and the United States (n=1). Age (years) was reported in 7 cases and ranged between 2 and 10 years old.

Case outcome was not reported/unknown in all 14 cases.

Nine of the 14 cases reported off-label use, 7 of which involved children aged between 2 and 10 years old. Age (in years) was not specified in the remaining 2 cases, however both referred to use in children <12 years old. A further case described treatment of children with higher than recommended doses of DTG (PTs: Overdose, Product use issue). All cases were non-serious and no clinical AEs were reported, with the exception of 1 case which reported abnormal blood count. This poorly documented case involved a 9-year-old female who experienced abnormal leucocyte count (not further specified) on an unknown date which improved from 4300 cells/µl to 6400 cells/ µl after DTG was discontinued (positive de-challenge). Other concomitant medication included TDF and 3TC. This was considered off-label use as the child received 30 mg per day rather than 35 mg per day for children weighing between 30-40 kg per the German SmPC.

Of the remaining 4 cases, 3 were a cluster of poorly documented cases from Sweden involving children of unspecified age who experienced tiredness, headache and decreased appetite an unknown time after starting DTG. The remaining case was a serious report involving a child of unspecified age and reports increased HIV RNA following a stem cell transplant and cessation of ART.

Limited data available suggest that post-marketing use of 25 mg and 10 mg, which support pediatric dosing in children weighing <40 kg, is low. It is therefore not unexpected that there were few reports in younger children (<12 years).

Adolescents ≥12 years to <18 years of age (N=37)

A total of 37 cases were identified in adolescents ≥12 years and <18 years of age. Cases were received between 2014-2019 and were derived from Brazil (n=7), France (n=6), United Kingdom (n=5), United States (n=4), Colombia (n=2), Israel (n=2), Mexico (n=2) and 1 case each from Canada, Sweden, Romania, Ecuador, Switzerland, Estonia, Portugal, Netherlands and Kazakhstan.

There were 2 fatal cases, 1 of which reported pulmonary hypertensive crisis in a 14-year-old patient one month after RAL was switched to DTG. The patient had medical history of pulmonary hypertension and heart disease. Other ARVs included ABC, 3TC, and DRV/r. The case was poorly documented with no information on HIV status or viral load provided. The second case involved a 17-year-old female who was hospitalized due to pneumonia and later died due to multi-organ failure, cardiac failure and general physical health deterioration an unknown time after starting DTG and FTC + TDF. The patient previously suffered from chronic lung disease, from HIV and had not been compliant with ARV medication at the start of treatment with viral load reported in the hundreds of thousands (unit not specified). Viral load decreased as the subject received treatment to 400-440 (unit not specified) and was later undetectable. Decreasing lymphocytes was reported in the weeks leading up to death (to below 200; units not specified) with CD4+comprising around 10% of total lymphocytes.

Psychiatric disorders: 15 events reported in 9 patients, the majority of which were nonserious. There were 3 serious events in 2 subjects including suicidal ideation in a 16-year-old male subject 12 days after initiating DTG containing therapy. The subject was placed under observation and a positive dechallenge was reported when treatment with DTG ceased. The patient had a prior history of depression and trauma. The second case involved a 16-year-old female who experienced persecutory delusion and olfactory hallucination 77 days after starting DTG and ATV. Both ARVs were discontinued and a positive de-challenge was reported. The subject had a history of persecutory delusion.

Gastrointestinal disorders: 14 events reported in 9 patients, mainly consisting of nonserious listed events (vomiting, diarrhoea, abdominal pain, nausea) or non-specific terms (gastrointestinal disorder). There were 2 serious pancreatitis events one of which was poorly documented although normalization of lipase was reported following discontinuation of DTG-containing regimen. The second case reports acute pancreatitis and abdominal pain in an adolescent male 11 days after starting DTG, ABC and 3TC. ARV treatment was discontinued, and clinical pancreatitis resolved over 3 days, with improving laboratory biomarkers and symptom resolution. The reporter considered the acute pancreatitis to be related to DTG, ABC and 3TC. Pancreatitis is included in the product information for 3TC.

Renal disorders: no serious renal events were reported. There was 1 poorly documented case reporting non-serious events of glycosuria, proteinuria and renal disorder in a 16-year-old male.

Hepatobiliary disorders: 1 poorly documented case of serious hepatitis in an adolescent an unknown time after starting DTG and RAL. Hepatitis is a listed event for DTG.

Hypersensitivity and rash: 1 poorly documented serious case reported anaphylactic reaction in 17-year-old female 1 day after starting DTG and an unknown time after starting co-suspect FTC + TDF. DTG was withdrawn and the outcome was unknown. Two further poorly documented cases reported hypersensitivity, both of which were nonserious events. 1 case described an allergic reaction in a 17-year-old female due to an unspecified work accident. The second case described allergic reaction in an adolescent, which was considered related to co-suspect RAL. Hypersensitivity is a listed event for DTG.

Pregnancy: exposure during pregnancy was reported in 4 patients aged between 15-17 years of age, 3 of which resulted in live births without apparent congenital anomalies. The final case resulted in a spontaneous abortion at 22 weeks gestation with no apparent congenital anomaly. Concurrent didelphic uterus was reported as a factor in this case.

2.6.1. Discussion on clinical safety

The dolutegravir paediatric study programme is not powered to generate a comprehensive safety database in children and in the data currently presented, no control arm is available for comparison. Rather, given that exposure is comparable, safety will be extrapolated through a PK/PD-bridge which is in line with EMA guidance.

It is agreed that the established safety profile of dolutegravir does not raise any serious concerns regarding increased Cmax levels in children. However, it cannot be excluded that currently listed ADRs such as headache, insomnia and gastrointestinal discomfort have an exposure response related to Cmax.

PK data from P1093 and ODYSSEY trials were analysed against clinical AE and laboratory events and found no relationship between DTG Cmax or AUC0-24h and selected AEs. However, due to the limited number of participants the model does not lend itself to any firm conclusions. Further review of participants in the 20 to < 25 kg weight band, with the highest Cmax, didn't reveal any safety signal but given the limited data in each weight band this provides only limited reassurance.

The limited safety data from dosing 50 mg BID in adults are of limited relevance when assessing Cmax, and rather speaks to the benefits of BID dosing to meet the PK variable most important for efficacy (Cmin) without having to increase the total daily dose, and subsequently AUC and Cmax, beyond acceptable limits.

However, as the current safety concerns are non-serious, the above must be weighed against the clear benefits of once daily dosing, including long-term adherence. Also, there is regulatory precedence from the darunavir paediatric development programme. For darunavir the Cmin, Cmax, and AUC24h values for DRV in treatment-experienced HIV-1 infected paediatric subjects from 3 to <6 years of age were 1.33-, 1.81-, and 1.62-fold higher, respectively, than in adults receiving DRV/rtv 800/100 mg QD (sub-study of TMC114-C211).

Hence, in view of the CHMP, the QD posology is acceptable but an alternative BID dosing scheme is needed to guide subscribers who wish to split the daily dose to better match the adult PK profile . The Applicant has provided a separate table with an alternative BID dosing scheme in the SmPC Section 4.2 and the CHMP agrees with this approach with minor linguistic adjustments.

2.6.2. Conclusions on the clinical safety

In the limited paediatric safety dataset, there are no signs of a different safety profile of dolutegravir in paediatric HIV patients from 4 weeks of age compared to adults.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Hypersensitivity reactions Hepatobiliary disorders Depression (including suicidal ideation and behaviours, particularly in patients with a pre-existing history of depression or psychiatric illness)

Important potential risks	Serious rash (DAIDS Grade 3 or 4) Neural tube defects
Missing information	Use in the elderly Use in pregnancy/ breastfeeding Long term safety data

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Prospective Observational Cohort Study in Patients Receiving DTG (EuroSIDA Cohort) Ongoing	To investigate the risk of HSR, hepatotoxicity and serious rash (DAIDS category 3 or 4)	Hypersensitivity Hepatobiliary disorders Serious Rash (DAIDS Grade 3 or 4)	Final protocol submission[1]	Final protocol submitted June 2014
			Study Start	June 2014
			Study completion (data collection completion)	June 2019
			Final Report	April 2020 (extended time to allow for bio specimen collection from suspected HSR cases).
A Prospective, Interventional Pharmacokinetic and Safety Study of DTG/ABC/3TC in Pregnant Women Study[2] (study 200336) On hold	To investigate the use of DTG during pregnancy	Pregnant/breastfeeding women	Protocol effective date	23 December 2013
			Study start	16 January 2015
			Final Report	End of study CSR anticipated 2022[1]

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.	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 Feb 2018
			Study start	08 March 2019
			Final Report	June 2023
Study 208759 DOLOMITE NEAT ID Network Planned	To assess the safety and effectiveness of DTG in pregnancy in the NEAT-ID network of approximately 40 sites across Europe and Canada.	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
			Expected Study start	1 March 2019 or after EC approval
			Expected Final Report	October 2022
Study ING112578 (P1093)	To assess the safety, tolerability and antiviral activity of DTG, in combination regimens in HIV-1 infected infants, children and adolescents	Long term safety data	Interim report	48 Week CSR expected Q4 2021
			Final data	Expected 2025 (includes 3-year follow-up period).

Risk minimisation measures

Safety concern (risk/ missing information)	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reactions (Identified risk)	**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:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EuroSIDA cohort study
Hepatobiliary disorders (Identified risk)	**Routine risk minimisation measures:** Sections 4.4 and 4.8 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:** None **Additional pharmacovigilance activities:** EuroSIDA cohort study
Depression including suicidal ideation and behaviours (particularly in patients with a pre-existing history of depression or psychiatric illness) (Identified risk)	**Routine risk minimisation measures:** Section 4.8 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:** Target Follow-up questionnaire for suicidal events **Additional pharmacovigilance activities:** None
Serious Rash (DAIDS Grade 3 or 4) (Potential Risk)	**Routine risk communication:** Rash is included as an ADR in section 4.8 of the SmPC. A warning and precaution around rash as part of a hypersensitivity reaction is included in section 4.4 of the SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EuroSIDA cohort study

Safety concern (risk/ missing information)	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for discontinuation of DTG, and liver function monitoring, in patients developing hypersensitivity reactions are included in SmPC Section 4.4.**Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV	
Neural tube defects (potential risk)	**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:** Direct health care professional communication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Target Follow-up questionnaire Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy **Additional pharmacovigilance activities:** Review of the APR Study 208613 -DOLOMITE EPPICC Study 208759- DOLOMITE NEAT ID Network Study
Use in the elderly (missing information)	**Routine risk minimisation measures:** Sections 4.2 and 5.2 of the SmPC. Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern (risk/ missing information)	Risk minimisation measures	Pharmacovigilance activities
	Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** None
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:** None **Additional pharmacovigilance activities:** Review of the APR Study 200336 - A Prospective, Interventional Pharmacokinetic and Safety Study of DTG/ABC/3TC in Pregnant Women[1] Study 208613 -DOLOMITE EPPICC Study 208759- DOLOMITE NEAT ID Network Study
Long term safety data (missing information)	**Routine risk minimisation measures:** 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:** None **Additional pharmacovigilance activities:** Study ING112578 (P1093)

Conclusion

The CHMP and PRAC considered that the risk management plan version 16.2 is acceptable.

2.8. Pharmacovigilance

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.

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. Significance of paediatric studies

Not applicable.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The global burden of HIV and the specific paediatric challenges are well-known. In 2018, 160,000 (110,000–260,000) children aged 0-14 acquired HIV infection globally. In the Western and Central Europe and North America region, the estimated number of children living with HIV in 2013 was 2,800 (2,300–3,600), and it is estimated that over 95% of these children were receiving antiretroviral therapy [UNAIDS, 2014].

Globally, deaths among children younger than 15 years of age are reported to be declining. At the end of 2018, an estimated 100,000 (64,000–160,000) children aged 0-14 years had died from AIDS- related causes, representing 52% fewer deaths in this age group than in 2012 [UNAIDS, 2019]. In North America, Western and Central Europe, fewer than 200 children died from AIDS-related illnesses in 2012 [UNAIDS, 2013].

3.1.2. Available therapies and unmet medical need

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

Given the more limited pharmacological armamentarium in the treatment of paediatric patients below 6 years of age, there is an unmet medical need for additional antiretroviral agents from the integrase inhibitor class.

3.1.3. Main clinical studies

Study P1093 (ING112578) is an ongoing Phase I/II multi-center, open-label non-comparative, dose-finding study of at least 120 HIV-1 infected infants, children, and adolescents ages ≥4 weeks to <18 years to evaluate the PK parameters, safety, tolerability, and antiviral activity of DTG when administered both prior to starting and in combination with optimized background therapy (OBT). This study enrolled children in age-defined cohorts sequentially from oldest to youngest.

Study ODYSSEY (201296) is an ongoing, open-label, multi-center, randomized (1:1), non-inferiority, Phase II/III, 96-week, 2-arm clinical trial to compare the efficacy and safety of DTG plus 2 NRTI vs. SoC in ~700 HIV-infected children aged less than 18 years who are starting first-line ART or switching to second-line ART.

Both P1093 and ODYSSEY include patients between 4 weeks and 18 years of age. The original enrolment in P1093 was based on age but data has post hoc been regrouped based on weight. In the ODYSSEY study patients are grouped according to weight bands.

In this application only safety and PK data have been presented from the ODYSSEY study while the efficacy data are from the P1093 study only.

3.2. Favourable effects

The favourable effects of dolutegravir are well-known from the adult pivotal trials and extensive post marketing experience since approval. In this paediatric application, the efficacy is established through a PK/PD-bridge. The key PK target for efficacy is expected to be Cmin, while AUC and Cmax are more important for bridging to the adult safety database. Hence, if exposure is comparable to what is seen in adults (or higher), dolutegravir is expected to be effective in the treatment of HIV in children from 4 weeks of age.

3.3. Uncertainties and limitations about favourable effects

It is well-known that the treatment of HIV in younger children is more challenging than in adolescents and adults. The proportion of patients reaching HIV-RNA below 50 copies/mL is substantially lower than what was seen in the dolutegravir adult pivotal trials. This may partly be explained by the greater virological challenge in younger children due to higher baseline viral loads, but also due to apparent issues with treatment adherence. In the P1093 study, there were at least 5 patients with treatment-emergent key integrase inhibitor RAVs (G118R) which has not been seen in a similar extent in adults, outside of the failed monotherapy dolutegravir trials. This is in contrast to protease inhibitors such as lopinavir, where virologic

failure in children has not been associated with resistance development to the same extent. Development of integrase inhibitor resistance, and further NRTI resistance that is expected in these cases, can severely limit future treatment options.

3.4. Unfavourable effects

The safety profile of dolutegravir is well-established in adults and given that exposure is comparable, it is not expected to be substantially different in a paediatric setting. The limited paediatric safety dataset does not raise any age-specific issues other than an apparently treatment-emergent decrease in bicarbonate in the younger age groups, most likely related to technical blood sampling issues.

3.5. Uncertainties and limitations about unfavourable effects

The main safety issue in this application is that with the proposed QD dosing and the formulations used, Cmax need to be higher (up to two-fold) to achieve AUC and Cmin comparable to the PK profile seen in adults. Hence, it cannot be excluded that dolutegravir ADRs such as insomnia, headache, nausea and other GI ADRs are more common in children than adults and that such events could possibly be underreported in younger patients.

However, as the safety concerns related to dolutegravir are non-serious, the above must be weighed against the clear benefits of once daily dosing, including long-term adherence. Also, there is regulatory precedence from the darunavir paediatric development programme. For darunavir the Cmin, Cmax, and AUC24h values for DRV in treatment-experienced HIV-1 infected paediatric subjects from 3 to <6 years of age were 1.33-, 1.81-, and 1.62-fold higher, respectively, than in adults receiving DRV/rtv 800/100 mg QD (sub-study of TMC114-C211).

Hence, in view of the CHMP , the QD posology was acceptable and an alternative BID dosing was presented by the Applicant in order to guide subscribers who wish to split the daily dose to better match the adult PK profile, which was accepted by the CHMP. The Applicant has provided a separate table with an alternative BID dosing scheme in the SmPC Section 4.2 and the CHMP agrees with this approach.

3.6. Effects Table

Table 70: Favourable effects for Tivicay in paediatric patients

Paediatric Weight Band (kg) / Adults reference	DTG Dosage Form	Once Daily Dose (mg)	PK Parameter GM (90% CI)			Uncertainties / Strength of evidence
			Cmax (μg/mL)	AUC0-24h (μg*h/mL)	C24h (ng/mL)	
3 to <6	DT	5	4.02 (2.44, 6.78)	49.4 (25.4, 95.4)	1070 (357, 3010)	Model predicted
6 to <10 & <6 months	DT	10	5.90 (3.67, 9.57)	67.4 (35.9, 127)	1240 (392, 3630)	Model predicted

6 to <10 & ≥6 months	DT	15	6.67 (4.24, 10.6)	68.4 (36.4, 128)	964 (262, 3210)	Model predicted
10 to <14	DT	20	6.61 (4.30, 10.2)	63.1 (34.3, 115)	719 (184, 2560)	Model predicted
14 to <20	DT	25	7.17 (4.63, 11.2)	69.5 (37.8, 127)	824 (212, 2870)	Model predicted
14 to <20	FCT	40	6.96 (4.38, 11.0)	72.6 (39.6, 132)	972 (254, 3250)	Model predicted
20 to <25	DT	30	7.37 (4.77, 11.4)	72.0 (39.3, 133)	881 (227, 3020)	Model predicted
20 to <25	FCT	50	7.43 (4.73, 11.8)	78.6 (43.2, 145)	1080 (289, 3620)	Model predicted l
25 to <30	FCT	50	6.74 (4.26, 10.6)	71.4 (39.3, 131)	997 (272, 3320)	Model predicted
30 to <35	FCT	50	6.20 (3.94, 9.78)	66.6 (36.5, 121)	944 (256, 3100)	Model predicted
≥35	FCT	50	4.93 (3.07, 7.93)	54.0 (29.2, 99.1)	814 (233, 2590)	Model predicted
Adults	FCT	50*	3.7 (2.9-6.7) *	46 (37 – 134)**	995 (697 – 2260)**	Observed/model predicted

Notes:

* The GM target of 3.67 µg/mL represents a post hoc GM estimate in treatment naïve participants following 50 mg FCT QD DTG dosing. The lower limit (2.94 µg/mL) is selected as 80% of the GM Cmax (3.67 µg/mL). The upper limit (6.7 ug/mL) represents the 95th percentile of post hoc estimates in treatment experienced participants following 50 mg FCT BID dosing.

** The upper range target is the 95th percentile observed in adults in Study ING112961 in which DTG was dosed twice daily

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given the natural course of HIV, ultimately leading to AIDS and death within years for the vast majority of patients, there is no doubt that the overall benefits of ART vastly exceed the associated risks.

The addition of dolutegravir to the pharmacological armamentarium for children between 4 weeks and 6 years of age must be seen in relation to the currently limited paediatric ART armamentarium. Second-generation integrase strand transfer inhibitors are overall well-tolerated, without extensive interaction issues and with a relatively high barrier to resistance.

Hence, dolutegravir is anticipated to be an important drug for children aged 4 weeks and above.

3.7.2. Balance of benefits and risks

Given that the approval is based on a PK-bridge to the adult efficacy and safety data, the key issue for approval is whether exposure is comparable with the QD dosing proposed by the Applicant.

Regarding efficacy, the frequency of patients with HIV-RNA above the target level of 50 cop/mL is higher than in adults and risk of de novo INSTI resistance appear substantially higher. However, these issues appear to be mainly related to adherence. Regarding resistance, the Applicant has proposed additional wording in SmPC section 5.1 which is considered acceptable.

The Cmax levels are up to approximately two-fold of those seen in adults, but as the safety concerns related to dolutegravir are non-serious this must be weighed against the clear benefits of once daily dosing, including long-term adherence. Also, there is regulatory precedence from the darunavir paediatric development programme to accept somewhat higher Cmax levels in favour of once daily dosing. Hence, in view of the CHMP, the QD posology is acceptable but an alternative BID dosing scheme is needed to guide subscribers who wish to split the daily dose to better match the adult PK profile. In the SmPC Section 4.2 the Applicant has provided a separate table with an alternative BID dosing scheme and the CHMP agrees with this approach with minor linguistic adjustments.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

Given that the Applicant accepts the proposed SmPC, the overall B/R balance for Tivicay is positive also for children from 4 weeks to 6 years of age.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Tivicay 5 mg dispersible tablets is favourable in the following indication:

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg. The CHMP therefore recommends the extension(s) of the marketing authorisation for Tivicay 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 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0017/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.