15 December 2016
EMA/601663/20177
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tivicay

International non-proprietary name: dolutegravir

Procedure No. EMEA/H/C/002753/X/0018/G

Note

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

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List of abbreviations

%RSE	Percent relative standard error of the estimate
ω2	Variance of inter-individual random effect
σ2add	Additive component of the residual error model
σ2prop	proportional component of the residual error model
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALAG	Absorption lag time
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AT	All Treated
ATV	Atazanavir
AUC24	Area under the drug plasma concentration curve over time of the 24-hour dosing interval
BCS	Biopharmaceutics Classification System
BID	Twice daily
c/mL	Copies per milliliter
C24h	Drug plasma concentration at the end of the 24-hour dosing interval
cfu	Colony Forming Units
CI	Confidence interval
CL/F	Apparent clearance
COBI	Cobicistat
CQA	Critical Quality Attribute
CSR	Clinical Study Report
CV	Coefficient of variation of proportional error
CYP	Cytochrome P450
DoE	Design of experiments
DTG	Dolutegravir, TIVICAY
EC95	95% effective concentration (i.e., 95% of maximum virologic response)

EC	European Commission
EFV	Efavirenz
Emax	Maximum effect
EU	European Union
EVG	Elvitegravir
F	Relative bioavailability;
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FMEA	Failure mode effects analysis
FPV	Fosamprenavir
FTC	Emtricitabine
GDS	Global Data Sheet
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GM	Geometric mean
GSK	GlaxoSmithKline
HDPE	High Density Polyethylene
Hill	Slope of maturation; model;
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HPLC	High performance liquid chromatography
HSR	Hypersensitivity reaction
ICH	International Conference on Harmonisation
IIV	Inter-individual variability
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IMS	Intercontinental Medical Statistics
IN	Integrase
INI	Integrase inhibitor
IOV	Inter-occasion variability
IP	Investigational product
IPC	In-process control

IRIS	Immune reconstitution inflammatory syndrome
Ka	First-order rate of absorption
KF	Karl Fischer titration
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NMT	Not more than
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OBT	Optimized background therapy
OCT	Organic cation transporter
PD	Pharmacodynamic
PDVF	Protocol-defined virologic failure
Ph. Eur.	European Pharmacopoeia
PI	Protease inhibitor
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PP	Polypropylene
PT	Preferred term
q.s.	Quantum satis (amount which is needed)
QbD	Quality by design
QC	Quality control
QTPP	Quality Target Product Profile
RAL	Raltegravir
RH	Relative Humidity
RNA	Ribonucleic acid
rpm	rotations per minute
RSI	Reference Safety Information
RTV	Ritonavir

SAE	Serious adverse event
SD	Standard deviation
SDS	sodium dodecyl sulphate
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TM50	Maturation half-life
TPV	Tipranavir
UGT	Uridine diphosphate glucuronosyltransferase
USNF	United States Pharmacopoeia National Formulary
UPLC-MS/MS	Ultra performance liquid chromatography tandem mass spectrometry
US	United States (of America)
UV	Ultraviolet
V/F	Apparent volume of central compartment

1. Background information on the procedure

1.1. Submission of the dossier

ViiV Healthcare UK Limited submitted on 11 December 2015 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation:

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

The MAH applied for addition of two new strengths (10mg and 25mg film-coated tablets) to support the extension of the target population covered by the authorised therapeutic indication for Tivicay to treat paediatric patients from 6 years of age infected with HIV.

In addition, the MAH proposed to extend the indication for Tivicay to treat paediatric patients from 6 years of age infected with HIV with the approved 50mg film-coated tablets.

The MAH has updated section 4.2 of the SmPC with dose recommendations for the use of Tivicay in children 6 to less than 12 years of age.

Sections 4.5, 4.7, 4.8 and 5.1 and 5.2 of the SmPC have also been updated to include relevant information about the clinical trial ING112578 in support of the new therapeutic indication.

Section 5.3 of the SmPC was updated to reflect the non-clinical investigations performed for the paediatric development program.

The MAH applied for the following indication for Tivicay 10mg, 25mg film-coated tablets:

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children above 6 years of age.

The legal basis for this application refers to:

Article 7(2) of Commission Regulation (EC) No 1234/2008- Grouping of variations.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on MAH's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0061/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0061/2015 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 applicant 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 applicant 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: Kristina Dunder Co-Rapporteur: Philippe Lechat

- The application was received by the EMA on 11 December 2015.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2016 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2016 (Annex 2). The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 25 April 2016 (Annex 3).
- During the meeting on 13 May 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 16 May 2016 (Annex 4).
- During the meeting on 23-26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 May 2016 (Annex 5).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 July 2016.
- The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
- A GCP inspection at two investigator sites in South Africa and Thailand respectively, between 24 May and 7 July 2016. The outcome of the inspection carried out was issued on 24 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 August 2016 (Annex 6).
- During the PRAC meeting on 02 September 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. (Annex 7).
- During the meeting on 12-15 September 2016, the CHMP agreed on the consolidated List of outstanding issues to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 September 2016 (Annex 8).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 November 2016.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 November 2016 (Annex 9).
- During the PRAC meeting on 1 December 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. (Annex 10).
- During the meeting on 12-15 December 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for the group of variations, including the extension of the marketing authorisation and an extension of indication for Tivicay.

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.

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 12 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 10 mg, 25 mg or 50 mg of dolutegravir (as dolutegravir sodium) as active substance. The 10 mg and 25 mg strengths are being introduced to the already authorised 50 mg film-coated tablets with this line extension.

Other ingredients of the tablet core are: mannitol (E421), microcrystalline cellulose, povidone K29/32, sodium starch glycolate and sodium stearyl fumarate. Ingredients of the film-coating are: polyvinyl alcohol-partially hydrolysed, titanium dioxide (E171), macrogol, talc, and, for 25 mg tablets only, iron oxide yellow (E172).

The product is available in high density polyethylene (HDPE) bottles closed with polypropylene (PP) screw closures, with a polyethylene faced induction heat seal liner. Each bottle of Tivicay 10 mg film-coated tablets contains a desiccant, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance dolutegravir sodium, used to manufacture Tivicay 10 mg and 25 mg film-coated tablets, is the same as that used for the manufacture of the authorised Tivicay 50 mg film-coated tablets.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of this grouped type II variation and line extension is to extend the therapeutic indication for Tivicay to include children from 6 to 12 years of age, and to introduce two new film-coated tablet strengths: 10 mg and 25 mg, in order to facilitate dosing to children.

The finished product is presented as immediate release film-coated tablets for oral administration. The 10 mg strength is presented as white, round, biconvex tablets, approximately 6 mm in diameter, debossed with 'SV 572' on one side and '10' on the other side. The 25 mg strength is presented as pale yellow, round, biconvex tablets approximately 7 mm in diameter debossed with 'SV 572' on one side and '25' on the other side. The 10 mg and 25 mg film-coated tablets are distinguishable by their colour, size and debossing both between themselves and from the previously authorised 50 mg film-coated tablets.

The size and shape of the 10 and 25 mg film-coated tablets, as well the composition in excipients, is considered appropriate for the target age groups (6 to 12 years of age). The acceptability of the finished product is validated by its use in the paediatric clinical trials.

The composition of the 10 and 25 mg core tablets includes dolutegravir (as dolutegravir sodium), mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate and sodium stearyl fumarate. The film-coating includes polyvinyl alcohol-partially hydrolysed, titanium dioxide, macrogol, talc, and, iron oxide yellow (25 mg tablets only).

The pharmaceutical development approach that was used for the design and development of Tivicay film-coated tablets contains quality by design (QbD) elements. A combination of risk based assessments using structured methodologies such as failure mode and effects analysis (FMEA), laboratory studies, and prior knowledge and product specific understanding based on development history was used to gain a comprehensive understanding of the formulation and process conditions and their impact on the quality attributes of the finished product. No design space was proposed.

The formulations of Tivicay 10 mg, 25 mg and 50 mg film-coated tablets share the same principal composition. The excipients used in the 10 mg and 25 mg film-coated tablets are the same as in the authorised 50 mg film-coated tablets. Therefore, no additional drug / excipient compatibility studies were performed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards or the EC Regulation 231/2012. 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 primary packaging consists of HDPE bottles closed with PP screw closures, with a polyethylene faced induction heat seal liner. The bottles for 10 mg contain a desiccant. The primary packaging material complies with Ph. Eur. and EC requirements. Confirmation of the child-resistant closure compliance with EN ISO 8317 has been provided. 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 is considered to be a standard manufacturing process and includes granulation, blending, compression, and film coating. 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 this type of manufacturing process and pharmaceutical form.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: description (visual), identification of dolutegravir (UV and HPLC), dolutegravir content (HPLC), impurities (HPLC), uniformity of content (HPLC), dissolution (UV), microbial enumeration test (Ph. Eur.) and water content (KF).

A test for impurities is not included in the finished product release specification, which was justified in accordance with ICH Q6A.

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

Batch analysis results are provided for three production scale batches of 10 mg and 25 mg film-coated tablets confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications.

Stability of the product

Stability data on three commercial scale batches of each strength of the finished product stored under long term conditions at 25 ºC / 60% RH for up to 36 months and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Based on available stability data, the proposed shelf-life of 3 years with no special storage conditions, as stated in the SmPC (section 6.3) is acceptable. The 10 mg tablet strength should be stored in the original package in order to protect form moisture and the desiccant should not be removed.

Comparability exercise for finished medicinal drug product

Not applicable.

Adventitious agents

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

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space was claimed for the manufacturing process. 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.

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. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

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 IC_{50} of DTG against the purified enzyme HIV-1 integrase ranged from 2.7 nM to 12.6 nM.

Secondary pharmacodynamics

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

In summary, the pharmacology of DTG was thoroughly evaluated during the marketing authorisation application for Tivicay. No new non-clinical pharmacology studies were submitted in support of the present application. The CHMP considered this as 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.

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.

Bioavailability of DTG in rat and monkey ranged from 25 to 34% and increased to levels of 76 to 87% after fasting. Distribution studies in rats indicated highest levels of radiolabel at 6 hours post dose. 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.

In conclusion, the non-clinical pharmacokinetic aspects of DTG were thoroughly evaluated during the original approval procedure for Tivicay. No new non-clinical pharmacokinetic studies were submitted in support of the present application.

2.3.4. Toxicology

The toxicological profile of DTG was investigated during the marketing authorisation application of Tivicay. No new preclinical toxicology studies have been conducted in support of the present application. This is acceptable. In view of the new paediatric indication, the results of the previously conducted reproductive and developmental toxicity studies, in particular the juvenile toxicity studies are of special interest.

Repeat-dose toxicity

The toxicity of DTG was investigated in repeat-dose studies in rat up to 26 weeks, in monkey up to 38 weeks, and in mouse up to 13 weeks. 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 2 week 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 treated with doses of DTG up to 1000 mg/kg. Male and female fertility did not appear to be affected at doses up to 1000 mg/kg providing exposure multiples of approximately x27 the expected clinical value at a dose of 50 mg BID.

Embryo-fœtal development

Table 1. Summary of EFD studies with DTG

Study Type / Study ID / GLP	Species; No / sex / group	Route & dose, Study design	Major findings
Embryofoetal development (XD2009/00367) GLP	Rat (Sprague-Dawley, 20 F)	0, 100, 300, 1000 mg/kg PO GD6-GD17	Preimplantation loss (%) slightly increased at 1000 mg/kg. Litter parameters not affected. NOAEL F0 females, F1 litters: 1000 mg/kg
Embryofoetal development (XD2009/00366) GLP	Rabbit (Japanese white, 20 F)	0, 40, 200, 1000 mg/kg, PO GD6-GD18	≥200 mg/kg: Bw gain, food intake decreased. Scant faeces/urine incidence increased. NOAEL F0 females: 200 mg/kg (general toxicity) 100 mg/kg (reproductive toxicity) F1 litters: 1000 mg/kg.

Dose formulated in 0.5% HPMC, 0,1% Tween 80

Prenatal and postnatal development, including maternal function

In a pre-and post-natal development study, DOL was administered to rat dams (Crl:CD(SD)) orally at doses of 5, 50 or 1000 mg/kg/day from Day 6 of gestation (GD) to postnatal day (PND) 20 of lactation.

Table 2. Overview of pre- and postnatal development study in rats

Study type/ Study ID / GLP	Species/ Sex/ No./Group	Dose (mg/kg)	Duration	Major findings
Pre and postnatal development including maternal function (2011N121663) GLP	Rat Sprague-Dawley 22 dams	0, 5, 50, 1000	GD6 to PND20	**NOAEL F0:** 50 mg/kg (BW gain ↓ in dams) **NOAEL F0:** 1000 mg/kg (Repro. function) **NOAEL F1:** 50 mg/kg **LOAEL F1:** 1000 mg/kg (BW, food intake ↓ in females.)

The F_1 generation was evaluated with respect to clinical signs, viability day on PND of lactation, weaning index, body weights, physical development (pinna unfolding, growth of hair, eruption the upper incisors and eyelid opening) early behaviour (back rightning, negative geotaxis) sensory functions (visual placing response, papillary reflex, Preyer's reflex and pain response), open field test, conditioned avoidance response (shuttle box test), genital development (preputial separation and vaginal opening), vaginal smears, mating ability, fertility, gross pathology and implantation and viability of embryos (F_2) on GD13. Overall, no test-substance related adverse effects where discovered in the F_0 dams. In the F_1 generation, one new-born had external malformations (meningocele and eye bulge aplasia) in the 1000 mg/kg/day dose group. Due to overall low incidence of developmental anomalies, this defect was considered not to be treatment-related by the Applicant. Statistically significant decreases were noted in the body weights of female offspring (F_1) in the 1000 mg/kg group at PND11, 14, 18, 21, 28, 35 and 42 as compared to the control group.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

In the first dose range finding (DRF) and tolerability study (CD2009/00409; Table 3), survival, clinical signs, body weight, body lengths and toxicokinetics were monitored. The dose range of DOL was between 5 and 1000 mg/kg/day and administration was by gavage between PND4 and PND21 with endpoint observations on PND21-22.

Table 3. Overview of Juvenile toxicity studies in rats

Study ID	Species/ Sex/ No./ Group	Dose (mg/kg)	Duration	Major Findings
CD2009/ 00409	Rat Sprague-Dawley 10-20 M, 10-20 F	5, 50, 100, 500, 1000	PND4 to PND21	**$LOAEL_1$ F1**: 1000 mg/kg /day (*deaths, alopecia, loss of skin elasticity, discoloration of organs*) **$LOAEL_2$ F1**: 500 mg/kg /day (*growth retardation*) **NOAEL F1:** 100 mg/kg/day
CD2009/ 00770	Rat Sprague-Dawley 20 M, 20 F	2, 25, 75, 300	PND4 to PND31	**$LOAEL_1$ F1**: 300 mg/kg /day (*deaths* PND9 to PND22, *alopecia, loss of skin elasticity, cytoplasmic rarefaction hepatocytes liver*) **$LOAEL_2$ F1**: 75 mg/kg /day (*body weight gain*↓, *trend of peripheral blood T cell count*↓, *decrease of spleen lymphocytes* ↓, *eosinophilic infiltrate in mucosa of glandular stomach*↑, *extramedullary haematopoiesis*) **NOAEL F1**: 25 mg/kg/day

Study ID	Species/ Sex/ No./ Group	Dose (mg/kg)	Duration	Major Findings
CD2010/ 00023 (GLP)	Rat Sprague-Dawley 10-20 M, 10-20 F	0, 0.5, 2, 75	PND4 to max PND66	**$LOAEL_1$ F1**: 75 mg/kg (*two deaths on PND12-17, body weight gain↓ from PND15 that was transient in males and consistent in females*) **NOAEL F1**: 2 mg/kg

Formulated in 0.5% HPMC with 0.1 w/w% Tween 80.

Systemic exposure levels were similar at 100 and 500 mg/kg/day. At doses > 500 mg/kg/day, deaths occurred starting on PND14. Macroscopic observations were yellow discoloration of the intestines, liver and skin and small adrenals. Growth retardation was noted at 500 mg/kg with decreases in body weight and body length. There were no marked differences between male and female offspring for C_{max} and AUC at PND21 (Table 4). C_{max} peaked at the 100 mg/kg/day dose. A 10-fold increase in dose from 5 mg/kg/day corresponded approximately to a 2- to 3-fold increase in systemic exposure. A 20-fold increase in dose from 5 mg/kg/day gave a 3- to 4-fold increase in systemic exposure.

Table 4. Toxicokinetic data from PND21 in the first DRF juvenile toxicity study (CD2009/00409)

Dose (mg/kg/day)	Cmax (µg/ml) PND21	AUC_{0-24} (µg x h/ml) PND21
5	M- 30.1 F-31.8	M-398 F-366
50	M- 79.2 F-76.3	M-1079 F-934
100	M- 107 F-101	M-1411 F-1420
500	M- 82.2 F-89.1	M-1628 F-1520
1000	M- NR* F-NR*	M-NC** F-NC**

*NR: Not reported since only 1 and 3h samples were available, **NC: not calculated due to insufficient data.

In the second DRF study (CD2009/00770, Table 5) parameters monitored included survival, clinical signs, body weight, in life photographs, gross and histopathology (stomach, liver, spleen, thymus, lymph), clinical chemistry, haematology, toxicokinetics and B and T cells via flow cytometry. The dose range was between 2 and 300 mg/kg/day and applied by gavage between PND4 and PND31 with endpoint observations on PND13, PND21 and PND32.

Deaths occurred at 300 mg/kg. Increased rarefaction of hepatocytes at this dose level was probably related to increased glycogen and lack of fasting prior to euthanasia in this group. There was a non-dose related decrease in peripheral T cells at doses ≥25 mg/kg. The number of B cells was not affected.

Table 5. Toxicokinetic data at PND13 in the second DRF juvenile toxicity study (CD2009/00770)

Dose (mg/kg/day)	Cmax PND13 (µg/ml)	AUC_{0-24} PND13(µg x h/ml)
2	M-11.5 F-14.5	M-257 F-286
25	M-58.3 F-57.3	M-1166 F-1160
75	M-72.6 F-75.4	M-1314 F-1517
300	M-73.1 F-59.4	M-1484 F-1169

No clear differences between males and females could be seen for toxicokinetic parameters on PND13. A 12.5-fold increase in dose from 2 mg/kg/day corresponded approximately to a 4- to 5-fold increase in systemic exposure. A 37.5-fold increase in dose from 2 mg/kg/day led also to an approximately 4- to 5-fold increase in systemic exposure.

In the third, pivotal, juvenile toxicity study (CD2010/00023, Table 6), the endpoints were body weight, food intake, physical development (vaginal opening, balano-preputial skin fold separation), haematology, coagulation, urinalysis, gross and histopathology, stage-dependent evaluation of spermatogenesis, organ weights, femur length and T cell dependent antibody response and immune-phenotyping of lymphocyte subsets and CD4 or CD8 T cell receptor V beta usage. The doses used were 0.5, 2 and 75 mg/kg/day and they were applied by gavage between PND4 and PND66 with toxicokinetic endpoint observations on PND13 and PND32, clinical observations on PND21, PND28 and PND66 and 67, and terminal body weight and necropsy on PND67. The offspring was gradually weaned from maternal removal on PND21 (2 to 3 animals per sex and box) to individual housing on PND28 (1 animal per sex and box).

Two pre-weaning male pup deaths occurred on PND12 and PND17 in the 75 mg/kg/day dose group and were considered test-substance linked. Nasal degeneration was observed at all dose levels, being ascribed to a local irritant effect. 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). No effects on immunological competence or on lymphocyte subsets counts were reported. NOAEL was set at 2 mg/kg, corresponding to a C_{max} of 15.8 µg/ml (Male 15.2 + female 16.4 / 2) and an AUC_{0-24} of 309.5 µg x h/ml (male 303 + female 316 / 2) at PND 13 (Table 6). Corresponding levels on day 32 were C_{max} 7.585 µg/ml (male 7.71 + female 7.46 / 2) and AUC_{0-24} 89.5 µg x h/ml (male 85.7 + female 93.3 / 2). No apparent gender differences could be seen at the NOAEL and the LOAEL.

Table 6. Toxicokinetic data from PND13 and PND32 in the third pivotal juvenile toxicity study (CD2010/00023)

Dose (mg/kg/day)	Cmax (µg/ml) PND13	Cmax (µg/ml) PND32	AUC_{0-24} (µg x h/ml) PND13	AUC_{0-24} (µg x h/ml) PND32
0.5	M-4.55 F-4.69	M-1.5 F-2.41	M-92 F-86.5	M-9.9 F-27.1
2	M-15.2 F-16.4	M-7.71 F-7.46	M-303 F-316	M-85.7 F-93.3
75	M-88 F-85.4	M-69.9 F-77.4	M-1540 F-1549	M-917 F-1044

The estimated therapeutic target exposure in human children for AUC_{0-24} is 46 µg x h/ml, with an acceptable systemic exposure range between a lower limit of 37 µg x h/ml and a upper limit of 67 µg x h/ml (The maximal lower limit is estimated to 25 µg x h/ml and the upper maximal limit is 92 µg x h/ml). Based on the pre-weaning values from PND13 (, this gives an AUC-based dosing marginal of:

- NOAEL (2 mg/kg/day) : 8.4x (lower limit) and 4.6x (upper limit)
- LOAEL (75 mg/kg/day) : 41.7x (lower limit) and 23.1x (upper limit)

Based on the post-weaning values from PND32, this gives an AUC-based dosing marginal of:

- NOAEL (2 mg/kg/day) : 2.4x (lower limit) and 1.3x (upper limit)
- LOAEL (75 mg/kg/day) : 26.5x (lower limit) and 14.6x (upper limit)

The Applicant presented two main arguments why the observed pre-weaning deaths in male pups, as well as the body weight reduction in both sexes during the pre-weaning period, should not constitute a safety concern for 6-year old children. It could be concluded that that the pre-weaning deaths and negative effect on body weight gain at 75 mg/kg/day in the pivotal juvenile rat study are not of concern for children 6 years of age. The results and conclusions are reflected in the SmPC. If there would be a future indication in children < 6 years, these data will required a careful re-evaluation, especially in light of the low margins to NOAEL (4.6-8.4-fold for PND13 and

1.3-2.4-fold for PND32). The Applicant may, in that case, consider conducting a new study using 1-2 intermediate dose groups between 2 and 75 mg/kg, to further establish the NOAEL.

2.3.5. Ecotoxicity / environmental risk assessment

No new environmental information has been introduced in the present Tivicay submission and the ERA is therefore conducted on the previously submitted data. Based on the information, DTG is not classified as a PBT or vPvB compounds and is most likely to accumulate in STP sludge and sediment. Overall, DTG is found to be able to generate toxicity in both aquatic ecosystems (algae toxicity) and terrestrial ecosystems (phytotoxicity in pea). While not remarked upon in the original submission ERA, 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. As this effect is stimulatory rather than inhibitory (specified in the OECD TG216) this finding will not influence the present ERA.

In the original application for DTG's use in adults and juveniles, the overall conclusion was that DTG is not expected to pose a risk to the environment. While acknowledging the general increase (a near doubling of HIV diagnoses during the last decade in different regions of Europe, see ECDC-WHO report for HIV/AIDS surveillance in Europe 2014) it is deemed unlikely to that the new target population (6-12 years of age) strongly influences the size of the overall patient population and consequently the eco-toxicological calculations (and dependent conclusions) from the original application.

In summary, as with the original submission, DTG is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

No new non-clinical pharmacology, pharmacokinetics, toxicological or eco-toxicological studies were submitted in support of the present application. This is acceptable. The Applicant has provided a thorough discussion concerning the adverse findings in the juvenile rat toxicity studies. As stated above, it is agreed that the pre-weaning deaths and negative effect on body weight gain at 75 mg/kg/day in the pivotal juvenile rat study are not of concern for children 6 years of age.

With regard to the ERA, DTG is not expected to pose a risk to the environment. That being said, it can be noted that the Applicant calculates the surface water PEC based on sales prediction market penetration forecast (sp-Fpen) based on the whole EU population. As there are regional differences in HIV infection prevalence in the European Union (e.g. between eastern and western Europe), these Fpen-dependent values are misleading. These regional differences were also made clear in the scientific advice for the original submission (the 2nd follow-up) given in 2011 which demonstrated a WHO/ECDC-specified member-state range in HIV/AIDS prevalence between 0.1% (e.g. Germany) and 1.2% (Estonia) with most member states reporting an incidence <1%.

The Applicant committed to recalculate and correct the Fpen (for the member state with the highest HIV prevalence) and all associated parameters at the first opportune moment and/or future renewal of the ERA. In a similar manner, regarding the Phase IIB assessment of sediment-dweller toxicity, the Applicant committed to recalculate the $NOEC_{SED}$ into a standardized $NOEC_{SED}$ with an organic carbon content of 10% (and all downstream dependent parameters) at the first opportune moment and/or renewal of the ERA.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considered that here is no objection to approval of Tivicay from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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.

Table 7. Tabular overview of clinical studies

Study Identifier	Study Objective	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]
ING112578 (P1093)	To select a DTG dose for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG adult dose and to evaluate safety, tolerability, and steady-state PK of DTG in combination with other ARTs	Phase I/II, multicenter, open label, non comparative intensive PK and safety study	HIV- infected infants, children and adolescent subjects	DTG once-a-day doses with target dose of ~1 mg/kg and with 4 weight bands, and maximum dose of 50 mg[b]; 48 weeks	Cohort I (Stage I & IIa): 23 Enrolled 11 Ongoing Cohort IIa (Stage I & Stage II) 23 enrolled 19 ongoing

a. For ongoing study, the number of ongoing subjects reported as of data cut-off date (14Feb2015)

b. For subjects receiving concomitant rifampin, EFV, FPV/r, or TPV/r it was recommended that the dose of DTG be increased to twice daily administration

The extension of indication of Tivicay is supported by PK and clinical efficacy/safety data derived from study ING112578 (P1093). This is an ongoing Phase I/II multi-centre, open-label non-comparative study with a targeted enrolment of approximately 160 HIV-1 infected infants, children, and adolescents ages ≥4 weeks to <18 years in age-defined cohorts sequentially from oldest to youngest:

- Cohort I: Adolescents ≥12 to <18 years of age (tablet formulation)
- **Cohort IIA: Children ≥6 to <12 years of age (tablet formulation)**
- Cohort IIB: Children ≥6 to <12 years of age (granules for oral suspension)
- Cohort III: Children ≥2 to <6 years of age (granules for oral suspension)
- Cohort IV: Children ≥6 months to <2 years (granules for oral suspension)
- Cohort V: Infants ≥4 weeks to <6 months (granules for oral suspension)

The submitted data include:

- PK, efficacy and safety results from Cohort I (≥12 to <18 years – Week 48 results) and Cohort IIA (≥6 to <12 years – Week 24 efficacy results),

- A population PK (POPPK) analysis from Cohort I and Cohort IIA, and preliminary data from Cohort IIB.

Subjects of Cohorts I and IIA of study P1093 received oral tablets of dolutegravir (10 mg, 25 mg or 50 mg). Clinical data from Cohorts IIB, III, IV and V (with the oral suspension of dolutegravir) are not available at this stage and therefore not included in this application.

During the evaluation, the MAH confirmed that the development of oral suspension has been stopped and is replaced by the development of dispersible tablets.

2.4.2. Pharmacokinetics

The recommended adult dose of DTG is 50 mg once daily in patients infected with HIV-1 without resistance to the integrase class. In patients infected with HIV-1 with resistance to the integrase class the recommended dose of DTG is 50 mg twice daily. DTG is currently approved in adolescences (12 years or older and weighing at least 40 kg), infected with HIV-1 without resistance to the integrase class. The recommended dose of DTG in adolescences is 50 mg once daily.

Data from the two first cohorts (I, ≥12 to <18 years, and IIa, ≥6 to <12 years) from an on-going paediatric study (P1093 also named ING112578), provided new data (cohort IIA) on DTG in a total of 23 children between the ages of 6 to 12 years. Efficacy, safety, and pharmacokinetic data, as well as modelling and simulation data are being used to support the proposed paediatric dosing strategy to expand the paediatric indication for DTG to include patients 6 to 12 years of age.

Analytical methods

Human plasma samples were analyzed for DTG concentration using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for DTG was 5 ng/mL with a higher limit of quantification (HLQ) of 10000 ng/mL. Linear regression analysis calculations were performed using MultiQuant 2.0.2.

A summary of the bioanalytical method used for the study ING112578 is given in Table 8.

Table 8. Bioanalytical Methods Summary

Validation Report	Clinical Study No	Summary of Method and Validation Parameters
Dolutegravir (GSK1349572) Human Plasma (EDTA) Title: Assay Method for the Analysis of Dolutegravir (DTG) in Human Plasma by High Performance Liquid Chromatography coupled with Tandem Mass Spectrometry.	IMPAACT P1093 (GSK Study ING112578)	Dolutegravir was extracted from 20 precipitation using acetonitrile containing [2H715N]- dolutegravir as an internal standard. Extracts were analyzed by HPLC-MS/MS using positive ion electrospray. Lower Limit of Quantification: 5 ng/mL Validated Range: 5 -10000 ng/mL QC Levels: 5a, 15, 450, 900 and 10000a ng/mL Within-run Precision (%CV): ≤2.1% Between-run Precision (%CV): ≤9.1% Inter Day Accuracy (% Bias): -6.5 – 5.4% Intra Day Accuracy (% Bias): -9.8 – 10.3% Stability in Human Plasma: 36 month at -80°C Recovery: 96.5 – 99.3% Freeze-Thaw Stability: 3 cycles from -80°to ambient temperature Processed Extract Stability: 3 days at 15°C

Pharmacokinetic data analysis

The pharmacokinetic parameters were determined using both non-compartmental analysis (NCA) and population PK analysis. WinNonlin version 5.3 or Phoenix 6.4 (Pharsight Corporation, Mountain View, CA) was used for all NCA pharmacokinetic analyses. NONMEM® program version VII level 3.0 was used for the population PK analysis (ICON, Ellicott City, Maryland, USA). PK parameters were estimated using the first-order conditional estimation method with interaction (FOCEI).

ADME properties

ADME studies have only been performed in adults. The absolute bioavailability of dolutegravir has not been established. Food has an influence on the bioavailability of dolutegravir and depends on meal content: low, moderate, and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Dolutegravir is highly bound (>99%) to human plasma proteins. In adults the terminal half-life was ~14 hours and the apparent oral clearance (CL/F) was approximately 1 L/hr in HIV-infected patients based on a population pharmacokinetic analysis. The intra- and inter-individual variability in exposure to DTG in adult patients was low to moderate (20-39% (%CV) for CL/F).

Renal elimination of unchanged active substance is low (<1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronide conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine.

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma. Metabolites found in the urine are 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).

Bioequivalence

No new bioequivalence or relative bioavailability data was provided for the new 10 and 25 mg tablet strengths.

Dose proportionality and time dependency

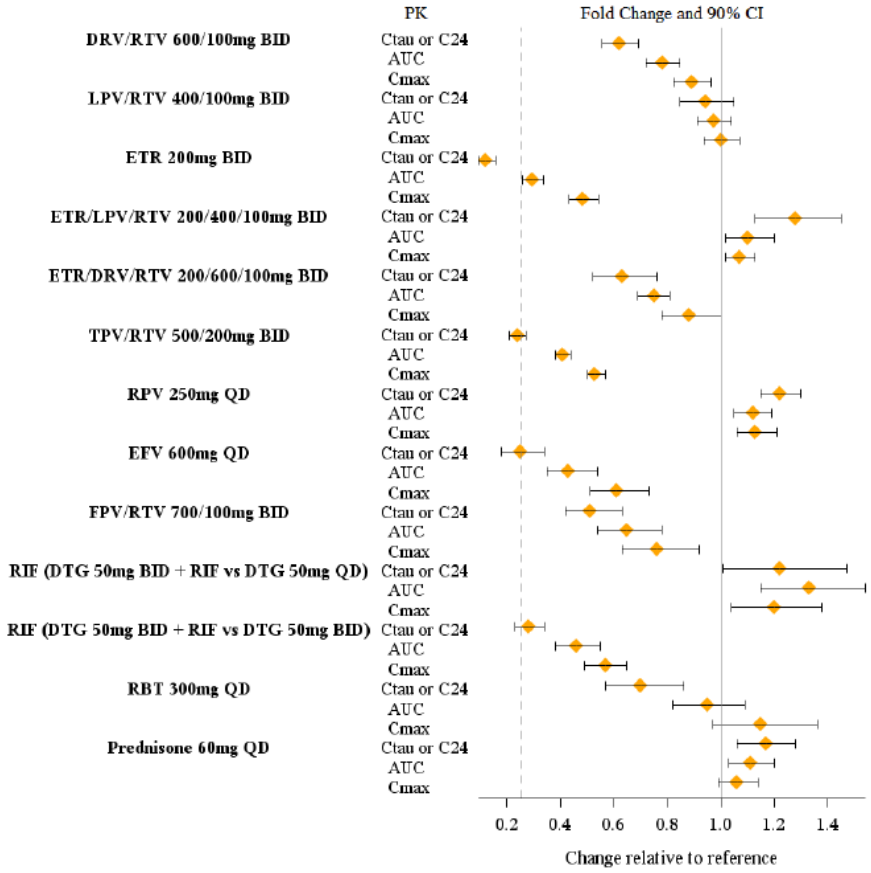
In adults there is dose-proportional increase in exposure between 25 mg and 50 mg tablets while the increase is less than proportional between 50 mg and 100 mg, due to limitations in solubility. No time dependency in PK has been observed.

Interactions

Effects of other medicinal products on the PK of DTG

DTG is a substrate of UGT1A1 and CYP3A4 as well as of the transporter proteins P-pg and BCRP. No mechanistic studies aimed to investigate the relative importance of the elimination pathways have been performed, however a number of co-medications commonly used in clinical practice have been studied. The effects of selected co-administered drugs on the PK of DTG are given in Figure 3.

Figure 1. Relative effect of co-administered drugs on DTG exposure (C_{tau}, AUC, C_{max})



DRV=darunavir; EFV=efavirenz; ETR=etravirine;FPV=fosamprenavir; LPV=lopinavir; RBT=rifabutin; RIF=rifampin; RPV=rilpivirine; RTV=ritonavir; TLV=telaprevir; TPV= tipranavir

Effects of DTG on the PK of other drugs

The risk of clinically relevant DDIs due to inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2D6 or general enzyme/transporter induction by DTG is considered low. For CYP3A4 clinically relevant DDIs due to inhibition or induction by DTG at systemic level are considered to be low.

DTG did not inhibit BCRP, BSEP, MRP2, MRP4, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and P-pg *in vitro* to any clinically relevant extent. DTG inhibited OCT2 in vitro, which is supported by the *in vivo* observation of a decrease in creatinine clearance. DTG inhibited OAT1 and OAT3 in vitro. In vivo, OAT1 (tenofovir as substrate) was not inhibited by DTG. OAT3 has not been studied in vivo and DTG may increase exposure of OAT3 substrates.

Special populations

No dose adjustment is required in in subjects with renal or mild or moderate hepatic impairment. Severe HI has not been studied.

Gender, race and elderly population had no clinically relevant effects on the PK of DTG. PK in adolescents 12 to 18 years of age was similar to adults.

Previously in adults, the exposure was found to decrease with increasing body weight. For the range of weights in the treatment-naïve population (39-135 kg), CL/F ranged from 0.67-1.2 L/h which was 23% lower to 33% higher compared to a 70-kg subject, and V/F ranged from 11-29 L which was 36% lower to 66% higher compared to a 70-kg subject. A similar result was obtained in the analysis of treatment-experienced patients. The predicted exposure is approximately 25% higher for low weight patients (40 kg) and 25% lower for high weight patients (135 kg) compared to a 70 kg reference patient.

Pharmacokinetics in the target population

The pharmacokinetics of dolutegravir has been determined previously in adult and adolescent (≥12 to <18 years of age) HIV 1 infected patients. The exposure in adults was previously found to be related to body weight, but not considered to be clinically relevant in adults. The paediatric study P1093/ING112578 was included in the original submission, but only data from the first cohort (12-18 years) was available. A clear relation between oral clearance and body weight was not observed in the adolescent PK and it was at the time of approval concluded that more data from children with lower body weight was needed before any conclusion could be drawn. The study is ongoing with sequential inclusion of cohorts from higher to lower age.

The PK data generated in the paediatric study originates from both frequent PK sampling (Table 9) as well as sparse sampling. Consequently, population PK modelling is employed in order to describe the PK profile regardless of sampling schedule and to determine factors that influence exposure. Information regarding included subjects in population PK and baseline demographics is given in Tables 10 and 11. In total 18 subjects aged between 6 and <12 years was included in the initial popPK analysis.

An additional 47 DTG concentrations from 11 subjects (all Cohort IIA) that were not available at the time of the initial Pop PK model was developed were included during the procedure based on a request from the CHMP. A further 5 additional DTG concentrations from 1 subject (Cohort IIB) became available during the late stage of the current analysis and was used to update the final model parameters.

Pharmacokinetic data from administration of the granule formulation was included in the popPK analysis, but was specifically assessed since this formulation was not a part of the current application.

Table 9. Summary of Study Information Included in the Population PK Analysis

Cohort (Status)	Cohort Description / No. Subjects	DTG Dose / Treatment Duration	DTG Formulation	PK Data Included in the Interim / Initial / Final Analysis
I (Completed)	Age cohort: Adolescents 12 to <18 years of age N=23 (10 on Stage I and 13 on Stage II)	· Stage I: Approximately 1 mg/kg QD using weight band based fixed doses with continuation of the current failing ARV or as monotherapy for those not taking ARV then in combination with OBR for minimum of 24 weeks · Stage II: Dose based on Stage data with OBT simultaneously for a minimum of 24 weeks	Tablet	·23 subjects for the interim and current analysis
IIA (Completed)	Age cohort: Children 6 to < 12 years of age N=22 (10 on Stage I and 12 on Stage II)		Tablet	·11 subjects for the interim analysis ·13 out of 22 subjects completed study contributed data for the initial analysis .23 subjects for the Final analysis (including 1 subject switched from cohort IIB)
IIB (On-going)	Age cohort: Children 6 to < 12 years of age N=~14 (all on Stage I; 4 on Mini-1 cohort and ~10 on Mini-2 cohort*)		Granule suspension Switch to tablet allowed after Week 4	·Not in the interim analysis ·5 out of 7 subjects (4 subjects from Mini-1 cohort and 3 subjects from Mini-2 cohort) completed study contributed data for the initial and final analyses

Table 10. Subject Characteristics by Weight Band

Covariate	Statistic or Category	15 to <20 kg	20 to <30 kg	30 to <40 kg	≥40 kg	Overall
Number of subjects		4	7	6	24	41
Number of samples* N (%)	Tablet	7 (30)	51 (68)	59 (100)	231 (100)	348 (90)
	Granule	16 (70)	24 (32)	0 (0)	0 (0)	40 (10)
Age at baseline (yrs)	Median [Min-Max]	6 [6-6]	7 [6-9]	14 [10-15]	13 [10-17]	12 [6-17]
	Mean (SD)	6.00 (0)	7.14 (1.07)	13.0 (2.28)	13.5 (2.27)	11.6 (3.58)
Weight at baseline (kg)	Median [Min-Max]	18.5 [17.0-19.5]	22.1 [21.4-24.5]	34.4 [32.4-37.7]	52.3 [39.7-91.0]	46.4 [17.0-91.0]
	Mean (SD)	18.4 (1.24)	22.5 (1.17)	34.8 (2.37)	56.4 (13.8)	43.7 (19.0)

Table 11. Summary of intensive PK results

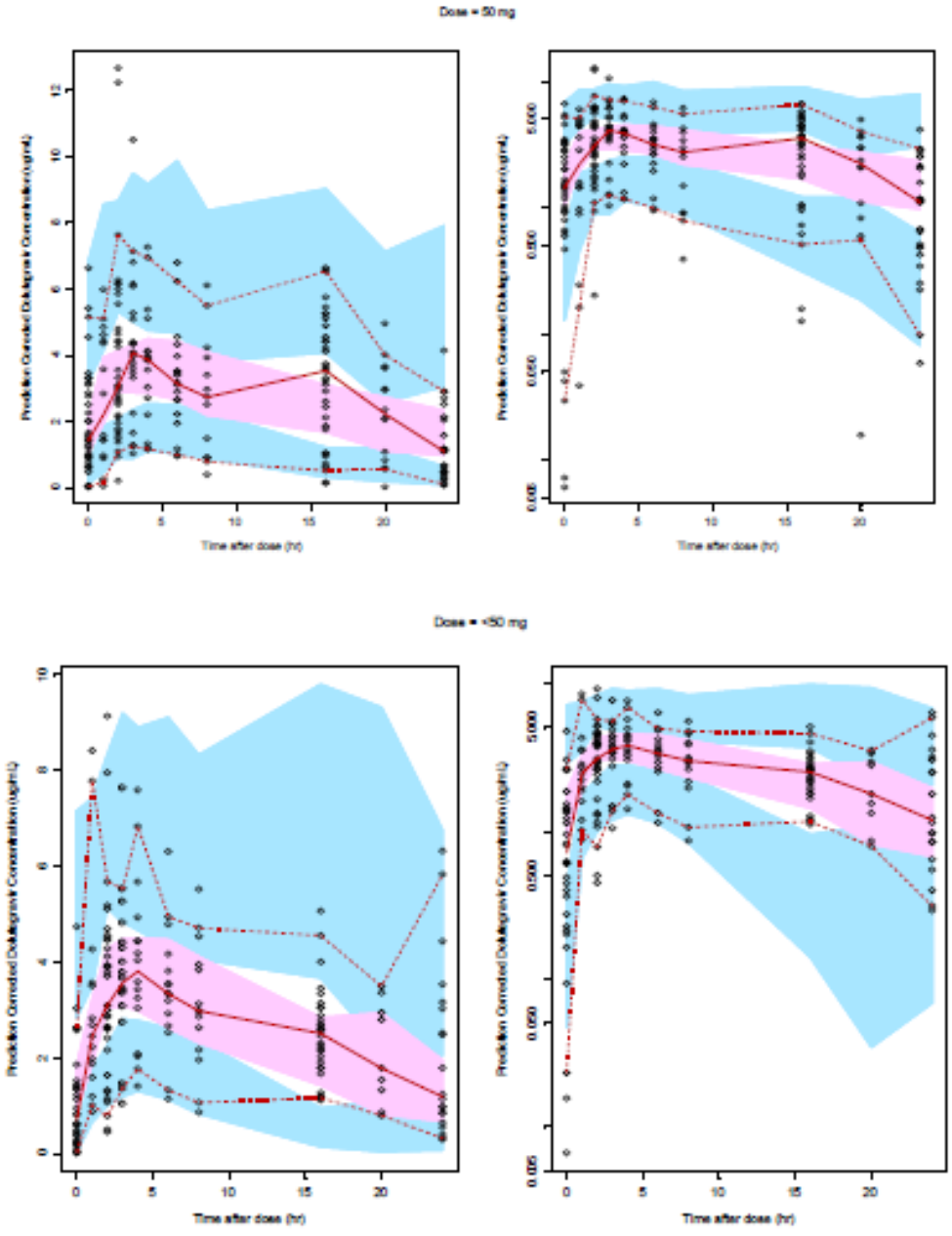
Age	Cohort	Formulation	Final Recommended Dose (FRD)	N	Mean Weight (kg)	Mean Dose mg (mg/kg)	Geometric Mean AUC_{24} (µg*h/L)	Geometric Mean C_{24} (ng/mL)
≥ 12 to <18y	I	Adult tablet	1 mg/kg QD	10	57.16	48.50 (0.90)	45.97	902.21
≥6 to <12y	IIA	Adult tablet	1 mg/kg QD	11	35.15	38.18 (1.10)	50.46	926.06

Results of PopPK analysis

The PK of dolutegravir following oral administration of tablets and granules was described by a one-compartment model with first order absorption, absorption lag time and first-order elimination; absorption rate constant, absorption lag time, and relative bioavailability were formulation-specific. Body weight was found to be a covariate on both clearance and volume of distribution of the central compartment. Model-estimated

final parameters are listed in Table 12. The prediction corrected Visual Predictive Check (pcVPC) for the final model for all data are given in Figure 2. In general, the 5th, median, and 95th percentiles of observed dolutegravir concentrations were confined within the corresponding prediction bands. Over-prediction was observed around the absorption phase for the 5th percentile.

Figure 2. Prediction-Corrected VPCs for the Final PopPK Model by Sampling Scheme



Open Circle: Observed concentrations

Solid Line: Median of observed concentrations

Dashed Line: 5th and 95th of observed concentrations

Shaded Region: 90% prediction interval of the 5th, median, and 95th percentiles of predictions

Dose = <50 includes all doses less than 50mg (20mg, 25mg and 35mg)

Table 12. Parameter Estimates of the Final DTG Paediatric Pop PK Model (Run 035)

Parameter [Units]	NONMEM Estimates					Bootstrap Estimates[a]	
	Point Estimate	RSE %		95% CI		Median	95% CI
CL/F [L/hr]	1.05	7.24		0.901-1.20		1.06	0.927-1.24
V/F [L]	19.0	5.15		17.1-20.9		19.3	16.7-23.1
Ka, tablet [hr^{-1}]	0.808	41.0		0.159-1.46		0.867	0.401-3.05
Ka, gran [hr^{-1}]	1.43	12.2		1.09-1.77		1.45	1.07-2.08
ALAG, tabl [hr]	0.620	59.8		-0.107-1.35		0.604	0.101-0.884
ALAG, gran [hr]	0 FIX	-		-		-	-
F, granule	1.50	7.60		1.28-1.72		1.53	1.24-1.83
CL/F~WT	0.750 FIX	-		-		0.75 FIX	-
V/F~WT	1.00 FIX	-		-		1.00 FIX	-
TM_{50} [wk][b]	52.2 FIX	-		-		-	-
Hill[b]	3.43 FIX	-		-		-	-
Inter-individual or inter-occasion variability			**Shrinkage %**		**CV% ***		
ω^2_{CL}	0.122	33.4	24.3	0.0422-0.202	34.9	0.118	0.0475-0.215
$\omega^2_{Ka,\ tablet}$	1.76	51.8	46.7	-0.0275-3.55	219	2.18	0.711-8.97
$\omega^2_{IOV\text{-}CL}$	0.188	23.7	19.2-48.8	0.101-0.275	45.5	0.190	0.112-0.301
$\omega^2_{IOV\text{-}Ka,\ tablet}$	2.39	50.2	47.3-58.4	0.0380-4.74	315	1.96	1.00E-5-4.75
Residual variability					**CV% / SD[c]**		
σ^2_{prop}	0.0221	43.4	20.6	0.00330-0.0409	14.9	0.0255	0.00550-0.0678
σ^2_{add}	0.112	43.0	20.6	0.0175-0.206	0.335	0.0920	0.0124-0.208

Abbreviations: %RSE = percent relative standard error of the estimate (standard error/parameter estimate*100); 95% CI = 95% confidence interval of the parameter; CL/F = apparent clearance; V/F = apparent volume of central compartment; Ka = absorption rate constant; ALAG = absorption lag time; F=relative bioavailability; WT = baseline body weight; TM50 = maturation half-life; Hill = slope of maturation; ω2 = variance of inter-individual random effect; CV = coefficient of variation of proportional error (=[σ2prop]0.5*100); IOV = inter-occasion variability; SD = standard deviation; σ2prop = proportional component of the residual error model; σ2add = additive component of the residual error model.

The reference population is a 70 kg person.

From 1000 bootstrap runs.

Parameters were used in the simulation model with maturation function.

Residual errors are expressed as CV% for proportional error and SD for additive error.

* $CV_{TV_p} = \sqrt{e^{\omega^2_P} - 1}$ when ω2P exceeds 0.15

Simulations of the recommended doses for children 6-12 years (15 to >40 kg)

Simulations using Monte-Carlo approach were performed to evaluate the appropriateness of the proposed dolutegravir (DTG) dosing regimen. DTG concentrations were predicted at 0, 1, 2, 3, 4, 6, 8, and 24 h following steady-state once-daily doses of DTG.

The percentage of children below the 10th percentile of adult concentration was 12% and 18% in the ≥40 kg and 15 to <20 kg weight group, respectively. However, the central tendency in exposure was similar to the adult exposure, but the variability greater leading to both higher and lower exposure in children compared to adults.

Table 13. Simulated steady-state DTG exposures with allometric scaling by weight band with tablet formulation

Weight Band	Statistic	C_τ (µg/mL)	$AUC_{0-\tau}$ (µg·hr/mL)
15 to <20 kg	N	114	114
	Dose (mg)	20	20
	Geomean Median (95% PI)	1.06 (0.861, 1.32)	51.6 (46.3, 57.2)
	% <10th of Adult[1]	18.4	14.0
	% >90th of Adult[1]	25.4	26.3
20 to <30 kg	N	226	226
	Dose (mg)	25	25
	Geomean Median (95% PI)	1.11 (0.959, 1.25)	51.1 (47.1, 55.4)
	% <10th of Adult[1]	17.0	14.2
	% >90th of Adult[1]	27.0	27.0
30 to <40 kg	N	179	179
	Dose (mg)	35	35
	Geomean Median (95% PI)	1.23 (1.03, 1.39)	54.5 (49.8, 60.0)
	% <10th of Adult[1]	14.0	11.7
	% >90th of Adult[1]	30.7	30.2
≥40 kg	N	213	213
	Dose (mg)	50	50
	Geomean Median (95% PI)	1.32 (1.17, 1.52)	55.8 (51.7, 60.9)
	% <10th of Adult[1]	11.7	11.3
	% >90th of Adult[1]	32.9	31.9

1PK parameters at 10th and 90th percentiles of adults at 50mg daily dose were post hoc estimates derived from the Pop PK model based on HIV-1 infected treatment-experienced adults. The 10th and 90th percentiles were 0.323 and 2.07µg/mL for Cτ, and 26.7 and 75.1 µg·hr/mL for AUC0-τ, respectively.

Adult plasma exposure of DTG

The observed plasma exposure in adult DTG exposure from phase II/III studies is given in Table 14.

Table 14. Summary of Key DTG Pharmacokinetic Parameters following 50 mg Once and Twice Daily Dosing in adult HIV-infected Subjects

Population	DTG Dosing Regimen	Data Source	Cmax (µg/ml)	AUC(0-τ) (µg·h/mL)	Cτ (µg/mL)
HIV-1 infected	50 mg once daily (no food restriction)	Population PK in Treatment-naive[a]	3.67 (20)	53.6 (27)	1.11 (46)

Data presented are geometric mean (%CV)

aPopulation PK analysis using pooled data from Phase II/III studies in treatment-naive subjects including ING111521, ING112276, and ING113086.

2.4.3. Pharmacodynamics

Mechanism of action

Dolutegravir is a HIV integrase inhibitor (INI). 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.

Primary and Secondary pharmacology

The viral replication cycle involves integration of the viral genome into host cell chromatin in two separate steps; 3' processing and strand transfer. During 3' processing a dinucleotide is excised by integrase from the 3' terminus of viral cDNA. The 3' processed viral DNA is then covalently linked to host DNA during strand transfer. Since integrase inhibitors appear to act at later stages of the viral replication cycle than viral entry or reverse transcriptase inhibitors, a larger proportion of productively infected cells may be inhibited. Dolutegravir has been shown to inhibit the strand transfer reaction, demonstrated as an accumulation of 2-long terminal repeat (2-LTR) circles at nanomolar concentrations. Dolutegravir has shown activity against most clones resistant to raltegravir and elvitegravir.

Relationship between plasma concentration and effect

The applicant argues as following concerning PK targets for dose selection:

Since paediatric PK tends to be more variable than adults, a lower threshold range for both the AUC24 and C24h was identified. Using maximum effect (E_{max}) models, the estimated AUC_{24} required to produce 95% of the maximum virologic response (i.e., the 95% effective concentration [EC95]) is 25 µg*h/mL, and the EC95 for the C_{24h} is 0.5 µg/ml. Therefore, all subjects had to meet these minimum exposure targets. These were considered the lowest threshold exposures acceptable in the paediatric study. This lower threshold is in place to ensure minimum exposure criteria are met, for some reason the targeted range cannot be met in an individual using the selected dose for the population. Similarly, the maximal exposure (upper threshold) is also defined to ensure subjects are not exposed to extremely high drug concentrations which may cause safety concerns.

Based on accumulated data in adults (in Phase I and IIb) to date, DTG is generally well tolerated with no significant safety issues identified. A dose of DTG 50 mg twice daily (BID) was evaluated in studies ING112961 (VIKING) and ING112574 (VIKING-3) in adult, HIV-infected subjects with resistance to RAL; exposures up to 2-fold higher are expected with co-administration of ATV with DTG, which is allowed in adult Phase III studies. Therefore, the maximal exposure target is 92 µg*h/mL for AUC_{24}, which is 2 times the geometric mean (GM) value at 50 mg once daily in adults (46 µg*h/mL) and is comparable to exposures anticipated with 50 mg BID or co-administration of DTG 50 mg once daily with ATV. Such upper thresholds may be adjusted upon availability of further clinical data. A dose-limiting toxicity has not been identified to date.

The 50 mg adult dose AUC_{24} target value is 46 µg*h/mL and the C_{24h} is 0.96 µg/mL, which represent geometric means. However, there will be variability around these targets. Therefore, the target range was defined as follows: the lower limits are 80% of the geometric means (37 µg*h/mL for AUC_{24} and 0.77 µg/mL for C24h); the upper limits are the 90th percentiles around the AUC_{24} and C24h (67 µg*h/mL for AUC_{24} and 2.26 µg/mL for C24h) observed in adult subjects in ING112276 (SPRING-1).

In summary, the target exposure for AUC_{24} was set to 46 μg*h/mL, targeting average adult exposure, with an acceptable range of 37-67 μg*h/mL. The target exposure for C24h was 960 ng/mL with an acceptable range of 770-2260 ng/mL.

Table 15. Study P1093 protocol defined target exposures

Protocol-Defined Targets		
	AUC_{24} (μg*h/mL)	C24h (ng/mL)
Targets:	46	960
Target Range	37-67	770-2260
Max Lower Limit	25	500
Max Upper Limit	92	-

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

ADME

No new data on general pharmacokinetic properties has been submitted. All ADME studies have only been performed in adults. Given the nature of this application, this is considered acceptable.

Formulation

No new bioequivalence or relative bioavailability data for the new tablet strengths 10 and 25 mg was provided in the present submission. A major objection was raised related to a lack of sufficient PK characterisation of the new tablet strengths 10 and 25 mg. Furthermore, an in vivo relative bioavailability study in adults comparing the exposure of the 10, 25 and 50 mg tablets was requested unless otherwise justified by the Applicant. The Applicant stated that a relative bioavailability in adults study comparing the different tablet strengths is not necessary. The main reason for this would be that the new tablet strengths are sufficiently studied in the present paediatric study (ING112578) and also that there is no intent to interchange the tablet strengths. Furthermore, the Applicant states that bioavailability of the formulations will not be similar in paediatric subjects as compared to adults because of differences in clearance by body weight in paediatric subjects. However, the most common way forward for development of paediatric formulation is to perform a formulation study in adults which then is extrapolated to paediatric population, even though the absolute BA might differ, the relative BA should be possible to extrapolate to children in age range 6-12 years.

The 25 mg tablet is considered sufficiently characterised for the intended use in children. This is based on the combined in vivo data in adults and paediatrics in addition to in vitro dissolution data and is therefore approvable. The Applicant refers to a previously submitted study (SPRING 1/ING112276) where steady state PK data from 10 mg and 25 mg tablets was investigated in adults. In this study the dose-normalised AUC_{TAU} and C_{TAU} were comparable for 25 mg and 50 mg. The 25 mg tablet used in SPRING1/ING112276 was of a different composition compared to the paediatric study ING112578; however it was shown to be bioequivalent to the 25 mg tablet composition used in the paediatric study in PK study submitted in the original marketing authorisation (study ING113674). The 25 mg tablet intended for market was administered in the paediatric study ING112578 in 7 subjects (weight range 20-30 kg), where intensive PK sampling was available in 4 subjects and sparse in remaining 3. The mean exposure obtained from non-compartmental analysis of rich PK data in subjects receiving the 25 mg dose was lower compared to the mean exposure after a 50 mg dose. However, the overall

variability in exposure is substantial and individuals with even lower exposure are observed in the group treated with the 50 mg tablet. This means that a mean value calculated separately for a small sample of subjects is associated with a large uncertainty. However, the composition of the 25 mg tablet is proportional to the approved 50 mg tablet and the in vitro dissolution profiles are generally considered similar to the approved 50 mg tablet (see quality). Thus the 25 mg tablet is considered sufficiently characterised based on the combined in vivo data in adult and paediatric patients in addition to in vitro dissolution data and is therefore approvable.

Regarding the 10 mg tablet, the composition is not proportional to the 50 mg tablet and also behaves differently compared to the 50 mg tablet in the in vitro dissolution assay (see section on quality). As stated above the number of paediatric subjects in the present clinical study receiving the 10 mg tablet where exposure data is available is notably low. However, as response to Day 120 List of Questions from the CHMP the Applicant submitted additional PK data from 15 subjects that received the 10 mg tablet, either alone (n=4) or in combination with the 25 mg tablet (n=11). The new data were in line with previous PK observations and considered supportive of the paediatric PopPK model for dolutegravir.

The 10 mg tablet is considered to be sufficiently characterized for its purpose, i.e. the 10 mg tablet can only be used as the posology given in SmPC section 4.2 Table 1. It is reflected in Section 4.2 of the SmPC that the 10 mg table is not interchangeable.

Interactions

Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A component. Both UGT1A1 and CYP3A4 enzyme activities are low at birth. CYP3A4 is expected to be fully mature at 6 years of age and approximate the adult activity at 6 months (Johnson et al Clin. Pharmacokinetics 2006; 45 (9): 931-956). There is less data on maturation of UGT1A1, but it known to rapidly increase to adult activity. UGT1A1 activity will be further discussed when data from younger aged groups will be submitted. No new interaction studies have been performed. The SmPC contains extensive information on the DDI potential of DTG from the initial application. There is no proposed change in SmPC Section 4.5, except for the dosing recommendation when DTG is co-administrated with inducers (Etravirine, Efavirenz, Nevirapine, Tipranavir/r, Carbamazepine, Oxcarbazepine/Phenytoin/Phenobarbital, St John's wort and Rifampicin). The applicant proposed that the paediatric daily dose should be administered twice daily, in line with the adult recommendation. Dolutegravir is primarily metabolized through glucuronidation via UGT1A1 with a minor CYP3A and both enzymes are mature at age of 6 years according to the Applicant, which is agreed. The popPK analysis included inducers (categorised as mild and moderate/strong) as a covariate, but was not found significant. DTG is also a P-pg and BCRP substrate and the Applicant was asked to discuss the maturation of these. The Applicant has provided literature data supporting that there are no overt differences in BCRP and P-gp expression in the 6-12 year age group compared to adults and thus extrapolation of adult DDI results to the 6 to 12 year age group is adequate.

PopPK analysis

The PK data generated in the paediatric study results from both frequent PK sampling as well as sparse sampling. Consequently, population PK modelling is employed in order to describe the PK profile regardless of sampling schedule and to determine factors that influence exposure.

The population PK model is pivotal in this application. It is used to support the dosing regimen by simulations. The model contributes with quantification of the risk of over/under exposure and provides evidence for weight based dosing. The optimal dose levels and weight bands may be deduced from the model by simulation of exposure in the target population. However, in order to trust the model it needs to be qualified for its purpose.

The response from the Applicant was lacking important information and additional questions were raised regarding:

- importance that the relation between clearance and body weight is well defined,
- that the between- and within subject variability in model parameters is accounted for
- that influence of study design is accounted for in the model (e.g. rich/sparse sampling as covariate in the residual error model).
- The absorption phase should be properly described in order to regard the disposition parameters, and ultimately the predicted C_{tau}, as unbiased by the absorption model.

It is assumed in the model that the eliminating capacity is related to body weight to the power of ¾ according to allometry. The allometric exponents were evaluated in the original modelling analysis. Estimated values were relatively close to theoretical (0.68 vs 0.75 and 0.952 vs 1, for CL and V respectively) and therefore they were fixed. This was later confirmed by the Applicant's additional modelling.

Several alternative models including a more flexible absorption model and alternative handling of intra-individual variability was explored by the Applicant. None of the models provided a better fit to the data and it was concluded that the original updated PopPK model was sufficient to describe data.

To summarize, the Applicant has shown that alternative models does not describe the data better than the current model. The model still seems to over predict variability but is in general acceptable for description of the data and simulation of exposure within the range of studied doses and range of body weight. To improve the precision in modelling for the remaining parts of the P1093 study, the CHMP recommended performing a relative bioavailability study to compare the 10 mg and the dispersible dolutegravir tablet formulations, to the 50 mg tablet. The MAH committed to perform this study.

Posology

During the procedure the applicant was requested to substantiate the dosing regimen including weight bands, or consider an alternative posology to provide an adequate exposure. The Applicant provided simulations of an alternative posology excluding the 10 mg tablet strength, making use only of the 25 mg and 50 mg strengths. The Applicant chose to simulate using a WHO standard for weight category (14 to <20 kg, 20 to <25 kg, 25 to <35 kg and >35 kg). As expected, the exposure was considerably higher for subjects where the greatest increase in dose was seen. The alternative posology would lead to some subjects experiencing exposure well above what has been observed in adults at a dose level of 50 mg bid. Although the risk of under exposure would be somewhat reduced, the consequences of over exposure in children are not known and the alternative posology could not be recommended.

Similarly, the original dose levels were applied to the WHO weight categories. Compared to the original dosing regimen, a larger proportion of subjects would have an exposure above the 90th percentile of adult data while approximately the same proportion would run the risk of having a C_{tau} below the 10th percentile of adult data.

Table 16. Comparison of originally proposed and alternative dolutegravir weight-band doses

Original Dosing Scheme		Alternative Posology		
Weight Band (kg)	P1093 Dose (mg)	Weight Band (kg)	Scheme 1 Dose (mg)	Scheme 2 Dose (mg)
15 to <20	20	14 to <20	20	25
20 to <30	25	20 to <25	25	25
30 to <40	35	25 to <35	35	50
≥40	50	≥35	50	50

Table 17. Simulated steady-state dolutegravir exposures using alternative posologies

Weight Band	Statistic	C_T (µg/mL)	AUC_{0-T} (µg·hr/mL)
15 to <20 kg	**N**	114	114
	Dose (mg)	20	20
	Geomean Median (95% PI)	1.06 (0.861, 1.32)	51.6 (46.3, 57.2)
	% <10th of Adult[1]	18.4	14.0
	% >90th of Adult[1]	25.4	26.3
20 to <30 kg	**N**	226	226
	Dose (mg)	25	25
	Geomean Median (95% PI)	1.11 (0.959, 1.25)	51.1 (47.1, 55.4)
	% <10th of Adult[1]	17.0	14.2
	% >90th of Adult[1]	27.0	27.0
30 to <40 kg	**N**	179	179
	Dose (mg)	35	35
	Geomean Median (95% PI)	1.23 (1.03, 1.39)	54.5 (49.8, 60.0)
	% <10th of Adult[1]	14.0	11.7
	% >90th of Adult[1]	30.7	30.2
≥40 kg	**N**	213	213
	Dose (mg)	50	50
	Geomean Median (95% PI)	1.32 (1.17, 1.52)	55.8 (51.7, 60.9)
	% <10th of Adult[1]	11.7	11.3
	% >90th of Adult[1]	32.9	31.9

1PK parameters at 10th and 90th percentiles of adults at 50mg daily dose were post hoc estimates derived from the Pop PK model based on HIV-1 infected treatment-experienced adults. The 10th and 90th percentiles were 0.323 and 2.07µg/mL for C_T, and 26.7 and 75.1 µg·hr/mL for AUC_{0-T}, respectively.

The Population model used in simulation mode is considered to provide conservative estimates of over exposure. This is partly due to that correlation between variability parameters cannot always be estimated. Simulating without correlated parameters may lead to inflation of the variability in exposure and therefore the simulations may be considered conservative with respect to fraction of subjects outside the predefined exposure limits. It is agreed that the original (studied) posology is likely to provide safe and efficacious exposure in children above 6 years of age.

To conclude, the alternative posologies that have been considered do not appear to be better in terms of efficacy or safety compared to the original posology.

2.4.5. Conclusions on clinical pharmacology

The 10 mg tablet is considered to be sufficiently characterised with regards to PK. The updated population PK model adequately describes the data from the paediatric subjects included in this application. The proposed posology is anticipated to exposures reasonably similar to those seen in adults treated with 50mg/d, and is acceptable given the presumed broad therapeutic index of dolutegravir.

2.5. Clinical efficacy

The current application is based on one ongoing paediatric study (P1093/ING112578) to support the extended therapeutic indication in children 6-12 years. The study is being conducted by an academic research organization IMPAACT under the sponsorship of DAIDS.

2.5.1. Dose response and main study

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

This is an ongoing Phase I/II multi-center, open-label, non-comparative study of with an inclusion target of approximately 160 HIV-1-infected paediatric subjects ages ≥4 weeks to <18 years (enrolled sequentially in age-defined cohorts), 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).

The current application is based on data from two sub-cohorts of the P1093 study: Cohort IIA containing children 6-12 years, which is the scope of the current application, and Cohort I containing adolescents 12-18 years and are considered supportive to the current application.

Methods

Study Participants

Key inclusion criteria include antiretroviral therapy (ART)-experienced, INI-naïve infants, children, and adolescents age ≥4 weeks to <18 years at study entry, with confirmed HIV-1 infection, and an optimized background regimen that contains at least one fully active drug.

Key exclusion criteria include known resistance to an integrase inhibitor, presence of any active AIDS-defining opportunistic infections, known ≥Grade 3 and Grade 4 lab toxicities, evidence of pancreatitis, liver toxicity, and known exposure to an integrase inhibitor.

There are five age-defined groups in P1093 (enrolled in six cohorts) as follows:

- Cohort I: Adolescents ≥12 to <18 years of age (tablet formulation)
- **Cohort IIA: Children ≥6 to <12 years of age (tablet formulation)**
- Cohort IIB: Children ≥6 to <12 years of age (paediatric formulation)
- Cohort III: Children ≥2 to <6 years of age (paediatric formulation)
- Cohort IV: Children ≥6 months to <2 years (paediatric formulation)
- Cohort V: Infants ≥4 weeks to <6 months (paediatric formulation)

Seven investigators in the US and 1 investigator in Thailand enrolled all subjects in Cohort I. Eleven investigators in the US, 2 investigators in Thailand, and 1 investigator in South Africa enrolled all subjects in Cohort IIA. The first subject enrolled in Cohort I on 20 Apr 2011.

Paediatric subjects in Cohorts I and IIA receive DTG tablets (10 mg, 25 mg, and 50 mg) once daily according to weight-based dosages, whereas those in Cohorts IIB through V receive the paediatric formulation.

Each age cohort consists of two sequential stages: Stage I and II. The objectives of Stage I were to examine PK parameters after intense sampling and evaluate the short term tolerability and safety of DTG in approximately 10 subjects, allowing the selection of a dose for further study in Stage II. Those enrolled into Stage I remain in Stage I for the duration of the study. Longer-term safety and antiviral activity of DTG will be assessed from data obtained from those enrolled in Stage I as well as those in Stage II who initiated treatment at the chosen dose for the cohort and remained on this dose. Subjects in Stage I or Stage II will progress to the Long Term Safety Follow-up once 48 weeks of drug is completed and if they are deriving benefit from the study drug.

Treatments

For those subjects enrolling in Stage I, DTG treatment was added to a stable, failing ARV regimen or started as monotherapy for those not taking ARVs. Intensive PK was performed between Days 5 to 10; after obtaining the 24-hour PK sample, the background ARV regimen was immediately optimized. To minimize the impact of drug-drug interactions on PK variability, the use of ATV, nevirapine (NVP), ATV/RTV, EFV, fosamprenavir (FPV), FPV/RTV, and tipranavir (TPV), TPV/RTV was not allowed prior to the initial PK evaluation but could be added as part of optimized background therapy. All ARV regimens must have contained at least one fully active drug and one additional drug in the OBT, in addition to DTG. An initial starting DTG dose was approximately 1 mg/kg once daily, with a maximum daily dose of 50 mg.

Table 18. Initial dosing table for subjects enrolled in P1093

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

All subjects in both Cohort I and Cohort IIA were treated exclusively at the final selected dose. The treatment dosing regimen assignments used in this study were based on DTG tablet once daily doses, with target dose of ~1 mg/kg across 4 weight bands, and maximum dose of 50 mg. Note, for subjects receiving concomitant rifampin, EFV, FPV/RTV, or TPV/RTV, it was recommended that the dose of DTG be increased to twice-daily administration.

The treatment dosing assignments used in Cohort I and Cohort IIA were:

- Cohort I: 19 subjects received 50 mg/day and 4 subjects received 35 mg/day.
- Cohort IIA: 1 subject received 70 mg/day (taken as 35 mg BID), 5 subjects received 50 mg/day, 6 subjects received 35 mg/day, 8 subjects received 25 mg/day and 3 subjects received 20 mg/day.

Objectives

Primary Objectives

- To select a DTG dose for chronic dosing in infants, children, and adolescents that achieves similar exposure to the DTG adult dose selected from the Phase IIb clinical trial in ART-naïve adult subjects
- 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 other antiretrovirals (optimized background therapy, [OBT]) in treatment-experienced, HIV-1-infected infants, children, and adolescents, and to determine the dose of DTG that achieves a targeted AUC24 (primary PK endpoint) and C24h (secondary PK endpoint) in this population

Secondary Objectives

- To evaluate the antiviral activity of DTG in combination with 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 subjects 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 population PK analysis
- To determine the extended long-term (⩾48 weeks) safety and tolerability of DTG in HIV-1-infected infants, children, and adolescents
- To explore the relationship between DTG exposure and the antiviral activity

Outcomes / endpoints

Safety Assessments

Safety assessments included monitoring and recording all AEs and serious adverse events (SAEs), laboratory parameters including haematology, fasting lipid profile, and blood chemistry. Toxicity through Week 24 was a primary endpoint and included all AEs or laboratory toxicities of Grade 3 or higher severity, AEs or laboratory toxicities of Grade 3 or higher judged to be at least possibly attributable to the study medication, termination from treatment due to a suspected adverse drug reaction (SADR) and Death.

Efficacy Assessment

Key secondary efficacy analyses include virologic outcomes based on HIV-1 RNA (c/mL) at Week 24 and Week 48. At both of these time points, the primary definition of virologic outcome was calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA's snapshot algorithm. Subjects were classified as virologic failures if they had missing HIV-1 RNA data throughout the window surrounding the time point of interest.

Sample size

The enrolment estimate assumes an approximate 35% dropout rate, and allows for a minimum of 100 evaluable subjects with at least 24 weeks of safety data for those treated exclusively with the selected dose.

Randomisation

This was an open-label single-arm study; hence no randomisation or blinding was performed.

Statistical methods

Safety Analyses

It is stated that the primary population for the safety analyses is the all-treated (AT) Population. However, it is also stated that the primary safety analysis includes only subjects whose starting doses have been those judged to be optimal for their groups. Stage I subjects whose doses have been adjusted for inadequate PK are excluded. Stage I subjects who have been removed from treatment due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis.

AEs were summarized overall and by treatment group: 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.

Efficacy Analyses

The all-treated (AT) population was the primary population of interest for all efficacy endpoints and was defined as all randomized subjects who received at least one dose of study medication.

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

Results

Recruitment

At this time P1093 is ongoing; results presented throughout this clinical study report include Cohort I Stage I and Stage II through Week 48 and Cohort IIA Stage I and Stage II through Week 24, both with a data cut-off date of 14 February 2015. The first subject in Cohort I was enrolled 20 April 2011; the first subject in Cohort IIA was enrolled 25 January 2012.

A total of 23 subjects from South Africa (n = 4), Thailand (n = 3), and the US (n = 16) were enrolled in Cohort IIA (Stage I, n = 11; Stage II, n = 12) and received dolutegravir. Twenty-two subjects completed Week 24 and 16 subjects have completed Week 48.

Table 19. Subject disposition

Population	DTG Once Daily + OBT	
	Cohort I[a]	Cohort IIA[b]
Enrolled, N	**23**	**23**
Safety (treated with IP), N	23	23
Subjects completed Week 24, n	23	22
Subjects completed Week 48, n	21	16
Off Study Drug, n	13	4
Completed Treatment	1	0
Protocol Defined Clinical Event[c]	0	1
Pregnancy	1	0
Unable to attend clinic visits	5	1
Non-compliance	4	1
Lost to Follow-up	1	1
Other[d]	1	0

a. Cohort I = ages ≥12 to <18 years of age

b. Cohort IIA = ages ≥6 to <12 years of age

c. Protocol Defined Clinical Event in this case is a virologic failure

d. Family moved out of state; subject withdrew consent

Baseline data

Table 20. Baseline Demographics and Characteristics – AT Population

Demographics	DTG Once Daily + OBT	
	Cohort I[a] N=23	Cohort IIA[b] N=23
Age in Years, median (range)	15 (12 – 17)	10 (6 – 11)
Sex, n (%)		
Male	5 (22)	16 (70)
Female	18 (78)	7 (30)
Weight, mean kg (range)	55 (33 – 91)	30 (18 – 54)
Ethnicity, n (%)		
Hispanic or Latino	6 (26)	6 (26)
Race, n (%)		
African American/African Heritage	12 (52)	12 (52)
American Indian or Alaskan Native	0	0
Asian	3 (13)	3 (13)
Native Hawaiian or other Pacific Islander	0	1 (4)
White – White/Caucasian/European Heritage	8 (35)	4 (17)
More than one race	0	1 (4)
Unknown	0	2 (9)

a. Cohort I = ages ≥12 to <18 years of age

b. Cohort IIA = ages ≥6 to <12 years of age

Table 21. Summary of Baseline Characteristics – AT Population

Baseline Characteristics	DTG Once Daily+ OBT	
	Cohort I[a] N=23	Cohort IIA[b] N=23
Median (range) Baseline HIV-1 RNA (log_{10} c/mL)	4.3 (3.1 – 5.4)	5.0 (2.9-7.0)
Median (range) Baseline CD4+ (cells/mm^3)	466 (11 – 1025)	645 (9 – 1700)
Median (range) Baseline CD4+ Percent	22 (1 - 39)	24 (<1 – 44)
CDC Category C[c] or HIV Stage 3, n (%)	9 (39)	6 (26)

a. Cohort I = ages ≥12 to <18 years of age

b. Cohort IIA = ages ≥6 to <12 years of age

c. only c category was collected

All subjects in both Cohort I and Cohort IIA were treatment-experienced. At study entry, all subjects were on a failing ART regimen or were currently off therapy; no subjects were receiving background ART that was not permitted according to the protocol.

Results

Data from two sub-cohorts of the P1093 study are available: Cohort IIA containing children 6-12 years, which is the scope of the current application, and Cohort I containing adolescents 12-18 years and are considered supportive to the current application. All efficacy endpoints are secondary in the P1093 study.

Table 22. Virologic (Snapshot algorithm) and Immunologic Activity of Treatment for Subjects 6 Years and Older in P1093

	TIVICAY ~1 mg/kg Once Daily + OBR	
	Cohort I (12 to 18 years) (n=23)	Cohort IIA (6 to <12 years) (n=23)
HIV-1 RNA <50 copies/mL at 24 weeks, n (%)	16 (70%)	14 (61%)
HIV-1 RNA <50 copies/mL at 48 weeks, n (%)	14 (61%)	-
HIV-1 RNA <400 copies/mL at 24 weeks, n (%)	19 (83%)	18 (78%)
HIV-1 RNA <400 copies/mL at 48 weeks, n (%)	17 (74%)	-
Virologic non response	6	3
CD4+ Cell Count Median Change from Baseline, cells/mm^3 Median Percent Change from Baseline	 84[a] 5%[a]	 209[b] 8%[b]

a. 22 subjects contributed Week 48 CD4+ cell count data

b. 21 subjects contributed Week 24 CD4+ cell count data

Table 23. Study Outcomes Based on Plasma HIV-1 RNA <400 c/mL (AT Population)

	DTG Once Daily + OBT		
	Cohort I[a] Week 24 N=23 n (%)	Cohort I[a] Week 48 N=23 n (%)	Cohort IIA[b] Week 24 N=23 n (%)
Virologic Success[c]	19 (83)	17 (74)	18 (78)
Virological Failure	4 (17)	6 (26)	4 (17)
Data in window not below threshold	4 (17)	4 (17)	4 (17)
Discontinued while not below threshold	0	2 (9)	0
No Virologic Data	0	0	1 (4)
Discontinued for Other Reasons while below threshold	0	0	1 (4)

a. Cohort I = ages ≥12 to <18 years of age

b. Cohort IIA = ages ≥6 to <12 years of age

c. Virologic success was defined as plasma HIV-1 RNA <400 c/mL; MSDF Snapshot Algorithm was used in HIV-1 RNA analysis

In Cohort IIA, the rate of virologic success at 24 weeks (61% when defined as <50 c/mL) is lower than what is seen in ART experienced adults treated with dolutegravir (79 % in the SAILING study at 24 weeks). In both cohorts, there was an increase in absolute and relative CD4 count.

Protocol defined virologic failure (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 two consecutive measurements at least 1 week but no more than 4 weeks apart.

- Cohort I: Six (26%) subjects met PDVF criteria (had confirmed plasma HIV-1 RNA >400 c/mL) through Week 48, 4 of whom had met PDVF criteria at Week 24; 2 additional subjects met PDVF subsequent to Week 48 (at Week 96 and at Week 156).
- Cohort IIA: Three (13%) subjects met PDVF criteria (confirmed plasma HIV-1 RNA >400 c/mL) at Week 24; 1 additional subject met PDVF subsequent to Week 24 (at Week 32).

Evidence of treatment-emergent resistance to a PI, nucleoside reverse transcriptase inhibitor (NRTI), or non-nucleoside reverse transcriptase inhibitor (NNRTI) was seen in a few subjects.

One subject (Cohort I) had emergent protease (PR) minor mutations M36I and L89M at Week 48 and a reverse transcriptase (RT) major mutation, K103N, detected later at Week 96. Concomitant ART records indicate no use of an NNRTI for this subject while on study.

Two additional subjects (one in Cohort I and Cohort IIA each) had emergent minor ART resistance-associated mutations to either a PI or NRTI.

One subject (Cohort I) had treatment-emergent IN resistance at both the initial virologic failure visit (Week 32) and at a subsequent virologic failure visit (Week 132) with lack of adherence to study treatment reported throughout her participation. At Week 32, population integrase genotyping showed the presence of mutation R263R/K and a DTG FC of 1.2. At Week 132, IN mutations E138 A/E/K/T, S147S/G, and R263K were detected with a DTG fold change (FC) of 5.1. A clonal analysis was performed at the pre-treatment, Week 32, and Week 132 time points to better understand the IN resistance acquisition in this subject (Table 13). Results indicated at Week 32 the viral population was composed of approximately 50% mutant R263K and that this mutation led to the slight increase in median DTG FC (DTG FC=2). The clonal analysis at Week 132, showed the majority of the viral population harbouring R263K. In addition, a new emerging minor population with linked IN mutations at positions 138, 147, and 263 were seen. When present, these linked mutations resulted in a median DTG FC of 6.3.

Table 24. Clonal Analysis for one subject

Timepoint on Study	HIV-1 RNA (c/mL)	Total Clones Tested	IN Linked Substitutions / Number of Clones	Clonal DTG Median FC
Pre-treatment	7739	8	L74V / 4 clones	0.97
			L74I / 1 clone	0.97
			L74L / 3 clones	1.16
Week 32	9778	8	R263K / 4 clones	2.0
			V201I / 3 clones	1.19
			V201I, R263R / 1 clone	1.26
Week 132	1367	16	A49G, M50V, V201I, R263K / 12 clones	4.17
			A49G, M50V, E138T, S147G, V201I, R263K / 4 clones	6.33

The R263K mutation in combination with other secondary mutations described above is associated with a significant fold change but also reduced viral fitness. Similar findings have previously been described also in treatment experienced, but INI naïve, adult subjects in the SAILING study.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The P1093 study is of single-arm open design, intended for ART-experienced but INI-naïve pediatric subjects. The MAH has confirmed that only ART experienced patients were included in the study.

Efficacy data and additional analyses

Overall, dolutegravir is known to be a potent inhibitor of HIV-1 replication with well-established clinical efficacy in adult subjects. This application concerns children aged 6-12 years (Cohort IIA), where the clinical efficacy data is based on 24-week data from 22/23 study subjects and to some extent can be supported by 48-week data from subjects aged 12-18 years.

The virologic response in Cohort IIA at 24 weeks is numerically inferior to what is seen in comparable adult subjects, but the low number of subjects and the greater uncertainty on treatment compliance in lower age groups makes a direct comparison impossible. Rather, the clinical efficacy should be inferred from PK/PD-data to ensure that the dolutegravir exposure in terms of AUC24 and C24 are comparable to what is seen in adult subjects.

2.5.3. Conclusions on the clinical efficacy

In line with EMA guidelines, the P1093 study has not been dimensioned to establish direct clinical efficacy in the age group 6-12 years. As the pharmacologic target is of viral origin, there is little doubt that dolutegravir will be efficient in inhibiting HIV-1 replication also in this subset of patients as long as drug exposure is comparable to what is seen in adults.

In contrast to adult patients, where a doubling of the dose to 50 mg x 2 is recommended, there is insufficient data to recommend a dose for dolutegravir in children and adolescents in the presence of INI resistance.

2.6. Clinical safety

The safety data presented in this section support the primary objective of determining the safety and tolerability of DTG through Week 48 for Cohort I and Week 24 for Cohort IIA.

The data cut-off for this analysis is 14 February 2015; the primary population for the safety analyses is the AT Population. Dolutegravir use was not associated with any safety events during the dose-finding period for either Cohort I or Cohort IIA (Stage I) that led to withdrawal or modification of any dose.

Patient exposure

As of the 15 January 2016 analysis cut-off date, a total of 46 subjects were exposed to at least one dose of DTG. In Cohort I, the median extent of exposure to DTG was 1198 days, ranging from 280 to 1387 days. In Cohort IIA, the median extent of exposure to DTG was 842 days, ranging from 84 to 1377 days.

Table 25. Clinical Trial Exposure by Duration and Cohort All Treated Population – Cut-off 15 January 2016

	Cohort I (N=23)#	Cohort IIA (N=23)##	Total (N=46)
Minimum Exposure	n	n	n
>0 days	23	23	46
>4 weeks	23	23	46
>12 weeks	23	22	45
>24 weeks	23	22	45
>48 weeks	20	21	41
>72 weeks	20	21	41
>96 weeks	18	14	32
>120 weeks	16	12	28
>144 weeks	14	10	24
>168 weeks	12	7	19
>192 weeks	6	6	12

#Per target dose of ~1 mg/kg and weight bands, 19 subjects received 50mg/day and 4 subjects received 35mg/day.

##Per target dose of ~1 mg/kg and weight bands, 1 subject received 70mg/day, 5 subjects received 50mg/day, 6 subjects received 35mg/day, 8 subjects received 25mg/day, and 3 subjects received 20mg/day.

Adverse events

The primary population for the safety analyses is the all-treated (AT) Population. The MAH also stated that the primary safety analysis includes only subjects whose starting doses have been those judged to be optimal for their groups, as stage I subjects whose doses have been adjusted for inadequate PK are excluded. However, the MAH has confirmed that all subjects that have received at least one dose of dolutegravir have been included in the safety data set.

Stage I subjects who have been removed from treatment due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis.

The MAH states that DAIDS collects SAEs (which meet ICH criteria) through what has been submitted to the DAIDS Regulatory group while all other events are reported and collected via the Data Management Center from the clinical database. Therefore, SAEs reported may not show up in the AE database. For example, the suicide attempt below was not reported in the Diagnoses CRF but was reported as a secondary event in the Event Evaluation Form with Depression as the primary diagnosis. Only primary events from the Event Evaluation Form are summarized in the reports.

The MAH has confirmed that there are no further SAEs that have been recorded as secondary events to a primary SAE diagnosis and therefore concludes that SAEs have not been underestimated in the study report or tabulated summaries.

Table 26. Adverse events in Cohort I - ages ≥12 to <18 years of age

Preferred Term	DTG Once Daily + OBT Cohort I[a] N=23				
	Grade				Total (any Grade) n (%)
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	
Number of subjects with one or more AEs	9 (39)	9 (39)	4 (17)	1 (4)	23 (100)
Cough	13 (56)	1 (4)	0	0	14 (61)
Oropharyngeal pain	6 (26)	3 (13)	0	0	9 (39)
Diarrhea	6 (26)	2 (9)	0	0	8 (35)
Nasal congestion	6 (26)	2 (9)	0	0	8 (35)
Rhinorrhea	7 (30)	0	0	0	7 (30)
Headache	5 (22)	2 (9)	0	0	7 (30)
Pyrexia	5 (22)	2 (9)	0	0	7 (30)
Lymphadenopathy	6 (26)	0	1 (4)	0	7 (30)
Decreased appetite	4 (17)	3 (13)	0	0	7 (30)
Pain in extremity	4 (17)	2 (9)	0	0	6 (26)
Abdominal pain	1 (4)	3 (13)	1 (4)	0	5 (22)
Dizziness	4 (17)	0	0	0	4 (17)
Sinus congestion	4 (17)	0	0	0	4 (17)
Vomiting	4 (17)	0	0	0	4 (17)
Back pain	2 (9)	2 (9)	0	0	4 (17)
Arthralgia	3 (13)	0	0	0	3 (13)
Musculoskeletal pain	3 (13)	0	0	0	3 (13)
Nausea	2 (9)	1 (4)	0	0	3 (13)
Pharyngitis	2 (9)	1 (4)	0	0	3 (13)
Depression	0	2 (9)	0	1 (4)	3 (13)
Fatigue	1 (4)	2 (9)	0	0	3 (13)
Peripheral swelling	1 (4)	2 (9)	0	0	3 (13)
Vaginal discharge	1 (4)	2 (9)	0	0	3 (13)
Conjunctival pallor	2 (9)	0	0	0	2 (9)
Dyspnea	2 (9)	0	0	0	2 (9)
Gingival inflammation	2 (9)	0	0	0	2 (9)
Influenza like illness	2 (9)	0	0	0	2 (9)
Metrorrhagia	2 (9)	0	0	0	2 (9)
Muscle spasms	2 (9)	0	0	0	2 (9)
Musculoskeletal chest pain	2 (9)	0	0	0	2 (9)
Neck Pain	2 (9)	0	0	0	2 (9)
Papule	2 (9)	0	0	0	2 (9)
Pharyngeal erythema	2 (9)	0	0	0	2 (9)
Proteinuria	2 (9)	0	0	0	2 (9)
Rash pustular	2 (9)	0	0	0	2 (9)
Skin induration	2 (9)	0	0	0	2 (9)
Toothache	2 (9)	0	0	0	2 (9)
Acarodermatitis	0	2 (9)	0	0	2 (9)
Laceration	0	2 (9)	0	0	2 (9)
Rash	0	2 (9)	0	0	2 (9)
Rash generalized	0	2 (9)	0	0	2 (9)
Urticaria	0	2 (9)	0	0	2 (9)
Wheezing	0	2 (9)	0	0	2 (9)
Body tinea	1 (4)	1 (4)	0	0	2 (9)
Bronchitis	1 (4)	1 (4)	0	0	2 (9)
Dysuria	1 (4)	1 (4)	0	0	2 (9)
Joint swelling	1 (4)	1 (4)	0	0	2 (9)
Oral candidias	1 (4)	1 (4)	0	0	2 (9)
Oral pain	1 (4)	1 (4)	0	0	2 (9)
Productive cough	1 (4)	1 (4)	0	0	2 (9)
Respiratory tract congestion	1 (4)	1 (4)	0	0	2 (9)
Deep vein thrombosis	0	1 (4)	1 (4)	0	2 (9)

Table 27. Adverse events in Cohort IIA - ages ≥6 to <12 years of age

Preferred Term	DTG Once Daily + OBT Cohort IIA[a] N=23				
	Grade				Total (any Grade) n (%)
	1 (n%)	2 (n%)	3 (n%)	4 (n%)	
Number of subjects with one or more AEs	6 (26)	14 (61)	2 (9)	0 (0)	22 (96)
Cough	12 (52)	0	0	0	12 (52)
Nasal Congestion	5 (22)	2 (9)	0	0	7 (30)
Rash	4 (17)	3 (13)	0	0	7 (30)
Skin lesion	4 (17)	1 (4)	0	0	5 (22)
Diarrhea	3 (13)	2 (9)	0	0	5 (22)
Lymphadenopathy	4 (17)	0	0	0	4 (17)
Pyrexia	3 (13)	1 (4)	0	0	4 (17)
Rhinorrhea	3 (13)	1 (4)	0	0	4 (17)
Pruritus	3 (13)	1 (4)	0	0	4 (17)
Tinea capitis	2 (9)	2 (9)	0	0	4 (17)
Dermatitis atopic	1 (4)	3 (13)	0	0	4 (17)
Headache	2 (9)	1 (4)	0	0	3 (13)
Oropharyngeal pain	2 (9)	1 (4)	0	0	3 (13)
Vitamin D deficiency	2 (9)	0	0	0	2 (9)
Weight decreased	2 (9)	0	0	0	2 (9)
Vomiting	2 (9)	0	0	0	2 (9)
Papule	2 (9)	0	0	0	2 (9)
Abdominal pain upper	1 (4)	1 (4)	0	0	2 (9)
Oral herpes	1 (4)	1 (4)	0	0	2 (9)
Rales	1 (4)	1 (4)	0	0	2 (9)
Wheezing	0	2 (9)	0	0	2 (9)
Otorrhea	0	2 (9)	0	0	2 (9)

The MAH has also provided an updated summary of clinical adverse events as of Jan 15, 2016. As expected, the cumulative frequencies of adverse events rise with increased total exposure within the study but the overall profile is consistent with the tabulated summaries above.

The new Grade 3 AEs reported were: pelvic inflammatory disease, sinusitis bacterial, vaginal discharge and nasal congestion in Cohort I; stomatitis necrotising, abscess limb and pain in extremity in Cohort IIa. All these new AEs were reported only once. No safety signal may be highlighted.

The new Grade 4 AEs reported were intentional overdose and suicide attempt in both cohorts. All these new AEs were reported only once, without additional cases of depression. It is likely that these cases of suicide attempt were those previously reported as Grade 4 depression in the previous report.

Adverse Events of Special Interest (AESIs)

For DTG, AESIs have been identified based on non-clinical and/or clinical safety data for (e.g., GI disorders, renal disorders, hepatobiliary disorders), labelling and/or regulatory authority interest for INIs and/or the INI class (e.g., psychiatric disorders, rhabdomyolysis and myositis, serious rash and/or hypersensitivity), increased incidence of immune reconstitution inflammatory syndrome (IRIS); and/or regulatory requirements.

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.

Psychiatric Disorders Including Suicidality

Across Cohort I and Cohort IIA, 7 subjects reported one or more AEs from the Psychiatric Disorders SOC.

Four subjects (3 in Cohort I and 1 in Cohort IIA) experienced depression or major depression. Three of these four subjects had a medical history of depression or other relevant risk factors. One subject also reported a Grade 4 suicide attempt. The suicide attempt was not considered related to study drug by the investigator and DTG was continued uninterrupted. Another also developed aggression while on study. This subject had a history of attention deficit hyperactivity disorder (ADHD) and defiant and destructive behaviours since a young age.

One Cohort I subject with a history of behavioural problems, difficulty concentrating, and learning disabilities was diagnosed with ADHD. Of the final two subjects, one was reported to have flat affect and the other reported difficulty sleeping.

Gastrointestinal Disorders

In Cohort I and Cohort IIA, AEs were commonly reported from the GI disorders SOC, with abdominal pain, diarrhoea, nausea, and vomiting being the most commonly reported AEs. Most GI adverse events were Grade 1 or Grade 2. The commonly reported GI events are consistent with those observed in adult subjects receiving DTG. One subject experienced Grade 3 gastritis and abdominal pain, which was considered not related to study drug by the investigator. No change was made to the study drug and the subject was reported as recovered.

There were no events indicative of GI erosion or ulceration. One subject experienced Grade 2 gastroesophageal reflux disease (GERD), abdominal pain, and diarrhoea. This event was not considered by the investigator to be related to the study drug.

Musculoskeletal Disorders

In Cohort I and Cohort IIA, no Grade 3 or Grade 4 events from the Musculoskeletal and Connective Tissues Disorders SOC were reported. The most commonly reported Grade 1 and Grade 2 events were pain in extremity, muscular pain (e.g., back pain, musculoskeletal pain, and myalgia), and joint pain. There were no cases of rhabdomyolysis reported, and there was only 1 report of creatine phosphokinase elevation (Grade 1).

Renal Disorders

Renal laboratory data and relevant clinical event data are discussed under laboratory findings.

Serious adverse event/deaths/other significant events

There were no deaths reported in Cohort I or Cohort IIA.

In Cohort I, 5 subjects (22%) reported at least one SAE:

- One subject developed a Grade 3 deep vein thrombosis.

- One subject developed herpes simplex, herpes zoster, and deep vein thrombosis (all Grade 2), and lymphadenopathy (Grade 3).

- One subject reported a Grade 4 suicide attempt.
- One subject developed Grade 3 pelvic inflammatory disease.
- One subject developed Grade 3 gastritis.

In Cohort IIA, 3 subjects (13%) reported at least one SAE:

- One subject developed Grade 3 aggression and abnormal behaviour.
- One subject developed Grade 1 respiratory distress.
- One subject developed Grade 3 pneumonia.

The intensity of most SAEs in Cohort I and IIA was considered Grade 3 by reporting investigators. None of the SAEs resulted in permanent discontinuation from IP and withdrawal from the study. None of the SAEs were deemed related to study drug by the investigators.

With a limited number of study subjects and without a comparator, it is not possible to directly ascertain whether the serious adverse events reported from Cohort IIA are caused by dolutegravir treatment. Most subjects either had pre-existing conditions, belonged to a group with increased baseline risk regarding the events described or that the event was of a nature where a causal link to dolutegravir treatment is unlikely. Depression and suicidal ideation are currently listed in the Tivicay SmPC. Regarding the two cases of deep vein thrombosis in Cohort I, 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.

Laboratory findings

Clinical chemistry analyses were carried out on the AT population and were not carried out under fasted conditions. However, if triglycerides were Grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting lipid profile (triglycerides, cholesterol, high density lipoprotein [HDL], and low density lipoprotein [LDL]) was to be drawn.

Laboratory events were reported by 21 (91%) subjects in Cohort I and by 22 (96%) subjects in Cohort IIA. In Cohort I, two laboratory events, lipase increased and neutrophil count decreased were considered serious or clinically significant by the investigator. In Cohort IIA, no laboratory events were considered serious or clinically significant by the investigator. Three subjects (13%) in each cohort experienced a laboratory event that was of Grade 3 or higher intensity. None of the serious or Grade 3 or higher laboratory events in either cohort were considered related to study drug by the investigator.

Table 28. All Laboratory Events by Cohort Worst Grade for Each Subject on Each Subcategory Reported (Incidence >0% in One or More Cohorts) - All Treated Population – Curt-off date 15 January 2016

	Cohort I (N=23)#				Cohort IIA (N=23)##				Total (N=46)			
	Grade				Grade				Grade			
	1	2	3	4	1	2	3	4	1	2	3	4
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients with one or more events	11 (47.8)	6 (26.1)	3 (13.0)	1 (4.3)	7 (30.4)	12 (52.2)	3 (13.0)	0 (0)	18 (39.1)	18 (39.1)	6 (13.0)	1 (2.2)
Investigations	11 (47.8)	6 (26.1)	3 (13.0)	1 (4.3)	7 (30.4)	12 (52.2)	3 (13.0)	0 (0)	18 (39.1)	18 (39.1)	6 (13.0)	1 (2.2)
Alanine aminotransferase increased	4 (17.4)	1 (4.3)	0 (0)	0 (0)	2 (8.7)	2 (8.7)	0 (0)	0 (0)	6 (13.0)	3 (6.5)	0 (0)	0 (0)
Aspartate aminotransferase increased	3 (13.0)	0 (0)	0 (0)	0 (0)	5 (21.7)	1 (4.3)	0 (0)	0 (0)	8 (17.4)	1 (2.2)	0 (0)	0 (0)
Blood albumin decreased	3 (13.0)	0 (0)	0 (0)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	4 (8.7)	1 (2.2)	0 (0)	0 (0)
Blood alkaline phosphatase abnormal	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)
Blood alkaline phosphatase increased	1 (4.3)	0 (0)	0 (0)	0 (0)	3 (13.0)	1 (4.3)	0 (0)	0 (0)	4 (8.7)	1 (2.2)	0 (0)	0 (0)
Blood bicarbonate decreased	11 (47.8)	0 (0)	0 (0)	0 (0)	8 (34.8)	1 (4.3)	0 (0)	0 (0)	19 (41.3)	1 (2.2)	0 (0)	0 (0)
Blood bilirubin increased	3 (13.0)	1 (4.3)	1 (4.3)	0 (0)	1 (4.3)	3 (13.0)	2 (8.7)	0 (0)	4 (8.7)	4 (8.7)	3 (6.5)	0 (0)
Blood calcium decreased	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)
Blood calcium increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)
Blood cholesterol increased	1 (4.3)	1 (4.3)	0 (0)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	2 (4.3)	2 (4.3)	0 (0)	0 (0)
Blood creatine phosphokinase increased	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)
Blood creatinine increased	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)
Blood glucose decreased	4 (17.4)	3 (13.0)	0 (0)	0 (0)	8 (34.8)	3 (13.0)	0 (0)	0 (0)	12 (26.1)	6 (13.0)	0 (0)	0 (0)
Blood glucose increased	2 (8.7)	0 (0)	0 (0)	0 (0)	3 (13.0)	0 (0)	0 (0)	0 (0)	5 (10.9)	0 (0)	0 (0)	0 (0)
Blood phosphorus decreased	2 (8.7)	1 (4.3)	0 (0)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	3 (6.5)	2 (4.3)	0 (0)	0 (0)
Blood potassium decreased	4 (17.4)	0 (0)	0 (0)	0 (0)	2 (8.7)	0 (0)	0 (0)	0 (0)	6 (13.0)	0 (0)	0 (0)	0 (0)
Blood potassium increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)

Blood sodium decreased	6 (26.1)	0 (0)	0 (0)	0 (0)	7 (30.4)	0 (0)	0 (0)	0 (0)	13 (28.3)	0 (0)	0 (0)	0 (0)
Blood sodium increased	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7)	0 (0)	0 (0)	0 (0)	2 (4.3)	0 (0)	0 (0)	0 (0)
Haemoglobin decreased	1 (4.3)	0 (0)	0 (0)	0 (0)	4 (17.4)	1 (4.3)	0 (0)	0 (0)	5 (10.9)	1 (2.2)	0 (0)	0 (0)
Lipase increased	0 (0)	0 (0)	1 (4.3)	0 (0)	2 (8.7)	0 (0)	0 (0)	0 (0)	2 (4.3)	0 (0)	1 (2.2)	0 (0)
Low density lipoprotein increased	0 (0)	1 (4.3)	0 (0)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	1 (2.2)	2 (4.3)	0 (0)	0 (0)
Neutrophil count decreased	1 (4.3)	2 (8.7)	1 (4.3)	1 (4.3)	4 (17.4)	1 (4.3)	1 (4.3)	0 (0)	5 (10.9)	3 (6.5)	2 (4.3)	1 (2.2)
Platelet count decreased	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (2.2)	0 (0)	0 (0)
White blood cell count decreased	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (2.2)	0 (0)

#Per target dose of ~1 mg/kg and weight bands, 19 subjects received 50mg/day and 4 subjects received 35mg/day. ##Per target dose of ~1 mg/kg and weight bands, 1 subject received 70mg/day, 5 subjects received 50mg/day, 6 subjects received 35mg/day, 8 subjects received 25mg/day, and 3 subjects received 20mg/day. N = Number of patients in each cohort. n (%) = Number (percent) of patients in each subcategory. Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Potentially Life-Threatening.

In Cohort I, there were 2 subjects with a Grade 3 laboratory AE (blood bilirubin increased and lipase increased) and 1 subject with a Grade 3 and Grade 4 laboratory AE (white blood cell decreased and neutrophil count decreased).

In Cohort IIA, there were 3 subjects with a Grade 3 laboratory AE (2 blood bilirubin increased and 1 neutrophil count decrease). There were no Grade 4 laboratory AEs in Cohort IIA

Liver Chemistries/Hepatobiliary Adverse Events

Small increases in mean total bilirubin were observed. Nine subjects had increases in blood bilirubin greater than or equal to Grade 1 (three Grade 1, three Grade 2, and three Grade 3). Eight out of the nine subjects were taking atazanavir, for which asymptomatic bilirubin elevations are a recognized/listed adverse reaction in the product labelling. One event of blood bilirubin increased was considered possibly related to DTG. The only AE reported from the Hepatobiliary disorders SOC was Grade 1 hepatomegaly in one subject. All liver enzymes and haematology values were normal for this subject so no underlying cause was suspected.

Renal Findings

In Cohort I and Cohort IIA, no cases of renal failure were reported. Two subjects experienced Grade 1 proteinuria. One of these experienced Grade 1 proteinuria that was associated with haematuria. This subject had an elevated albumin/creatinine ratio of 265.5 µg/mg at Baseline, which had decreased to 87.2 µg/mg at Week 48. The subject is being followed in a renal clinic, but no underlying cause has so far been identified. The second subject experienced Grade 1 proteinuria, which was considered possibly related to DTG. This subject had a normal albumin/creatinine ratio of 2.3 µg/mg at Baseline and it remained normal at Week 24 (2.6 µg/mg). There was no result reported for this subject at Week 48.

Table 29. Mean Change from Baseline in Serum Creatinine – AT Population

Cohort	Actual Relative Time	N	Baseline Mean	Mean	Mean Change from Baseline (min, max)	Median Change from Baseline
Cohort I[a]	Baseline	23	0.58	0.58		
	Week 2	23	0.58	0.65	0.07 (-0.10, 0.19)	0.09
	Week 4	22	0.58	0.65	0.07 (-0.10, 0.27)	0.09
	Week 12	21	0.59	0.69	0.10 (-0.08, 0.33)	0.10
	Week 24	23	0.58	0.73	0.15 (-0.07, 0.35)	0.16
	Week 48	22	0.57	0.68	0.12 (-0.10, 0.40)	0.10
Cohort IIA[b]	Baseline	21	0.42	0.42		
	Week 2	21	0.42	0.49	0.05 (-0.26, 0.29)	0.06
	Week 4	20	0.42	0.49	0.06 (-0.26, 0.35)	0.05
	Week 12	20	0.40	0.49	0.07 (-0.08, 0.30)	0.03
	Week 24	19	0.40	0.52	0.11 (-0.02, 0.27)	0.10
	Week 48	14	0.43	0.53	0.09 (-0.03, 0.24)	0.09

The non-progressive increase in serum creatinine is well-described in adult patients and considered related to dolutegravir blocking the organic cation transporter 2 (OCT-2).

Immunological events

In Cohort I and Cohort IIA, there were no cases of hypersensitivity or IRIS reported. No Grade 3 or Grade 4 rashes and no serious skin reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or erythema multiform were reported. There were two cases of stomatitis reported.

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 AEs

There were no adverse events that resulted in discontinuation of study drug.

2.6.1. Discussion on clinical safety

The overall safety profile of dolutegravir is considered favourable in adult subjects, with comparable or superior tolerability compared to the active control agents used in pivotal studies. The spectrum and frequency of clinical adverse reactions in this small sample do not raise any new safety signals.

Potential hepatotoxicity has previously been investigated in detail, as this was seen in primates exposed to high doses of dolutegravir, but has not been verified in clinical studies. The laboratory findings regarding bilirubin increase is likely often related to concomitant treatment with atazanavir.

In the specific laboratory paediatric safety data set, there is an increased frequency of hypoglycaemia and low bicarbonate. After reviewing the response from the MAH on the aetiology and confounding factors of these observations it is concluded that they do not currently indicate a safety issue, but the MAH should ensure that bicarbonate levels are measured adequately in future cohorts of the P1093 study to exclude possible causes of *pseudo* hypobicarbonatemia and allow adequate monitoring of participants.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

No new or paediatric-specific safety issues have emerged from this very small sample.

2.7. Risk Management Plan

The CHMP and PRAC endorsed the Risk Management Plan version 12.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions Hepatic disorders Drug Interaction with dofetilide Drug resistance 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) Renal disorders Gastrointestinal intolerance/erosions Lipase elevations (Grade 3 and 4) Musculoskeletal events/elevated CK Increased occurrence of IRIS
Missing information	Use in the elderly Use in pregnancy/breastfeeding Use in patients with severe hepatic impairment Long term safety

The list of safety concerns were not changed in the context of the extension of indication.

Pharmacovigilance plan

No new or additional pharmacovigilance activity was requested within the procedure.

Risk minimisation measures

The risk minimisation measures remain the same.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tivicay (dolutegravir) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal products authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

DTG has a well-documented effect in inhibiting HIV-1 replication in adult patients, is generally well-tolerated and offers a decreased risk of viral resistance development compared to other currently available INIs. As the pharmacologic target is of viral origin, there is little doubt that DTG will be also efficient in children aged 6-12 years, providing that drug exposure and viral susceptibility is comparable to what is seen in adults. The data provide sufficient reassurance in this sense.

Uncertainty in the knowledge about the beneficial effects

Relevant uncertainties regarding the beneficial effects of dolutegravir in treating children aged 6-12 years pertain to the PK/PD bridge necessary to infer efficacy from the pivotal studies in adult subjects.

The composition of the 10 mg in SPRING-1 is different compared to the tablets used in the paediatric study ING112578. In addition the composition is not proportional to the 50 mg tablet. It also behaves differently compared to the 50 mg tablet in the in vitro dissolution assay. The number of paediatric subjects in the present clinical study receiving the 10 mg tablet where exposure data is available is notably low. The relative bioavailability of the 10 mg tablet versus the approved 50 mg tablet has not been determined in a dedicated study. A difference in relative bioavailability cannot be ruled out, although not identified in the modelling analysis. Should such a difference exist, it could confound the estimated drug disposition parameters even though the model fits the data.

For this application, where the amount of PK data is notably limited it is crucial to use both rich and sparse PK data to draw conclusions. Further, the data needs to be viewed or analysed simultaneously to assess the influence of age/body weight and to manage the imbalance between age groups. The model takes rich PK data as well as sparse PK data into account and estimates both an average PK profile and the associated variability. As such, this is a post hoc analysis and there is an inherent uncertainty which cannot be avoided.

Risks

Unfavourable effects

In adults, dolutegravir has a favourable safety profile at the once daily dose, used as PK reference in this application, as well as with the dose of 50 mg b.i.d. used in patients with prior INI resistance. The clinically observed adverse events are in line with what has been previously described in adults, and are generally benign.

Uncertainty in the knowledge about the unfavourable effects

Due to the limited size of the sub-cohorts in the P1093 study and sparse post-marketing data available from children treated within the current paediatric indication (12-18 years), it cannot be formally excluded that there are age-specific unfavourable effects that have not been detected.

Benefit-risk balance

Importance of favourable and unfavourable effects

Dolutegravir is an important part of the pharmacological armamentarium in the treatment of HIV-1 in adults and will likely become so also in children, provided that the dosing scheme ensures adequate exposure in children from 6 years of age. Due to the established safety profile, the negative consequences of potential PK overexposure versus the 50 mg tablet in adults are judged to be less important compared to potential under exposure. With too low exposure in terms of trough concentration, there is a concern of reduced efficacy and development of resistance relevant to all available drugs in the INI class, and also development of resistance to the co-treating agents. That said, it is also recognised that dolutegravir at the exposures seen with 50 mg in the adult population has a robust barrier to resistance and an impressive therapeutic margin.

Benefit-risk balance

This application relies on the pharmacokinetic bridge that would allow the inference of efficacy and safety data from pivotal adult studies. Due to the limited data, population modelling is needed for drawing conclusions about dolutegravir pharmacokinetics in children between 6 years and 12 years of age.

The population model of dolutegravir PK in children is an interpretation of existing data. It relies on previous knowledge obtained in the adult population as well as basic principles of clinical pharmacokinetics, especially in children. The model is similar to the adult Population PK model for dolutegravir. In addition, the 70 kg reference values for oral clearance and volume of distribution are similar for the adult and paediatric model.

The PK data are sparse, variable and heterogeneous in terms of age, body weight, doses and PK sampling but can nevertheless be described by the model. The population PK model is considered qualified for its purpose and the proposed dosing appears adequate although there is an added level of uncertainty regarding the relative bioavailability of the 10 mg tablet. This is considered acceptable in this particular case, given the wide therapeutic window of dolutegravir.

To improve the precision in modelling for the remaining parts of the P1093 study, the MAH committed to perform a relative bioavailability study to compare the 10 mg and the dispersible dolutegravir tablet formulations, to the 50 mg tablet.

3.1. Conclusions

The overall Benefit/Risk balance of Tivicay in children aged ≥6 to <12 years is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tivicay 10mg, 25mg film-coated 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 above 6 years of age.

The CHMP therefore recommends the granting of the extension to the marketing authorisation subject to the following conditions:

Other 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.

These conditions fully reflect the advice received from the PRAC.

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

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

Extension of Indication to include paediatric patients from 6 years of age infected with HIV for Tivicay 50mg film-coated tablets; as a consequence, sections 4.1, 4.2, 4.5, 4.7, 4.8, 5.1, 5.2, and 5.3 of the SmPC are updated based on the analysis of the pivotal study ING112578 and the non-clinical investigations performed for the paediatric development program. The Package Leaflet is updated in accordance.