Module 1.8.2

European Union Risk Management Plan (EU-RMP) for TIVICAY (dolutegravir)

STATEMENT REGARDING LICENSE AGREEMENTS

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RMP version to be assessed as part of this application	
RMP Version number	22.0
Data lock point for this RMP	28 February 2025
Date of final sign off	15 May 2025

Rationale for submitting an updated RMP
The RMP has been updated to include the 2024 Antiretroviral Pregnancy Registry data. Update to the submission date for the final CSR for category 3 PASS study DOLOMITE-NEAT ID (208759) to September 2026. Post-authorisation exposure has been updated to the latest available data.

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in the present EU-RMP**
Part I: Product(s) Overview		No change
Part II: Safety Specification	Module SI: Epidemiology of the Indication(s) and target population(s).	No change
	Module SII: Non-Clinical part of the Safety Specification	No change
	Module SIII: Clinical trial exposure	No change
	Module SIV: Populations not studied in clinical trials.	No change
	Module SV: Post authorisation experience	Post-authorisation exposure data updated
	Module SVI: Additional EU requirements for the safety specification	No change
	Module SVII: Identified and Potential Risks.	Updated to add 2024 Antiretroviral Pregnancy Registry data.
	Module SVIII: Summary of Safety Concerns	No change
Part III: Pharmacovigilance Plan (including post authorisation safety studies).		Update to DOLOMITE NEAT ID (208759) Category 3 PASS study CSR submission date
Part IV: Plans for post-authorisation efficacy studies		No change
Part V: Risk minimization measures (including		No change

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in the present EU-RMP**
evaluation of the effectiveness of risk minimization activities).		
Part VI: Summary of RMP		Update to DOLOMITE NEAT ID (208759) Category 3 PASS study CSR submission date

Other RMP versions under evaluation		
RMP Version number	Submitted on	Procedure number
Not applicable		

Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
21.0	EMEA/H/C/002753/II/0093	28 November 2024

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

AAG	Alpha-1 acid glycoprotein
ABC	Abacavir
ADR	Adverse drug reaction
AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
AKI	Acute kidney injury
ALT	Alanine aminotransaminase
APR	Antiretroviral pregnancy registry
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransaminase
ATV	Atazanavir
AUC	Area under the concentration curve
BID	Twice daily
BMD	Bone mineral density
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CART	Combined antiretroviral therapy
CDC	Centre for disease and prevention control
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
Cmax	Maximum plasma concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disorder
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CSR	Clinical study report
CVD	Cardiovacular disease
DDI	Didanosine
DDI	Drug-drug interaction
DHPC	Direct Health Care Professional communication
DILI	Drug induced liver injury
DM	Diabetes Mellitus
DRV	Darunavir
DT	Dispersible tablet
DTG	Dolutegravir
EACS	European AIDS Clinical Society
ECG	Electrocardiogram
EEA	European Economic Area
EFV	Efavirenz
EMA	European Medicines Agency
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
ESRD	End stage renal disease
ETV	Etravirine
EU	European Union
EVG	Elvitegravir

FCT	Film coated tablet
FDA	Food and Drug Administration
FDC	Fixed dose combination
FTC	Emtricitabine
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
GTP	Guanosine triphosphate
GVP	Good Pharmacovigilance Practice
HAART	Highly active antiretroviral therapy
HAND	HIV associated neurocognitive disorders
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HSR	Hypersensitivity reaction
IMS	Intercontinental Medical Statistics
INSTI	Integrase inhibitor
IP	Investigational product
IRIS	Immune reconstitution inflammatory syndrome
IRR	incidence rate ratio
ISO	Integrated safety output
KS	Kaposi's sarcoma
LPV	Lopinavir
MAA	Marketing authorization application
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for regulatory activities
MI	Myocardial infarction
MRP	Multi drug resistant protein
NADM	Non-AIDS associated malignancy
NNRTI	Non- nucleoside reverse transcriptase inhibitor
NOAEL	No observable adverse effect level
NVP	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitor
NTD	Neural tube defects
OCT2	Organic cation 2 transporter
OI	Opportunistic infection
PASS	Post-authorisation safety study
PBRER	Periodic benefit risk evaluation report
PDVF	Protocol defined virological failure
PI	Protease inhibitor
PJP	Pneumocystits jiroveci pneumonia
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred term
PY	Patient or Person years
QD	Once daily

RAL	Raltegravir
RMP	Risk management plan
RNA	Ribonucleic acid
RSI	Reference Safety information
RTV	Ritonavir
SAE	Serious adverse event
SD	Standard deviation
SE	Single entity
SJS	Stevens Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
TBDR	Texas Birth Defects Registry
TDF	Tenofovir
TFQ	Targeted Follow up Questionnaire
TNF	Tumour necrosis factor
TB	Tuberculosis
TEN	Toxic epidermal necrolysis
UGT1A1	UDP glucuronsyltransferase 1A1
ULN	Upper limit of normal
USA	United States of America
WHO	World Health Organisation
WOCBP	Women of child-bearing potential
VH	ViiV Healthcare Ltd
3TC	Lamivudine

Trademark Information

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 Product Overview

Active substance(s) **(INN or common name)**	Dolutegravir
Pharmacotherapeutic group(s) (ATC Code)	Integrase inhibitor, J05AX12
Marketing Authorisation Holder/ Applicant	ViiV Healthcare Limited
Medicinal products to which this RMP refers	Dolutegravir
Invented name(s) in the European Economic Area (EEA)	TIVICAY
Marketing authorisation procedure	Centralised procedure
Brief description of the product	2-metal-binding integrase inhibitor
	Integrase inhibitors (INSTIs) are designed to block the action of the integrase viral enzyme, which catalyzes two key steps in the Human Immunodeficiency Virus (HIV) life cycle and is responsible for insertion of the viral genome into the DNA of the host cell.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD)
Indication(s) in the EEA	Current: <u>Film coated tablets</u> Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents and children of at least 6 years of age or older and weighing at least 14 kg. <u>Dispersible tablets</u> Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

<table>
<tr><td></td><td>Proposed: no changes proposed.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
<u>Film coated tablets</u>
Adults
Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class.
The recommended dose of dolutegravir is 50 mg orally once daily.
Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)
The recommended dose of dolutegravir is 50 mg twice daily.
Adolescents aged 12 and above, to less than 18 years, and weighing at least 20 kg
In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is 50 mg once daily. Alternatively, if preferred 25 mg may be taken twice daily. In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in adolescents.
Children aged 6 and above, to less than 12 years, and weighing at least 14 kg
In patients infected with HIV-1 without resistance to the integrase class, the recommended dose of dolutegravir is determined according to the weight of the child.
Pediatric dose recommendations for film-coated tablets
<table><tr><th>Body weight (kg)</th><th>Dose</th></tr><tr><td>14 to less than 20</td><td>40 mg once daily</td></tr><tr><td>20 or greater</td><td>50 mg once daily</td></tr></table>Alternatively, if preferred the dose may be divided equally into 2 doses, with one dose taken in the morning and one dose taken in the evening.
Alternative pediatric dose recommendations for film-coated tablets
<table><tr><th>Body weight (kg)</th><th>Dose</th></tr><tr><td>14 to less than 20</td><td>20 mg twice daily</td></tr><tr><td>20 or greater</td><td>25 mg twice daily</td></tr></table></td></tr>
</table>

In the presence of integrase inhibitor resistance, there are insufficient data to recommend a dose for dolutegravir in children.

Dispersible tablets

Adults

Patients infected with HIV-1 without documented or clinically suspected resistance to the integrase class

The recommended dose of dolutegravir is 30 mg (six 5 mg dispersible tablets) orally once daily.

Patients infected with HIV-1 with resistance to the integrase class (documented or clinically suspected)

The recommended dose of dolutegravir is 30 mg (six 5 mg dispersible tablets) twice daily.

Adolescents, children and infants aged 4 weeks and above and weighing at least 3 kg

Patients infected with HIV-1 without resistance to the integrase class

The recommended dose of dolutegravir is determined according to weight and age.

Pediatric dose recommendations for dispersible tablets

Body weight (kg)	**Dose**
3 to less than 6	5 mg once daily
6 to less than 10 < 6 months ≥ 6 months	 10 mg once daily 15 mg once daily
10 to less than 14	20 mg once daily
14 to less than 20	25 mg once daily
20 or greater	30 mg once daily

Alternatively, if preferred the dose may be divided equally into 2 doses, with one dose taken in the morning and one dose taken in the evening.

<table>
<tr><td></td><td>Alternative pediatric dose recommendations for dispersible tablets
<table><tr><th>Body weight (kg)</th><th>Dose</th></tr><tr><td>3 to less than 6</td><td>---</td></tr><tr><td>6 to less than 10
< 6 months
≥ 6 months</td><td>
5 mg twice daily
10 mg twice daily</td></tr><tr><td>10 to less than 14</td><td>10 mg twice daily</td></tr><tr><td>14 to less than 20</td><td>15 mg twice daily</td></tr><tr><td>20 or greater</td><td>15 mg twice daily</td></tr></table>
Patients infected with HIV-1 with resistance to the integrase class
There are insufficient data to recommend a dose for dolutegravir in integrase inhibitor resistant adolescents, children and infants
Proposed: no changes proposed.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td><u>Current:</u>
<u>Film-coated tablet (tablet).</u>
<u>Tivicay 10 mg film-coated tablets</u>
White, round, biconvex tablets approximately 6 mm in diameter debossed with ‘SV 572’ on one side and ‘10’ on the other side.
<u>Tivicay 25 mg film-coated tablets</u>
Pale yellow, round, biconvex tablets approximately 7 mm in diameter debossed with ‘SV 572’ on one side and ‘25’ on the other side.
<u>Tivicay 50 mg film-coated tablets</u>
Yellow, round, biconvex tablets approximately 9 mm in diameter debossed with ‘SV 572’ on one side and ‘50’ on the other side.
<u>Dispersible tablet.</u>
White, round, biconvex tablets approximately 6 mm in diameter debossed with ‘SV H7S’ on one side and ‘5’ on the other side.
Proposed: no changes proposed.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

SI.1 Human Immunodeficiency Virus (HIV)

TIVICAY is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents and children.

INCIDENCE AND PREVALENCE

Worldwide, in 2023, an estimated 39.9 million (range: 31.6–44.6 million) people were living with HIV infection, with a median prevalence among adults aged 15-49 years of 0.8% globally [UNAIDS, 2024a]. However, the global burden of HIV varies by country and region. In Western and Central Europe and North America, 2.3 million people (2.0-2.7 million) were living with HIV in 2023, with an adult prevalence of 0.2% [UNAIDS, 2024b]. In the United States alone, the CDC estimated that 1,238,000 people aged 13 and older were living with HIV in 2022, with an estimated prevalence of 0.4% [Centers for Disease Control and Prevention, 2024a].

Eastern and Southern Africa remains the most severely HIV-affected region, with approximately 1 in 17 adults (5.7%; 20.8 million) living with HIV, and accounting for the majority (52%) of people living with HIV worldwide [UNAIDS, 2024a; UNAIDS, 2024c]. Eastern and Southern Africa also accounted for 35% of the estimated 1.3 million new HIV infections globally in adults and children in 2023 [UNAIDS, 2024a]. Western and Central Africa does not trail far behind the rest of the sub-continent, with an adult HIV prevalence of 1.2% (5.1 million), and 15% of all new HIV infections in adults and children globally in 2023 [UNAIDS, 2024a; UNAIDS, 2024d]. The number of people living with HIV in sub-Saharan Africa is nearly 4 times the number in Asia and the Pacific, where 6.7 million people (0.2% among adults aged 15-49 in the region) are living with HIV [UNAIDS, 2024e]. After sub-Saharan Africa, the regions with the highest adult HIV prevalence in 2023 were the Caribbean (1.2%) and Eastern Europe and Central Asia (1.2%) [UNAIDS, 2024f; UNAIDS, 2024g]. The lowest HIV prevalence in adults (<0.1%) is found in the Middle East and North Africa region [UNAIDS, 2024h].

Globally, about 39% fewer people acquired HIV in 2023 compared with 2010, but progress has been uneven across regions. Approximately 1.3 million (1.0-1.7 million) adults and children acquired HIV in 2023, down from approximately 2.1 million (1.7-2.7 million) people who acquired HIV in 2010 [UNAIDS, 2024a]. The sharpest decline in new HIV infections in all ages occurred in Eastern and Southern Africa (59%) between 2010 and 2023, dropping from 1.1 million (880,000-1.4 million) annual HIV infections in 2010 to 450,000 (360,000-580,000) new infections in 2023 [UNAIDS, 2024c]. However, the incidence of HIV infection in the Middle East and North Africa, and Eastern Europe and Central Asia regions has increased (by 116% and 20% respectively) since 2010 [UNAIDS, 2024h; UNAIDS, 2024g]. Incidence is also increasing in Latin America (by 9% between 2010 and 2023) [UNAIDS, 2024i]. In 2023, an estimated 140,000 (120,000-160,000) new infections occurred in Eastern Europe and Central Asia. By comparison,

the estimated 2023 incidence in Western and Central Europe and North America was 56,000 new infections (45,000-67,000) [UNAIDS, 2024a]. In the United States, the CDC estimates that there were 31,800 new HIV infections in 2022, a 12% decline in annual infections from 2018 (36,200) [Centers for Disease Control and Prevention, 2024a].

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease

Globally, certain populations such as young women and girls, sex workers, men who have sex with men, transgender people and injection drug users have a higher burden of disease compared with the general population. For instance, data show that HIV prevalence among men who have sex with men is approximately 7.7% higher than that in the general population [UNAIDS, 2024a]. HIV prevalence is 2.3% higher than the general population prevalence among women and girls aged 15-24 years in eastern and southern Africa. Among injection drug users HIV prevalence was approximately 5% higher than for the general population [UNAIDS, 2024a]. Sex workers have an estimated HIV prevalence 3% higher than that of the general population and transgender people have an estimated HIV prevalence 9.2% higher than that of the general population [UNAIDS, 2024a].

Globally, the steepest declines in numbers of new HIV infections have been among children aged 0–14 years. In 2023, an estimated 120,000 (83,000–170,000) children aged 0-14 acquired HIV infection globally. This represents a 62% decline since 2010, when 300,000 (220,000–440,000) children acquired HIV infection [UNAIDS, 2024a]. The decreased incidence has been greatest in Eastern and Southern Africa, where new infections declined by 73% between 2010 and 2023. The majority of new HIV infections in children in 2023, however, were still reported in Eastern and Southern Africa (50,000; 34,000-79,000), followed by Western and Central Africa (48,000; 36,000 – 63,000) [UNAIDS, 2024a]. In 2023, the estimated number of children aged 0-14 living with HIV globally was 1.4 million (1.1–1.7 million) [UNAIDS, 2024a]. In the United States, a total of 1,126 children ≤13 years old were living with diagnosed HIV in 2022 [Centers for Disease Control and Prevention, 2024b]. In 2022, 62 children aged <13 were newly diagnosed with HIV in the United States and 6 territories and freely associated states [Centers for Disease Control and Prevention, 2024b].

In high-income countries, racial minorities typically have a higher burden of disease. In the US for instance, racial minorities are disproportionately affected, with African Americans bearing a higher burden of the epidemic. In 2022, the rate of diagnosis among Black /African American persons aged ≥13 years was 7.8 times the rate among White persons [Centers for Disease Control and Prevention, 2024a]. African Americans made up 12% of the US population, and 37% of new HIV diagnoses [Centers for Disease Control and Prevention, 2024c]. In the United States 22% of people newly diagnosed with HIV infection in 2022 acquired through heterosexual transmission [Centers for Disease Control and Prevention, 2024e].

Globally, 72% (95% CI: 65-80) of individuals living with HIV are estimated to have suppressed viral loads in 2023, up from 38% in 2015 [UNAIDS, 2024a]. The proportions of people living with HIV who were virally suppressed in 2023 were highest in Western

& Central Europe and North America (70%), East and Southern Africa (78%), Western and Central Africa (70%), Asia and the Pacific (65%), and Latin America (67%) [UNAIDS, 2024b; UNAIDS, 2024c; UNAIDS, 2024d; UNAIDS, 2024e; UNAIDS, 2024i]. The lowest rates of viral suppression were in the Middle East and North Africa (45%) and Eastern Europe and Central Asia (42%) [UNAIDS, 2024h; UNAIDS, 2024g].

In the United States, 65% of individuals diagnosed with HIV were virally suppressed in 2022 [Centers for Disease Control and Prevention 2024c]. The lowest percentages of viral suppression were among Black/African American persons (61%) and women overall (64%) [Centers for Disease Control and Prevention, 2024d]. In the European Union, 93% of people living with HIV on treatment are virally suppressed [European Centre for Disease Prevention and Control, 2024].

Risk factors for the disease

Only specific fluids, such as blood, semen, vaginal secretions, and breast milk, from an HIV-infected person can transmit HIV. These specific fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the bloodstream (from a needle or syringe) for transmission to possibly occur. Primary risk factors for HIV transmission include unprotected vaginal and anal sex, as well as the transfusion of contaminated blood or tissue transplantation and the sharing of contaminated needles and/or syringes, particularly between injection drug users. Out of 31,800 estimated new HIV infection in the US in 2022, 67 % were among gay, bisexual and men who reported male-to-male sexual contact; 22% were among people who reported heterosexual contact and 7% were among people who inject drugs [Centers for Disease Control and Prevention, 2024e]. HIV can also be transmitted to a child during pregnancy, delivery, and breastfeeding. People living with HIV who are taking ART and have an undetectable viral load will not transmit HIV to their sexual partners [World Health Organization, 2023].

SI.1.2 The main existing treatment options

Treatment of HIV requires use of combination antiretroviral therapy. The choice of the combination regimen depends on the status of the patient, particularly in terms of plasma HIV viral load, CD4 cell counts, any previous treatment(s), prior treatment failure, and intolerance to treatment. Treatment guidelines have been developed to guide clinicians in selecting appropriate treatments for patients. The most commonly used guidelines are those developed by the World Health Organization (WHO) [World Health Organization, 2021], the European AIDS Clinical Society (EACS) [EACS, 2023] and the Department of Health and Human Services (DHHS) in the USA [Department of Health and Human Services, 2023a]. These global guidelines recommend an INSTI (specifically DTG) plus 2 NRTIs as part of preferred first line therapy for treatment-naïve adults. However, many countries have developed their own national guidelines to reflect the local epidemiological situation.

The management of treatment-experienced patients is a different process from that of treatment-naïve patients. Treatment-experienced patients may require different combinations of drugs due to adverse events, consideration of drug-drug interactions

(DDIs) for patients requiring concomitant medication due to co-morbidities, drug resistance and the desire to lower pill burden, simplifying dosing and regimen. Special populations, such as pregnant women and patients co-infected with tuberculosis or hepatitis B or C infection may also require different regimens based on their specific situations to decrease the risk of adverse outcomes such as congenital anomalies (in the case of pregnant women), or DDIs in the case of co-infected patients.

Treatment options in children are more limited compared to adults. Recommended treatment regimens are available for children in the EU [EACS, 2023] and US [DHHS, 2023b]. The WHO guidelines are often used in other countries where there is a high level of paediatric HIV [World Health Organization, 2021].

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

The number of people dying from Acquired Immune Deficiency Syndrome (AIDS)-related causes began to decline in the mid-2000s because of scaled-up antiretroviral therapy and the steady decline in HIV incidence since the peak in 1997. In 2023, an estimated 630,000 (500,000– 820,000) people died from AIDS-related causes worldwide, representing a 51% decline in AIDS-related mortality from 2010, when 1.3 million (95% CI: 1.0 million–1.7 million) AIDS-related deaths occurred [UNAIDS, 2024a]. Western and Central Europe and North America experienced a 34% decline in AIDS-related deaths from 2010 to 2023; in contrast, Eastern Europe and Central Asia experienced a 34% increase in AIDS-related mortality [UNAIDS, 2024b; UNAIDS, 2024g]. In 2023 there were an estimated 13,000 (9,400-17,000) AIDS-related deaths in Western and Central Europe and North America, and 44,000 (35,000-54,000) AIDS-related deaths in Eastern Europe and Central Asia [UNAIDS, 2024b; UNAIDS, 2024g]. Western and Central Africa experienced a 55% decline in AIDS-related deaths between 2010 and 2023 and Asia and the Pacific experienced a 51% decline in AIDS-related deaths between 2010 and 2023 [UNAIDS, 2024d; UNAIDS, 2024e]. More modest declines occurred in Latin America (28%) and Middle East and North Africa (6%) during the same period [UNAIDS, 2024i; UNAIDS 2024h].

Globally, deaths among children younger than 9 years of age are reported to also be declining. Compared to 2010 there was a decline of 60% in AIDS-related deaths among children aged 0-9 years by the end of 2020, while among adolescents (aged 10 to 19 years) the decline was only of 37% [UNAIDS, 2021].

SI.1.4 Important co-morbidities

Opportunistic infections

Hepatitis C virus (HCV) / Hepatitis B virus (HBV) co-infection and liver disease

Malignancies

Cardiovascular disease

Metabolic conditions

Musculoskeletal disorders

HIV-Associated Neurocognitive Disorders (HAND)

Pulmonary disorders

Kidney disease

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

Table 1 Key safety findings from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Single and repeat dose toxicity	
Gastrointestinal intolerance: Gastrointestinal (GI) intolerance was seen in repeat dose toxicity studies up to 38 weeks in monkeys and 26 weeks in rats. In monkeys, the most sensitive species, GI intolerance was characterized primarily by vomiting, diarrhoea, and associated mortality as well as GI lesions, and by gastric lesions in the rat. The GI intolerance is believed to be the result of local irritation by the drug and not systemic toxicity. The fact that affected animals had comparable exposures to animals at dose levels which were not affected is supportive of the conclusion that the GI toxicity is due to the larger local exposure in the GI tract in those dose groups. The no observable adverse effect level (NOAEL) for the monkey 38 week dosing period was 15 mg/kg/day (Day 270 gender mean area under the concentration curve (AUC) 0-24 and Cmax of 39 μg.h/mL and 5.1 μg/mL, respectively), which corresponds to: 0.7x and 1.4x the human AUC and Cmax exposure, respectively, at a 50 mg once daily dose (AUC0-24 of 53.6 μg.h/mL and Cmax of 3.7 μg/mL); and 0.5x and 1.2x the human AUC and Cmax exposure, respectively, at a 50 mg twice daily dose (AUC0-24 of 75.1 μg.h/mL and Cmax of 4.2 μg/mL).	These non-clinical findings have not translated into significant clinical findings in clinical studies to date. (See SVII.2). GI effects seen in non-clinical studies are likely due to local effect and local exposure in these studies which have provided significant cover. The NOAEL for the monkey 38-week dosing period (15 mg/kg/day) is 15x and 8x the human mg/kg equivalent dose (based on 50 kg human), and 5x and 3x the human mg/m^2 equivalent dose for a 50 mg once daily and 50 mg twice daily dose, respectively.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Renal findings: Renal tubule dilatation occurred in monkeys given 1000 mg/kg/day in the 14-day study. blood urea nitrogen (BUN) and creatinine were increased while serum sodium and chloride were decreased in these monkeys. In the 38 week monkey toxicity study, renal findings were restricted to increased BUN (12.5x) and creatinine (3.7x), and slight dilatation of distal renal tubules of the kidneys and cellular and hyaline casts in the moribund animal in the 50 mg/kg/day group (euthanized on Day 55). These findings (in both the 14 day and 38 week monkey toxicity studies) were considered secondary to the moribund condition related to GI toxicity. The NOAEL in the 38-week toxicity study was 15 mg/kg/day. Exposure (end of study, gender mean) at 15 mg/kg/day was 39 μg.h/mL, which corresponds to ~0.7x the anticipated human exposure for a 50 mg once daily dose or ~0.5x the anticipated human exposure for a 50 mg twice daily dose.	See SVII.2
Hepatology findings: Hepatocellular single cell necrosis and diffuse hepatocellular hypertrophy and/or vacuolation occurred in male monkeys given 1000 mg/kg/day in the 14 day study. Additional changes included transient alanine aminotransaminase (ALT) increases at ≥300 mg/kg/day, increased aspartate aminotransaminase (AST), bilirubin, γGTP (guanosine triphosphate), and triglycerides at 1000 mg/kg/day and decreased total cholesterol at 1000 mg/kg/day. The NOAEL was 100 mg/kg/day (~4x or 3x above the expected human exposure for a 50 mg once daily or twice daily (BID) dose, respectively). There were no treatment related findings in longer studies at lower doses.	See SVII.2

Key Safety findings (from non- clinical studies)	Relevance to human usage
Reproductive Toxicity	
DTG had no effects on male or female fertility in rats and no effect on embryofetal development in pregnant rats or rabbits at ≤1000 mg/kg/day. In animal reproductive toxicity studies, no adverse development outcomes, including neural tube defects (NTDs), were identified. Based on animal data, DTG is not anticipated to increase the risk of adverse developmental (or reproductive) outcomes in humans when used in accordance with dosing information in the product label.	There is a large amount of observational data on DTG use in pregnancy available from sources including the APR (over 1800 exposures), and two large birth outcome surveillance studies in Botswana (Tsepamo) and Eswatini (over 14,000 women) In Version 15 of the RMP, NTDs were added to the RMP as a potential risk for DTG based on data from a birth outcomes surveillance study conducted in Botswana (see Module SVII for further information). Data updating the characterisation of this risk supported RMP update to Version 19. See SVII.2 for further information
Developmental toxicity	
Juvenile toxicity	
In a juvenile toxicity study in rats DTG administration from Day 4 postpartum (pp) through Day 63 pp resulted in two preweaning deaths at 75 mg/kg/day. Over the preweaning treatment period, mean body weight gain was decreased in this group and the decrease persisted throughout the entire study for females during the post weaning period. Although the 75 mg/kg/day females gained weight at a comparable pace with the control group, the decrease in gain that occurred in the preweaning period was not regained; the 75 mg/kg males gained weight at a faster pace than the control group and essentially caught up to the control group. These body weight effects did not result in an effect on growth as measured by length of a long bone at the end of the study. There were no test article-related differences among the groups for the age at which offspring attained physical signs of sexual maturation (vaginal opening or balano-preputial skinfold separation) and no treatment related changes in stage-dependent evaluation	These data do not suggest an increased risk to the pediatric patient population of 6 years and older. The juvenile toxicity study in rats was conducted to support enrollment of children as young as a preterm infant. The findings of the preweaning deaths and decreased body weight gain were limited to the preweaning period (earlier than Day 21 pp, during which there were higher systemic exposures; this period is not applicable to 6-year-old children). There were no toxicity findings in the rat after weaning at the highest dose tested of 75 mg/kg/day. The systemic exposure at 75 mg/kg/day in the older rats (gender averaged Day 32 pp AUC = 980 μg.h/mL) is more comparable to 6-year-old children given DTG and is ~ 21 times higher than humans at the current target pediatric exposure of 46 μg.h/mL. There were no new target organs identified in juveniles compared to adults.

Key Safety findings (from non- clinical studies)	Relevance to human usage
of spermatogenesis. There were no new target organs identified in juveniles compared to adults and the NOAEL in juvenile rats was 2 mg/kg/day.The systemic exposure values in males on Day 13 pp were as follows: $AUC_{[0-24]}$ 303 µg.h/mL, C_{max} 15.2 µg/mL .On Day 32 pp the $AUC_{[0-24]}$ was 85.7 µg.h/mL and the C_{max} was 7.71 µg/mL with no appreciable difference in gender. This study supports the clinical use of DTG in children ≥ 6 years of age. DTG was not immunotoxic, as assessed by TDAR, in adult rats at doses ≤1000 mg/kg/day. In juvenile rats, there were no test article-related effects on TDAR, and no effects on lymphocyte subsets (T cells, both CD4 and CD8 subsets, and B cells) and CD4 or CD8 T cell receptor Vβ usage in peripheral blood.	
DTG administration resulted in suppressed body weight gain and decreased food consumption during the lactation period in a pre- and postnatal development study in rat dams (F0) receiving 1000 mg/kg/day. Associated with the maternal toxicity, decreased body weights were noted in the offspring (F1) in the 1000 mg/kg group from pre-weaning until adolescence. There were no effects on pregnancy, parturition or nursing behaviour. Due to the decreased body weights of the offspring observed at higher doses the NOAEL for postnatal development of the offspring (F1) was 50 mg/kg/day. At this dose the anticipated human exposure is ~ 25x or 18x above a 50 mg once daily or BID dose, respectively. Based on the fact that effects on offspring body weights were noted at doses where maternal toxicity was observed, and the presence of considerable safety margins expected at the proposed clinical doses, there is minimal risk for adverse effects on post-natal development in offspring of mothers receiving DTG.	There is a large amount of observational data on DTG use in pregnancy available from sources including the APR (over 1800 exposures), and two large birth outcome surveillance studies in Botswana (Tsepamo) and Eswatini (over 14,000 women). See SVII.2 for further information.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Genotoxicity	
DTG did not cause gene mutations or chromosomal damage in two definitive in vitro tests (bacterial mutation assay and mouse lymphoma L5178Y cell assay), or in an in vivo oral rat micronucleus test. Therefore, based on these data, DTG does not pose a genetic toxicity risk to humans.	Not applicable
Carcinogenicity	
DTG was not carcinogenic to mice at doses up to 500 mg/kg/day or rats at doses up to 50 mg/kg/day following oral administration for 104 consecutive weeks. In both species, DTG administration had no effect on survival, there were no treatment related clinical signs, and there were no neoplastic or non-neoplastic findings attributed to DTG. The NOAEL for non-neoplastic findings after chronic oral administration was the high dose of 500 mg/kg/day for mice and 50 mg/kg/day for rats. When compared to the expected human exposure for a 50 mg once daily (QD) or BID dose, the systemic exposures were ~20X or ~14X higher for mice and ~17X or ~12X higher rats.	Not applicable
General safety pharmacology:	
No treatment-related behavioral or overt pharmacological effects were noted in conscious male rats at ≤500 mg/kg (the highest dose tested). Systemic exposure at 500 mg/kg is estimated to be ~24X or 21X above the expected human C_{max} of DTG administered 50 mg QD or BID, respectively Single oral doses of DTG at ≤500 mg/kg did not produce any effect on respiratory functional parameters in male rats when monitored for up to 6 hours following dosing. Systemic exposure at 500 mg/kg is estimated to be approximately 32X or 23X above the	There were no findings from safety pharmacology studies that would indicate an unacceptable risk for oral administration of DTG to patients

Key Safety findings (from non- clinical studies)	Relevance to human usage
expected human AUC_{0-24} of DTG administered 50 mg QD. In male monkeys, single oral doses of DTG at doses up to 1000 mg/kg had no effect on arterial blood pressures, heart rate or electrocardiographic (ECG) parameters when monitored for 24 hours after dosing at a C_{max} ~5X above the expected human C_{max} of DTG when administered 50 mg QD or BID. Additionally, there were no treatment related effects in ECG parameters measured during the repeat dose monkey toxicity studies up to 38 weeks at doses ≤1000 mg/kg/day. The effect of a series of DTG concentrations (≤8.38 µg/mL) on hERG tail current was studied. An IC_{50} could not be determined as only 16.1% inhibition of hERG channel tail current occurred at the highest concentration, 20 µM. The high dose (20 µM or 8.4 µg/mL) is approximately 227X and 200X, respectively, above the free C_{max} obtained with a 50 mg QD or 50 mg BID oral dose of DTG (based on 99% protein binding). Dolutegravir up to 10 µM was evaluated *in vitro* for off target effects in a selectivity profile screen including various receptors, ion channels and enzymes. A 64% inhibition was recorded in the melanocortin receptor binding assay. Receptor binding assays demonstrated that DTG inhibited MC1, MC3, MC4, and MC5 receptors with IC50 values of 56.1 uM, 5.77 uM, 5.31 uM, and 14.7 uM, respectively. Substantial exposure margins exist for each of these IC50s: MC1, MC3, MC4, and MC5 is ~5610X, 577X, 531X, and 1470X the free clinical Cmax exposure (~0.01uM), respectively. The Cmax for DTG when administered at the maximal dose of 50mg BID is 4.2 ug/mL = ~10uM (MW = 419). DTG is ~99% protein bound, therefore, 0.042 ug/mL =	These data do not alter the risk assessment of DTG.

Key Safety findings (from non- clinical studies)	Relevance to human usage
0.01uM is the maximal free unbound concentration. In an in vivo phototoxicity study, oral gavage administration of GSK1349572, up to 1000 mg/kg/day for three consecutive days, to female Crl:LE (Long-Evans) rats followed by a single dose of UVR, approximately 2 hours after administration, elicited no evidence of cutaneous phototoxicity.	There have been no reports suggesting photosensitivity in the clinical data.
Mechanisms for drug interactions	
In vitro, DTG demonstrated little or no inhibition (IC50>30 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT1 or MRP2. Based on in vitro data, DTG is not a substrate of human organic anion transporting polypeptide (OATP) 1B1, OATP 1B3 or organic cation transporter (OCT) 1.	DTG is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.
In vitro, DTG did not induce CYP1A2, CYP2B6 or CYP3A4. In humans, DTG did not have an effect on the pharmacokinetics of midazolam, a CYP3A4 probe.	Drugs that induce these enzymes/transporters may theoretically decrease DTG plasma concentrations and reduce the therapeutic effect of DTG. Inhibition of these enzymes/transporters may theoretically increase DTG plasma concentration. In vivo, inhibition did not result in a clinically meaningful change in DTG systemic concentrations.
DTG is eliminated mainly through metabolism by UGT1A1. DTG also is a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP.	As a substrate of UGT1A1 DTG may result in a small increase in total or unconjugated bilirubin through competition for a common clearance pathway. Although the in vitro inhibition potential of DTG against UGT1A1 was weak (IC50 >100μM), the UGT1A1 enzyme is expressed on the inside of the microsomal membrane and bilirubin possessing low solubility and low permeability

Key Safety findings (from non- clinical studies)	Relevance to human usage
	is expected to have difficult access to the enzymatic site.
In vitro, DTG inhibited the renal organic cation transporter 2 (OCT2; IC_{50} = 1.9μM).	DTG may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 such as dofetilide and metformin. Co-administration of DTG and dofetilide (which has a narrow therapeutic index) is therefore contraindicated. Co-administration of DTG has the potential to increase metformin plasma concentrations via inhibition of OCT2 transporter, however, transport of metformin to the liver is unlikely to be affected. Patients should be monitored during therapy and a dose adjustment of metformin may be required. Administration of DTG may result in mild, nonprogressive increases (10-14%) in serum creatinine, which is believed to be due to inhibition of OCT2 mediated creatinine tubular secretion.
The absorption of DTG is reduced by certain anti-acid agents	Administration with antacids containing polyvalent cations requires separation of dosing times. DTG should be administered 2 hours before or 6 hours after antacids.

NEED FOR ADDITIONAL NON-CLINICAL INFORMATION IN SPECIAL POPULATIONS

PEDIATRICS

No new target organ toxicities were observed in the definitive juvenile rat toxicology study, and no signal indicating potential immunotoxicity was identified. The NOAEL for DTG in juvenile rats is considered to be 2 mg/kg/day. These findings support dosing of DTG in pediatric subjects at ~1 mg/kg once daily up to a maximum dose of 50mg.

Based on the available data in children and adolescents in pediatric studies (see Module SIII) there are no additional concerns considering the safety profile of DTG in pediatric patients compared to that observed in the clinical studies of DTG in adults.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Dolutegravir has been approved as a once daily antiretroviral product for the treatment of HIV-1 infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

ADULT SUBJECTS

The safety specification for DTG in adult subjects supporting the initial application involved 41 completed and ongoing interventional clinical trials (30 Phase I, 4 Phase II, 4 Phase III, 3 Phase IIIb) and 2 compassionate use programmes.

Six Phase IIb and Phase III studies with DTG had complete, interim or final statistical analyses available to support the application. These comprised four Phase III studies [Study ING113086 (SPRING-2), ING111762 (SAILING), ING112574 (VIKING-3) and ING114467 (SINGLE)] and two Phase IIb studies [Studies ING112276 (SPRING-1) and ING112961 (VIKING)] conducted with DTG in HIV-infected antiretroviral therapy naïve and experienced adults. The final data cut-off dates for individual studies included in the initial application are listed in Table 2

Table 2 Data Cut-off Dates for Studies supporting the safety specification included in the initial application

	Study	Study Time Point of Analysis	Data Cut-off Date[a]
Pivotal and Supportive Clinical Trials			
Studies in ART-Naïve Adults	ING112276	Post Week 96[b]	25 June 2012
	ING113086	Post Week 48[b]	18 June 2012
	ING114467	Week 48[c]	04 June 2012
Studies in ART-Experienced (INSTI-Naïve) Adults	ING111762	Week 24[c]	04 September 2012[e]
Studies in ART-Experienced (INSTI-Resistant) Adults	ING112961	Post Week 96[b]	08 June 2012
	ING112574	Week 24[c, d]	18 June 2012[e]

VI.4.1 This data cut-off date is the date when the data used in the analysis was extracted. This could either be Database Freeze (DBF) or Database Release (DBR), depending whether a new extraction was needed at DBF.

VI.4.2 The completed interim statistical analysis was more than six months prior to the planned submission date, so a new safety data cut was taken for reporting in this submission; thus, the data reported individually for these studies is not represented in a clinical study report.

VI.4.3 Safety data for this submission are reported based on the latest Clinical Study Report available.

VI.4.4 The interim analysis was planned to assess the first approximately 100 subjects that completed 24 weeks on study, and recruitment continued to allow enrolment of a further 50 to 100 subjects, as per protocol. All available safety data, as of the data cut, from all subjects enrolled contributed to the safety analysis. Thus, the planned interim analysis data cut was based on 114/183 subjects through Week 24.

VI.4.5 Since the initial application further analyses have been conducted on these two studies.

In the Safety Specification, the studies in ART-naïve subjects (ING112276, ING113086 and ING114467) were considered separately to studies in ART Experienced (INSTI-Naive) subjects (study ING111762) and ART Experienced (INSTI-resistant) subjects (studies ING112961 and ING112574) due to the different patient populations being studied and the different doses of DTG being administered (i.e., DTG 50 mg once daily versus DTG 50 mg twice daily).

ADDITIONAL ANALYSES CONDUCTED SINCE THE INITIAL APPLICATION

Since the initial application, the following further analyses have been completed:

- Week 48 primary endpoint analysis for ING111762 (data-cut 25 February 2013, (N= 719; DTG 357, RAL 362)
- A second interim analyses through Week 24 for all subjects enrolled in study ING112574 (data-cut 17 December 2012, N=183)
- Week 144 data from Phase III study ING114467 in antiretroviral therapy (ART)-naïve subjects (data-cut 07 April 2014, N= 833; DTG 414, Atripla 419)
- Week 96 data from Phase IIIb study ING114915 in ART-naïve subjects (data-cut 02 April 2014, N= 484, DTG 242, DRV/r 242))

Safety data from these additional analyses have been included in Section SVII.3 of the RMP where relevant. These data have not been integrated and are provided in text format. Exposure data from ING114467 and ING114915 to 144 and 96 weeks respectively have been included in exposure tables below where possible (Table 4, Table 6, Table 7 and Table 11).

Information on exposure to DTG in the pivotal and supporting Phase IIb/III Studies is presented in Table 3.

Table 3 Exposure to DTG in the pivotal and supporting Phase IIb/III Studies with Adult Subjects

Study Number	Phase	Patient type	Age range	No. on DTG	No. on comparator	Total
ING112276 (SPRING-1)	IIb	ART-Naive	≥18 years	155	50	205
ING112961 (VIKING)	IIb	ART-experienced INSTI resistant	≥18 years	51	N/A	51
ING113086 (SPRING-2)	III	ART-Naive	≥18 years	411	411	822
ING114467 (SINGLE)	III	ART-Naive	≥18 years	414	419	833
ING111762 (SAILING)	III	ART-experienced, INSTI-Naive	≥18 years	357	362	719
ING112574 (VIKING-3)	III	ART-experienced INSTI resistant	≥18 years	183	N/A	183
ING114915 (FLAMINGO)	III	ART-Naive	≥18 years	242	242	484

Data source ISO Table 2.501, ING114915, Week 96 CSR, Table 8.

Randomised Blinded Trial Population

Exposure in ART Naïve Adult Subjects

Table 4 Exposure to DTG once daily[a] in ART-Naïve Adult Subjects

	ING112276 DTG[1] (n=155)	ING112276 EFV (n=50)	ING113086 DTG 50 mg Q24 (n=411)	ING113086 RAL (n=411)	ING114467 DTG 50 mg Q24 (n=414)	ING114467 Atripla (n=419)	ING114915 DTG 50mg Q24 (n=242)	ING114915 DRV/r (n=242)
N	155	50	411	411	414	419	242	242
<2 weeks	2 (1)	2 (4)	3 (<1)	2 (<1)	7 (2)	14 (3)	1 (<1)	4 (2)
2 to <4 weeks	0	2 (4)	2 (<1)	1 (<1)	0	8 (2)	0	2 (<1)
4 to <8 weeks	0	1 (2)	5 (1)	4 (<1)	4 (<1)	9 (2)	3 (1)	0
8 to <12 weeks	2 (1)	0	1 (<1)	1 (<1)	4 (<1)	3 (<1)	1 (<1)	3 (1)
12 to <16 weeks	1 (<1)	0	2 (<1)	7 (2)	3 (<1)	10 (2)	2 (<1)	2 (<1)
16 to <20 weeks	0	0	3 (<1)	3 (<1)	3 (<1)	3 (<1)	0[c]	2 (<1)[c]
20 to <24 weeks	1 (<1)	0	1 (<1)	4 (<1)	1 (<1)	5 (1)	-	-
24 to <32 weeks	0	0	6 (1)	11 (3)	7 (2)	5 (1)	3 (1)[d]	9 (4)[d]
32 to <40 weeks	2 (1)	0	10 (2)	14 (3)	10 (2)	11 (3)	-	-

	ING112276 DTG[1] (n=155)	ING112276 EFV (n=50)	ING113086 DTG 50 mg Q24 (n=411)	ING113086 RAL (n=411)	ING114467 DTG 50 mg Q24 (n=414)	ING114467 Atripla (n=419)	ING114915 DTG 50mg Q24 (n=242)	ING114915 DRV/r (n=242)
40 to <48 weeks	0	0	7 (2)	5 (1)	37 (9)	38 (9)	5 (2)[e]	4 (2)[e]
48 to <96 weeks	41 (26)	13 (26)	371 (90)	359 (87)	338 (82)	313 (75)	62 (28)	68 (28)
>=96 weeks	106 (68)	32 (64)	0	0	345 (83)[b]	311 (74)[b]	165 (68)	148 (61)
N	155	50	411	411	414	419	242	242
Mean	642.0	598.9	451.7	441.7	877.4	788.8	631.5	601.3
Sd	128.95	202.10	104.77	113.91	287.5	356.75	136.0	173.79
Median	672.0	672.5	504.0	504.0	1009.0	1007.0	673.0	672.0
Q1	669.0	667.0	421.0	421.0	998.0	608.0	670.0	664.0
Q3	679.0	675.0	505.0	505.0	1012.0	1009.0	675.0	674.0
Min.	1	5	7	8	1	3	8	1
Max.	716	700	529	532	1073	1046	733	723
Duration (Subject-years)	272.4	82.0	508.3	497.0	994.5	904.9	418.4	398.4

a. Table summarises exposure during the randomized phase In ING112267 for the first 96 weeks 53 subjects were on 10 mg, 51 subjects were on 25 mg and 51 subjects were on 50 mg; all doses administered once daily. Post week 96 subjects on 10 mg and 25 mg switched to 50 mg once daily open-label and is not included in this summary. DTG= dolutegravir, EFV = efavirenz RAL= raltegravir, Atripla = EFV /Tenofovir(TDF)/ Emtricitabine(FTC) Q24= once daily. Data Source ISO Table 2.2, ING114467, Week 144 CSR, Table 8.1., Adhoc Table 1, ING114915 Week 96 CSR, Table 8.1, Adhoc Table 4

b. DTG 96 to <132 weeks 19 (5%), 132 to <144 weeks 86 (21%), >144 weeks 240 (58%), Atripla 96 to <132 weeks 28 (7%), 132 to <144 weeks 83 (20%), >144 weeks 200 (48%). Data Source ING114467, Week 144 CSR, Table 8.1,

c. 16 to <24 weeks

d. 24 to <36 weeks

e. 36 to <48 weeks

Exposure in ART Experienced (INSTI Naïve) Adult Subjects

Table 5 Exposure to DTG 50 mg once daily in ART Experienced (INSTI-Naïve) Adult Subjects

	ING111762 DTG (n=357)	ING111762 RAL (n=362)
Exposure (weeks), n (%)		
N	357	362
<2 weeks	2(<1)	2(<1)
2 to <4 weeks	7(2)	1(<1)
4 to <8 weeks	3(<1)	8(2)
8 to <12 weeks	6(2)	1(<1)
12 to <16 weeks	3(<1)	6(2)
16 to <20 weeks	6(2)	11(3)
20 to <24 weeks	19(5)	23(6)
24 to <32 weeks	73(20)	67(19)
32 to <40 weeks	40(11)	55(15)
40 to <48 weeks	78(22)	70(19)
48 to <96 weeks	120(34)	118(33)
>=96 weeks	0	0
Exposure (days)		
N	357	362
Mean	256.1	252.3
Sd	86.73	84.05
Median	281.0	281.0
Q1	172.0	170.0
Q3	336.0	337.0
Min.	10	10
Max.	370	360
Duration (Subject-years)	250.3	250.0

Table summarises exposure during the randomized phase.
Data Source ISO Table 2.501

Table 6 Summary of Age, Gender and Ethnic Origin of Randomised Blinded Trial Population -ART Naïve and ART Experienced (INSTI-Naïve) Adult Subjects

	ART Naive								ART Experienced (INSTI-Naïve)		Total
	ING112276 DTG (n=155)	ING112276 EFV (n=50)	ING113086 DTG (n=411)	ING113086 RAL (n=411)	ING114467 DTG (n=414)	ING114467 Atripla (n=419)	ING114915 DTG (n=242)	ING114915 DRV/r (n=242)	ING111762 DTG (n=357)	ING111762 RAL (n=362)	Total DTG (n=1579)
Age category, years, n (%)											
<50	145 (94)	43 (86)	370 (90)	365 (89)	361 (87)	375 (89)	214 (88)	206 (85)	272(76)	278(77)	1362 (86)
50-64	10(6)	5(10)	40(10)	41(10)	52(13)	38(9)	25 (10)	35 (14)	79(22)	78(22)	206 (13)
65-74	0	1(2)	1(<1)	4(<1)	1(<1)	5(1)	3 (1)	1 (<1)	6(2)	6(2)	11 (<1)
75-84	0	1(2)	0	1(<1)	0	0	0	0	0	0	0
85+	0	0	0	0	0	1(<1)	0	0	0	0	0
Gender (n, %)											
Male	133 (86)	44 (88)	348 (85)	355 (86)	347 (84)	356 (85)	211 (87)	201 (83)	249 (70)	238 (66)	1288 (82)
Female	22 (14)	6 (12)	63 (15)	56(14)	67 (16)	63 (15)	31 (13)	41 (17)	108 (30)	124 (34)	291 (18)
Racial origin, n (%)											
White	121 (78)	43 (86)	346 (84)	352 (86)	284 (69)	285 (68)	173 (72)	176 (73)	181 (51)	176 (49)	1105 (70)
Black	21 (14)	4 (8)	49 (12)	39 (9)	98 (24)	99 (24)	60 (25)	53 (22)	143 (40)	160 (44)	371 (23)
Asian	0	1 (2)	6 (1)	10 (2)	9 (2)	9 (2)	2(<1)	1 (<1)	9 (3)	6 (2)	26 (2)
Other	13 (8)	2 (4)	10 (2)	10 (2)	23 (6)	26 (6)	6 (2)	12 (5)	23 (6)	19 (5)	75 (5)

Data source ISO Table 2.557, ISO Table 1.10, ISO Table 1.12 and ISO Table 2.525, ING11915 Week 96 CSR Table 6.10 and 6.11, Adhoc Table 6

Table 7 Exposure to DTG once daily in Special Populations in ART Naïve and Art Experienced (INSTI-Naïve) Adult Subjects

	ART Naive								ART Experienced (INSTI-Naïve)		Total
	ING112276		ING113086		ING114467		ING114915	ING114915	ING111762		
	DTG (n=155) n(%)	EFV (n=50) n(%)	DTG (n=411) n(%)	RAL (n=411) n(%)	DTG (n=414) n(%)	Atripla (n=414) n(%)	DTG (n=242) n(%)	DRV/r (n=242) n(%)	DTG (n=357) n(%)	RAL (n=362) n(%)	Total DTG (n=1579) n(%)
HCV and/or HBV infected,	13(8)	6(12)	49(12)	43(10)	28(7)	30(7)	26 (11)	20 (8)	50(14)	65(18)	166 (11)
Renal impairment[1]											
Mild 60-<90 mL/min/1.73m2	20(13)	8(16)	26(6)	36(9)	34(8)	20(5)	19(8)	15(6)	65(18)	54(15)	164 (10)
Moderate 30-<60 mL/min/1.73m2	2(1)	0	0	2(<1)	2(<1)	2(<1)	0	1(<1)	6(2)	7(2)	10(<1)
Severe <30 mL/min/1.73m2	0	0	0	0	0	0	0	1(<1)	1(<1)	1(<1)	1(<1)

Note: This table includes all subjects who received at least one dose of study medication.

Data source ISO Table 2.227, ISO Table 2.534 and ISO Table 2.559, ING114915 Week 96 Adhoc Table 7, Week 96 CSR Table 6.13.

VI.3.1 Renal impairment categories based on Creatinine Clearance, estimated – Cockcroft-Gault formula at Baseline. Subjects with normal renal function are not presented in this summary,

Open-label Trial Population – Adult Subjects

Exposure in ART Experienced (INSTI-Resistant) Adult Subjects

Table 8 Exposure to DTG 50mg BID in ART Experienced (INSTI-Resistant) Adult Subjects

	ING112961 DTG BID (n=24) n(%)	ING112574 DTG BID (n=183) n(%)	TOTAL DTG BID (n=207) n(%)
Exposure (weeks)			
N	24	183	207
<2 weeks	0	0	0
2 to <4 weeks	0	2 (1)	2 (<1)
4 to <8 weeks	0	9 (5)	9 (4)
8 to <12 weeks	0	12 (7)	12 (6)
12 to <16 weeks	0	19 (10)	19 (9)
16 to <20 weeks	2 (8)	24 (13)	26 (13)
20 to <24 weeks	0	12 (7)	12 (6)
24 to <32 weeks	0	38 (21)	38 (18)
32 to <40 weeks	1 (4)	27 (15)	28 (14)
40 to <48 weeks	2 (8)	29 (16)	31 (15)
48 to <96 weeks	15 (63)	11 (6)	26 (13)
>=96 weeks	4 (17)	0	4 (2)
Exposure (days)			
N	24	183	207
Mean	511.0	177.3	216.0
Sd	172.86	87.54	146.88
Median	586.5	169.0	172.0
Q1	430.5	112.0	113.0
Q3	595.5	239.0	281.0
Min.	114	14	14
Max.	678	341	678
Duration of dosing in Subject-years	33.6	88.8	122.4

Data Source: ISO Table 2.3

Table 9 Summary of Age, Gender and Ethnic Origin of Open Label Trial Population, ART Experienced (INSTI-Resistant) Subjects

	ING112961 DTG BID (n=24) n(%)	ING112574 DTG BID (n=183) n(%)	Total DTG BID (n=207) n(%)
Age category, years,			
<50	17 (71)	110 (60)	127 (61)
50-64	6(25)	69(38)	75(36)
65-74	1(4)	4(2)	5(2)
75-84	0	0	0
85+	0	0	0
Gender			
Male	18 (75)	141 (77)	159 (77)
Female	6 (25)	42 (23)	48 (23)
Racial origin			
White	19 (79)	130 (71)	149 72)
Black	5 (21)	49 (27)	54 (26)
Asian	0	1 (<1)	1 (<1)
Other	0	3 (2)	3 (1)

Data Source ISO Table 2.557, ISO Table 1.11 and ISO Table 1.13

Table 10 Exposure to DTG 50mg BID in Special Populations in ART Experienced (INSTI-Resistant) Subjects

	ING112961 DTG BID (n=24) n(%)	ING112574 DTG BID (n=183) n(%)	Total DTG BID (n=207) n(%)
HCV and/or HBV infected	8(33)	38(21)	46(22)
Renal impairment[a]			
Mild 60-<90 mL/min/1.73m^2	0	35(19)	35(17)
Moderate 30-<60 mL/min/1.73m^2	0	9(5)	9(4)
Severe <30 mL/min/1.73m^2	0	1(<1)	1(<1)

Note: This table includes all subjects who received at least one dose of study medication.
Data source: ISO Table 2.228 and ISO Table 2.559

a. Renal impairment categories based on Creatinine Clearance, estimated – Cockgroft-Gault formula at Baseline. Subjects with normal renal function are not presented in this summary

All Clinical Trial Adult Subject Population (PhIIb/III studies)

Table 11 Exposure to DTG (all doses) in all PhIIb/III studies – Adult Subjects

	DTG (all doses) (n=1813) N(%)
Exposure (weeks)	
N	1813
<2 weeks	15 (<1)
2 to <4 weeks	11(<1)
4 to <8 weeks	27(1)
8 to <12 weeks	27(1)
12 to <16 weeks	31(2)
16 to <20 weeks	40(2)[a]
20 to <24 weeks	36(2)
24 to <32 weeks	131(7)[b]
32 to <40 weeks	89(5)
40 to <48 weeks	130(7)[c]
48 to <96 weeks	643(35)
>=96 weeks	633(35)
Duration of dosing in Subject-years	Not available

Data Source ISO Table 2.501, ING114467, Week 144 CSR, Table 8.1, ING114915 Week 96 CSR, Table 8.1,
a. For study ING114915 this represents 16 to <24 weeks
b. For study ING114915 this represents 24 to <36 weeks
c. For study ING114915 this represents 36 to <48 weeks

PEDIATRIC SUBJECTS

Study P1093 (ING112578)

Study P1093 was a Phase I/II multicenter, open-label, non-comparative study designed to evaluate the pharmacokinetic parameters, safety, tolerability and antiviral activity of DTG once daily in combination regimens in HIV-1 infected infants, children and adolescents aged ≥4 weeks to <18 years.

Participants were enrolled into the study into one of five age-based cohorts:

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

a. Cohort I: Adolescents ≥12 to <18 years of age (Film coated tablet (FCT));
b. Cohort IIA: Children ≥6 to <12 years of age (FCT);
c. Cohort IIB: Children ≥6 to <12 years of age (granules for suspension);
d. Cohorts III: Children ≥2 to <6 years of age (granules for suspension);
e. Cohort III-DT: Children ≥2 to <6 years of age (Dispersible tablet (DT));
f. Cohort IV: Children ≥6 months to <2 years (granules for suspension);
g. Cohort IV-DT: Children ≥6 months to <2 years of age (DT);
h. Cohort V-DT: Infants ≥4 weeks to <6 months (DT).

However, due to an increasing international interest in pediatric dosing independent of age, enrollment of sufficient participants to analyze by weight band for those in Cohorts III-DT, IV-DT and V-DT was incorporated into the protocol (v5.0) as shown below:

i. 3 to <6 kg;
j. 6 to <10 kg;
k. 10 to <14 kg;
l. 14 to <20 kg.

Week 24 data (pharmacokinetic, safety and efficacy) from Cohort I, comprising 23 participants, were available at the time of the Marketing authorisation application (MAA) (study cut-off date 17 Dec 2012) and supported the use of DTG in adolescents (≥ 12 to <18 years of age). Interim results from this study subsequently supported regulatory filings for DTG use across the pediatric age spectrum.

The study achieved LSLV on 18 October 2023 and is now complete. A total of 181 participants were exposed to at least 1 dose of DTG. A breakdown of baseline demographics and exposure by enrollment weight is presented in Table 12.

Table 12 Baseline demographics and Exposure to DTG once daily by Enrollment Weight Band in Pediatric Study P1093

Minimum Exposure	3 to <6kg (N=18)	6 to <10kg (N=47)	10 to <14kg (N=27)	14 to <20kg (N=35)	20 to <25kg (N=14)	25 to <35kg (N=12)	≥35kg (N=28)	Total (N=181)
>0 day	18	47	27	35	14	12	28	181
>4 weeks	18	47	26	35	14	12	28	180
>12 weeks	17	47	26	35	14	12	28	179
>24 weeks	17	45	26	35	13	12	28	176
>48 weeks	14	42	25	34	13	11	25	164
>72 weeks	14	39	25	33	13	11	25	160
>96 weeks	14	39	25	33	12	9	23	155
>120 weeks	14	39	25	33	12	9	22	154
>144 weeks	14	38	25	32	12	8	19	148
>168 weeks	14	38	24	32	11	8	17	144
>192 weeks	11	24	16	20	9	4	11	95
>216 weeks	0	0	0	0	2	1	2	5
>240 weeks	0	0	0	0	0	1	1	2
>264 weeks	0	0	0	0	0	1	1	2
Days Exposed								
Mean (SD)	1095 (494)	1166 (403)	1253 (331)	1283 (244)	1229 (417)	1149 (466)	1109 (419)	1189 (385)
Median	1346.5	1345	1345	1346	1347.5	1342	1306.5	1345
Range	60 - 1373	128 - 1427	10 - 1426	243 - 1454	85-1672	232-1946	281-1993	10-1993
Q1, Q3	1336, 1352	1316, 1359	1338, 1365	1332, 1370	1341, 1376	819.5, 1345.5	846, 1362.5	1316, 1361
Age in Months, mean (SD)	3.7 (2.2)	13.5 (11.2)	33.7 (11.3)	57.8 (17.0)	93.1 (18.1)	132.8 (17.8)	167.5 (27.5)	62.0 (59.0)

Minimum Exposure	3 to <6kg (N=18)	6 to <10kg (N=47)	10 to <14kg (N=27)	14 to <20kg (N=35)	20 to <25kg (N=14)	25 to <35kg (N=12)	≥35kg (N=28)	Total (N=181)
Sex, n (%)								
Male	6 (33.3)	25 (53.2)	12 (44.4)	25 (71.4)	13 (92.9)	6 (50.0)	8 (28.6)	95 (52.5)
Female	12 (66.7)	22 (46.8)	15 (55.6)	10 (28.6)	1 (7.1)	6 (50.0)	20 (71.4)	86 (47.5)
Race, n (%)								
Asian	2 (11.8)	6 (12.8)	5 (18.5)	3 (8.6)	2 (14.3)	4 (33.3)	3 (10.7)	25 (13.8)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	1 (0.6)
Black or African American	13 (72.2)	35 (74.5)	20 (74.1)	27 (77.1)	8 (57.1)	5 (41.7)	14 (50.0)	122 (67.4)
White	0 (0)	2 (4.3)	2 (7.4)	1 (2.9)	1 (7.1)	1 (8.3)	8 (28.6)	15 (8.3)
Other	3 (16.7)	4 (8.5)	0 (0)	4 (11.4)	2 (14.3)	2 (16.7)	3 (10.7)	18 (9.9)

Data Source: P1093 EoS CSR Tables 12 and 18, Safety outputs, Table 1.202

ODYSSEY (PENTA 20)

ODYSSEY was an open-label, multicenter, randomized (1:1), non-inferiority, Phase II/III, 96-week, 2-arm clinical study to compare the efficacy and toxicity of DTG plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) vs. standard of care in Human Immunodeficiency Virus (HIV)-infected children aged less than 18 years who were starting first-line ART (ODYSSEY A) or switching to second-line ART (ODYSSEY B). The study included three pharmacokinetic sub-studies including two evaluating DTG dosing according to WHO weight bands (WB-PK 1 and WB-PK 2).

Participants were enrolled in 2 different strata depending on their previous ART experience:

- ODYSSEY A: children starting first-line ART
- ODYSSEY B: children starting second-line ART

Within each stratum, children were randomized 1:1 to either DTG-based ART (DTG Arm) or standard of care (boosted PI-, or NNRTI- or INSTI-based ART; Standard of Care Arm). Treatment was open-label and dispensed at randomization for 4 weeks and then at maximum 12-week intervals.

Presented in this RMP are the safety data from the two weight band pharmacokinetic sub-studies from the ODYSSEY clinical trial (N=99). Data available to 28 February 2019 is presented in Table 13.

Table 13 Baseline demographics and Exposure to DTG by Enrollment Weight Band once daily in ODYSSEY PK sub-studies

	3 to <6 kg (n=1)	6 to <10 kg (n=10)	10 to <14 kg (n=5)	14 to <20 kg (n=33)	20 to <25 kg (n=28)	25 to <30 kg (n=16)	30 to <40 kg (n=6)	Total (n=99)
Exposure (weeks), n(%)								
<2	0	0	0	0	0	0		0
2 to <4	0	0	1 (20)	0	0	0		1 (1)
4 to <8	0	0	0	0	0	0		0
8 to <12	0	0	0	0	0	0		0
12 to <16	1 (100)	4 (40)	3 (60)	0	0	0		8 (8)
16 to <20	0	1 (10)	0	0	0	0		1 (1)
20 to <24	0	2 (20)	0	1 (3)	0	0		3 (3)
24 to <28	0	3 (30)	1 (20)	0	0	0		4 (4)
28 to <32	0	0	0	0	0	0		0
32 to <36	0	0	0	1 (3)	0	0		1 (1)
36 to <40	0	0	0	3 (9)	0	0		3 (3)
40 to <48	0	0	0	2 (6)	2 (7)	0		4 (4)
48 to <60	0	0	0	12 (36)	3 (11)	0		15 (15)
60 to <72	0	0	0	7 (21)	3 (11)	0		10 (10)
72 to <84	0	0	0	6 (18)	7 (25)	2 (13)	1 (17)	16 (16)
84 to <96	0	0	0	1 (3)	4 (14)	5 (31)	2 (33)	12 (12)
≥96	0	0	0	0	9 (32)	9 (56)	3 (50)	21 (21)
Days Exposed								
n	1	10	5	33	28	16	6	99
Mean (SD)	84.0	130.5 (40.66))	92.0 (50.97)	387.7 (100.02)	563.0 (153.85)	669.7 (113.08)	663.0 (99.75)	455.6 (215.43)
Median (range)	84.0 (84-84)	145 (85-169)	85.0 (26-169)	371.0 (165-594)	508.0 (335--841)	672.5 (505-842)	643.0 (568-841)	466.0 (26-842)
Age,								
4 weeks to <6 months, n (%)	1 (100)	0	0	0	0	0	0	1 (1))

	3 to <6 kg (n=1)	6 to <10 kg (n=10)	10 to <14 kg (n=5)	14 to <20 kg (n=33)	20 to <25 kg (n=28)	25 to <30 kg (n=16)	30 to <40 kg (n=6)	Total (n=99)
6 months to <2 years, n (%)	0	9 (90)	2 (40)	0	0	0	0	11 (11))
2 years to <6 years, n (%)	0	1 (10)	3 (60)	15 (45)	0	0	0	19 (19)
6 years to <12 years, n (%)	0	0	0	18 (55)	27 (96)	13 (81)	2 (33)	60 (61)
12 years to <18 years, n (%)	0	0	0	0	1 (4)	3 (19)	4 (67)	8 (8)
Gender								
Female, n (%)	1 (100)	8 (80)	4 (80)	17 (52)	13 (46)	4 (25)	4 (67)	51 (52)
Male, n (%)	0	2 (20)	1 (20)	16 (48)	15 (54)	12 (75)	2 (33)	48 (48)
Race								
Black-African, n (%)	1 (100)	10 (100)	5 (100)	33 (100)	28 (100)	16 (100)	6 (100)	99 (100)

Data Source: ODYSSEY CSR (data cut 28 February 2019) Table 12 and safety outputs table 3.4

Note: All weight band and DTG formulations/doses are included. Duration of exposure in days = (treatment stop date - treatment start date + 1) summed over all dosing periods for a particular dose/formulation and weight band, where dose interruptions are not taken into account. When IP stop date is missing, duration is calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever is the earlier.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The specific exclusion criteria applied during each phase of development reflected DTG data available at that time and are therefore slightly different for the Phase IIb studies compared to the Phase III studies. Additionally, there are some differences amongst the Phase III studies based on the patient population enrolled or the background regimens administered.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
History or presence of allergy or intolerance to the study drugs or their components or drugs of their class	Hypersensitivity is a rare but recognized risk for ART containing DTG, regardless of dose and is contraindicated in patients receiving DTG.	No	DTG is contraindicated in anyone with hypersensitivity to DTG or to any of the excipients and a warning around hypersensitivity reactions (HSR) is included in section 4.4 of the Summary of Product Characteristics (SmPC).
Concomitant use of dofetilide	Dofetilide is prohibited as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity	No	The use of DTG and dofetilide is contraindicated in the SmPC
Anticipated need for HCV therapy during the study	HCV therapy at present includes the use of interferon, which is an immune modulator and thus may affect CD4+ cell count or other responses to treatment	No	Patients with HIV infection receiving DTG may have a HCV co-infection. Safety data across all patient populations supports the administration of DTG in HIV infected patients co-infected with HCV.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			Treatment with DTG will be guided by established guidance and medical practice.
Subjects positive for HBV at screening (+HbsAg)	Hepatitis B surface antigen positivity was an exclusion criterion for ING114467 due to the blinded use of ABC/lamivudine (3TC) in the DTG arm, whereas treatment guidelines (e.g., EACS guidelines) recommend ART initiation with tenofovir (TDF)-based therapy for HBV-co-infected patients in need of anti-HBV therapy and/or with CD4+ cell counts <500. This exclusion only applied to study ING114467.	No	Patients with HIV infection receiving DTG may have a HBV co-infection. Safety data across all patient populations supports the administration of DTG in HIV infected patients co-infected with HBV. Treatment with DTG will be guided by established guidance and medical practice.
Moderate to severe hepatic impairment as determined by Child-Pugh	Pharmacokinetic data from subjects with mild to moderate hepatic impairment was not available at the start of the Phase III studies.	No	See SVII.2
ALT >5 times the upper limit of normal (ULN) ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin)	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition	No	Patients with HIV infection receiving DTG may have other conditions which result in laboratory abnormalities. On review of safety data across all patient populations, there is no reason to suggest that there

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	exacerbated during the study.		are additional risks in these patients. Treatment with DTG will be guided by established guidance and medical practice
Any verified Grade 4 laboratory abnormality	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Patients with HIV infection receiving DTG may have other conditions which result in laboratory abnormalities. On review of safety data across all patient populations, there is no reason to suggest that there are additional risks in these patients. Treatment with DTG will be guided by established guidance and medical practice.
Subject has estimated creatinine clearance <50 mL/min via Cockroft-Gault method	This exclusion applied to ING113086, ING114467 and ING112276 only due to use of fixed-dose combination nucleos(t)ide reverse transcripase inhibitors. Dose adjustments could not be applied to these background medications. No creatinine clearance restriction applied to treatment-experienced studies (ING111762 and ING112574).	No	In a phase I, open-label, parallel-group study to evaluate the pharmacokinetics and safety of a single 50 mg dose of DTG in HIV-negative subjects with severe renal impairment (CrCl <30 mL/min, not on dialysis), compared to healthy controls; severe renal impairment had a relatively moderate effect on DTG pharmacokinetics, reducing Cmax and AUC by around 23-40%, which is not considered clinically significant.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			No creatinine clearance restriction applied to treatment-experienced studies (ING111762 and ING112574). Patients with mild to severe renal impairment can therefore take DTG and no dose adjustment is considered necessary. Treatment with DTG will be guided by established guidance and medical practice
History of malignancy within the past 6 months (ING113086) or 5 years	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Patients with HIV infection receiving DTG may have a history of malignancy. On review of safety data across all patient populations, there is no reason to suggest that there are additional risks in these patients. Treatment with DTG will be guided by established guidance and medical practice.
Recent history (≤3 months) of any upper or lower GI bleed, with the exception of anal or rectal bleeding	GI intolerance (severe diarrhoea and gastric erosion) was observed in the 6- and 9-month long term animal (rat and monkey, respectively) toxicity studies conducted for DTG. To avoid putting the safety of the subject at risk through participation, and to	No	See SVII.2

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study		
Evidence of an active CDC Category C disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm3	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	On review of safety data across all patient populations, there is no reason to suggest that there are additional risks in these patients. Treatment with DTG will be guided by established guidance and medical practice.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	At the data-cut for the initial submission, DTG had been used in 2026 adult patients with HIV infection for periods up to ≥96 weeks in doses up to 50mg daily (INSTI-Naïve population) and 50mg twice daily (ART-experienced INSTI resistant population).	Given that over 2,000 subjects had been exposed to DTG at the time of the initial submission, then there was a >99% probability that very common (>1 in 10) and common (>1 in 100) Adverse events (AEs) would have been observed and a >85% probability that uncommon (>1 in 1000) AEs would have been observed during clinical development (based on CIOMS criteria for common).
Due to prolonged exposure	With antiretroviral therapies, some toxicities have taken considerable time/ years to manifest. The MAA for the initial DTG submission included clinical safety data for approximately 1400 adult subjects receiving DTG at the recommended dose or higher for 24 weeks or longer. There is now safety data in adults available for over 1600 subjects receiving DTG at the recommended dose for 24 weeks or longer, approximately 600 subjects receiving DTG for 96 weeks or longer and approximately 240 subjects receiving DTG for 144 weeks or longer. The programme is also informed by the accumulated clinical experience with raltegravir (RAL), which has been approved for use since 2007.	No long-term adverse effect of DTG is apparent from clinical studies to date. In addition, no long-term toxicities, have been noted for the first in class INSTI RAL, which has been marketed since 2007. Longer term data from study ING114467 demonstrated that DTG had long term durability with a low rate of discontinuation due to virologic failure; as well as a safety and tolerability profile that was generally favourable to that of comparator (Atripla) through Week 144. In addition, longer term data from pediatric study P1093 (which enrolled children aged ≥ 4 weeks to < 18 years of age) demonstrated that DTG was well tolerated as chronic therapy through Week 192 and showed no additional safety concerns compared to adults. The long term safety of DTG will be monitored through routine pharmacovigilance

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Due to cumulative effects	With antiretroviral therapies, some toxicities have taken considerable time/ years to manifest. The MAA for the initial DTG submission included clinical safety data for approximately 1400 adult subjects receiving DTG at the recommended dose or higher for 24 weeks or longer. There is now safety data available in adults for over 1600 subjects receiving DTG at the recommended dose for 24 weeks or longer, approximately 600 subjects receiving DTG for 96 weeks or longer and approximately 240 subjects receiving DTG for 144 weeks or longer. The programme is also informed by the accumulated clinical experience with RAL, which has been approved for use since 2007.	There were no new safety concerns identified during longer term treatment with DTG that might have been due to cumulative effects. No specific organ toxicity was detected. In addition, no long-term toxicities, have been noted for the first in class INSTI, RAL, which has been marketed since 2007. The long term safety of DTG will be monitored through routine pharmacovigilance
Which have a long latency	The assessment of longer-term toxicities seen with CART, such as bone disorders and lipodystrophy require a considerably extended follow up period. The MAA for the DTG submission included clinical safety data for approximately 1400 adult subjects receiving DTG at the recommended dose or higher for 24 weeks or longer. There is now safety data in adults available for over 1600 subjects receiving DTG at the recommended dose for 24 weeks or longer, approximately 600 subjects receiving DTG for 96 weeks or longer and approximately 240 subjects receiving DTG for 144 weeks or longer.	No long term adverse effect of DTG is apparent from clinical studies to date. In addition, no long term toxicities, have been noted for the first in class INSTI RAL, which has been marketed since 2007. The long term safety of DTG will be monitored through routine pharmacovigilance

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
	The programme is also informed by the accumulated clinical experience with RAL, which has been approved for use since 2007.	

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 14 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant and breast-feeding women	At the time of the MAA, pregnant women were excluded from DTG clinical studies. Subjects that became pregnant (intrauterine) were required to discontinue from the studies. Clinical experience of DTG use during pregnancywas therefore limited (see SVII.3.2). Breastfeeding women were not included in the clinical development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with severe hepatic impairment were excluded from the phase III clinical studsies.
Patients with renal impairment	Subjects with estimated creatinine clearance (CrCl) <50 mL/min (Cockroft-Gault method), indicative of moderate (<60 mL/min) and severe (<30 mL/min) renal impairment, were excluded from studies ING113086, ING114467 and ING112276 Table 7 and Table 10).
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical programme covered the full spectrum of HIV disease (i.e., no CD4+ cell count restrictions and no upper limit on viral load) and therapy experience.
Population with relevant different ethnic origin	All clinical studies were conducted internationally. Although the majority of patients in the clinical studies were white, no ethnicities were excluded (Table 6).
Subpopulations carrying relevant genetic polymorphisms	Subjects with genetic polymorphisms were not excluded from the clinical studies.
Pediatrics	At the time of the initial MAA, there was limited information regarding the use of DTG in pediatric subjects (data was available for 23 subjects ≥12 to <18 years of age through to 24 weeks). Data is now available from 181 pediatrics exposed to at least 1 dose of DTG in study P1093 (Table 12).
Elderly	There is limited information regarding the use of DTG in the elderly (>65 years old). Only 13 subjects on DTG across 6 studies were 65 years of age or older at the time of the initial MAA (all 65-74 years old) Table 6 and

Type of special population	Exposure
	Table 9.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for DTG.

SV.1.1 Method used to calculate exposure

Post-marketing exposure was based on IQVIA sales volume (IQVIA data can be up to 6 months in arrears from the cut-off date). The algorithm used to derive post-approval exposure data from IQVIA assumes a standard daily dose of one tablet of DTG, irrespective of tablet strength (DTG 50 mg, 25 mg, 10 mg film-coated tablets, or 5 mg dispersible tablets).

The post-marketing exposure data do not include sales through generic companies or licensing partners and therefore do not capture use in some countries where DTG is provided through licensing agreements between VH and generic companies.

SV.1.2 Exposure

Cumulative post-marketing exposure to DTG is estimated to be 4,803,179 patient years up to 31 December 2024. The majority of exposure (>99%) is estimated to be to 50 mg film-coated tablets. The estimated exposure to DTG dispersible tablets up to 31 December 2024 is 6439 patient years.

In the EU/EEA* total cumulative exposure to 31 December 2024 is 591 314 patient-years.

*The EU/EEA for the purposes of exposure data includes the following countries (as at 31 December 2024): Spain, Italy, France, United Kingdom, Germany, Portugal, Netherlands, Belgium, Switzerland, Sweden, Austria, Norway, Romania, Finland, Latvia, Bulgaria, Serbia, Czech Republic, Denmark, Hungary, Croatia, Slovakia, Slovenia, Luxembourg, Belarus, Poland, Ireland.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The MAH does not consider that there is a potential for misuse for illegal purposes with DTG.

The INSTI class of compounds has no known drug abuse potential. There are no data suggesting that DTG has the potential to imply illicit use, abuse, or dependency. In a secondary pharmacology evaluation, DTG did not significantly bind to any receptors or ion channels that would be considered relevant to neuropsychological stimulation (including monoamine oxidase A and B, cannabinoid CB1 or CB2, nicotinic cholinergic, dopamine D1 or D2L, dopamine transporter, GABA A or GABA B, glutamate NMDA, opiate, serotonin 5-HT1, 5-HT2, or 5-HT3) [GlaxoSmithKline Document Number RH2007/00072/00].

No studies to investigate the potential for abuse or dependency with DTG have been performed given that: a) DTG is not centrally active, b) there is clear evidence that this compound has very low blood brain barrier penetration, c) mechanistically, DTG does not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, and d) preclinical and clinical data available are not indicative of a potential for drug abuse.

In summary, there are no data suggesting that DTG has the potential to imply illicit use, abuse, or dependency.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

This section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no important identified or potential risk or missing information proposed to be added, removed or reclassified as part of this RMP update.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

IMPORTANT POTENTIAL RISK: NEURAL TUBE DEFECTS

Potential Risk	**Neural tube defects**
MedDRA terms (PT)	Neural tube defect
Evidence source(s) and strength of evidence	In May 2018, preliminary findings from a birth outcomes surveillance study (the Tsepamo Study) conducted in Botswana showed a higher than expected number of NTDs among newborns whose mothers were exposed to DTG-based ART at conception. Since the NTD signal was first observed in the Tsepamo study, as the number of infants exposed to DTG at conception has increased, there has been a marked decline in the prevalence of NTDs, from 0.94% in 2018 to 0.11% in the 2022 [Zash 2022]. The early signal, which suggested an approximate ten-fold increased risk of NTDs, has not been confirmed by subsequent data. The latest analysis (data to 31 March 2022) reports a prevalence rate of 0.11% in infants exposed to DTG at conception, compared with 0.11% in infants exposed to non-DTG regimens at conception and 0.07% in infants delivered to women without HIV. There is no longer evidence of a statistically significant difference in NTD rates between infants exposed to DTG and non-DTG regimens at conception, or any other exposure group in this study. In a large ongoing birth surveillance study in Eswatini, which includes over 4,800 exposures to dolutegravir at conception (data through September 2022), the prevalence of NTDs in infants delivered to women taking DTG at conception was 0.08%, which was the same as in infants delivered to women without HIV (0.08%). Since the initial identification of this signal, information on the use of DTG during pregnancy has been gained from a number of other sources, which

Potential Risk	Neural tube defects
	have not shown any evidence of a congenital abnormality signal and exposures are now sufficient to refute the NTD signal. Large surveillance studies including the Tsepamo and Eswatini studies, together include over 14,000 women with periconceptional exposure to DTG. The exposure threshold of over 2000 needed to confirm or rule out a three-fold or higher increased risk of NTDs with DTG is therefore reached. Based on the latest data from these studies, the prevalence of neural tube defects in infants born to women taking dolutegravir at conception did not differ significantly from the background rate in women without HIV, or other exposure groups. The DOLOMITE EPPICC study was an additional pharmacovigilance activity for this risk and it is now completed. After 833 pregnancy exposures, the results showed no increased risk of birth defects following DTG pregnancy exposure compared to background rates. Although the sample size was too small to exclude associations with NTDs, no NTDs were reported. The APR has received reports of over 1800 exposures to DTG in pregnancy resulting in live births, including 1160 first trimester exposures to DTG. Data from the APR through 31 July 2024 do not demonstrate an increased risk of overall birth defects with DTG use above population expected rates of birth defects. The number of periconception exposure outcomes in the APR are not yet sufficient to evaluate the potential association of DTG with NTDs. [APR 2024].
Characterisation of the risk	**Frequency** Latest analysis to 31st March 2022 in the Tsepamo Study, reports 10 NTDs out of 9,460 pregnancies exposed to DTG at conception which gives a prevalence rate of 0.11% (95% CI: 0.06, 0.19). This compares with 0.11% (95% CI: 0.07, 0.16) for non-DTG ART exposures from conception (prevalence difference: 0.00%, 95% CI: –0.07, 0.10) and 0.07% in women without HIV infection (prevalence difference 0.04%, 95% CI: -0.01, 0.13). The Eswatini Study from Sept 2021 to Sept 2022 shows a NTD DTG prevalence was 0.08% compared to 0.08% for HIV-negative women and 0.16% for women on EFV at conception. **<u>Seriousness/ outcomes</u>** The 10 NTDs identified among 9460 deliveries to women taking DTG at conception in the Tsepamo study included 4 myelomeningoceles, 2 anencephales, 3 encephaloceles, and 1 iniencephaly. From the data currently available on these cases, there are no obvious confounders. However, some relevant information is missing, for example, it is not known if there was any family history of NTDs or if vitamin B12 or folic acid supplementation was provided. Vitamin B12 or folic acid supplementation is

Potential Risk	Neural tube defects
	not routine practice in Botswana, nor is folate food fortification but there is no reason to suggest that there would be any differences between treatment groups with respect to supplementation that might explain the observed difference in risk. **<u>Severity and nature of risk:</u>** Neural tube defects result from failure of complete closure of the neural tube, a process which is normally complete by the end of the first month of pregnancy, often before a woman even knows that she is pregnant. This potential risk therefore affects women of childbearing potential and those actively seeking to become pregnant as it affects babies exposed at conception and very early in pregnancy. The two most common neural tube defects are spina bifida and anencephaly. In spina bifida, the foetal spinal column does not close completely. These forms of neural tube defects are compatible with life, but those affected usually have problems with mobility, as well as bladder and bowel function. In anencephaly, most of the brain and skull do not develop. Babies with anencephaly are usually either stillborn or die shortly after birth [Wilde 2014].
Potential mechanisms	There is no known mechanism linking DTG with these types of birth defects, and there are no relevant findings in pre-clinical studies. It is notable that the ten cases reported as NTDs among infants exposed to DTG at conception in the Tsepamo study are heterogeneous in terms of their presentation and pathophysiology, which is unusual. Anencephaly and myelomeninogocele arise as a result of primary failure of neural tube closure (which occurs within 28 days of conception), the presentation of other cases (encephalocele and iniencephaly) suggests that they are not defects due to failure of neural tube closure, but they are post neurulation defects [Copp, 2013]. Animal research suggests that encephaloceles are a post-neurulation defect which involve herniation of the brain through a skull defect. Iniencephaly, which is a rare condition characterised by an occipital bone defect and often confused with anencephaly with spinal retroflexion, is also likely to be a post-neurulation disorder and not part of the typical NTD spectrum [Copp, 2013].
Risk factors and risk groups	The pathophysiology of these various defects is based on animal studies and the relevance in humans has not been clearly established, therefore, the timing of occurrence of some of these defects, and how a potential teratogen might impact their development is not well understood. Although the exact timing of various types of defect may not be known it is thought they occur early in pregnancy and therefore the potential risk would concern women exposed to DTG at the time of conception and first trimester of pregnancy. The exact causes of NTDs are not known but environmental and genetic factors are known to play a part. Risk factors include: folate and Vitamin

Potential Risk	Neural tube defects
	B12 deficiency, obesity, diabetes, certain medicines such as some anti-epileptic medications (e,g, sodium valproate, carbamazepine), maternal age and hyperthermia/febrile illness. [Wilde 2014]. There is no evidence that neural tube defects occur more commonly in women living with HIV [Ford 2011]. Taking folic acid, before and during pregnancy is known to substantially reduce the occurrence of neural tube defects, by up to 70% [Relton 2004]. However, some NTDs appear to be resistant to folic acid, with perhaps a different aetiology to those which are sensitive to folic acid [Copp, 2013]. Neural tube defects affect an average of about 1 in 1000 established pregnancies worldwide although the incidence varies greatly from country to country, as well as within countries, and is dependent on numerous factors such as ethnicity, genetic make-up, geography, and nutrition, including folate intake [Copp, 2013]. A systematic review of the published literature [Zaganjor, 2016] highlighted a wide variation in prevalence estimates and suggests that there is some geographic variation. In the United Kingdom reported rates range from 0.12% to 0.18%, whilst in Europe as a whole, estimates range from 0.01% to 0.36%, with a median of 0.09%. Rates across the Americas ranged from 0.03% to 0.28%; median 0.12%. Prevalence in India and Pakistan appears to be higher (range 0.07% to 1.24%) with all five studies in Pakistan reporting rates between 0.39% and 1.24%. Data from Africa are relatively scarce, and the rates vary widely from 0.05% to 0.75%, but the median rate reported is around 0.12%.]
Preventability	Dolutegravir can be used during pregnancy if the expected benefit justifies the potential risk to the foetus. If a woman plans pregnancy, the risks of their disease and the benefits and risks of any medical treatment should be discussed with the patient. The SmPC includes information on DTG use in pregnancy (see Part V).
Impact on the risk-benefit balance of the product	The MAH considers that the NTD signal has been refuted by the latest data from the Tsepamo and Eswatini studies, and is supported by the data from the APR and other sources. The absolute risk of NTDs associated with DTG periconceptual exposure is reported to be similar to that in non-HIV populations. The DOLOMITE EPPICC study was an additional Pharmacovigilance Activity for this risk and is now complete with no safety concerns identified. The MAH will continue to monitor reports of NTDs, and intends to remove the potential risk of NTD when the EPPICC NEAT ID study is completed. The product information will inform prescribers and patients on up to date information on NTD risk based on more than 14 000 DTG pregnancy

Potential Risk	**Neural tube defects**
	exposures. Because this signal has been refuted, the label advice is altered accordingly. The MAH does not consider that the information about NTDs alters the overall benefit risk assessment for DTG in the treatment of HIV.
Public health impact	The SmPC contains appropriate information around this potential risk in women of child-bearing potential in order to prevent a major public health impact

SVII.3.2 Presentation of the missing information

USE IN PREGNANCY AND BREAST FEEDING:

Evidence Source:

Use in Pregnancy

At the time of the initial MAA, no studies had been conducted with DTG in pregnant women and pregnant/breastfeeding women were excluded from the DTG clinical studies. Subjects that became pregnant (intrauterine) were required to discontinue from the studies. Clinical experience of DTG use during pregnancy was therefore limited and use in pregnancy and breast feeding has been considered missing information for DTG in the RMP since the initial MAA approval.

The MAH initiated an open-label interventional study for women who become pregnant whilst receiving DTG/ABC/3TC (Study 200336). The study is an MAH-sponsored, prospective, interventional pharmacokinetic and safety study of DTG/ABC/3TC in Pregnant Women in which DTG/ABC/3TC is being made available to women who inadvertently become pregnant while participating in study ING117172 [open-label, active-controlled, non-inferiority study of DTG in a single tablet regimen as DTG/ABC/3TC compared to atazanavir plus ritonavir and tenofovir disoproxil fumarate/ emtricitabine (fixed dose combination) in women] in order that they may continue to maintain virologic suppression. The study was initiated on 17 December 2014. Only four women enrolled into the study; all had live births and infant outcomes were normal. Enrollment was placed on hold on 23 May 2018 due to a potential safety issue related to neural tube defects in infants born to women with exposure to DTG at the time of conception. In June 2020, the MAH took the decision to terminate the study as it was unclear if or when the enrolment hold may be lifted, and it was deemed unlikely that there would be further participants eligible for enrolment from study ING117172. Other larger studies were ongoing addressing Use in pregnancy as missing information (see Part III). A final study report was completed on 25 February 2022. The maternal and infant outcome data did not show any risk in the use of DTG/ABC/3TC in pregnancy or to the developing fetus. This study has not resulted in any new or updated safety concerns or missing information.

On 21 August 2012, following the MAA approval, DTG was added to the list of the ARVs monitored by the Antiretroviral Pregnancy Registry (APR). The APR was initially established in January 1989 and is an ongoing, collaborative effort of multiple companies [Antiretroviral Pregnancy Registry, 2018]. The objective of the APR is to detect an early signal of any major teratogenic effect of antiretroviral drugs included in the programme. The registry is a passive surveillance system designed to address the effect of ART in neonates exposed to ART in utero. This programme collects voluntary reports of ART exposure during pregnancy, which includes background and risk information and birth outcome associated with antiretroviral drugs, including ViiV Healthcare's marketed antiretroviral products. Registration is voluntary. Healthcare professionals are strongly encouraged to enroll their ART- exposed pregnant patients into the Registry as early in the pregnancy as possible, preferably before prenatal testing is done. Patients are followed through health care providers who provide information on maternal risk factors, pregnancy outcome, and neonatal health. In the month of expected delivery, a short follow-up form is sent to the health care provider to ascertain the pregnancy outcome and completion of the antiviral therapy information. Additional follow-up is not sought from health care providers. Data are reviewed periodically by an advisory board. Data and analysis from the APR are submitted within the PBRER for DTG.

A cumulative review of all the pharmacokinetic / safety data (including pregnancy outcomes) available for DTG during pregnancy was presented in the DTG PBRER covering the period 17 July 2016 to 16 January 2017, at the request of PRAC. On review of all the available data at that time, the MAH concluded that no change to the RSI for DTG was warranted with respect to use in pregnancy and pregnancy outcomes and that more pharmacokinetic data in pregnant women and safety data in infants are needed before DTG can be recommended for clinical use during pregnancy. Available data suggest that total DTG levels may be lower in the second and third trimesters of pregnancy compared to post-partum, but exposure is above that needed to suppress viral replication (Bollen 2017, Mulligan, 2018). More recently, Bollen et al (2018) reported that the unbound DTG plasma Cmin, which is thought to mediate the therapeutic effect of DTG, was unchanged in the third trimester compared to post-partum. Collectively, available data suggests that acceptable DTG exposures can be achieved in pregnancy with standard dosing thereby maintaining maternal HIV-1 RNA <50 copies/mL at delivery with no maternal-infant HIV transmission.

In May 2018, preliminary findings from a birth outcomes surveillance study conducted in Botswana showed a higher than expected number of NTDs, among newborns whose mothers were exposed to DTG-based ART at conception (Tsepamo study). On the basis of this data, NTDs were added to the RMP as a potential risk (see Section Identified and potential risks for further information).

The MAH conducted a review in 2018 of available data relating to the use of DTG in pregnancy, from the time of conception through all trimesters of pregnancy. The early signal, has been refuted by subsequent data from two large birth surveillance studies. The MAH has reviewed data from two key studies, the APR, as well as a number of other data sources including the DOLOMITE studies which are considered additional Pharmacovigilance Activities. The most recent data from the Tsepamo study in Botswana (over 9000 pregnancies with DTG peri-conception exposure as of March 2022), show no

evidence of a statistically significant difference in NTD prevalence between infants exposed to DTG and non-DTG ART nor with any other exposure groups. The Eswatini birth outcome surveillance study including over 4800 exposures to DTG at conception through to September 2022 reported no difference in NTD prevalence when mothers take DTG at conception compared to women without HIV. Taken together these 2 large birth surveillance studies, undertaken in countries without folate food fortification, include a total of over 14 000 women taking DTG at conception through to September 2022, and provide evidence that there is no increased risk of NTDs following peri-conception DTG exposure. The exposure threshold of over 2000 needed to confirm or rule out a three-fold or higher increased risk of NTDs with DTG is therefore reached. Based on the latest data from these studies, the prevalence of NTDs in infants born to women taking DTG at conception did not differ significantly from the background rate in women without HIV, or other exposure groups.

The DOLOMITE EPPICC study was an additional pharmacovigilance activity for this risk (for DTG) and it is now completed. After 833 pregnancy exposures, the results showed no increased risk of birth defects following DTG pregnancy exposure compared to background rates. Although the DOLOMITE-EPPICC and ongoing DOLOMITE NEAT ID PASS studies are not powered with sufficient DTG exposures to detect rare events (>500 and <190 respectively), there have been no NTDs reported.

The APR has received reports of over 1800 exposures to DTG in pregnancy resulting in live births. Data from the APR through 31 July 2024 do not demonstrate an increased risk of overall birth defects with DTG use above population expected rates of birth defects.

Birth defects were reported in 38/1160 live births with first trimester DTG exposure . The first trimester prevalence rate was 3.3% (95% CI: 2.3, 4.5). Birth defects were reported in 31/642 second/third trimester DTG exposures with a prevalence rate of 4.8% (95% CI: 3.3, 6.8). Overall, 69/1802 (3.8%) birth defects were reported with any DTG exposure, compared with population expected rates from birth defects registries of 2.7% (MACDP, Atlanta) and 4.2% (TBDR, Texas). Therefore APR data have not demonstrated an increased risk of overall birth defects, or by trimester of exposure, with DTG use compared with population-based surveillance systems. [APR 2024].

Other studies including literature and VH database information reviewed, did not show any evidence of NTDs that would contradict the primary data from the birth outcome driven African studies mentioned above. Further studies are currently ongoing to collect additional information on the use of DTG during pregnancy (see Part III for further information). Data and analysis from these sources are submitted in the PBRER for DTG as they become available.

Use in Breastfeeding

Dolutegravir is excreted in human milk in small amounts. There is insufficient information on the effects of dolutegravir in neonates/infants. European and U.S. guidelines recommend that HIV infected women do not breast feed their infants in order to avoid transmission of HIV. However, the WHO guideline for infant feeding states that in geographic regions where formula feeding is not feasible women can breastfeed while

receiving appropriate antiretroviral therapy during breastfeeding to reduce the risk of HIV transmission [World Health Organization, 2010].

Population in need of further characterisation:

Further information is required to understand the safety profile (e.g. pregnancy outcomes and risk of birth defects) in pregnant women taking DTG.

Further studies are currently ongoing to collect additional information on the use of DTG during pregnancy (see Part III for further information).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 15 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Neural tube defects
Missing information	Use in pregnancy/ breastfeeding

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are required:

Specific adverse reaction follow-up questionnaires for neural tube defects

- Neural tube defects are a potential risk in infants whose mothers were exposed to DTG-based ART at the time of conception. A Targeted Follow Up Questionnaire (TFQ) for cases reporting NTDs has been created for all DTG containing products to ensure the collection of consistent detailed information on these events and the pregnancy exposure. A copy of the TFQ is provided in ANNEX 4.

Other forms of routine pharmacovigilance activities

- Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy will be reviewed as part of routine pharmacovigilance. Results will be provided to regulatory agencies as appropriate as they become available.

III.2 Additional pharmacovigilance activities

A summary of the studies that are planned/ongoing for DTG, to address specific safety concerns, is presented below. Copies of relevant protocols are provided in ANNEX 3 where available.

ANTIRETROVIRAL PREGNANCY REGISTRY (APR)

STUDY SHORT NAME AND TITLE:

Antiretroviral Pregnancy Registry (APR)

RATIONALE AND STUDY OBJECTIVES:

The APR is an international registry that monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a MAH sponsored study involving the collaborative effort of multiple companies [Antiretroviral Pregnancy Registry 2024].

Data from the APR is used to monitor use of the DTG in pregnancy.

STUDY DESIGN:

Clinicians register pregnant women with prenatal exposures to any ARV before the outcome of pregnancy is known, report data on exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential. Defects are reviewed by a teratologist, and all data are reviewed semiannually by an independent

Advisory Committee. Exposure is classified and analysed by the earliest trimester of exposure to each individual ARV medication. Birth defect prevalence (any pregnancy outcome > 20 weeks of gestation with a defect/live births) is compared to both internal and external comparator groups. The external comparators used are two population-based surveillance systems – Metropolitan Atlanta Congenital Defects Program MACDP) [Correa, 2008; Correa-Villasenor, 2003] by the CDC and the Texas Birth Defects Registry (TBDR) [TBDR, 2012]. Internal comparators include exposures to other drugs and exposures in the 2nd or 3rd trimester of pregnancy relative to 1st trimester exposures when organogenesis occurs.

STUDY POPULATION:

Annually, the Registry enrolls approximately 1,000 pregnant women exposed to antiretroviral drugs for the treatment of HIV and HBV infection and prevention of HIV infection. During the last 6 month report period, 471 new prospective enrollments were received bringing the total number of enrolled people to 27,338 [Antiretroviral Pregnancy Registry 2024].

MILESTONES:

The registry reviews data every six months and publishes interim reports semi-annually summarizing the data. These updated data from the APR are presented in the DTG PBRER. The semiannual interim report does not differentiate ARV exposures at conception from post conception-first trimester exposures. The MAH will work with the APR to conduct additional analyses to provide data on DTG exposure at conception among prospectively reported pregnancies.

Data Summary:

As of 31 July 2024, birth defects were reported in 38 out of 1160 live births with first trimester DTG exposure with a first trimester prevalence rate of 3.3% (95% CI: 2.3, 4.5). Birth defects were reported in 31 out of 642 second/third trimester DTG exposures with a prevalence rate 4.8% (95% CI: 3.3, 6.8). Overall, 69/1802 (3.8%) birth defects were reported with any DTG exposure, compared with population expected rates from birth defects registries of 2.7% (MACDP, Atlanta) and 4.2% (TBDR, Texas). The number of pregnancies enrolled in the APR with DTG peri-conception exposure are currently insufficient for definitive conclusions of any potential association of DTG with NTDs. APR data have not demonstrated an increased risk of overall birth defects, or association by trimester of exposure, with DTG use compared with population-based surveillance systems.

DOLOMITE

DOLOMITE, the DTG in pregnancy program is set up to provide comprehensive data on pharmacokinetics, usage, safety and effectiveness of DTG in pregnancy in real world settings in Europe. With PENTA Foundation functioning as the coordinating centre, the MAH is working with two partners, NEAT-ID Network and PANNA Network to design and conduct two studies of DTG in pregnancy; the DOLOMITE NEAT ID Network Study (208759) has the ability to capture pregnancies exposed to DTG at conception. The DOLOMITE EPPICC study which was a Category 3 post-authorisation safety study (PASS) addressing Important Potential Information on 'Neural Tube Defects' has now been completed. This study has not resulted in any new safety concerns or missing information.

STUDY SHORT NAME AND TITLE:

DOLOMITE NEAT ID Network Study (208759)

A non-interventional, multi-site observational study to define the safety and effectiveness of Dolutegravir use in HIV positive pregnant women

RATIONALE AND STUDY OBJECTIVES:

The study aims to assess the safety and effectiveness of DTG in pregnancy in a network of approximately 40 sites across Europe and Canada. DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

STUDY DESIGN:

Multi-site observational study

STUDY POPULATION:

Data on all consenting, DTG exposed pregnant women since its approval and availability in, from participating clinical sites across Europe and Canada will be included in the study.

MILESTONES:

Expected Final report: 30 September 2026

III.3 Summary Table of additional Pharmacovigilance activities

There are no category 1 or 2 studies for DTG.

Table 16 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry Ongoing	Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnancy, NTDs	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR is presented in the PBRER.	-
Study 208759 DOLOMITE NEAT ID Network Ongoing	To assess the safety and effectiveness of DTG in pregnancy in the NEAT-ID network of approximately 40 sites across Europe and Canada.	Use in pregnancy, NTDs DTG exposure relative to conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.	Expected Final Report	30 September 2026

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorization efficacy study required for this product.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 17 Description of routine risk minimization measures by safety concern

Safety concern (risk/ missing information)	Routine risk minimization activities
Neural tube defects (Potential Risk)	**Routine risk communication:** Information on NTDs is included in section 4.6 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for use of DTG containing products in women of childbearing age are included in section 4.6 of the SmPC. **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV
Pregnant/ breastfeeding women (Missing Information)	**Routine risk communication:** Information on the use of DTG in pregnant/ breastfeeding women is included in section 4.6 of the SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for use of DTG containing products in women of childbearing age are included in section 4.6 of the SmPC **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Removal of additional risk minimization activities for neural tube defects

The DHPC was completed in 2018 and therefore has been removed from the EU RMP as this is no longer considered a current additional risk minimization activity for the potential risk of NTD. In addition, the NTD risk has been refuted by the latest data from the Tsepamo and Eswatini Studies, and is supported by the data from the APR and other sources.

V.3 Summary of risk minimization measures

Table 18 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern (risk/ missing information)	**Risk minimization measures**	**Pharmacovigilance activities**
Neural tube defects (potential risk)	**Routine risk minimization measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Target Follow-up questionnaire Review of data from ongoing/planned external and MAH supported studies investigating the use of DTG during pregnancy **Additional pharmacovigilance activities:** Review of the APR Study 208759- DOLOMITE NEAT ID Network Study
Pregnant/ breastfeeding women (missing information)	**Routine risk minimization measures:** Section 4.6 of the SmPC. Prescription only medicine Prescribed by physicians experienced in the treatment of HIV **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Review of the APR Study 208759- DOLOMITE NEAT ID Network Study

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for TIVICAY (Dolutegravir)

This is a summary of the RMP for TIVICAY. The RMP details important risks of TIVICAY, how these risks can be minimized, and how more information will be obtained about TIVICAY's risks and uncertainties (missing information).

TIVICAY 's SmPC and its package leaflet give essential information to healthcare professionals and patients on how TIVICAY should be used.

This summary of the RMP for TIVICAY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TIVICAY's RMP.

I. The medicine and what it is used for

TIVICAY is authorized for the treatment of HIV infected adults, adolescents and children, in combination with other anti-retroviral medicinal products (see SmPC for the full indication). It contains dolutegravir as the active substance and it is given by oral route.

Further information about the evaluation of TIVICAY’s benefits can be found in TIVICAY’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/tivicay

II. Risks associated with the medicine and activities to minimize or further characterise the risks

Important risks of TIVICAY, together with measures to minimize such risks and the proposed studies for learning more about TIVICAY's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of TIVICAY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TIVICAY are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TIVICAY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Neural tube defects
Missing information	Use in pregnancy/ breastfeeding

II.B Summary of important risks

Important potential risk: Neural tube disorders	
Evidence for linking the risk to the medicine	Preliminary findings from a birth outcomes surveillance study conducted in Botswana showed a higher than expected number of neural tube defects (NTDs), among newborns whose mothers were exposed to dolutegravir -based antiretroviral therapy at conception. Review of further data from large observational studies (Eswatini and Tsepamo) also with other sources such as APR, literature and MAH database as well as the completed DOLOMITE EPPICC study, have refuted this signal.
Risk factors and risk groups	Although the exact timing of types of defect may not be known it is thought they occur early in pregnancy and therefore the potential risk would concern women exposed to dolutegravir at the time of conception and first trimester of pregnancy.

Important potential risk: Neural tube disorders	
	The exact causes of NTDs are not known but environmental and genetic factors are known to play a part. Risk factors include: folate and Vitamin B12 deficiency, obesity, diabetes, certain medicines such as some anti-epileptic medications (e,g, sodium valproate, carbamazepine), maternal age and hyperthermia/febrile illness. There is no evidence that NTDs occur more commonly in women living with HIV. Taking folic acid, before and during pregnancy is known to substantially reduce the occurrence of neural tube defects, by up to 70%.
Risk minimization measures	**Routine risk minimization measures:** Section 4.6 of the SmPC. **Additional risk minimization measures:** No additional risk minimization measures
Additional pharmacovigilance activities	Antiretroviral pregnancy registry Study 208759 -DOLOMITE NEAT ID Network Study- ongoing See section II.C of this summary for an overview of the post-authorization development plan

Missing Information: Use in pregnancy/breastfeeding	
Risk minimization measures	**Routine risk minimization measures:** Section 4.6 of the SmPC **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Antiretroviral Pregnancy Registry - ongoing Study 208759- DOLOMITE NEAT ID Network Study See section II.C of this summary for an overview of the post-authorization development plan

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TIVICAY.

II.C.2 Other studies in post-authorisation development plan

Study/Activity (including study number)	Objectives	Safety concerns/efficacy issue addressed	Status	Planned date for submission of (interim and) final study results
Antiretroviral Pregnancy Registry	Monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort.	Use in pregnancy, neural tube defects	Ongoing	A registry interim report is prepared semi-annually summarising the aggregate data which are included in the PBRER..
Study 208759 DOLOMITE NEAT ID Network	To assess the safety and effectiveness of dolutegravir in pregnancy in the NEAT-ID network of approximately 40 sites across Europe.	Use in pregnancy, neural tube defects	Ongoing	Final Report Expected 30 September 2026

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific adverse reaction follow-up questionnaire for neural tube defects

Targeted Follow Up Questionnaire

Dolutegravir; Dolutegravir/abacavir/lamivudine; Dolutegravir/rilpivirine; Dolutegravir/lamivudine and Neural Tube Defects

Patient/subject ID: **DOB/initials:**	**Sex/weight/(is patient obese if weight unknown)** **/Body Mass Index (if known):**	**GSK CASE No:**

Description of the Event:

	Yes	**No**
Was there a neural tube defect? If yes, please describe type, nature and outcome	☐	☐
Did the pregnancy go to full term? If the pregnancy resulted in a spontaneous abortion/miscarriage, please provide week of gestation this occurred.	☐	☐
Were there any other adverse events? If yes, please specify	☐	☐
Please provide information on antiretroviral drug exposure at time of conception and during pregnancy? Specify all drugs and start and stop dates relevant to pregnancy		
If the suspect drug was discontinued, was it subsequently restarted? If *yes*, please specify date and outcome:	☐	☐

Diagnostic Tests:

Please provide a summary of main results of abnormal laboratory values / investigations (or provide copies of relevant results):

	Yes	**No**
Was an ultrasound performed? If yes, please indicate date and results:		

Was the triple or combined screening test performed? If yes, please indicate date and results:	☐	☐
Were any other relevant laboratory investigations such as genetic tests, free fetal DNA performed? If yes, please indicate date and results:	☐	☐
Please provide relevant information regarding the diagnosis method for the neural tube defect		

History:

Social:

Is there a history or current use of (please include details, frequency and amount):	**Yes**	**No**
Smoking	☐	☐
Alcohol	☐	☐
Recreational drugs	☐	☐
Occupation: Please provide details		

Medical history

Is there a family history of birth defects? If yes, please provide details	☐	☐
Is there a history of: (If yes, please provide details)	**Yes**	**No**
Diabetes	☐	☐
Epilepsy	☐	☐
Other relevant history: Please provide details	☐	☐

HIV specific medical history (please provide details)		
Date of initial diagnosis of HIV		
Viral load, CD4 count, CD4 nadir		
Toxoplasma/CMV		
Tuberculosis and Tuberculosis therapy		
Concurrent medications (Please provide drug and duration of use relative to pregnancy)		
Sodium valproate		
Opioids		
Obstetric history		
Serology: Rubella/CMV/toxo/HSV/HCV and HBV Please provide details		
Antenatal screening. Please provide details		
Combined test (age, nuchal, PAPP-A, BHCG		
Triple test: AFP, BHCG, UE3		
Anomaly scan		
Please provide detail of folate use.		
Number of live births (Please provide GP+2 [G is gravida (amount of times pregnant), P is number of live births, with +2 relating to any other pregnancy e.g. medical termination or miscarriage). For live births please provide gestational age.		
Number of spontaneous abortions		
Number of elective terminations		
Previous birth defects including neural tube defects		
Was there exposure to any antiretroviral before or during the previous pregnancies? If yes, please confirm antiretroviral and outcome.		

Travel history to area where Zika prevalent		
	Yes	**No**
Is there history of travel to an area where Zika is prevalent? If yes, please provide Zika Serology	☐	☐

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.