European Union Risk Management Plan (EU-RMP)
REZOLSTA (Darunavir/Cobicistat Fixed Dose Combination)

Data lock point for current RMP	13 December 2023	Version number	7.1

CHMP Opinion Date: 22 May 2025

QPPV Sign-off Date:	22 May 2024
RMP Version Number:	7.1
Supersedes Version:	6.1
EDMS Number:	EDMS-ERI-1293396, 1.0

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	7.1
Rationale for submitting an updated RMP	Extension of the currently approved indication for REZOLSTA to pediatric patients aged 6 years and older, weighing at least 25 kg.
Summary of significant changes in this RMP:	Indication extended from “adults and adolescents (aged 12 years and older, weighing at least 40 kg)” to “adults and pediatric patients (aged 6 years and older, weighing at least 25 kg)”.

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	6.1
Approved within procedure	EMEA/H/C/002819/II/0033
Date of approval (EC decision date)	09 March 2020

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW

Part I. - Product Overview

Active substance(s) **(INN or common name)**	Darunavir/cobicistat
Pharmacotherapeutic group(s) (ATC Code)	Antiviral for systemic use, Antiviral for treatment of HIV infection Combinations ATC code: J05AR14
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	REZOLSTA® (further referred to as REZOLSTA)
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** Darunavir (DRV): protease inhibitor (PI) Cobicistat (COBI): pharmacokinetic (PK) enhancer **Summary of mode of action** DRV is an inhibitor of the dimerization and of the catalytic activity of the human immunodeficiency virus type 1 (HIV-1) protease. It selectively inhibits the cleavage of HIV-encoded Gag-Pol polyproteins in virus-infected cells, thereby preventing the formation of mature infectious virus particles. COBI is a mechanism-based inhibitor of cytochrome P450 (CYP) of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, such as DRV, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism. **Important information about its composition** Not applicable
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet

Indication(s) in the EEA	**Current:** REZOLSTA is indicated, in combination with other ARV medicinal products, for the treatment of HIV-1 infection in adults and pediatric patients (aged 6 years and older, weighing at least 25 kg).
Dosage in the EEA	**Current:** ***Adults and pediatric patients weighing at least 40 kg*** *Antiretroviral therapy-naïve patients* The recommended dose regimen is one 800 mg darunavir/150 mg cobicistat film-coated tablet of REZOLSTA once daily taken with food. *Antiretroviral therapy-experienced patients* In ART-experienced patients with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L, one 800 mg darunavir/150 mg cobicistat film-coated tablet of REZOLSTA once daily taken with food may be used. *All other ART-experienced patients or if HIV-1 genotype testing is not available* REZOLSTA should not be used. Another ARV regimen should be used. ***Pediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg*** *Antiretroviral therapy-naïve pediatric patients* The recommended dose regimen is one 675 mg darunavir/150 mg cobicistat film-coated tablet of REZOLSTA once daily taken with food. *Antiretroviral therapy-experienced pediatric patients* In ART-experienced pediatric patients with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L, one 675 mg darunavir/150 mg cobicistat film-coated tablet of REZOLSTA once daily taken with food may be used. *All other ART-experienced pediatric patients or if HIV-1 genotype testing is not available* REZOLSTA should not be used. Another ARV regimen should be used.

Pharmaceutical form(s) and strengths	**Current:** ***REZOLSTA 800 mg/150 mg film-coated tablets*** Film-coated, pink oval shaped tablet of 23 mm x 11.5 mm, debossed with "800" on one side and "TG" on the other side. The REZOLSTA tablet contains 800 mg of DRV (as ethanolate) and 150 mg of COBI. ***REZOLSTA 675 mg/150 mg film-coated tablets*** Film-coated, green to dark green oval shaped scored tablet of 20 mm x 10 mm, debossed with "675" on one side and "TG" on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The REZOLSTA tablet contains 675 mg of DRV (as ethanolate) and 150 mg of COBI.	
Is/will the product be subject of additional monitoring in the European Union?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

SI.1. Epidemiology of the Indication(s) and Target Population(s)

Indication: Human immunodeficiency virus type 1 infection

Adult Population

Incidence:

The 2023 report from the Joint United Nations Programme on HIV/Acquired Immune Deficiency Syndrome (AIDS) (UNAIDS) states that in 2022, there were approximately 1.3 million (range: 1.0-1.7 million) new (incident) HIV infections, which represents a 38% decline from 2010. Adults aged ≥15 years accounted for 1.2 million (range: 900,000-1.6 million) of these new infections. The incidence and prevalence of all-age HIV infection estimates by region are presented below (UNAIDS 2023a). New HIV infections declined the most in countries within sub-Saharan Africa (UNAIDS 2023b).

Estimated Incidence and Prevalence of HIV by Region, 2022

Region	New HIV infections (range)	People living with HIV (range)
Eastern and Southern Africa	500,000 (370,000 - 670,000)	20,800,000 (17,400,000 - 24,500,000)
Asia and the Pacific	300,000 (220,000 - 400,000)	6,500,000 (5,300,000 - 7,800,000)
Western and Central Africa	160,000 (110,000 - 250,000)	4,800,000 (4,200,000 - 5,500,000)
Eastern Europe and Central Asia	160,000 (140,000 - 180,000)	2,000,000 (1,800,000 - 2,100,000)
Latin America	110,000 (94,000 - 130,000)	2,200,000 (2,000,000 - 2,500,000)
Western Europe, Central Europe, and North America	58,000 (46,000 - 69,000)	2,300,000 (1,900,000 - 2,600,000)
Middle East and North Africa	17,000 (13,000 - 23,000)	190,000 (160,000 - 220,000)
Caribbean	16,000 (11,000 - 21,000)	330,000 (290,000 - 380,000)
Global	**1,300,000 (1,000,000 - 1,700,000)**	**39,000,000 (33,100,000 - 45,700,000)**

Source: UNAIDS 2023a, UNAIDS 2023b.

In 2022, the HIV diagnosis rate was 5.1 cases per 100,000 population in the European Union (EU)/European Economic Area (EEA) and 19.9 cases per 100,000 population in the non-EU/EEA countries. The EU/EEA countries with the highest rates (per 100,000 population) in 2022 were Cyprus (24.1) and Estonia (18.8), and the Russian Federation had the highest rate (38.4) among non-EU/EEA countries (ECDC 2023).

Prevalence:

Of the 39 million (range: 33.1-45.7 million) people living globally with HIV in 2022, 37.5 million (range: 31.8-43.6 million) were adults aged ≥15 years. Over 65% of the people living with HIV resided in sub-Saharan Africa. Western and Central Europe and North America accounted for 2.3 million (range: 1.9-2.6 million) people living with HIV in 2022 (UNAIDS 2023b).

Demographics of the Population in the Authorized Indication and Risk Factors for the Disease

Risk factors for acquiring HIV include geography, sex, injection drug use, and sexual activity. The World Health Organization (WHO) recommends a harm reduction strategy to reduce HIV transmission in key populations with increased HIV risks (WHO 2022).

Geography

Sub-Saharan Africa still accounts for the majority of new global HIV infections (51%). In comparison with 2010, new HIV infections have increased in other regions including Eastern Europe and Central Asia (49% increase) and the Middle East and North Africa (61% increase) (UNAIDS 2023b), but the absolute numbers of new HIV cases are low in these regions (Eastern Europe and Central Asia: 160,000 [range: 140,000-180,000] and the Middle East and North Africa: 17,000 [range: 13,000-23,000]) (UNAIDS 2023a).

Sex and Gender Identity

Of persons newly infected with HIV in 2022, 46% were female (UNAIDS 2023a). Young adult females are at particularly high risk. Among those aged 15-24 years, 160,000 (range: 93,000-230,000) females acquired HIV in 2022 versus 47,000 (range: 9,300-75,000) males (UNAIDS 2023b). For adults living with HIV, slightly more females were accessing antiretroviral therapy (ART) (82%, range: 69-95%) than males (72%, range: 60-84%) (UNAIDS 2023a).

Globally in 2022, the median prevalence of HIV was 10.3% among transgender persons, which is higher than 0.7% in the general adult population. This prevalence varies across regions but accounts in almost every region for the highest proportion of transmission of all key groups including persons who inject drugs, sex workers, and men who have sex with men (MSM) (UNAIDS 2023b).

Injection Drug Use

Globally in 2022, the median HIV prevalence among persons who inject drugs was 5.0% among those aged 15-49 years compared to 0.7% for the general population (UNAIDS 2023a). In the EU/EEA in 2022, transmission related to injection drug use accounted for 4.3% of new HIV diagnoses. Injection drug use accounts for more new HIV infections in the non-EU/EEA countries (ECDC 2023).

Sexual Activity

Globally in 2022, the median HIV prevalence was 2.5% among sex workers and 7.5% for MSM (UNAIDS 2023a). In the EU/EEA in 2022, sex between men accounted for the highest proportion of HIV transmission (33.3%) of considered modes of transmission. In Eastern Europe/non-EU/EEA countries, heterosexual contact accounted for the majority of HIV transmission (>70%) in 2022 (ECDC 2023).

Main Existing Treatment Options:

The 2021 update of the WHO HIV Treatment Guidelines recommends ART to treat all people (including pregnant women, infants, and children) living with HIV regardless of WHO clinical stage or CD4+ cell count (WHO 2021).

Current treatment options include HIV nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists, integrase strand transfer inhibitors (INSTIs), attachment and post-attachment inhibitors, capsid inhibitors, and pharmacokinetic (PK) enhancers (NIH 2023a). An initial ART regimen for a treatment-naïve patient generally consists of 3 ART medicines from 2 or more drug classes. Given the large number of options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as side effects and drug-drug interactions (NIH 2021).

In the 2022 UNAIDS report, it was noted that 76% (range: 65%-89%) of those living with HIV have access to ART. Access to ART was higher among adults (77%, range: 65%-90%) than for children (57%, range: 44%-78%). ART usage among HIV-infected adults in Western Europe and North America was 76% (range: 64%-87%) in 2022 (UNAIDS 2023a).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

HIV is transmitted through certain body fluids and attacks the CD4+ cells of the body's immune system. Over time, HIV can destroy so many CD4+ cells that the body cannot fight off infections. If not treated, individuals once infected with HIV will typically progress through 3 stages of disease (CDC 2022). Treatment can slow or prevent progression to further stages and can reduce the risk of transmission to others (NIH 2023b).

Within 2 to 4 weeks after infection, the acute HIV infection stage (Stage 1) occurs, which can be marked by an extended flu-like prodrome. Due to the high amount of HIV in the blood during the acute stage, people are very contagious but often are unaware because they may not feel sick right away or at all (CDC 2022, NIH 2023b).

During Stage 2 (known as asymptomatic or chronic HIV infection), HIV is still active but reproduces at very low levels (clinical latency). People may not have symptoms during this stage. With good adherence to ART, Stage 2 lasts for several decades. Without ART, this period often lasts about 10 years. At the end of this stage, HIV viral loads start to increase as CD4+ cell counts decline, and people can develop symptoms (CDC 2022, NIH 2023b).

AIDS is Stage 3, the most severe stage of HIV infection. People are diagnosed with AIDS when their CD4+ cell count drops below 200 cells/mm^3 and/or they develop certain opportunistic illnesses that evade the failing immune system. Without treatment, AIDS patients typically survive about 3 years. Viral loads can be high during AIDS, which can allow for the spread of HIV (CDC 2022, NIH 2023b).

Globally in 2022, approximately 630,000 (range: 480,000-880,000) AIDS-related deaths occurred, which is a 51% decrease from 1.3 million (range: 970,000-1.8 million) in 2010 (UNAIDS 2023a). In 2022, with 2,349 AIDS diagnoses, the AIDS diagnosis rate was 0.6 per 100,000 population in the EU/EEA. The highest rate (3.8 per 100,000 population) for the EU/EEA was in Cyprus. There were 767 AIDS-related deaths in the EU/EEA in 2022 (ECDC 2023).

Important Comorbidities:

Important comorbidities in adult patients with HIV infection include chronic hepatitis secondary to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, renal disease, malignancies, tuberculosis, opportunistic infections, lipid abnormalities, coronary artery disease, dementia, peripheral neuropathy, pancreatitis, and progressive multifocal leukoencephalopathy.

Pediatric Population

Incidence:

Approximately 130,000 children aged <15 years were newly infected with HIV in 2022, which is a 58% decline from 2010 (UNAIDS 2023a). The number of children aged <15 years newly infected with HIV (incidence) and those living with HIV (prevalence) in 2022, by geographic region, is as follows:

Estimated Incidence and Prevalence of HIV for Children Aged <15 Years by Region, 2022

Region	New HIV infections (range)	Children living with HIV (range)
Eastern and Southern Africa	58,000 (38,000 - 100,000)	930,000 (710,000 - 1,400,000)
Western and Central Africa	51,000 (34,000 - 69,000)	400,000 (310,000 - 490,000)
Asia and the Pacific	12,000 (8,600 - 18,000)	130,000 (110,000 - 160,000)
Latin America	3,800 (2,900 - 4,700)	31,000 (26,000 - 36,000)
Middle East and North Africa	1,700 (1,300 - 2,100)	10,000 (8,700 - 12,000)
Caribbean	1,500 (1,100 - 2,100)	11,000 (8,600 - 13,000)
Eastern Europe and Central Asia	Not reported	Not reported
Western Europe, Central Europe, and North America	Not reported	Not reported
Global	**130,000 (90,000 - 210,000)**	**1,500,000 (1,200,000 - 2,100,000)**

Source: UNAIDS 2023a, UNAIDS 2023c.

Prevalence:

In 2022, there were 1.5 million (range: 1.2-2.1 million) children aged <15 years living with HIV (UNAIDS 2023b).

Demographics of the Population in the Authorized Indication and Risk Factors for the Disease

Mother-to-child transmission is the main driver for new HIV infections in children. In 2022, approximately 220,000 pregnant or breastfeeding women living with HIV globally were not receiving ART (UNAIDS 2023a). Of the estimated 133,000 children infected through vertical transmission globally in 2022, nearly half (65,000) were born to mothers who were not receiving ART. Similar numbers of children had mothers who stopped ART (29,000) or became infected during pregnancy or breastfeeding (27,000), with the remaining transmissions being due to viral suppression issues (12,000). The majority of these 130,000 vertical transmissions in 2022 occurred in sub-Saharan Africa (UNAIDS 2023b).

In 2022, 1.2% of newly diagnosed HIV infections in the EU/EEA were transmitted from mother to child (ECDC 2023). In the United Kingdom and Ireland, the Collaborative HIV Paediatric Study (CHIPS) follows virtually all children receiving HIV-related care (total = 2,212 children, as of

March 2021). Since 2015, 76% of the children enrolled in CHIPS were virally suppressed (≤200 or ≤lower assay limit) 12 months after starting ART (CHIPS 2021).

Main Existing Treatment Options:

Of the HIV-infected children aged <15 years globally, 57% (range: 44%-78%) had access to ART and 46% had suppressed viral loads (UNAIDS 2023b).

Similar to adults, ART initiation in treatment-naïve children should consider patient-specific factors, including characteristics of the patient and the drug regimens being considered, and family preference. In the United States, the recommendation for children is a combination therapy with 3 drugs: dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone plus an INSTI, an NNRTI, or a boosted PI (NIH 2023c). The EU recommendation for initiation of treatment in children is similar to the one in the United States (Bamford 2018). For other countries, the WHO announced that the recommended, preferred first-line ART (dolutegravir) for young children and infants as young as 4 weeks of age and weighing >3 kg was more readily available in 2020 (WHO 2020).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Progression of HIV infection in children is similar to adults, although for some, it may also advance more rapidly. Vertically transmitted HIV can cause rapidly progressive, chronically progressive, or adult-like disease in which a significant clinical latency period occurs before symptoms appear (Rivera 2020).

Without treatment, about one third of infants living with HIV die by their first birthday and half of them die by their second birthday (UNAIDS 2014). Infected infants are often asymptomatic for the first few months of life regardless of ART initiation. Symptoms often start around 3 years (median) with outliers remaining asymptomatic at >5 years of age. Untreated infants can experience failure to thrive, neurologic problems (eg, loss or delay in motor skills, irritability, poor head growth), and *Pneumocystis* pneumonia infections. Older children who remain untreated can have additional issues related to other opportunistic infections (Weinberg 2023). Globally, there were 84,000 AIDS-related deaths among children aged <15 years in 2022, which is a 64% reduction from 2010 (UNAIDS 2023b).

Important Comorbidities:

Important comorbidities in children with HIV infection include encephalopathy, psychiatric disorders, pain, HBV and/or HCV infection, renal disease, respiratory diseases, cardiomyopathy/ventricular dysfunction, reduced bone density/osteoporosis/osteonecrosis, cytopenia, malignancies, tuberculosis, opportunistic infections, progressive multifocal leukoencephalopathy, lipid abnormalities, and sexual maturity and growth abnormalities.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings From Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Toxicity findings include:	
Developmental toxicity	
There was no evidence of an effect of DRV on fertility or early embryonic development. There was neither teratogenicity with DRV in rabbits when treated alone, nor in rats and mice when treated alone or in combination with rtv. The exposure levels were lower in mice and rabbits and higher in rats than those with the recommended clinical dose in humans. In a pre- and postnatal development assessment in rats, DRV with and without rtv caused a transient reduction in body weight gain of the offspring pre-weaning, and there was a slight delay in the opening of eyes and ears. DRV in combination with rtv caused a reduction in the number of pups that exhibited the startle response on Day 15 of lactation and a reduced pup survival during lactation. These effects may be secondary to pup exposure to the active substance via the milk and/or maternal toxicity. No post-weaning functions were affected with DRV alone or in combination with rtv.	The nonclinical data do not indicate a safety concern for humans and therefore do not indicate a safety concern for REZOLSTA.
No teratogenic effects were observed in rat and rabbit developmental toxicity studies with COBI. Exposures were approximately 1.9- and 4.7-fold higher, respectively, than human therapeutic exposure. In rats, ossification changes in the spinal column and sternebra of fetuses occurred at a dose that produced significant maternal toxicity.	

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Juvenile toxicity In rats, from 23 days of age, DRV has a toxicity profile and exposure that is comparable to that observed in adult animals. In studies where dosing commenced at less than 23 days of age (equivalent to less than 2 years of age in humans), mortality was observed and in some animals, convulsions and other apparent central nervous system effects preceded these deaths. Within this age range, high plasma, liver, and brain area under the plasma concentration-time curve (AUC) values were observed, which were both dose- and age-dependent and considerably greater (approximately more than 3-fold in plasma) than those observed in adult animals. These findings were attributed to the immaturity of the liver enzymes and of the blood brain barrier. The above observations in juvenile rats provide evidence of a potential safety risk as a result of drug-brain accumulation in young children (below 2 years of age). No clinically relevant adverse effects were observed in the juvenile toxicity studies with COBI. Above the no observed adverse effect level of COBI, exposures were 2.7-fold higher (for males and females) than therapeutic adult human exposure.	The observations with DRV are considered relevant for REZOLSTA. An age range of 1 to 3 weeks in rats generally corresponds to a human age range of between 0.1 and 2 years. The observations with DRV in juvenile rats in this age range provide evidence of a potential safety risk due to high drug exposure and accumulation in the brain. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, DRV should not be used in pediatric patients below 3 years of age. A cumulative review of the available clinical data for DRV and DRV/COBI through 19 February 2016 allowed concluding that convulsions is not considered an important potential risk for REZOLSTA.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Nephrotoxicity After 2 years of DRV administration at exposures at or below the human exposure, nephrosis with tubular pigmentation was recorded in mice and linked to an increase in kidney weight. This finding occurred in a limited number of animals, and in the absence of any significant changes in the parameters of renal function (serum creatinine), it is not considered a risk for humans. Chronic progressive nephropathy was also noted in female rats and was accompanied by changes in urinalysis and serum creatinine. This finding is commonly seen in ageing rats and reported to be exacerbated by the administration of xenobiotics. In studies with COBI in rats and dogs urinalysis and urine chemistry changes were noted, including higher urine volume, lower urine specific gravity, and increases in electrolyte excretions. These changes were reversible, were not associated with remarkable clinical chemistry changes, including serum creatinine and blood urea nitrogen, and were without histopathological correlates and were seen at higher exposures than therapeutic human exposure. COBI is an inhibitor of the renal efflux transporter multidrug and toxic compound extrusion protein 1 (MATE1) and organic cation transporter novel, type 1. Organic cation transporter type 2 (OCT2) and MATE1 transporters appear to play a role in the active tubular secretion of creatinine by the kidney (Urakami 2004, Sato 2008, Tanihara 2007).	These observations with DRV and COBI are not considered to be relevant for REZOLSTA. The DRV finding is commonly seen in ageing rats and reported to be exacerbated by the administration of xenobiotics. The COBI findings were without histopathological correlates and are not relevant for humans. In clinical trials, COBI has been shown to decrease estimated creatinine clearance (CrCl) due to inhibition of tubular secretion of creatinine without affecting glomerular function. These changes are consistent with nonclinical findings of COBI inhibition of the renal transporters, MATE1 and OCT2.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Hepatotoxicity	
Hepatocellular hypertrophy sometimes with vacuolation of centrilobular hepatocytes was seen in mice and rats treated with DRV. The hepatocellular hypertrophy was considered mild in nature and reflects an adaptive response to enzyme induction. Increases in cholesterol and total proteins and decreases in triglycerides were seen in rats. These lipid and protein changes were probably secondary to the effects on the liver. These findings were seen at exposure below the human therapeutic dose.	The observed effects of DRV and COBI on the liver are adaptive changes in response to liver enzyme induction effect of both compounds and are species specific. They are therefore considered to be of limited relevance to humans. In humans, no potentiation of toxic liver effects are expected.
In dogs, changes in the liver were observed only after 12 months of treatment with DRV and were limited to a slight increase in liver weight associated with hepatocellular vacuolation and pigmentation. Increases in liver transaminases in animal studies were generally mild or absent. These findings were seen at exposures higher than human therapeutic exposure.	
During studies with COBI in rats, increases in liver weight were associated with microsomal enzyme induction and hepatocellular hypertrophy. These changes are considered adaptive changes and were not considered adverse effects. COBI induces hepatic CYP3A activity in rats likely due to a species-specific activation of rat pregnane X receptor. In dogs, minimal to mild increases in bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase activities, increased liver weights, and hepatocyte vacuolation were noted after 4 weeks. All findings were seen at exposures higher than human therapeutic exposure.	
Mutagenicity and genotoxicity	
DRV was not mutagenic or genotoxic in a battery of in vitro and in vivo assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes and in vivo micronucleus tests in mice.	The nonclinical data do not indicate a safety concern for humans.
COBI was not genotoxic in the Ames test, mouse lymphoma assay, or rat micronucleus assay.	

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Carcinogenicity	
Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in male and female mice and rats. Thyroid follicular cell adenomas were noted in male rats. Administration of DRV did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. Repeated administration of DRV to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats to thyroid neoplasm. At the highest tested doses, the systemic exposures (based on AUC) to DRV were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses. Administration of COBI in mice resulted in no drug-related increase in tumor incidence. In rats, increases in follicular cell adenomas and/or carcinomas in the thyroid gland were observed. The follicular cell findings are considered to be rat specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the carcinogenicity study, COBI AUCs were between 10- and 23-fold (mice) and 2.6- to 3-fold (rats) the human systemic exposure at the therapeutic daily dose.	The observed hepatocellular (DRV) and thyroid tumors (DRV, COBI) in rodents are considered to be of limited relevance to humans. Hepatic microsomal enzyme induction and increased thyroid hormone elimination only predispose rats but not humans to thyroid neoplasm. During the clinical development programs of DRV/COBI 800/150 mg once daily and of the single agents, no safety concern was identified for carcinogenicity.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
General safety pharmacology findings:	
Thyroid effect	
In studies with DRV, thyroid homeostasis was altered to various extent in rats (and mice) as seen by diffuse follicular hypertrophy and hyperplasia. It is likely that this is a rodent-specific adaptive response to liver enzyme induction. This finding was seen at exposure below the human therapeutic dose. Thyroid changes were not observed in dogs at exposure higher than human therapeutic exposure.	These observations are considered not relevant for human use as they are species specific.
During studies with COBI in rats, increases in thyroid weight were associated with thyroid hormone imbalance, thyroid follicular cell hypertrophy, and thyroid follicular cell adenomas and/or carcinomas. These changes are considered adaptive changes, were not considered adverse, and were seen at exposure higher than human therapeutic exposure.	

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Hematopoietic system In studies with DRV, the hematopoietic system was affected in rats and mice, with slight decreases (about 10%) in red blood cell (RBC) counts, hemoglobin, and hematocrit. Increases in reticulocytes and bilirubin levels were also observed. These changes are indicative of an increased RBC turnover, which was confirmed microscopically by the presence of extramedullary hematopoiesis in the spleen, sometimes accompanied by an increase in spleen weight. These findings were seen at exposure below the human therapeutic exposure. No changes in RBC-related parameters have been observed in dogs at higher exposure than human therapeutic exposure. In studies with COBI, minimal changes in RBC parameters (not exceeding 10%) were noted for the high-dose in a 26-week rat study corresponding to higher exposure than human therapeutic exposure. There were no correlative effects (eg, symptoms of anemia, bone marrow suppression) and similar effects were not seen in mice dosed for 10 weeks or in dogs dosed for 39 weeks.	These observations are considered not relevant for human use as they are species specific. During the clinical development programs of DRV/COBI 800/150 mg once daily and of the single agents, no safety concern was identified for the hematopoietic system.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Blood coagulation system	
The blood coagulation system was affected during studies with DRV. Platelet counts were increased and prolongation in the activated partial thromboplastin time (APTT) was observed in rats. The observed increase in platelet counts was not associated with any gross or microscopic evidence of venous and arterial thromboembolism. The observed increase in APTT was not associated with any gross or microscopic evidence of bleeding. These findings were seen at exposure below the human therapeutic dose. In dogs, no such changes were seen at higher exposure than human therapeutic exposure. In studies with COBI in rats and dogs, increases in mean platelet counts were noted, with minimal prolongation in APTT also noted in dogs at exposure higher than human therapeutic exposure. In all cases, there were no associated effects on bleeding, the changes were reversible, and they were not considered adverse.	These observations with DRV are considered not relevant for human use as they are species (rat) specific. For COBI, these changes only occurred at high doses, they were considered not adverse, and not considered relevant to humans. During the clinical development programs of DRV/COBI 800/150 mg once daily and of the single agents, no safety concern was identified for blood coagulation.
Immune system	
No changes in the immune response were observed for DRV at higher exposure than human therapeutic exposure. In various immunotoxicity studies for COBI, decreased immunoglobulin G levels were noted in female rats at dose levels above the no observed adverse effect level for systemic toxicity in long term studies. However, in standard toxicity studies with COBI in mice, rats, and dogs, and at higher dose levels and exposures, no signs of immune function changes have been observed.	Nonclinical DRV data reveal no special hazard for humans based on repeat dose toxicity studies. During the clinical development program of DRV/COBI 800/150 mg once daily and the single agents, no safety concern was identified for toxicity on immunoglobulin G.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Cardiac effect	
DRV safety pharmacology studies did not detect any significant nonclinical safety signals. In vitro, concentrations tested corresponded to 13-fold the clinical concentration. Ex vivo rabbit studies and in vivo dog studies suggest that COBI may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than human exposure at the recommended 150 mg daily dose. These effects may be a consequence of interaction with cardiac calcium channels (Guth 2007, Dai 2005).	During the DRV clinical trial program, no safety concern was identified for prolonged PR and/or decreased left ventricular function. During the COBI clinical trial program, COBI at exposures approximately 2- or 4-fold above the recommended therapeutic dose in healthy volunteers was found to induce a dose-related increase of the PR interval (+9.6 msec), which was not considered to be clinically significant. No effect was observed on left ventricular function. No cardiac safety concern was identified during the DRV/COBI clinical development programs. Clinical trials excluded subjects with abnormal electrocardiogram (ECG) findings at screening judged by the investigator to be clinically significant. A cumulative review of the available clinical data for DRV and DRV/COBI through 19 February 2016 allowed concluding that cardiac conduction abnormalities is not considered an important potential risk for REZOLSTA.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Mechanisms for drug interactions	
For DRV, CYP3A was almost exclusively involved in the metabolism. DRV inhibited CYP3A in human liver microsomes with an inhibitory constant (K_i) value of 0.40 µM (0.22 µg/mL). The K_i values for the other CYP450 enzymes (CYP2B6, CYP2C9, CYP2C1, CYP2D6, CYP2C8, and uridine diphosphate glucuronosyltransferase [UGT] 1A1) were at least 60-fold higher, indicating a much lower affinity and less potential for clinically relevant interactions. DRV also showed a concentration dependent effect on CYP3A4 induction in vitro. In vitro, DRV has P-glycoprotein (P-gp) inhibitory properties with an apparent 50% inhibitory concentration of 32.9 µM (18.0 µg/mL). COBI is a potent inhibitor of human CYP3A, with inactivation kinetics similar to those of rtv. COBI does not inhibit human CYP1A2, CYP2B6, CYP2C8, CYP2C9, or CYP2C19 and is a weak inhibitor of CYP2D6. COBI is a weak inhibitor of human hepatic microsomal UGT1A1 activity, being less potent than rtv. COBI treatment should thus not raise serum bilirubin concentrations due to inhibition of UGT1A1. The transporters that COBI inhibits include P-gp, breast cancer resistance protein, organic anion-transport protein (OATP)1B1, and OATP1B3.	Coadministration of DRV and/or COBI and medicinal products primarily metabolized by CYP3A may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effects and adverse reactions. Coadministration of DRV/COBI with medicinal products that are highly dependent on CYP3A for their clearance and for which increased plasma concentrations result in serious and/or life-threatening reactions (narrow therapeutic index) is contraindicated. Coadministration of COBI with potent CYP3A inducers that may significantly decrease the plasma concentrations of DRV and COBI is also contraindicated. Unlike rtv, COBI is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP3A4, CYP2C9, CYP2C19, UGT1A1, or P-gp. If switching from rtv as a PK enhancer, caution is required during the first two weeks of treatment with REZOLSTA, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of rtv as a PK enhancer. During the clinical development program of DRV/COBI 800/150 mg once daily and of the single agents, no safety concern was identified for drug interactions.

Conclusion of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The REZOLSTA tablet is a combination of 2 single agents, DRV and COBI. DRV is an approved HIV-1 PI. COBI has been registered to be coadministered as a PK enhancer of atazanavir (ATV), DRV, and elvitegravir. The development of a fixed-dose combination (FDC) tablet of DRV with its PK enhancer in a once-daily regimen offers the option to simplify DRV-containing ARV regimens by reducing pill burden.

DRV (PREZISTA®, also known as TMC114) is an HIV-1 PI developed by Janssen Research and Development. It is currently indicated for the treatment of HIV-1 infection in adults and in pediatric patients 3 years of age and above in combination with rtv and with other ARVs. Low-dose rtv is coadministered with DRV (as a single agent) for its CYP3A inhibitor properties to enhance (boost) DRV concentrations. Once daily and twice daily dosing recommendations of DRV/rtv are available, and the approved dosing regimen and indications may vary per country where registered.

DRV 800 mg, in combination with 100 mg rtv once daily, is a registered dose regimen in the European Union that can be used for the treatment of:

- HIV-1 infection in ART-naïve adults and pediatric patients 3 to 17 years of age and weighing at least 40 kg, and
- HIV-1 infection in ART-experienced adults and pediatric patients 3 to 17 years of age and weighing at least 40 kg, with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

DRV 675 mg, in combination with 100 mg rtv once daily, is a registered dose regimen in the European Union that can be used for the treatment of:

- HIV-1 infection in ART-naïve pediatric patients 3 to 17 years of age and weighing at least 30 kg to less than 40 kg, and
- HIV-1 infection in ART-experienced pediatric patients 3 to 17 years of age and weighing at least 30 kg to less than 40 kg, with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

COBI (formerly known as GS-9350) has been developed by Gilead Sciences Inc. (Gilead) and is licensed for use as a PK enhancer to increase systemic exposure of coadministered ARVs metabolized by CYP3A enzymes, including the PIs DRV and ATV, and the INSTI elvitegravir. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of the substrates of CYP3A, such as DRV; this is useful in situations where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism. COBI itself does not show ARV activity in vitro and does not directly contribute to the efficacy of an ARV regimen. Its primary pharmacodynamic activity is to enhance the exposure of drugs that are metabolized by CYP3A in order to achieve appropriate therapeutic exposures.

DRV 800 mg, in combination with 150 mg COBI once daily, is a registered dose regimen in the European Union for the treatment of:

- HIV-1 infection in ART-naïve adults and adolescents (aged 12 years and older, weighing at least 40 kg), and
- HIV-1 infection in ART-experienced adult and adolescents (aged 12 years and older, weighing at least 40 kg) with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

Additionally, a lower dosage of DRV 675 mg, in combination with 150 mg COBI once daily, has been developed for the treatment of:

- HIV-1 infection in ART-naïve pediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg, and
- HIV-1 infection in ART-experienced pediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg, with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

COBI is also authorized in the European Union as part of a single tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (E/C/F/TDF, Stribild), a single tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF, Genvoya), and an FDC containing ATV and COBI (Evotaz).

The clinical development of the REZOLSTA tablet has been built on the information accrued from the development program for DRV in combination with rtv (conducted by the Marketing Authorization Holder) and on the development program for COBI (conducted by Gilead).

The clinical program consisted of a PK bridging program, with the aim to support the development of an FDC formulation and to bridge the comprehensive datasets of the individual agents to the FDC formulation.

No clinical trials were performed with the DRV/COBI FDC tablet in HIV-1-infected pediatric or adolescent patients.

- For the adolescent population (12 to ≤18 years weighing at least 40 kg), results from the following trials with the components of the DRV/COBI FDC in HIV-1-infected adolescents allow extrapolation of the established safety, efficacy, and resistance clinical data from DRV and COBI to the DRV/COBI FDC:
    - TMC114-C230 (DRV in combination with ritonavir [rtv] in ART-naïve subjects)
    - GS-US-216-0128 (DRV in combination with COBI [as single agents] in ART-experienced, virologically-suppressed subjects; Cohort 1)
    - GS-US-292-0106 (COBI, as part of the E/C/F/TAF FDC).

  The available data for DRV and COBI indicate that the overall safety profile in adolescent subjects aged 12 to <18 years and weighing at least 40 kg is similar to that observed in the adult population.

- For the pediatric population 6 to ≤12 years weighing at least 25 kg, results from one trial with the components of the DRV/COBI FDC in HIV-1-infected children allow extrapolation of the established safety, efficacy, and resistance clinical data from DRV and COBI to the DRV/COBI FDC:
    - GS-US-216-0128 (DRV in combination with COBI [as single agents] in ART-experienced, virologically-suppressed subjects; Cohort 2).

  The available data for DRV and COBI indicate that the overall safety profile in pediatric subjects aged 6 to <12 years and weighing at least 25 kg is similar to that observed in the adult population.

The following completed Phase 3 and Phase 3b trials from the DRV/COBI Clinical Development Program are included in this European Union Risk Management Plan (EU-RMP):

- 1 Phase 3 trial: GS-US-236-0118 (HIV-infected subjects)
- 2 Phase 3b trials: GS-US-216-0130 (HIV-infected subjects), of which results showed that the safety profile of DRV/COBI is comparable to the established safety profile of DRV/rtv; and TMC114HIV3015 (HIV-1-infected pregnant women).

SIII.2. Clinical Trial Exposure

Exposure in Randomized Trials

During the clinical development program of REZOLSTA, there were neither placebo-controlled trials, nor fully randomized blinded trials with REZOLSTA or with DRV/COBI coadministered as single agents.

Exposure in All Clinical Trials

Exposure to DRV/COBI in the all clinical trials population is summarized in Tables SIII.1 through SIII.4 for all subjects by duration, by age and sex, by race, and variable stratifications relevant to the product (pregnant women, breast-feeding women, renal impairment at baseline, transaminase elevation at baseline, coinfection with HBV/HCV). These tables present the exposure of the 313 HIV-1-infected subjects included in the Phase 3b trial GS-US-216-0130 to DRV/COBI 800/150 mg once daily coadministered as single agents, based on the Week 48 analysis[1]. In addition, the tables also include exposure to DRV/COBI 800/150 mg once daily in 7 HIV-1-infected pregnant women included in the Phase 3b trial TMC114HIV3015.

In the Phase 3 trial GS-US-236-0118, 22 HIV-1-infected subjects with mild to moderate renal impairment were treated with DRV/COBI for a total duration of 96 weeks. This trial is not included in the exposure tables as the Marketing Authorization Holder (MAH) is not the sponsor of this trial and hence does not have access to the individual exposure data.

[1] The cut-off for this Week 48 analysis is when last subject reached Week 48 or discontinued earlier.

Table SIII.1: Exposure BY DURATION (Trials GS-US-216-0130 - Week 48 and TMC114HIV3015 DRV/COBI arm)

	Persons (n)	Person-Years
INDICATION HIV-1 infection	(N = 320)	
Exposure of at least 4 Weeks	303	23
Exposure of at least 12 Weeks	297	68
Exposure of at least 24 Weeks	284	131
Exposure of at least 48 Weeks	268	247
Total person time		353

[TRMPEX01.RTF] [/SAS/Z_TMC114/TMC114ZDSURPSURRMP/FILES/RE/RMP_DRV_COBI_OCT2017/MACROS/TRMPEX01.SAS]
31OCT2017, 14:41

Table SIII.2: Exposure BY AGE GROUP AND SEX (Trials GS-US-216-0130 - Week 48 and TMC114HIV3015 DRV/COBI arm)

	Men		Women	
	Persons	**Person - Years**	**Persons**	**Person - Years**
INDICATION HIV-1 infection	(N = 279)		(N = 41)	
<18 years	0	0	0	0
18 - 64 years	277	316	41	36
65 - 74 years	2	1	0	0
≥75 years	0	0	0	0
Total	279	317	41	36

[TRMPEX02.RTF] [/SAS/Z_TMC114/TMC114ZDSURPSURRMP/FILES/RE/RMP_DRV_COBI_OCT2017/MACROS/TRMPEX02.SAS]
31OCT2017, 15:24

Table SIII.3: Exposure BY ETHNIC OR RACIAL ORIGINS (Trials GS-US-216-0130 - Week 48 and TMC114HIV3015 DRV/COBI arm)

	Persons	Person - Years
INDICATION HIV-1 infection	(N = 320)	
White	188	215
Black	113	120
Asian	4	2
American Indian or Alaska Native	4	5
Other[a]	11	11
Total	320	353

[a] "Other" includes other Pacific islander and not specified other.

[TRMPEX03.RTF] [/SAS/Z_TMC114/TMC114ZDSURPSURRMP/FILES/RE/RMP_DRV_COBI_OCT2017/MACROS/TRMPEX03.SAS]
31OCT2017, 14:51

Table SIII.4: Exposure BY SPECIAL POPULATIONS (Trials GS-US-216-0130 - Week 48 and TMC114HIV3015 DRV/COBI arm)

	Persons	Person - Years
INDICATION HIV-1 infection	(N = 320)	
Pregnant Women	7	3
Breast-feeding Women	Not included in clinical trials	Not included in clinical trials
Renal Impairment [a]		
Normal (CrCl ≥80 mL/min)	299	337
Mild (CrCl >50 to <80 mL/min)	14	14
Moderate (CrCl >30 to ≤50 mL/min)	0	0
Severe (CrCl ≤30 mL/min)	0	0
Transaminase elevation		
ALT >2 times the ULN	10	9
ALT >3 times the ULN	1	0
Coinfection with HBV/HCV	13	15

ULN = upper limit of normal

[a] Based on baseline CrCl calculated with Cockcroft-Gault formula (CHMP 2004):

$$CrCl = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \ \{\times 0.85 \text{ for women}\}}{72 \times \text{serum creatinine (mg/dL)}}$$

[TRMPEX04.RTF] [/SAS/Z_TMC114/TMC114ZDSURPSURRMP/FILES/RE/RMP_DRV_COBI_OCT2017/MACROS/TRMPEX04.SAS] 20NOV2017, 08:59

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Medical history of clinically significant allergy or hypersensitivity to DRV or COBI**
Reason for being an exclusion criterion	The use of REZOLSTA is contraindicated in patients with hypersensitivity to one of the components to avoid possible severe and life-threatening allergic/hypersensitivity reactions.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The Summary of Product Characteristics (SmPC) states that hypersensitivity to the active substances or to any of the excipients is a contraindication to REZOLSTA use.
Criterion 2	**Clinical or laboratory evidence of severe hepatic impairment**
Reason for being an exclusion criterion	The PK and safety of DRV in patients with severe hepatic impairment have not been established.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The SmPC states that the use of REZOLSTA is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Criterion 3	**Pregnant women: Women of childbearing potential were requested to use effective birth control methods during and after the trials**
Reason for being an exclusion criterion	Per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, pregnant women should normally be excluded from clinical trials.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The SmPC states that therapy with REZOLSTA should not be initiated during pregnancy, and women who become pregnant during therapy with REZOLSTA should be switched to an alternative regimen.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 4	**Breast-feeding women**
Reason for being an exclusion criterion	Breast-feeding women are usually excluded from clinical trials. In addition, in order to avoid transmission of HIV to the infant, HIV-infected women should not breast-feed.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The SmPC states that HIV-infected women should not breast-feed if they are receiving REZOLSTA because of the potential for HIV transmission and the potential for adverse reactions in breast-fed infants.
Criterion 5	**Patients below 18 years of age**
Reason for being an exclusion criterion	These patients were excluded from the pivotal trials of the initial DRV/COBI clinical development program. Experience in adults was required before the safety and efficacy of REZOLSTA could be established in pediatric patients.
Considered to be included as missing information	No
Rationale (if not included as missing information)	REZOLSTA was initially only indicated for adults. Once the REZOLSTA profile in adults was determined, trials with the components of REZOLSTA conducted in adolescents (12 to ≤18 years of age) and children (6 to ≤12 years) allowed extrapolation of the established safety, efficacy, and resistance clinical data from DRV and COBI to the DRV/COBI FDC for these populations. REZOLSTA is not recommended for use in pediatric patients aged 3 to less than 6 years, or older than 6 years but weighing less than 25 kg. REZOLSTA should not be used in pediatric patients below 3 years of age.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical trial development program of DRV/COBI included 320 HIV-1-infected adult subjects (including 7 HIV-1-infected pregnant women), which is sufficient to detect, with 95% confidence, events that have an incidence of 1%. As a result, the target population may be at risk for ADRs not detected in clinical trials.

As limited data are available on the long-term use of DRV/COBI up to 64.3 weeks, the effects of prolonged exposure are unknown. However, it is expected that data can be extrapolated from the safety profiles of DRV/rtv and COBI. The clinical development program of DRV/rtv included 3,746 adult subjects, of which 373 subjects were treated up to 192 weeks. In these subjects, no additional ADRs were detected compared to Week-96 available safety datasets, suggesting that

longer exposure did not change the risk profile. In the clinical development program of COBI, 443 subjects were exposed to COBI used as a PK enhancer of ATV or DRV for more than 3 years, and no ADRs specifically associated with prolonged exposure to COBI have been identified.

The safety profile in the pediatric GS-US-216-0128 trial, in which 8 subjects aged 12 to ≤18 years and 8 subjects aged 6 to ≤12 years received DRV (dose based on body weight) and COBI (150 mg) as separate agents was consistent with that observed in the adult population. No new ADRs were identified.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pediatric population	*Adolescents (12 to ≤18 years old):* In Cohort 1 of the Phase 2/3 trial GS-US-216-0128, 8 HIV-1-infected, treatment-experienced, virologically-suppressed adolescent subjects aged 12 to <18 years and weighing at least 35 kg* received DRV**/COBI 150 mg once daily. In the Phase 2 trial TMC114-C230, 12 HIV-1-infected, ART-naïve adolescent subjects aged 12 to <18 years and weighing at least 40 kg were treated with DRV/rtv 800/100 mg once daily in combination with other ARV agents. In the Phase 2/3 trial GS-US-292-0106, 50 HIV-1-infected, treatment-naïve adolescent subjects aged 12 to <18 years and weighing at least 35 kg received E/C/F/TAF (150/150/200/10 mg) FDC once daily. * *While the protocol allowed enrollment of adolescents aged 12 to <18 years weighing at least 25 kg, no subject receiving DRV/COBI in the trial weighed less than 35 kg at screening.* ** *DRV dose according to applicable prescribing information, based on body weight.* *Children (6 to ≤12 years old):* In Cohort 2 of the Phase 2/3 trial GS-US-216-0128, 8 HIV-1-infected, treatment-experienced, virologically-suppressed pediatric subjects aged 6 to <12 years and weighing at least 25 kg received DRV**/COBI 150 mg once daily. ** *DRV dose according to applicable prescribing information, based on body weight.*
Elderly	Of the 320 subjects in the all clinical trials population, 2 (0.6%) subjects were 65 years of age or older, while no subjects were 75 years of age or older.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant women have been excluded from all clinical trials in the clinical development program to date, except for the Phase 3b trial TMC114HIV3015, which assessed the PK of DRV/rtv (twice daily and once daily regimens), DRV/COBI (once daily regimen), etravirine, and rilpivirine in HIV-1-infected pregnant women. In this trial, 7 pregnant women were treated with DRV/COBI.
Breast-feeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Of the 320 subjects in the all clinical trials population, 10 (3.1%) subjects had transaminase elevation at baseline defined as an ALT >2 times the upper limit of normal (ULN) and 1 subject had an ALT >3 times the ULN. Patients with severe hepatic impairment (Child-Pugh C) were not included in the clinical development program.
• Patients with renal impairment	Of the 320 subjects in the all clinical trials population, 14 (4.4%) subjects had mild (CrCl >50 to <80 mL/min; n=14), moderate (CrCl >30 to ≤50 mL/min; n=0), or severe (CrCl ≤30 mL/min; n=0) renal impairment at baseline. In the Phase 3 trial GS-US-236-0118, 22 HIV-1-infected subjects with mild to moderate renal impairment (screening estimated glomerular filtration rate calculated by the Cockcroft-Gault method between 50 and <90 mL/min) were treated with DRV/COBI plus 2 NRTIs.
• Patients with cardiac conduction disorders	Not included in the clinical development program.
• Immunocompromised patients	Not applicable
• Patients coinfected with HIV and HBV and/or HCV	Of the 320 subjects in the all clinical trials population, 13 (4.0%) HIV-1-infected subjects were coinfected with HBV and/or HCV.
Patients with relevant different racial and/or ethnic origin	Of the 320 subjects in the all clinical trials population, 188 (58.8%) were white, 113 (35.3%) were black, and 19 (5.9%) were American Indian, Asian, or other.
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable

Summary of Safety Concerns Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with cardiac conduction disorders

PART II: SAFETY SPECIFICATION

Module SV: Post-authorization Experience

SV.1. Post-authorization Exposure

SV.1.1. Method used to Calculate Exposure

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The recommended dose for REZOLSTA is 1 tablet taken once daily. Therefore, 30.4 tablets equal 1 person-month of exposure, and 12 person-months equal 1 person-year of exposure.

SV.1.2. Exposure

Considering that a total of 217,156,710 tablets of REZOLSTA were distributed worldwide from launch through 30 April 2023, the estimated non-study post-authorization exposure is 595,276 person-years, of which 228,948 person-years are in the European Union.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The potential for illegal use is unlikely given that the pharmacodynamic mode of action of REZOLSTA is virus specific.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No safety concerns have been newly added or reclassified in this updated RMP.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

There are no important identified risks or important potential risks for REZOLSTA.

Missing information for REZOLSTA are:

- Safety in patients with cardiac conduction disorders

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Missing information: Safety in patients with cardiac conduction disorders
Evidence source: Ex vivo rabbit studies and in vivo dog studies suggest that COBI may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the 150 mg daily dose of COBI. The available clinical study data from the COBI studies and the additional supporting data from the Stribild (E/C/F/TDF) studies do not support an increased risk of cardiac conduction disorders associated with the use of COBI in patients with preexisting nonclinically significant ECG abnormalities. Because of the aforementioned nonclinical data of COBI, patients with abnormal ECG results deemed to be clinically significant were excluded from clinical trials.
Population in need of further characterization: Patients with cardiac conduction disorders.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with cardiac conduction disorders

PART III: PHARMACOVIGILANCE PLAN (Including Post-Authorization Safety Studies)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are listed in the tables below.

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities
Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Post-authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing information	
Safety in patients with cardiac conduction disorders	Routine risk communication: • None Other routine risk minimization measures beyond the Product Information: • Legal status: restricted medical prescription

V.2. Additional Risk Minimization Measures

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

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Safety in patients with cardiac conduction disorders	Routine risk minimization measures: • Legal status: restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for REZOLSTA

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

REZOLSTA's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how REZOLSTA should be used.

This summary of the RMP for REZOLSTA 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.

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

I. The Medicine and What it is Used For

REZOLSTA is authorized in combination with other antiretroviral (ARV) medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients (aged 6 years and older, weighing at least 25 kg) (see SmPC for the full indication). REZOLSTA contains darunavir/cobicistat (DRV/COBI) as the active substance and is given as an oral FDC tablet (adults and pediatric patients weighing at least 40 kg: DRV 800 mg, COBI 150 mg; pediatric patients 6 years and older weighing at least 25 kg to less than 40 kg: DRV 675 mg, COBI 150 mg).

Further information about the evaluation of REZOLSTA’s benefits can be found in REZOLSTA’s European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage:

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

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of REZOLSTA, together with measures to minimize such risks and the proposed studies for learning more about REZOLSTA'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 PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized 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 (eg, 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 analyzed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report 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 REZOLSTA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of REZOLSTA 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 REZOLSTA. 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 (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with cardiac conduction disorders

II.B. Summary of Important Risks

Missing Information: Safety in patients with cardiac conduction disorders	
Risk minimization measures	Routine risk minimization measures: • Legal status: restricted medical prescription Additional risk minimization measures: • None

II.C. Post-authorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of REZOLSTA.

II.C.2. Other Studies in Post-authorization Development Plan

There are no other studies in the post-authorization development plan of REZOLSTA.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities

Not applicable.