European Union Risk Management Plan
REKAMBYS (Rilpivirine prolonged-release suspension)

Details of this RMP Submission

RMP version number: 6.1
Data lock point: 18 February 2023

Date: 23 September 2025
RMP Version Number: 6.1
Supersedes RMP Version Number: 5.2
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[redacted]

Rationale for Submitting an Updated RMP

Type IB variation to update the due date for the final report of the additional pharmacovigilance activity DUS study, following the favorable opinion to the PASS protocol amendment assessment (procedure EMA/PASS/0000247696).

Summary of Significant Changes in this RMP

Pharmacovigilance Plan:

Update of the due date for the final report of the additional pharmacovigilance activity "Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration with EuroSIDA" from September 2026 to September 2027.

Other RMP Versions Under Evaluation:

Version Number	Date Submitted	Procedure Number
Not applicable		

Details of the Currently Approved RMP

Version number: 5.2
Approved with procedure: EMEA/H/C/005060/II/0022
Date of approval: 13 January 2025 (EC decision date)

QPPV Details

QPPV Name: Dr. Laurence Oster-Gozet, PharmD, PhD

QPPV Oversight Declaration: The QPPV has reviewed and approved this RMP (electronic signature on file, as applicable).

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir sulfate
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ART-CC	Antiretroviral Therapy Cohort Collaboration
ARV	antiretroviral
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CAB	cabotegravir
cART	combination antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	creatinine clearance
CSR	Clinical Study Report
CYP	cytochrome P450
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DTG	dolutegravir
DUS	Drug Utilization Study
EACS	European AIDS Clinical Society
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	healthcare professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFU	instructions for use
IM	intramuscular(ly)
INI	integrase inhibitor
INN	international nonproprietary name
IR	incidence rate
IV	intravenous(ly)
LA	long acting injectable, extended-release suspension for injection, or prolonged-release suspension for injection
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities

MSM	men who have sex with men
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PBRER	Periodic Benefit-Risk Evaluation Report
PK	pharmacokinetic(s)
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
Q4W	dosing once every 4 weeks
Q8W	dosing once every 8 weeks
RMP	Risk Management Plan
RPV	rilpivirine
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
UDP-GT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Rilpivirine (INN: Rilpivirine free base, TMC278)
Pharmacotherapeutic group(s) (ATC Code)	Antiviral for systemic use NNRTI (ATC code: J05AG05)
Marketing Authorization Holder	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	REKAMBYS
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** NNRTI **Summary of mode of action:** RPV is a diarylpyrimidine NNRTI of HIV-1. RPV activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase. RPV does not inhibit the human cellular DNA polymerases alpha (α), beta (β), and gamma (γ). **Important information about its composition:** Not applicable
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labeling and Package Leaflet
Indication(s) in the EEA	**Current:** REKAMBYS is indicated, in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen, without present or past evidence of viral resistance to, and no prior virological failure with, agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class.
	Proposed: Not applicable

Dosage(s) in the EEA	**Current:** Therapy should be prescribed by a physician experienced in the management of HIV infection. Each injection should be administered by an HCP. Prior to starting REKAMBYS, the HCP should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses. Following discontinuation of REKAMBYS in combination with CAB injection, it is essential to adopt an alternative, fully suppressive ARV regimen no later than 1 month after the last every 1 month injection or 2 months after the last every 2 months injection. The prescribing information for CAB injection should be consulted for recommended dosing. Posology REKAMBYS (RPV injection) may be initiated with oral lead-in or without (direct to injection). The HCP and patient may decide to proceed directly to RPV injection. Alternatively, RPV tablets may be used as an oral lead-in prior to the initiation of RPV injections to assess tolerability to RPV. Refer to the SmPC Section 4.2 for the recommended oral lead-in dosing schedule table and monthly and every 2 months IM injection dosing schedule tables. *Oral lead-in* When used for oral lead-in prior to the initiation of REKAMBYS, RPV oral tablets, together with CAB oral tablets, should be taken for approximately 1 month (at least 28 days) to assess tolerability to RPV and CAB. One RPV 25-mg tablet should be taken with a meal with one CAB 30-mg tablet once daily. ***Every 1 month dosing*** *Initiation Injection (900 mg corresponding to 3 mL)* On the final day of current ART or oral lead-in, the recommended initiation injection dose of RPV is a single 900 mg IM injection. *Continuation Injections (600 mg corresponding to 2 mL)* After the initiation injection, the recommended continuation injection dose of RPV is a single 600 mg monthly IM injection. Patients may be given injections up to 7 days before or after the date of the monthly injection schedule.

	Missed Doses Patients who miss an injection visit should be clinically reassessed to ensure resumption of therapy is appropriate. If ≤2 months have elapsed since the last injection, continue with the monthly 600 mg injection schedule as soon as possible. If >2 months have elapsed since the last injection, re-initiate the patient on the 900 mg dose, and then continue to follow the monthly 600 mg injection schedule. ***Every 2 months dosing*** *Initiation Injections - 1 month apart (900 mg corresponding to 3 mL)* On the final day of current ART or oral lead-in, the recommended initial RPV injection dose is a single 900 mg IM injection. One month later, a second 900 mg IM injection should be administered. Patients may be given the second 900 mg injection up to 7 days before or after the scheduled dosing date. *Continuation Injections – 2 months apart (900 mg corresponding to 3 mL)* After the initiation injections, the recommended RPV continuation injection dose is a single 900 mg IM injection administered every 2 months. Patients may be given injections up to 7 days before or after the date of the every 2 months injection schedule. *Missed Doses* Patients who miss an injection visit should be clinically reassessed to ensure resumption of therapy is appropriate. **Missed Injection 2** If ≤2 months have elapsed since the last injection, continue with the 900 mg injection as soon as possible and continue with every 2 months injection schedule. If >2 months have elapsed since the last injection, re-initiate the patient on the 900 mg dose, followed by a second 900 mg initiation injection 1 month later. Then follow the every 2 months injection schedule. **Missed Injection 3 or later** If ≤3 months have elapsed since the last injection, continue with the 900 mg injection as soon as possible and continue with every 2 months injection schedule. If >3 months have elapsed since the last injection, re-initiate the patient on the 900 mg dose, followed by a second 900 mg initiation injection 1 month later. Then follow the every 2 months injection schedule. ***Dosing Recommendations When Switching From Monthly to Every 2 Months Injections*** Patients switching from a monthly continuation injection schedule to an every 2 months continuation injection schedule should receive a

	single 900 mg IM injection of REKAMBYS 1 month after the last 600 mg REKAMBYS continuation injection dose and then 900 mg every 2 months thereafter. ***Dosing Recommendations When Switching From Every 2 Months to Monthly Injections*** Patients switching from an every 2 months continuation injection schedule to a monthly continuation injection schedule should receive a single 600 mg IM injection of REKAMBYS 2 months after the last 900 mg REKAMBYS continuation injection dose and then 600 mg monthly thereafter. Method of administration For IM use. Care should be taken to avoid inadvertent injection of REKAMBYS into a blood vessel. For instructions on administration, see "Instructions for Use" in the PL. REKAMBYS should always be co-administered with a CAB injection. REKAMBYS and CAB injections should be administered at separate gluteal injection sites during the same visit. The order of injections is not important. When administering REKAMBYS, the HCP should take into consideration the BMI of the patient to ensure that the needle length is sufficient to reach the gluteus muscle.		
	Proposed: Not applicable		
Pharmaceutical form(s) and strength(s)	**Current:** Prolonged-release suspension[a] for injection. White to off-white suspension. 2 mL vial Each vial contains 600 mg RPV 3 mL vial Each vial contains 900 mg RPV		
	Proposed: Not applicable		
Is/will the product be subject of additional monitoring in the EU?		☑ **Yes**	☐ **No**

[a] further referred to as RPV LA

PART II: SAFETY SPECIFICATION

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

Indication

REKAMBYS is indicated, in combination with cabotegravir injection, for the treatment of HIV-1 infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen, without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class.

Incidence

The 2023 report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) on the global AIDS epidemic states that approximately 1.3 million (range: 1.0-1.7 million) individuals (all ages) were newly infected with HIV in 2022, which represents a decline of 38% from 2010 (UNAIDS 2023b). The steepest drops in numbers of new infections were observed in children (0-14 years) and young people (15-24 years). Globally, in 2022, approximately 210,000 (range: 130,000-300,000) adolescent girls and young women (15-24 years) and approximately 140,000 (range: 67,000-210,000) adolescent boys and young men (15-24 years) acquired HIV, a 49% and 44% reduction since 2010, respectively. Among the sub-Saharan African regions, the Eastern and Southern African region was most heavily affected by HIV in 2022. However, the number of new cases in the region significantly decreased compared to previous years. From 2010 to 2022, the number of new HIV infections among all ages declined by 57% in this region. On the contrary, the region Eastern Europe and Central Asia has the fastest growing HIV epidemic in the world. In 2022, 160,000 (range: 140,000-180,000) new HIV infections were reported, representing a 49% increase since 2010 (UNAIDS 2023a, 2023b). Incidence estimates for 2022 (>15 years of age) by region are presented in the below table (UNAIDS 2023b).

HIV incidence estimates with uncertainty bounds for the adult population (>15 years of age)

Region	Adults (15+) newly infected with HIV
Western and Central Africa	110,000 [66,000-190,000]
Eastern and Southern Africa	440,000 [330,000-590,000]
Eastern Europe and Central Asia	160,000 [130,000-180,000]
Asia and the Pacific	290,000 [210,000-380,000]
Latin America	110,000 [90,000-130,000]
Caribbean	14,000 [10,000-19,000]
Western and Central Europe and North America	57,000 [46,000-69,000]
Middle East and North Africa	16,000 [12,000-21,000]

Source: UNAIDS 2023b

In 2022, there were 22,995 HIV diagnoses in 30 European Union/EEA countries, with a rate of 5.1 per 100,000 population when adjusted for reporting delay. Cyprus and Estonia were the 2 countries with the highest rates of HIV diagnoses: 24.1 and 18.8 per 100,000 population, respectively (ECDC 2023). The table below shows the number of HIV cases (N) and rates per 100,000 population by country for Europe in 2022 (ECDC 2023).

HIV diagnoses (N) and rates per 100,000 population, by country in EU/EEA

Country	N	Rates per 100,000
Austria	189	2.1
Belgium	1,060	9.1
Bulgaria	328	4.8
Croatia	113	2.9
Cyprus	218	24.1
Czech Republic	870	8.3
Denmark	258	4.4
Estonia	250	18.8
Finland	273	4.9
France	4,158	6.1
Germany	3,239	3.9
Greece	565	5.4
Hungary	224	2.3
Iceland	40	10.6
Ireland	887	17.5
Italy	1,888	3.2
Latvia	229	12.2
Liechtenstein	1	2.5
Lithuania	252	9.0
Luxembourg	71	11.0
Malta	60	11.5
Netherlands	431	2.5
Norway	245	4.5
Poland	2,050	5.4
Portugal	804	7.8
Romania	670	3.5
Slovakia	197	3.6
Slovenia	42	2.0
Spain	2,937	6.2
Sweden	446	4.3
Total European Union/EEA	**22,995**	**5.1**

Source: ECDC 2023

Rates expressed as a ratio of the number of HIV diagnoses to the size of the population at risk for the year 2022

Prevalence

The global prevalence of HIV in 2022 for all ages was estimated at 39 million (range: 33.1-45.7 million) (UNAIDS 2023). In 2022, about 76% of all people with HIV (29.8 million people) were accessing ART, a significant increase from 2010 (7.7 million people) (UNAIDS 2023b). Approximately 20.8 million (range: 17.4-24.5 million) people, representing 53% of the global HIV-infected population in 2022, lived in Eastern and Southern Africa (UNAIDS 2023a). Western and Central Europe and North America had 2.3 million (range: 1.9-2.6 million) people with HIV in 2022 (UNAIDS 2023a).

In 2022, 37.5 million (range: 31.8-43.6 million) people living with HIV worldwide were adults (≥15 years of age), representing around 96% of the total number of people living with HIV worldwide (39 million), and 1.5 million (range: 1.2-2.1 million) were children (0-14 years) (UNAIDS 2023b). Eastern and Southern Africa accounted for the highest number of people (≥15 years of age) living with HIV in 2022 (19.8 million [range: 16.6-23.2 million]) (UNAIDS 2023b). The below table presents the number of adults (≥15 years of age) living with HIV by geographic region in 2022.

HIV prevalence estimates with uncertainty bounds for the adult population (≥15 years of age)

Region	Estimated adults (15+) living with HIV
Western and Central Africa	4,400,000 [3,800,000-5,100,000]
Eastern and Southern Africa	19,800,000 [16,600,000-23,200,000]
Eastern Europe and Central Asia	1,900,000 [1,700,000-2,100,000]
Asia and the Pacific	6,400,000 [5,200,000-7,600,000]
Latin America	2,200,000 [1,900,000-2,400,000]
Caribbean	320,000 [280,000-370,000]
Western and Central Europe and North America	2,300,000 [1,900,000-2,600,000]
Middle East and North Africa	180,000 [150,000-210,000]

Source: UNAIDS 2023b

Demographics of the Population with HIV-1 Infection and Risk Factors for the Disease

Of those people more than 15 years of age who were living with HIV in 2022, around 53% (20 million [range: 16.9-23.4 million]) were women (UNAIDS 2023b). In adults between 15 and 49 years of age, the global HIV prevalence rate was 0.7% in 2022. In younger adults between 15 and 24 years of age, the global HIV prevalence rate was 0.3% in women and 0.2% in men. The HIV prevalence rates by region for the adult population (15-49 years of age) in 2022 were 5.9% (range: 4.9%-6.9%) in Eastern and Southern Africa, followed by 1.2% (range: 1.0%-1.3%) in the Caribbean, and 1.1% (range: 1.0%-1.3%) in Western and Central Africa (UNAIDS 2023a).

Globally in 2022, 72% of individuals living with HIV (>15 years of age) are estimated to have suppressed viral loads, up from 41% in 2015 (UNAIDS 2023b). Viral suppression rates in 2022 in adults (>15 years of age) were highest in Eastern and Southern Africa (78%), and Western and Central Africa (74%) (UNAIDS 2023b). Viral suppression rates for this age group (>15 years of age) were only available by sex for Western and Central Europe and North America. The rates were 74% in women and 72% in men. The lowest rates of viral suppression were in the Middle East and North Africa (46%), Eastern Europe and Central Asia (48%), Asia and the Pacific (62%), and the Caribbean (58%) in 2021 (UNAIDS 2023b).

Risk factors for acquiring HIV include geography, sex, injection drug use, and sexual activity.

Geography

In 2022, Sub-Saharan Africa accounted for 66% of the total population living with HIV globally and 50% of the total number of new HIV infections (all ages). Eastern and Southern Africa had the highest IR for adults between 15 to 49 years of age (1.70 [range: 1.24-2.27] per 1,000 population) (UNAIDS 2023b). In Eastern Europe and Central Asia, new HIV infections have continued to rise with an IR per 1,000 population of 0.65 (range: 0.56-0.74) in 2010 to 1.02 (range: 0.88-1.17) in 2021 for adults between 15 to 49 years of age (UNAIDS 2023a, 2023b). The largest proportion of HIV-diagnosed people in the European Union/EEA belonged to the age group 30 to 39 years of age (31.7%), 8.9% were young people aged 15 to 24 years, and 19.9% were older adults aged 50 years or above at diagnosis (ECDC 2023). Based on data from 28 European Union/EEA countries, 11,103 diagnoses (48.3% of total diagnoses and 55.5% of those with known information on region of origin) were reported among people originating from outside the reporting country. Of these, 2,781(12.2% of total diagnoses and 13.9% of those with known information on region of origin), irrespective of transmission mode, were reported among people originating from countries with generalized HIV epidemics in sub-Saharan Africa. Among the

European Union/EEA countries, Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Iceland, Ireland, Luxembourg, the Netherlands, Norway, Slovakia, and Sweden had more than half of their HIV diagnoses among people originating from outside of the reporting country (ECDC 2023).

Sex

Globally, women and girls (all ages) constituted 53% of all people living with HIV (UNAIDS 2023b). The burden of HIV on women was especially high in high-prevalence regions. In Eastern and Southern Africa, women and girls accounted for 64% of the region's new HIV infections in 2022, being 3.4 times higher among adolescent girls and young women (15-24 years of age) than among males of the same age (UNAIDS 2023a). However, in the European Union/EEA, the male-to-female ratio of new HIV diagnoses in 2022 was 2.4 (ECDC 2023). The rate of HIV diagnoses was 7.3 per 100,000 population among men and 2.9 per 100,000 population among women. The 30- to 39-year-old age group had the highest rate of HIV diagnoses in the European Union/EEA at 12.5 per 100,000 population. However, for men the rates were highest in the 25- to 29- year-old age group at 17.5 per 100,000 population for men, while rates for women were highest in the 30-39-year-old age group at 7.7 per 100,000 population (ECDC 2023).

Injection drug use

In low-prevalence regions, injection drug users are a key population of people living with HIV, accounting for 14% of new HIV infections outside of sub-Saharan Africa, 1% in sub-Saharan Africa, and 8% globally (UNAIDS 2024). The WHO strongly recommends health interventions for injection drug users as a way of HIV prevention (WHO 2022). In the European Union/EEA, transmission due to injection drug use accounted for 5.9% of HIV diagnoses with a known route of transmission in 2022 (ECDC 2023). It is highly likely that 24.8% of HIV cases in Latvia, 20.9% of cases in Finland, and 18.8% of cases in Luxembourg were transmitted through injection drug use (ECDC 2023).

Sexual activity

Worldwide, median HIV prevalence among sex workers and MSM is higher than in the general population. Globally, these 2 groups accounted for 28% of new HIV infections, and outside sub-Saharan Africa, 8% of new infections occurred in sex workers and 34% in the MSM population (UNAIDS 2024). In the United States, MSM accounted for 68% of new HIV diagnoses in 2020, and 64% in the Western and Central Europe and North America region in 2021.

In the European Union/EEA in 2022, the highest proportion (33.3%) of HIV diagnoses was reported in the MSM population, while the second highest (19%) was reported in heterosexual women (ECDC 2023). In Europe, MSM accounted for more than 50% of HIV diagnoses in 10 European countries, namely Austria, Croatia, Greece, Hungary, Iceland, Ireland, Malta, the Netherlands, Slovenia, and Spain (ECDC 2023).

Main Existing Treatment Options

Treatment of HIV requires use of cART. 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 WHO (WHO 2021), the European AIDS Clinical Society (EACS 2023), and the Department of Health and Human Services in the US (DHHS 2024). 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 AEs, consideration of drug-drug interactions for patients requiring concomitant medication due to comorbidities, drug resistance and the desire to lower pill burden, simplifying dosing and regimen. Special populations, such as pregnant women and patients coinfected with tuberculosis or HBV or HCV 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 drug-drug interactions in the case of coinfected patients.

Natural History of HIV-1 Infection in the Untreated Population, Including Mortality and Morbidity

HIV is a virus that is transmitted through certain body fluids and attacks the body's immune system, specifically the CD4+ cells. Over time, HIV can destroy so many of these cells that the body cannot fight off infections and disease. Individuals who become infected with HIV and do not receive treatment will typically progress through 3 stages of disease (CDC 2022).

Stage 1 is the acute HIV infection stage, which occurs within 2 to 4 weeks after infection with HIV. Patients may experience a flu-like illness, which may last for a few weeks. Patients with acute HIV infection have a large amount of virus in their blood. These patients are often unaware that they are infected because they may not feel sick right away or at all (CDC 2022, NIH 2023).

Stage 2, the clinical latency period, is sometimes called asymptomatic HIV infection or chronic HIV infection. During this phase, HIV is still active but reproduces at very low levels. Patients may not have any symptoms or get sick during this time. For people who are not taking medicine to treat HIV, this period usually advances to Stage 3 in about a decade or more, but some may progress faster. On the other hand, people who adhere to HIV treatment can potentially remain in this stage for several decades. At the end of this phase, a person's viral load starts to increase as the CD4+ cell count begins to decrease. As this happens, the person may develop symptoms and progress to Stage 3 (AIDS) (CDC 2022, NIH 2023).

Stage 3, the most severe stage of HIV infection, is also called AIDS. People with AIDS have such inefficient immune systems that they develop an increasing number of severe illnesses. Without treatment, AIDS patients typically survive about 3 years. People are diagnosed with AIDS when

their CD4+ cell count drops below 200 cells/mm^3 or they develop certain opportunistic illnesses. People with AIDS can have a high viral load and be very infectious (CDC 2022, NIH 2023).

Treatment can slow or prevent progression from one stage to the next. It can also dramatically reduce the chance of transmitting HIV to someone else (CDC 2022, NIH 2023).

Globally, approximately 630,000 (range: 480,000-880,000) AIDS-related deaths occurred in 2022 (all ages), which is a 51% decrease from 1.3 million (range: 970,000 – 1.8 million) in 2010. Of these, 540,000 (range: 410,000-770,000) were adults >15 years of age (UNAIDS 2023b). In the European Union/EEA, 767 individuals with AIDS (all ages) were reported to have died during 2022. This figure has been consistently decreasing since 2013 (ECDC 2023). The ART-CC, which includes cohorts of HIV-positive patients from Canada and Europe, reported a mortality rate of 15.5 and 7.4 per 1,000 person-years for men and women, respectively and includes 20,784 patients and 104,649 person-years of follow-up, reported an overall mortality rate of 11.2 (95% CI: 10.6-11.9) per 1,000 person-years (ART-CC, 2016).

The mortality rate in the second and third years after initiating ART has declined over time, with an adjusted hazard ratio of 1.12 (range: 0.97-1.28) for those starting ART between 1996 and 1999, and 0.80 (range: 0.66-0.97) for those starting treatment between 2008 and 2010 (ART-CC, 2017). The ART-CC also reported that baseline CD4+ count was prognostic for unadjusted cumulative mortality. Patients who started ART with a CD4+ count <50 cells/µL experienced the greatest declines in mortality rates over time on ART, from 88 (95% CI: 78-99) per 1,000 person-years during the first 6 months to 15 (95% CI: 13-17) per 1,000 person-years after 10 years from start of ART (May, 2016).

Important Comorbidities

Important comorbidities in patients with HIV-1 infection include HIV-encephalopathy, psychiatric disorders, HBV and/or HCV infection, renal disease, respiratory diseases, cardiomyopathy/ventricular dysfunction, reduced bone density/osteoporosis/osteonecrosis, cytopenias, malignancies, tuberculosis, opportunistic infections, progressive multifocal leukoencephalopathy, malaria, and lipid abnormalities.

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The active drug moiety in the oral and injectable RPV formulations is the same, and much higher exposures can be achieved after oral than after IM administration of RPV in animals. Therefore, results obtained with oral RPV can be extrapolated to RPV LA. The nonclinical safety of RPV LA is therefore fully supported by the nonclinical findings from the oral RPV program, with some additional nonclinical toxicity studies performed specifically with RPV LA.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Toxicity (based on oral RPV data):	
Single & repeat dose toxicity	
Hepatotoxicity	
Hepatocellular hypertrophy in mice and rats was associated with liver enzyme (ie, UDP-GT) induction and an increase of the organ weight at exposures at ≥12 times the exposure in humans at 25-mg once daily in HIV-1-infected patients or 600-mg or 900-mg IM dose of RPV.	Careful clinical monitoring of hepatotoxicity was performed in clinical trials. Based on results from clinical trials with oral RPV and RPV LA, and postmarketing data with oral RPV, hepatotoxicity is not considered to be an important potential risk for RPV.
Mild to moderate perivascular inflammatory reactions together with fibrosis and single hepatic cell necrosis in the central part of the lobules were seen in dogs and were associated with an increase in cholesterol, bilirubin, alkaline phosphatase, and ALT at exposures at ≥8 times the exposure in humans at 25-mg oral RPV once daily in HIV-1-infected patients or 600-mg or 900-mg IM dose of RPV. Moreover, mononuclear phagocytic system aggregates and multifocal bile duct proliferation were noted.	
Thyroid and pituitary glands	
The thyroid gland effects in rats were characterized by an increased organ weight, hypertrophy of follicular epithelium, and reduced serum concentrations of thyroxine and were associated with liver enzyme (ie, UDP-GT) induction. Effects on the pituitary gland in rats comprised an increase of swollen and vacuolated cells in the pars distalis. These effects are considered secondary to the thyroid gland effects.	As the effects on thyroid and pituitary glands are secondary to the effects of RPV on rodent-specific thyroxine clearance, they are considered not relevant when RPV is used in humans.
Nephrotoxicity	
Minimal to moderate degenerative nephropathy was noted in mice at exposures ≥450 times the exposure in humans at 25-mg oral RPV once daily in HIV-1-infected patients or 600-mg or 900-mg IM dose of RPV. Moderate acute nephritis was observed in dogs at exposures ≥21 times the exposure in humans at 25-mg once daily in HIV-1-infected patients or 600-mg or 900-mg IM dose of RPV.	The kidney effects seen in mice and dogs are not indicative of an effect on glomerular filtration or proximal tubular resorption. For these reasons and in view of the safety margins, the nonclinical kidney effects are considered not relevant when RPV is used in humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Adrenal glands	
Changes in the serum concentrations of adrenal hormones or their precursors and of adrenocorticotropic hormone in rats, dogs, monkeys and likely the effects in dog testes and ovaries of mice and dogs are due to the apparent inhibition of CYP21 and CYP17, key enzymes in steroidogenesis.	These findings suggest a potential for changes in adrenal hormones and gonadal effects in humans and eventually for adrenal insufficiency. However, based on results from clinical trials with oral RPV (including clinical monitoring of decreased blood cortisol) and RPV LA, and postmarketing data with oral RPV, decreased blood cortisol is not considered to be an important potential risk for RPV.
Red blood cells	
A small decrease in red blood cell parameters was seen in mice, rats, and dogs at exposures respectively ≥224, 25, and ≥21 times the exposure in humans at 25-mg oral RPV once daily in HIV-1–infected patients or 600-mg or 900-mg IM dose of RPV. Signs of regeneration were noted and no signs pointed toward bone marrow suppression.	Given the absence of bone marrow suppression in rats, mice, and dogs, the red blood cell effects are considered not relevant when RPV is used in humans.
Coagulation system	
A mild to moderate increase of coagulation times of both the intrinsic and extrinsic pathways occurred only in male rats at exposures ≥4 times the exposure in humans at 25-mg oral RPV once daily in HIV-1-infected patients or 600-mg or 900-mg IM dose of RPV. There were no clinical manifestations of affected coagulation in this species.	Given the absence of clinical manifestations, this effect in rats only is considered not relevant when RPV is used in humans.
Reproductive toxicity	
RPV did not show a teratogenic potential or effect on reproductive function in rats and rabbits. The reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity, parturition, or maternal behavior.	The results of reproductive toxicity studies (in rats and rabbits) and developmental toxicity studies (in rats) did not suggest a risk when RPV is used in humans.
Developmental toxicity	
The reproductive and developmental toxicity studies in rats did not demonstrate any effects on the development of offspring from dams treated with RPV during pregnancy and lactation. In rats, the placenta was a partial barrier for RPV. Low exposure to RPV in rat pups nourished by dams treated with RPV indicated a low concentration of RPV in milk of rats.	The results of reproductive and developmental toxicity studies in rats did not suggest a risk when RPV is used in humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Genotoxicity	
No indications of a genotoxic potential of RPV were observed in genotoxicity tests (in vitro and in vivo).	The results of genotoxicity testing did not indicate a safety concern when RPV is used in humans.
Carcinogenicity	
Hepatocellular adenomas and carcinomas seen in mice were associated with induction of CYP4A and peroxisome proliferation. Hepatocellular adenomas and follicular adenomas and carcinomas in the thyroid gland in rats occurred as a result of induction of CYP3A and UDP-GT.	The liver enzyme inductions underlying the carcinogenic effects in rodents is considered species-specific and therefore considered not relevant when RPV is used in humans.
Toxicity (based on RPV LA data):	
Local tolerance	
After long-term repeated IM administration of RPV LA in dogs and minipigs, slight, short-lasting (ie, 1-4 days in minipigs) erythema was observed, and white deposits were noted at the injection sites at necropsy, accompanied by swelling and discoloration of draining lymph nodes. Microscopic examination showed macrophage infiltration and eosinophilic deposits at the injection sites. A macrophage infiltration response was also noted in the draining/regional lymph nodes. These findings were considered to be a reaction to the deposited material rather than a manifestation of local irritation.	Injection site reactions have been identified as ADRs during the RPV LA + CAB LA clinical development program, and are adequately described in the REKAMBYS SmPC (Section 4.8).
Safety pharmacology (based on oral RPV data):	
Cardiovascular system (including potential effect on QT interval)	
RPV demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization and to induce QT interval prolongation in the rabbit ventricular wedge assay. However, the observed mild QT interval prolongation contributed to only a marginal Torsade de Pointes score at unbound drug concentrations much higher than those achieved in humans with the approved 25-mg dose of oral RPV, indicating a low proarrhythmic risk of RPV. In the in vivo animal models, no significant effect on electrophysiological cardiovascular or hemodynamic parameters was noted.	Nonclinical data suggest a potential for QT interval prolongation with RPV when used in humans, as confirmed by the dose-dependent QT prolongation in the thorough QT trial with supratherapeutic doses. The mean RPV steady-state C_{max} for the recommended 600 mg Q4W dose of RPV LA is 143 ng/mL, which is, respectively, 4.4-fold and 11.6-fold lower than the mean steady-state C_{max} of the supratherapeutic oral RPV doses of 75 mg once daily and 300 mg once daily. The mean steady-state C_{max} for oral RPV 25 mg once daily, which is not associated with a clinically relevant effect on QTc, was 247 ng/mL.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
	Based on results from clinical trials with oral RPV (including careful clinical monitoring of QT interval prolongation) and RPV LA, and postmarketing data with oral RPV, QT interval prolongation is not considered to be a safety concern for RPV.

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Overview of Clinical Trials in the RMP

HIV-1 infection

Janssen Sciences Ireland UC in partnership with ViiV Healthcare Company (further referred to as ViiV Healthcare) developed the RPV LA + CAB LA regimen for the treatment of HIV-1 infection. The overall objective of the RPV LA + CAB LA clinical development program was to develop a novel, highly effective, well tolerated 2-drug LA injectable regimen. Such a regimen allows for reduced dosing frequency compared with daily oral ARVs. With less frequent dosing, the daily reminder of subjects' HIV status may be avoided and associated stigma related to taking oral treatment regimens may thereby be lessened. Since all injections are given by HCPs, such a regimen holds promise for increased patient compliance with dosing requirements. This novel treatment option may result in improved overall satisfaction with treatment and longer retention in care for individuals with HIV infection. In addition, this NRTI-sparing regimen avoids known NRTI-associated adverse reactions and long-term toxicities. Moreover, given the parenteral route of administration, a 2-drug LA injectable regimen may result in fewer gastrointestinal AEs, eliminates dosing restrictions with regard to food, and will not have the drug-drug interactions observed with oral ARVs at the level of the gastrointestinal tract.

RPV is a diarylpyrimidine derivative and a potent NNRTI with in vitro activity against wild type HIV-1 and specific NNRTI-resistant mutants, developed for the treatment of HIV-1 infection. Oral RPV is a globally available product, marketed as EDURANT 25-mg tablets and as part of several fixed-dose combination single tablet regimens. The subject of this EU-RMP is the RPV prolonged-release suspension for IM injection, referred to as RPV LA.

Data from the following clinical trials in HIV-1 infected subjects are included in this RMP for characterization of exposure and safety of the RPV LA + CAB LA 2-drug injectable regimen:

Adults:

Two Phase 2b clinical trials conducted and sponsored by ViiV Healthcare:

- LATTE trial (LAI116482; Completed): Open-label, randomized, dose ranging, Phase 2b trial evaluating oral CAB in combination with oral RPV.
- LATTE-2 trial (200056; Completed): Open-label, randomized, dose ranging, Phase 2b trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression.

Two Phase 3 clinical trials and 3 Phase 3b clinical trials conducted and sponsored by ViiV Healthcare:

- FLAIR trial (201584; Ongoing): Open-label, randomized, Phase 3 trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC.

- ATLAS trial (201585; Ongoing): Open-label, randomized, Phase 3 trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen.
- ATLAS-2M trial (207966; Ongoing): Open-label, randomized, parallel-group, non-inferiority Phase 3b trial evaluating efficacy, safety, and tolerability of CAB LA in combination with RPV LA administered every 8 weeks or every 4 weeks.
- SOLAR trial (213500; Completed): Phase 3b switch trial to demonstrate non-inferior antiviral activity of CAB LA in combination with RPV LA administered every 2 months compared with continuing bictegravir/emtricitabine/tenofovir alafenamide.
- CARISEL trial (213199; Completed): Open-label, hybrid type 3, Phase 3b trial evaluating implementation strategies for CAB LA plus RPV LA administered every 2 months in select European healthcare settings.

Additional supportive exposure data is available from 2 trials:

- POLAR trial (209035; Completed): Open-label, rollover Phase 2b trial evaluating CAB LA in combination with RPV LA administered once every 2 months or DTG/RPV in HIV-positive participants from the LATTE trial. (Note: subjects in the DTG/RPV group completed the study).
- CUSTOMIZE trial (209493; Completed): Phase 3b implementation trial to identify and determine best implementation practices for CAB LA in combination with RPV LA in the United States.

Adolescents:

One Phase 1/2 clinical trial sponsored by the National Institute for Health/Division of AIDS (NIH/DAIDS) and supported by ViiV Healthcare:

- MOCHA trial (208580; Ongoing): Multicenter, open-label, noncomparative, Phase 1/2 trial to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, LA injectable CAB, and LA injectable RPV in virologically suppressed HIV-infected children and adolescents aged 12 to less than 18 years and weighing at least 35 kg. This study consists of 2 cohorts. In Cohort 1, oral and injectable CAB (Cohort 1C) and oral and injectable RPV (Cohort 1R) are studied separately to confirm adult-matched exposure/PK and gather initial safety information. In Cohort 2, safety, tolerability, acceptability, PK, and antiviral efficacy of CAB LA plus RPV LA are assessed.

SIII.2. Clinical Trial Exposure

Clinical trial exposure to RPV LA in the Phase 1/2, Phase 2b, and Phase 3/3b clinical trials (ie, LATTE-2, FLAIR, ATLAS, ATLAS-2M, SOLAR, CARISEL, POLAR, CUSTOMIZE, and MOCHA) is summarized in Tables SIII.1 through SIII.4 for all subjects by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, ethnic origin). Exposure (expressed in person-time) was calculated up to the point of the subject's last dose administered or until a clinical cut-off date of 18 February 2023 for subjects still on treatment at that time. Person-time was calculated based on LATTE-2 End of Study, FLAIR Week 124, ATLAS Week 96, ATLAS-2M Week 152, SOLAR End of Study, CARISEL End of Study,

POLAR End of Study, CUSTOMIZE End of Study, and MOCHA Cohorts 1 and 2 Week 24 datasets. For injections, exposure can last up to a year or more after the last injection.

Table SIII.1: Duration of Exposure to RPV LA

HIV-1 Infection		
Duration of exposure	**Patients (n)**	**Person-time (years)**
<4 weeks	47	1.290
4 weeks to <6 months	231	58.850
6 months to <1 year	815	650.081
1 to <2 years	606	899.871
2 to <3 years	500	1,327.748
3 to <4 years	579	1,884.799
4 to <5 years	257	1,084.055
≥5 years	218	1,575.959
Total person-time for indication	3,253	7,482.653

Table SIII.2: Exposure to RPV LA by Age Group and Sex

HIV-1 Infection				
Age group	**Patients (n)**		**Person-time (years)**	
	Male	**Female**	**Male**	**Female**
<18 years	70	78	60.312	58.426
18-64 years	2,427	632	5,864.444	1,398.546
65-74 years	26	18	60.838	37.708
≥75 years	2	0	2.379	0.000
Total	2,525	728	5,987.973	1,494.680

Table SIII.3: Exposure to RPV LA by Dose

HIV-1 Infection		
Dose of exposure	**Patients (n)**	**Person-time (years)**
Up to 900 mg IM LA	3,253	7,482.653

Table SIII.4: Exposure to RPV LA by Ethnic Origin

HIV-1 Infection		
Ethnic origin	**Patients (n)**	**Person-time (years)**
Black or African American	703	1,412.200
White	2,276	5,505.736
American Indian or Alaska Native	77	188.819
Arabic	0	0.000
Asian	157	283.953
Native Hawaiian or Other Pacific Islander	5	18.579
Mixed	35	73.366
Missing	0	0.000
Total	3,253	7,482.653

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

All Phase 3/3b pivotal clinical trials were conducted with the RPV LA + CAB LA combination regimen, so the exclusion criteria of the Phase 3/3b clinical trials apply to the combination regimen and are not RPV LA-specific. All pivotal clinical trials are conducted and sponsored by ViiV Healthcare.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Subjects with advanced HCV or requiring treatment for HCV during the first 48 weeks of maintenance therapy.**
Reason for being an exclusion criterion	In the Phase 3/3b clinical trials for RPV LA + CAB LA, subjects with HCV with either advanced disease or requiring treatment could confound safety and efficacy results.
Included as missing information?	No
Rationale if not included as missing information	Asymptomatic subjects with stable HCV were allowed to enroll in the Phase 2b and 3/3b clinical trials for RPV LA + CAB LA provided that certain criteria were met, including that these subjects did not have advanced liver disease and were assessed by the investigator that HCV treatment was not necessary during the trial. Limited data are available and do not indicate that these stable coinfected patients show different efficacy and safety. The SmPC (Section 4.4) states that limited data is available in patients with hepatitis C coinfection. In patients coinfected with hepatitis C receiving oral RPV, the incidence of hepatic enzyme elevation was higher than in patients receiving oral RPV who were not hepatitis C coinfected. The PK exposure of oral and injectable RPV in coinfected patients was comparable to that in patients without hepatitis C coinfection. The SmPC (Section 4.2) states that REKAMBYS is not recommended in patients with severe hepatic impairment (Child-Pugh score C).
Criterion 2	**Women who are pregnant or plan to become pregnant.**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women are not routinely enrolled into clinical trials to avoid exposing the fetus to the study medication.
Included as missing information?	Yes (Use in pregnancy)

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale if not included as missing information	Not Applicable
Criterion 3	**Women who are breastfeeding or plan to breastfeed.**
Reason for being an exclusion criterion	Per ICH guidelines, breastfeeding women are not routinely enrolled into clinical trials to avoid exposing the breastfed infant to the study medication.
Included as missing information?	No
Rationale if not included as missing information	The SmPC (Section 4.6) recommends women living with HIV not to breastfeed in order to avoid transmission of HIV to the infant.
Criterion 4	**Subjects not fully suppressed on their current ART regimen, ie, with a viral load ≥50 copies/mL.** **(Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 copies/mL in 12 months prior to screening was required; one within the 6- to 12-month window and one within 6 months of screening.)**
Reason for being an exclusion criterion	Subjects should be virologically suppressed (HIV-1 RNA <50 copies/mL) before switching to the RPV LA + CAB LA regimen.
Included as missing information?	No
Rationale if not included as missing information	This exclusion criterion is consistent with the indication for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL).
Criterion 5	**Subjects positive for HBV at screening (+HBsAg).**
Reason for being an exclusion criterion	HBsAg positivity was an exclusion criterion for Phase 2b and 3/3b clinical trials for RPV LA + CAB LA, due to lack of an ART with HBV activity.
Included as missing information?	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale if not included as missing information	No conclusions can be made about the safety of RPV LA + CAB LA in HBV coinfected patients. The SmPC (Section 4.4) states that it is not recommended to initiate REKAMBYS in patients with hepatitis B coinfection. In patients coinfected with hepatitis B receiving oral RPV, the incidence of hepatic enzyme elevation was higher than in patients receiving oral RPV who were not hepatitis B coinfected. Physicians should refer to current treatment guidelines for the management of HIV infection in patients coinfected with HBV. These guidelines recommend NRTI-containing regimens with activity against HBV.
Criterion 6	**ALT ≥3 times ULN.**
Reason for being an exclusion criterion	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 trial.
Included as missing information?	No
Rationale if not included as missing information	Treatment with REKAMBYS will be guided by established global and local guidance and medical practice.
Criterion 7	**Any verified Grade 4 laboratory abnormality.**
Reason for being an exclusion criterion	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 trial.
Included as missing information?	No
Rationale if not included as missing information	Treatment with REKAMBYS will be guided by established global and local guidance and medical practice.
Criterion 8	**Subjects with severe hepatic impairment (score C) as determined by Child-Pugh Classification.**
Reason for being an exclusion criterion	PK trials investigating the use of RPV LA + CAB LA have only been performed in subjects with mild and moderate hepatic impairment (Child-Pugh score A and B, respectively).
Included as missing information?	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale if not included as missing information	The SmPC (Sections 4.2 and 5.2) states that no dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B), but caution is advised in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh score C); therefore, REKAMBYS is not recommended in these patients.
Criterion 9	**Subject has estimated CrCl <50 mL/min/1.73m^2 via CKD-EPI method.**
Reason for being an exclusion criterion	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 trial.
Included as missing information?	No
Rationale if not included as missing information	The effect of renal impairment on RPV PK has not been studied because renal elimination of RPV is negligible. Population PK analysis during the development of oral RPV indicated that RPV exposure was not altered in HIV-1 infected subjects with mild renal impairment. Given the negligible renal elimination of RPV, no significant effect of moderate renal impairment is anticipated. As metabolism and elimination is independent of administration route, this is also applicable for RPV LA. The SmPC (Sections 4.2 and 5.2) states that no dose adjustment of REKAMBYS is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, the combination of REKAMBYS with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. The SmPC (Section 4.2) states that subjects with estimated CrCl <50 mL/min/1.73m^2 were not included in the Phase 3 trials. The SmPC (Section 5.2) states that in patients with severe renal impairment or end-stage renal disease, REKAMBYS should be used with caution, as plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction.
Criterion 10	**Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, noninvasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia.**
Reason for being an exclusion criterion	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 trial.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Included as missing information?	No
Rationale if not included as missing information	Patients with HIV-1 infection receiving RPV LA + CAB LA 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 REKAMBYS will be guided by established global and local guidance and medical practice.
Criterion 11	**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/mm^3 or evidence of ongoing malignancy.**
Reason for being an exclusion criterion	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 trial.
Included as missing information?	No
Rationale if not included as missing information	Treatment with REKAMBYS will be guided by established global and local guidance and medical practice.

SIV.2. Limitations to Detecting Adverse Reactions in the Clinical Development Program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	At the data cut-off for the initial submission (20 December 2018), 1,667 HIV-infected subjects had been exposed to RPV LA.	Given that over 1,667 HIV-infected subjects had been exposed to RPV LA at the time of initial submission, there was a >99% probability that very common (>1 in 10) and common (>1 in 100) AEs would have been observed and a >85% probability that uncommon (>1 in 1,000) AEs would have been observed during clinical development (based on CIOMS criteria for common). Up to 18 February 2023, 3,253 HIV-infected subjects have been exposed to RPV LA in the RPV LA + CAB LA clinical development program.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Due to prolonged exposure	Up to 18 February 2023, there was safety data available for 606 HIV-infected subjects receiving RPV LA at the recommended dose for 1 year to <2 years, 500 HIV-infected subjects receiving RPV LA for 2 years to <3 years, 579 HIV-infected subjects receiving RPV LA for 3 years to <4 years, 257 HIV-infected subjects receiving RPV LA for 4 years to <5 years, and 218 HIV-infected subjects receiving RPV LA for 5 years or longer.	Longer term data from 218 subjects who have been exposed to RPV LA for ≥5 years, have not identified any long-term adverse effect of RPV LA to date. Longer term data continue to demonstrate that the combination of RPV + CAB has long-term durability with a low rate of discontinuation due to virologic failure; as well as a safety and tolerability profile that is generally favorable.
Due to cumulative effects	Up to 18 February 2023, there were long-term clinical safety data available for 606 HIV-infected subjects receiving RPV LA at the recommended dose for 1 year to <2 years, 500 HIV-infected subjects receiving RPV LA for 2 years to <3 years, 579 HIV-infected subjects receiving RPV LA for 3 years to <4 years, 257 HIV-infected subjects receiving RPV LA for 4 years to <5 years, and 218 HIV-infected subjects receiving RPV LA for 5 years or longer.	There were no new safety signals identified during the RPV LA + CAB LA clinical development program that might have been due to cumulative effects. No specific organ toxicity was detected. After 48 weeks of monthly RPV LA injections, approximately 80% of RPV steady-state exposure is achieved. After that, there is limited further accumulation, with RPV steady-state exposure reached after 2.2 years (90% after 1.5 years and 95% after 2 years).
Which have a long latency	The assessment of long-term toxicities seen with cART, such as bone disorders and lipodystrophy require a considerably extended follow-up period. Up to 18 February 2023, there were long-term clinical safety data available for 257 HIV-infected subjects receiving RPV LA at the recommended dose for 4 to <5 years and 218 HIV-infected subjects receiving RPV LA for 5 years or longer.	No long-term adverse effect of RPV LA is apparent from clinical trials to date.

SIV.3. Limitations With Respect to Populations Typically Under-represented in Clinical Development Programs

All Phase 3/3b clinical trials were conducted with the RPV LA + CAB LA combination regimen, so the populations typically underrepresented in the Phase 3/3b clinical trials apply to the combination regimen and are not RPV LA specific.

Table SIV.3: Exposure of Special Populations Included or Not in the Clinical Development Program

Type of Special Population	Exposure
Pregnant women	Pregnant women were excluded from the RPV LA + CAB LA clinical development program. Subjects that became pregnant (intrauterine) were required to discontinue the study medication (and discontinue the trial). Clinical experience of RPV LA use during pregnancy is therefore limited.
Breastfeeding women	Breastfeeding women were excluded from the RPV LA + CAB LA clinical development program.
Pediatrics/Adolescents	Children and adolescents <18 years of age were excluded from the RPV LA + CAB LA Phase 3/3b pivotal clinical trials. Since the pivotal trials, 148 adolescents have been studied in the Phase 1/2 multicenter, open-label, noncomparative MOCHA trial. The trial enrolled HIV-1-infected, cART-experienced adolescents (12 to <18 years of age) weighing at least 35 kg who were virologically suppressed on a stable ARV regimen. The safety and efficacy of RPV LA in children aged less than 12 years and adolescents weighing less than 35 kg have not been established. No data are available. The safety, tolerability, acceptability, and PK of CAB + RPV is being studied in an ongoing Phase 1/2 trial in children 2 to less than 12 years of age (CRAYON trial [214003]).
Elderly	There was no upper age limit for inclusion in the RPV LA+ CAB LA clinical development program. There is limited information regarding the use of RPV LA in the elderly. Of the 3,105 adult subjects in the Phase 2b (LATTE-2, POLAR) and Phase 3/3b (FLAIR, ATLAS, ATLAS-2M, SOLAR, CARISEL, CUSTOMIZE) clinical trials (up to 18 February 2023), 44 (1.4%) subjects were ≥65 years of age and 2 (0.1%) subjects were ≥75 years of age.
Population with relevant different ethnic origin	Not applicable.

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.
Patients with relevant comorbidities:	
Patients with hepatic impairment	In the Phase 1 trial TMC278-C130, 16 subjects with hepatic impairment were exposed to oral RPV, of which 8 subjects with mild hepatic impairment (Child-Pugh score A) and 8 subjects with moderate hepatic impairment (Child-Pugh score B). Patients with severe hepatic impairment (Child-Pugh score C) were excluded from the Phase 3/3b RPV LA clinical trials.
Patients with renal impairment	Subjects with estimated CrCl <50 mL/min/1.73m^2 (CKD-EPI method) indicative of moderate (<60 mL/min/1.73m2) and severe (<30 mL/min/1.73m2) renal impairment, were excluded from the RPV LA + CAB LA clinical development program.
Patients with cardiovascular impairment	Patients with clinically significant cardiovascular disease were excluded from the RPV LA + CAB LA clinical development program.
Immunocompromised patients	Not applicable.
Patients with a disease severity different from inclusion criteria in clinical trials	The majority of subjects who enrolled into the Phase 3/3b pivotal clinical trials with RPV LA were CDC stage of HIV disease 1 or 2, but there was a very limited number of subjects who were CDC category HIV infection stage 3 at baseline (approximately 6 [1%] subjects in the Phase 3/3b pivotal clinical trials).
Patients with HBV coinfection	Patients with hepatitis B were excluded from the RPV LA + CAB LA clinical development program.
Patients with symptomatic/advanced HCV coinfection	During the Phase 3/3b pivotal clinical trials with RPV LA, there were 41 subjects coinfected with HCV (based on HCV serology alone at baseline).

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Through a distribution agreement, Janssen supplies vials of RPV LA single entity (REKAMBYS) to ViiV Healthcare, which then distributes and sells together with CAB LA (Vocabria) for patient use.

Postmarketing exposure data is provided by ViiV Healthcare, which distributes RPV LA throughout the European Union and other markets. ViiV Healthcare derives postmarketing exposure data from IQVIA. This is consistent with how ViiV and GSK report postmarketing exposure data in their EU PBRERs/PSURs.

SV.1.2. Exposure

The total number of vials of RPV 300 mg/mL (REKAMBYS) for IM injection sold from first launch to 31 December 2022 is [redacted], which is equivalent to approximately [redacted] patient-years.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

There are no data to suggest that REKAMBYS has the potential for abuse or dependency, and abuse is not likely because the drug regimen is administered by an HCP.

Based on the pharmacology and mechanism of action of RPV, it is considered highly unlikely that RPV has the potential for abuse. No systematic examination of the abuse potential of RPV has been performed in nonclinical and clinical studies. There have been no reports of RPV dependence from any clinical trial.

No studies to investigate the potential for abuse or dependency with RPV LA have been performed because:

- RPV is not centrally active,
- There is evidence that RPV has low brain penetration,
- Mechanistically, RPV does not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, and
- Available preclinical and clinical data are not indicative of a potential for drug abuse.

In summary, there are no data suggesting that REKAMBYS has the potential for illicit use, abuse, or dependency.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks and Missing Information

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

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

Not all ADRs or safety concerns for RPV LA are considered important risks for inclusion in the list of safety concerns in the RMP. The majority of the ADRs that were identified from the Phase 3/3b clinical trials (FLAIR, ATLAS and ATLAS-2M) with RPV LA in combination with CAB LA, were non-serious and of low severity grade (Grade 1 or Grade 2). Further information on the RPV LA ADRs and the reason they are not considered important risks is provided below.

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns

Known risks with minimal impact on risk-benefit profile, given the severity of the underlying condition: injection site reactions, headache, nausea, vomiting, abdominal pain, rash (includes the MedDRA terms: rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic), transaminase increased, pyrexia (includes the MedDRA terms: body temperature increased, feeling hot), asthenia, fatigue, malaise, abnormal dreams, insomnia, dizziness, somnolence

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated: depression, vasovagal reactions (in response to injections)

Adverse reactions observed in the Phase 3/3b RPV LA + CAB LA clinical trials that are not considered risks for RPV LA, based on the established safety profile of RPV, and the safety profile of INIs, including CAB: anxiety, diarrhea, flatulence, weight increased, myalgia, hepatotoxicity

SVII.1.2. Important Risks and Missing Information for Inclusion in the List of Safety Concerns

Safety Concerns	Risk-Benefit Impact
Important potential risks	
Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)	
REKAMBYS should be administered in combination with CAB LA injection and in accordance with the recommended dosage and administration in the prescribing information (including IFU). If the regimen is not administered correctly (eg, incorrect route or incorrect dose) or the subject does not receive their follow-up injections within the specified window for dosing, this could lead to reduced therapeutic efficacy or an increased risk of AEs.	The frequency of inadequate compliance with the complete drug regimen/maladministration is anticipated to be low and should decrease over time as HCPs become more familiar with the treatment.
Missing information	
Use in pregnancy	
Pregnant women were excluded from the RPV LA + CAB LA clinical development program. Subjects that became pregnant (intrauterine) were required to discontinue from the study medication (and discontinue from the trial). Clinical experience of RPV LA use during pregnancy is therefore limited.	A moderate amount of data in pregnant women using oral RPV indicate no malformative or fetal/neonatal toxicity of RPV. However, the safety of RPV LA during human pregnancy has not been established, therefore it is not possible to define the risk in this patient population. REKAMBYS is not recommended during pregnancy unless the expected benefit justifies the potential risk. Data on the use of RPV LA during pregnancy will be collected through Antiretroviral Pregnancy Registry (APR) postauthorization, in addition to the ongoing data collection on oral RPV.

SVII.2. New, Reclassified, and Removed Safety Concerns with Submission of an Updated RMP

Not applicable.

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

Important identified risks:

Not applicable.

Important potential risks:

1. Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)

Missing information:

1. Use in pregnancy

MedDRA version 21.0 was used to classify the clinical trials AE information that is summarized in this Section.

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

Important Potential Risk: Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)

Potential Mechanisms

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A 2-drug LA injectable therapy represents a novel approach to HIV care, and as there are several steps in the drug delivery process of RPV LA and CAB LA that are unique, there is a potential for medication error. The dual regimen will be separately packaged and marketed, which could potentially be a risk for off-label use or administering an incomplete regimen. The requirement to administer both REKAMBYS and CAB LA at the same visit, as separate injections, could introduce potential risk for dosing or administration errors. For monthly dosing, the requirement for different injection volumes of REKAMBYS at initiation (900 mg, 3 mL) and continuation (600 mg, 2 mL) forms an additional risk. In every 2 months dosing (always 900 mg, 3 mL), there is a potential for error when initiating therapy, which requires an initial dose, a second dose 1 month later and then continuing to every 2 months dosing. Additionally, errors with preparation of the injection, dispensing or storage errors (eg, not stored at 2-8°C) could also negatively impact the effectiveness of RPV. Clinical consequences of medication errors for the RPV LA + CAB LA regimen could include reduced therapeutic efficacy or an increased risk of AEs.

Although IM injections are standard in modern healthcare, inadvertent (partial) IV injection is a recognized, yet uncommon, complication of the procedure. In the case of RPV LA, accidental injection into the venous system could lead to reduced efficacy due to rapid clearance of RPV from the systemic circulation instead of being slowly released into the systemic circulation providing sustained RPV plasma concentrations, as intended. Additionally, there may be a risk of AEs if medication designed for IM administration is delivered directly into the venous circulation.

Evidence Source(s) and Strength of Evidence

In the RPV LA + CAB LA clinical development program, investigators could report identified medication errors of any type; medication errors were reported infrequently during the clinical trials. It is known that documentation of medication errors from clinical trials is imperfect and may not represent the true rate of errors.

Human factor studies were conducted, assessing the monthly injection regimen, using commercially representative medicinal product kits. These included representative drug product vials, delivery devices and packaging, and to-be-marketed prescribing information with IFU for the dosing of RPV LA under simulated use conditions. The objective was to provide evidence that the user requirements were adequately met. Errors observed during the human factor studies were associated with incorrect dose selection, incorrect dose measured in syringe, and incorrect injection site chosen. The studies suggest that medication errors for the every 2 months injection regimen will be similar to those for the monthly injection regimen.

Characterization of the Risk

Overall, up to a clinical cut-off date of 21 February 2020, over 48,000 injections of RPV LA have been administered in the RPV LA + CAB LA clinical development trials LATTE-2, FLAIR, ATLAS, and ATLAS-2M.

At the time of the pooled Week 48 analysis of the Phase 3 pivotal clinical trials FLAIR and ATLAS, 14,682 injections have been administered (Data Source: Mod5.3.5.3/209522Tables/Tab3.110). Medication errors not associated with device malfunction were formally reported and were infrequent occurrences during these trials. These errors were reported to have occurred in 15 subjects, sometimes involving more than 1 drug, and sometimes involving more than 1 subject at the same investigation site. For most subjects (n=14), these involved receiving the wrong dose and in 1 subject this involved receiving the right dose and drug but from the wrong trial (reported as a protocol deviation only) (Data Source: Study 201584 CSR Listing 66, Study 201585 CSR Listing 2). Of the 14 subjects receiving the wrong dose, 8 involved an underdose and 6 an overdose. In 11 subjects, these errors occurred during the first 12 weeks of commencing RPV LA + CAB LA indicating an initial lack of familiarity with use of the product. No AEs were directly attributable to these errors.

At the time of the Week 124 analysis of the FLAIR trial, 17,392 injections of RPV LA had been administered to 278 subjects in the randomized RPV LA + CAB LA group during the Maintenance + Extension Phase (Data Source: Mod5.3.5.1/201584 W124 CSR/Table 3.97). An additional 4,442 injections of RPV LA had been administered to 230 subjects in the Extension Switch Population during the Extension Phase (ie, subjects switching at Week 100 from their current ARV regimen to either RPV LA + CAB LA injectable regimen after completing an oral lead-in [n=119, 2,128 injections], or to proceed directly with RPV LA + CAB LA injections [n=111, 2,314 injections]) (Data Source: Mod5.3.5.1/201584 W124 CSR/Table 3.23). In the randomized RPV LA + CAB LA group, 4 subjects had various dosing errors, ie, received the wrong dose of study drug (n=3) or received study drug from the wrong study (n=1). None of these dosing errors

occurred in the Extension Switch Population (Data Source: Mod5.3.5.1/201584 W124 CSR/Section 7.3.9 and Listing 53).

In the Phase 3/3b clinical trials, very limited evidence of lack of efficacy has been detected as determined by absence of suspected or confirmed virological failure following the occurrence of an error. In the Phase 2b clinical trial LATTE-2, there was 1 subject with accidental (partial) IV administration who remained asymptomatic, but subsequently developed confirmed virologic failure without the emergence of resistance.

Up to the clinical cut-off date of the full Cohort 1 analysis and Cohort 2 Week 24 primary analysis of the MOCHA trial (ie, 18 February 2023), 1,125 injections of RPV LA had been administered to 148 adolescent subjects (at least 12 years of age and weighing at least 35 kg). One subject in Cohort 1R received 900 mg of RPV LA instead of 600 mg at Week 8. In Cohort 2, 2 subjects received incorrect doses (CAB LA 400 mg and RPV LA 600 mg instead of CAB LA 600 mg and RPV LA 900 mg): 1 subject at Week 16 and 1 subject at both Week 16 and Week 24. Three subjects in Cohort 2 reported AEs potentially consistent with post-injection reactions. None of these AEs were serious or led to discontinuation of treatment.

There have been no reports of attempts to combine CAB LA and RPV LA into a single syringe.

In clinical trials, accidental (partial) IV administration has resulted in rare AEs immediately (within minutes) following injection. Up to the clinical cut-off date noted above for the Phase 2b and Phase 3/3b clinical trials LATTE-2, FLAIR, ATLAS, and ATLAS-2M (ie, 21 February 2020), out of 48,000 injections, 4 serious post-injection reactions were reported; 3 with confirmed PK values consistent with accidental (partial) IV injection, 1 without confirmatory PK values. These events were characterized by rapid onset of symptoms (such as dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure) and began to resolve within minutes after the injection.

Based on ad hoc analysis of the PK RPV plasma concentrations measured 2 hours post-dose at several visits during the Phase 2b/3/3b clinical trials, an additional low number of subjects that likely had accidental (partial) IV injections have been identified. No drug-related serious adverse outcomes have been identified in these subjects. No other clinically significant adverse outcomes are known to have occurred as a result of inadvertent (partial) IV administration or due to increased exposure in these trials.

During postmarketing experience, no new safety signal has been identified for this risk.

Risk Factors and Risk Groups

The injectable RPV LA + CAB LA regimen will initially be novel. Both the monthly and every 2 months injection regimens have 2 or 3 stages for dosing; optional oral lead-in dosing, IM initiation dosing, and IM continuation dosing, with both RPV LA and CAB LA being administered as separate injections. The initiation injection dose of RPV LA consists of a single injection for the monthly regimen, while it consists of 2 injections given 1 month apart for the every 2 months regimen. For both regimens, there is a risk of administering an incomplete regimen, potentially

resulting in sub-optimal therapeutic levels. For the monthly regimen, there is also a risk of overdosing when the 900-mg dose would be erroneously administered during the 600-mg continuation dosing.

Accidental (partial) IV injection, resulting initially in a higher than expected peak exposure, is an uncommon, but inherent, risk of IM administration.

Preventability

The prescribing information is clear concerning the requirement for the combined use and delivery of both REKAMBYS and CAB LA. The packaging for the different RPV LA dosing stages is color-coded to help ensure the correct dosage is given at each visit. The 900 mg (3 mL RPV LA) dose secondary packaging is distinguishable by the use of yellow color in its main design elements, whereas the 600 mg (2 mL RPV LA) dose secondary packaging utilizes grey color in its main design elements. Refer to the SmPC Section 4.2 for the recommended monthly and every 2 months IM injection dosing schedule tables.

Detailed IFU will be provided with each REKAMBYS injection kit, informed by user risk assessment, which identifies critical steps in the dispensing, preparation, and administration of the regimen. The ability to complete the critical steps according to the IFU without errors was evaluated through extensive human factor studies. The IFU has been developed through an iterative process with the goal of reducing errors. The outer packaging for REKAMBYS has been developed to differentiate between the 600-mg and 900-mg doses.

As stated in Section 4.2 of the SmPC, prior to starting REKAMBYS, the HCP should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits. Following discontinuation of REKAMBYS in combination with CAB injection, it is essential to adopt an alternative, fully suppressive ARV regimen.

Impact on the Risk-benefit Balance of the Product

The packaging, product labeling and IFU have been designed to minimize the risk for medication errors. The frequency of inadequate compliance with the complete drug regimen/maladministration is anticipated to be low and should decrease over time as HCPs become more familiar with the treatment.

Public Health Impact

Medication errors for the RPV LA + CAB LA regimen could lead to reduced therapeutic efficacy due to viral resistance. Considering that a very small number of subjects developed resistance in clinical trials, and that there are measures in place to manage those with observed or with potential resistance, the public health impact is considered low.

SVII.3.2. Presentation of the Missing Information

Missing information: Use in pregnancy

Evidence source:

Nonclinical embryofetal studies in rats and rabbits were conducted with oral RPV and no significant adverse effects directly related to the drug were noted in the offspring.

Pregnant women were excluded from the RPV LA + CAB LA clinical development program, and women of childbearing potential were required to use effective contraception methods. Subjects who became pregnant (intrauterine) were required to discontinue from the study medication (and discontinue from the trial). Clinical experience of RPV LA use during pregnancy is therefore limited. Due to the LA nature of the RPV injection, exposure could occur at the time of conception and throughout the time of the pregnancy even if injections were stopped before or as soon as pregnancy was identified.

The APR is a prospective exposure-registration cohort study that monitors prenatal exposures to ARV drugs for the detection of a potential increase in the risk of birth defects and provides an early signal on major teratogenicity. The APR interim report issued in December 2022 reviewed data through 31 July 2022.

The APR interim report includes RPV-containing products such as EDURANT, REKAMBYS, and CABENUVA, as these products contain the active moiety of RPV and are considered analyzed together for the purposes of detecting a signal for birth defects in the APR interim report.

A total of 643 first trimester exposure and 209 second/third trimester exposure prospective cases of live births involving exposure to RPV were presented. Twelve (12/643, 1.9% [95% CI: 1.0%, 3.2%]) cases of birth defects have been reported following the first trimester exposure and 2 (2/209, 1.0% [95% CI: 0.1%, 3.4%]) cases of birth defects have been reported following the second and third trimester exposure.

There were 7 first trimester exposures to CAB + RPV, and no second and third trimester exposures. No pregnancy outcome data following first trimester exposure to CAB + RPV could be identified from the APR interim report.

Population in need of further characterization:

As clinical experience of RPV LA use as part of an injectable regimen during pregnancy is limited, it is not possible to define the risk in this patient population. Further information is required to understand the safety profile (eg, pregnancy outcomes and risk of birth defects) in pregnant women taking RPV LA as part of the RPV LA + CAB LA regimen.

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	Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)
Missing Information	Use in pregnancy

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires

Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective(s)	Milestones
Cumulative review of medication error cases in adolescents (ie, non-adherence to the dosing schedule, incorrect route of administration) in the PBRER/PSUR.	To further characterize the important potential risk of medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration).	Ongoing cumulative safety review presentation in PBRERs/PSURs.

III.2. Additional Pharmacovigilance Activities

Study name and title	**Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration With EuroSIDA.**
Rationale and study objectives	This 5-year prospective Drug Utilization Study (DUS) aims to better understand the patient population receiving RPV LA and/or CAB LA containing injection regimens in routine clinical practice, usage patterns, adherence, postmarketing clinical effectiveness of this regimen, discontinuations, and monitor for resistance among virologic failures for whom data on resistance testing are available. The DUS will also evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of RPV LA and/or CAB LA containing injection regimens according to the SmPC recommendations. The study is conducted in collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 22,000 patients followed in over 100 hospitals in 31 European countries, Israel, and Argentina.
Safety concern(s) addressed	Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)
Study design	This is a prospective, observational cohort study nested in the EuroSIDA study, using electronic patient medical information from participating clinical sites over a period of 5 years. All patients who discontinue CAB + RPV LA regimens for any reason, will be followed up for 48 months after discontinuation, during which data will be collected on the ARV regimen the patients switch to, virological outcomes and data on resistance, where tested for and as available. Of note, the EuroSIDA study, and therefore also this study, will be unable to provide comprehensive data on HIV subtype and resistance testing, as the

	latter cannot be mandated across the EuroSIDA sites within the current framework of data collection.
Study population	The study population includes HIV-infected patients over the age of 18 years from EuroSIDA clinical sites who are new users of RPV LA and/or CAB LA containing injection regimens over a period of 5 years. Patients are eligible for inclusion from the date of starting the treatment regimen, and after approval and commercial availability of the regimens.
Milestones	Protocol submission: 31 December 2020 Interim data presenting the progress and status of the DUS will be discussed in the PBRER/PSUR and will be submitted as annual standalone reports. Final study report submission: September 2027
Study 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 an MAH co-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal and fetal outcomes following RPV LA use during pregnancy. Exposure to RPV relative to conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second, and third trimester exposures.
Safety concern(s) addressed	Use in pregnancy.
Study design	Voluntary, prospective, exposure-registration, observational study.
Study population	Pregnant people exposed to ARV drugs for the treatment of HIV and HBV infection and prevention of HIV infection.
Milestones	Protocol submission: 16 December 2021 A registry interim report will be prepared semi-annually summarizing the aggregate data. Data from the APR will be presented in the PBRER/PSUR.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.3: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration With EuroSIDA Ongoing	To better understand the patient population receiving RPV LA and/or CAB LA containing injection regimens in routine clinical practice, usage patterns, adherence, postmarketing clinical effectiveness of this regimen, discontinuations, and monitor for resistance among virologic failures for whom data on resistance testing are available. The DUS will also evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of RPV LA and/or CAB LA containing injection regimens according to the SmPC recommendations.	Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)	Protocol submission Regular updates Final study report submission	31 December 2020 Interim data presenting the progress and status of the DUS will be discussed in the PBRER/PSUR and will be submitted as annual standalone reports. September 2027
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				
Antiretroviral Pregnancy Registry (APR) 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	Protocol submission Regular updates	16 December 2021 A registry interim report will be prepared semi-annually summarizing the aggregate data. Data from the APR will be presented in the PBRER/PSUR.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

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

Study and Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorization				
COMBINE-2 for RPV LA+CAB LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance Ongoing	The study aims to gather data from 1,000 patients to assess clinical effectiveness, adherence, durability, and discontinuations after initiating the RPV LA + CAB LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched from the RPV LA + CAB LA regimen. The study population includes HIV-infected patients over the age of 18 years from NEAT ID Network clinical sites who are prescribed an RPV LA + CAB LA regimen. As per the SmPC, adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class, are eligible for inclusion.	Clinical effectiveness of the regimen Development of resistance	Protocol submission Regular updates Final study report submission	31 December 2020 Interim data presenting the progress and status of the study will be discussed in the PBRER/PSUR and will be submitted as annual standalone reports. September 2026
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 Measures)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

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

Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)	**Routine risk communication:** • SmPC Sections 4.2 and 4.4 • PL Sections 2 and 3 • IFU
	Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Sections 4.2 and 4.4 provide detailed instructions on the correct administration of the regimen, importance of adherence to the injection schedule, and how to handle treatment discontinuation. • PL Sections 2 and 3 include instructions on what to do when stopping treatment. • IFU are provided in the PL and include detailed information on the preparation and administration of an IM injection. **Other routine risk minimization activities beyond the Product Information:** • Administered by HCPs. • Different packaging designs to differentiate between dose and medication.
Use in pregnancy	**Routine risk communication:** • SmPC Sections 4.4 and 4.6 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation regarding the use of REKAMBYS during pregnancy is provided in SmPC Sections 4.4 and 4.6, and PL Section 2. **Other routine risk minimization activities beyond the Product Information** • This is a prescription only medicine. • Prescribed by HCPs.

V.2. Additional Risk Minimization Measures

Not applicable. Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of REKAMBYS.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures

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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)	**Routine risk minimization activities:** • SmPC Sections 4.2 and 4.4 • PL Sections 2 and 3 • IFU • SmPC Sections 4.2 and 4.4 provide detailed instructions on the correct administration of the regimen, importance of adherence to the injection schedule, and how to handle treatment discontinuation. • PL Sections 2 and 3 include instructions on what to do when stopping treatment. • IFU are provided in the PL and include detailed information on the preparation and administration of an IM injection. • Administered by HCPs. • Different packaging designs to differentiate between dose and medication. **Additional risk minimization activities:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cumulative review of medication error cases in adolescents (ie, non-adherence to the dosing schedule, incorrect route of administration) in the PBRER/PSUR. **Additional pharmacovigilance activities:** • Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration With EuroSIDA Final study report due date: September 2027

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in pregnancy	**Routine risk minimization activities:** • SmPC Sections 4.4 and 4.6 • PL Section 2 • Recommendation regarding the use of REKAMBYS during pregnancy is provided in SmPC Sections 4.4 and 4.6, and PL Section 2. • This is a prescription only medicine. • Prescribed by HCPs. **Additional risk minimization activities:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Review of Antiretroviral Pregnancy Registry (APR). A registry interim report will be prepared semi-annually summarizing the aggregate data. Data from the APR will be presented in the PBRER/PSUR.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for REKAMBYS (INN: Rilpivirine free base, TMC278)

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

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

This summary of the RMP for REKAMBYS 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 REKAMBYS's RMP.

I. The Medicine and What it is Used For

REKAMBYS is authorized, in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen, without present or past evidence of viral resistance to, and no prior virological failure with, agents of the non-nucleoside reverse transcriptase inhibitor and integrase inhibitor class (see SmPC for the full indication). It contains rilpivirine (RPV) as the active substance. REKAMBYS and cabotegravir (CAB) injections should be administered by intramuscular (IM) injection at separate gluteal injection sites during the same visit.

Further information about the evaluation of REKAMBYS's benefits can be found in REKAMBYS's EPAR, 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/rekambys.

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

Important risks of REKAMBYS, together with measures to minimize such risks and the studies for learning more about REKAMBYS'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 HCPs;
- 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 (PBRER)/Periodic Safety Update Report (PSUR) 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 REKAMBYS is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of REKAMBYS are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 REKAMBYS. 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	Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)
Missing information	Use in pregnancy

II.B. Summary of Important Risks

Important Potential Risk: Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration)	
Evidence for linking the risk to the medicine	In the REKAMBYS + CAB long acting (LA) clinical development program, investigators could report identified medication errors of any type; medication errors were reported infrequently during the clinical trials. It is known that documentation of medication errors from the clinical trials is imperfect and may not represent the true rate of errors. Human factor studies were conducted, assessing the monthly injection regimen, using commercially representative medicinal product kits. These included representative drug product vials, delivery devices and packaging, and to-be-marketed prescribing information with instructions for use (IFU) for the dosing of REKAMBYS under simulated use conditions. The objective was to provide evidence that the user requirements were adequately met. Errors observed during the human factor studies were associated with incorrect dose selection, incorrect dose measured in syringe, and incorrect injection site chosen. The studies suggest that medication errors for the every 2 months injection regimen will be similar to those for the monthly injection regimen.
Risk factors and risk groups	The injectable REKAMBYS + CAB LA regimen will initially be novel. Both the monthly and every 2 months injection regimens have 2 or 3 stages for dosing; optional oral lead-in dosing, IM initiation dosing, and IM continuation dosing, with both REKAMBYS and CAB LA being administered as separate injections. The initiation injection dose of REKAMBYS consists of a single injection for the monthly regimen, while it consists of 2 injections given 1 month apart for the every 2 months regimen. For both regimens, there is a risk of administering an incomplete regimen, potentially resulting in sub-optimal therapeutic levels. For the monthly regimen, there is also a risk of overdosing when the 900-mg dose would be erroneously administered during the 600-mg continuation dosing. Accidental (partial) intravenous injection, resulting initially in a higher than expected peak exposure, is an uncommon, but inherent, risk of IM administration.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2 and 4.4 • PL Sections 2 and 3 • IFU Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Sections 4.2 and 4.4 provide detailed instructions on the correct administration of the regimen, importance of adherence to the injection schedule, and how to handle treatment discontinuation.

	• PL Sections 2 and 3 include instructions on what to do when stopping treatment. • IFU are provided in the PL and include detailed information on the preparation and administration of an IM injection. Other routine risk minimization measures beyond the Product Information: • Administered by HCPs. • Different packaging designs to differentiate between dose and medication. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration With EuroSIDA. Final study report: September 2027 See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in pregnancy	
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation regarding the use of REKAMBYS during pregnancy is provided in SmPC Sections 4.4 and 4.6, and PL Section 2. Other routine risk minimization measures beyond the Product Information: • This is a prescription only medicine. • Prescribed by HCPs. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Review of Antiretroviral Pregnancy Registry (APR). See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

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

The following studies are conditions of the marketing authorization:

1. **Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration With EuroSIDA**

Purpose of the study: To better understand the patient population receiving RPV LA and/or CAB LA containing injection regimens in routine clinical practice, usage patterns, adherence, postmarketing clinical effectiveness of this regimen, discontinuations, and monitor for resistance among virologic failures for whom data on resistance testing are available. The Drug Utilization Study will also evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of RPV LA and/or CAB LA containing injection regimens according to the SmPC recommendations.

2. **COMBINE-2 for RPV LA+CAB LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance**

Purpose of the study: To gather data from 1,000 patients to assess clinical effectiveness, adherence, durability, and discontinuations after initiating the RPV LA + CAB LA regimen, and monitor for resistance and response to subsequent ARV regimen among patients who switched from the RPV LA + CAB LA regimen.

II.C.2. Other Studies in Postauthorization Development Plan

1. **Antiretroviral Pregnancy Registry (APR)**

Purpose of the study: Monitor prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective pregnancy exposure-registration cohort.

PART VII: ANNEXES

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Annex 4: Specific Adverse Reaction Follow-up Questionnaires

Not applicable.

Annex 6: Details of Additional Risk Minimization Activities

Key Messages of Additional Risk Minimization Activities

Not applicable.