Module 1.8.2

European Union Risk Management Plan (EU-RMP) for VOCABRIA (cabotegravir oral tablets and cabotegravir prolonged release suspension)

STATEMENT REGARDING LICENSE AGREEMENTS

This Risk Management Plan has been prepared by GlaxoSmithKline (GSK) on behalf of ViiV Healthcare (VH) and reviewed and endorsed by VH. GSK provide pharmacovigilance (PV) services under contract to VH from within their own PV system, details of which are settled in a pharmacovigilance agreement. GSK definitions, processes and/or systems are therefore referred to in this report. The integration of the data necessary for the management of safety for all products in VH is achieved via use of the GSK PV system; in GSK this is achieved by sharing an electronic global safety database. All adverse event (AE) reports for all VH marketed products and SAEs for investigational assets are collected into this GSK database, from which the information necessary for reporting to various competent authorities is obtained and constitutes a key body of data for signal management, risk management plans and aggregate safety report generation which is undertaken by GSK under the oversight of VH.

Whilst GSK are the providers of all operational PV services for VH marketed products, as product owner, sponsor of clinical trials and Marketing Authorization Holder (MAH) of Medicinal Products, VH is accountable for safety governance of each of its products. This includes the decisions on product safety issues and the action to be taken following identification and assessment of safety issues by the product review team, such as suspension of trials, updates to the product label, and other risk management actions.

RMP version to be assessed as part of this application	
RMP Version number	5.0
Data lock point for this RMP	10 April 2025
Date of final sign off	7 October 2025

Rationale for submitting an updated RMP

This RMP update reflects changes made to the milestone due dates in the PV Plan for the Category 1 post authorisation safety study: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA (DUS), in line with the latest approved protocol (10 April 2025).

Summary of significant changes in this RMP:

PART	MODULE	Changes made in EU RMP
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES	III.3 Summary Table of additional Pharmacovigilance activities	Addition of revised milestone due dates for DUS in line with approved protocol
PART VII ANNEXES	Annex 2	Addition of revised milestone due dates added for DUS in line with the approved protocol
	Annex 3	Addition of EMA approved amended protocol for DUS

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP

Version number	Approved with procedure	Date of approval
4.3	EMEA/H/C/004976 / II /0022	13 January 2025

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

Abbreviations

3TC	Lamivudine
ABC	Abacavir sulphate
ACCEPT	General Treatment Acceptance Score
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
BIK	Bictegravir/emtricitabine/tenofovir alafenamide
BMI	Body Mass Index
BCRP	Breast cancer resistance protein
BHIVA	British HIV Association
BSEP	Bile salt export pump
CAB	Cabotegravir
CAR	Continued/Current Antiretroviral Regimen
CI	Confidence Interval
CK	Creatine Kinase
CSF	Cerebrospinal Fluid
CVF	Confirmed Virologic Failure
CYP	Cytochrome P450
DAIDS	Division of AIDS
DILI	Drug-induced Liver Injury
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DTG	Dolutegravir
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EEA	European Economic Area
ETV	Etravirine
FC	Fold chain
FDC	Fixed-dose Combination
GCP	Good Clinical Practice
GD	Gestation Day
HAART	Highly Active Antiretroviral Therapy
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIVTSQc	HIV Treatment Satisfaction Questionnaire Change Version
HSR	Hypersensitivity Reaction
IFU	Instructions for Use
IM	Intramuscular

INI	Integrase Inhibitor
INSTI	Integrase Strand Transfer Inhibitor
ISR	Injection Site Reaction
ITTE	Intent-to-treat Exposed
Janssen	Janssen Sciences Ireland UC
LA	Prolonged Release Suspension for Injection
LCT	Liver Chemistry Test
LD	Lactation day
LSC	Liver Stopping Criteria
LSLV	Last Subject Last Visit
LTFU	Long Term Follow-up
MATE	Multidrug and toxin extrusion
MedDRA	Medical dictionary for regulatory activities
mg mkd	Milligram Mg/kg/day
mL	Milliliter
mm	Millimeter
MRHD	Maximum recommended human dose
MRP	Multidrug resistance-associated protein
ms	millisecond
ng	Nanogram
nm	Nanometre
NIH	National institute of Health
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAID	Nonsteroidal Anti-inflammatory Drugs
NTD	Neural Tube Defect
NVP	Nevirapine
OATP	Organic anion transporting polypeptides
OCT	organic cation transporter
OLI	Oral Lead-In
P-gp	Permeability glycoprotein
PhV	Pharmacovigilance
PI	Protease Inhibitor
PIN	Perception of Injection
PK	Pharmacokinetics
PL	Patient Leaflet
PLWH	People Living with HIV
PP	Per protocol
PPN	Pre- and Post-Natal
PrEP	Pre-exposure prophylaxis
PSUR	Periodic Safety Update Report
PTSD	Post-traumatic Stress Disorder
Q4W	Dosing once every 4 weeks
Q8W	Dosing once every 8 weeks
QTc	Corrected QT Interval
QTcB	Heart Rate-corrected QT Interval
QTcF	QT Interval Corrected using Fridericia's Formula
RAL	Raltegravir

RAM	Resistance-associated Mutations
RMM	Risk Minimisation Measure
RNA	Ribonucleic Acid
RPV	Rilpivirine
RT	Reverse Transcriptase
SJS	Stevens Johnson Syndrome
SOC	Standard of Care
TDF	Tenofovir
TdP	Torsades de pointes
TENS	Toxic Epidermal Necrolysis
UDPGA	Uridine 5'-diphospho-glucuronosyltransferase
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
WNL	Within Normal Levels
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of ViiV Healthcare
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EDURANT

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Cabotegravir
Pharmacotherapeutic group(s) (ATC Code)	J05AJ04
Marketing Authorisation Holder/ Applicant	ViiV Healthcare
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	VOCABRIA 30 mg Film-coated tablets, VOCABRIA 400 mg prolonged release suspension for injection (2 mL) VOCABRIA 600 mg prolonged release suspension for injection.(3 mL)
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical Class** CAB is an integrase strand transfer inhibitor (INSTI) formulated as a tablet for oral use and as a prolonged release suspension for intramuscular injection (IM).
	Summary of mode of action: CAB inhibits human immunodeficiency virus (HIV) integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle.
	Important information for its composition: None
Reference to the Product Information	Please refer to product information (module 1.3.1).
Indication(s) in the EEA	**Current**:

	Tablets Vocabria tablets are indicated in combination with rilpivirine tablets for the short-term 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 (see sections 4.2, 4.4 and 5.1) for: oral lead-in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting Vocabria injection plus long acting rilpivirine injection. oral therapy for adults and adolescents who will miss planned dosing with cabotegravir injection plus rilpivirine injection.
	Suspension for Injection: Vocabria injection is indicated, in combination with rilpivirine 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 in the EEA

Current:

The healthcare provider and patient may decide to use cabotegravir tablets as an oral lead-in prior to the initiation of Vocabria injection to assess tolerability (see Table 1) or may proceed directly to Vocabria injections (see Table 2 for monthly and Table 3 for every 2 month dosing recommendations).

Adults and adolescents (at least 12 years of age and weighing at least 35 kg)

Oral lead-in

When used for oral lead-in, Vocabria tablets together with rilpivirine tablets should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir and rilpivirine (see section 4.4).

One Vocabria 30 mg tablet should be taken with one rilpivirine 25 mg tablet, once daily When administered with rilpivirine, cabotegravir tablets should be taken with a meal (see cabotegravir tablet prescribing information).

Table 1 Oral Lead-in Dosing Schedule

	ORAL LEAD-IN
Drug	**For 1 month (at least 28 days), followed by the Initiation Injection[a]**
Cabotegravir	30 mg once daily
Rilpivirine	25 mg once daily

a) *see Table 2 for monthly injection dosing schedule and Table 3 for every 2 month dosing schedule*.

Monthly dosing

Initiation Injection (600 mg corresponding to 3 mL dose)

On the final day of current antiretroviral therapy or oral lead-in therapy, the recommended initial dose of Vocabria injection is a single 600 mg (3 mL) intramuscular injection. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit.

Continuation injection (400 mg corresponding to 2 mL dose) After the initiation injection, the continuation injection dose of Vocabria is a single 400 mg monthly intramuscular injection. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit. Patients may be given injections up to 7 days before or after the date of the monthly 400 mg injection schedule.

Table 2 Recommended monthly intramuscular dosing schedule in adults

Medicinal Product	INITIATION INJECTION	CONTINUATION INJECTION
	Direct to injection: Month 1 Or Following oral lead-in: Month 2 On	One month after initiation injection and monthly onwards
Vocabria	600mg	400mg
Rilpivirine	900mg	600mg

Every 2 Month Dosing

Initiation Injections - one month apart (600 mg dose)
On the final day of current antiretroviral therapy or oral lead-in, the recommended initial Vocabria injection dose is a single 600 mg (3 ml) intramuscular injection (month 2).

One month later, a second Vocabria 600 mg intramuscular injection should be administered. Patients may be given the second 600 mg initiation injection up to 7 days before or after the scheduled dosing date.

Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit.

Continuation Injections - 2- 2 months apart (600 mg)
After the initiation injections, the recommended Vocabria continuation injection dose is a single 600 mg intramuscular injection administered every 2 months. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit. Patients may be given

<table>
<tr><td></td><td>injections up to 7 days before or after the date of the every 2 month, 600 mg injection schedule.

Table 3 Recommended every 2 month intramuscular dosing schedule in adults

<table>
<tr><th></th><th>INITIATION INJECTION</th><th>CONTINUATION INJECTION</th></tr>
<tr><td>Drug</td><td>Initiate injection on the last day of either current ART therapy or oral lead-in (if used). One month later, a second initiation injection should be administered. Direct to injection:

months 1 and 2
OR
Following oral-lead in:
Month 2 and 3</td><td>Two months after last initiation injection and every 2 months onwards

Two months after final initiation injection and every 2 months onwards</td></tr>
<tr><td>Vocabria</td><td>600mg</td><td>600mg</td></tr>
<tr><td>Rilpivirine</td><td>900mg</td><td>900mg</td></tr>
</table>

Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current: Each tablet contains 30 mg cabotegravir (as cabotegravir sodium).

Film-coated tablets. White, film-coated, oval tablets (approximately 8.0 mm by 14.3 mm), debossed with ‘SV CTV’ on one side.

<u>400 mg (2 mL) Vial</u>

Each vial contains 400 mg cabotegravir in 2 mL.

<u>600 mg (3 mL) Vial</u>
Each vial contains 600 mg cabotegravir in 3 mL.</td></tr>
</table>

	Prolonged-release suspension for injection. White to light pink suspension. **Proposed:** Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

SI.1 Indication

Incidence of HIV

HIV incidence has been declining globally in the recent years. Approximately 1.3 million (1.0-1.7 million) adults and children were newly infected with HIV in 2024, 39% down from approximately 2.1 million (1.7-2.7million) new HIV infections in 2010 (UNAIDS, 2024). 44% of all new infections in 2023 were accounted for by women and girls (UNAIDS, 2024). In 2023, an estimated 210,000 (130,000 – 280,000) girls and young women aged 15-24 and an estimated 150,000 (82,000 – 210,000) boys and young men aged 15-24 acquired HIV, representing a 50% and 42% reduction since 2010, respectively (UNAIDS, 2024).

In 2022, 22,995 new HIV infections were reported in 30 countries of the EU/EEA, corresponding to a rate of 5.1 per 100 000 population (ECDC, 2023) which has increased 30.8% since 2021 but decreased 3.8% since 2019. 8.9% of these incident HIV infections occurred in individuals aged 15-24. The countries with the highest HIV incidence rate were Cyprus (24.1 per 100,000) and Estonia (18.8 per 100,000), and the country with the lowest rate was Slovenia (2.0 per 100,000) (ECDC, 2023).

The highest rate of new diagnoses in the 30 reporting countries were in the age group 30–39 years (12.5 per 100,000), while the lowest rate was among young people aged 15–24 years at 0.3 per 100,000. Of these incident HIV infections in 2022, 16,114 men (70.1%) and 6,676 women (29.0%) were diagnosed. The overall rates of diagnoses among men and women were 7.3 per 100,000 and 2.9 per 100,000, respectively (ECDC, 2023). The overall male-to-female ratio was 2.4:1, the highest male-to-female ratios were in Malta (11.0:1) and Slovenia (7.4:1) and lowest in Czechia (1:1).

Prevalence of HIV

About 39.9 million (36.1- 44.6 million) people were living with HIV globally in 2023, among whom 38.6 million (34.9-43.1 million) were adults 15 years and older and 1.4 million (1.1-1.7 million) were children aged 0-14 years. (UNAIDS, 2024).

In 2023, the ECDC estimated that 2.3 million people were living with HIV (PWH) in 47 countries within Europe (ECDC 2024). The burden of HIV varies greatly by country and region within Europe. The majority of individuals were located in Eastern European countries where the estimated number of people living with HIV was 1.43 million. Most of these people lived in either Russia (1,000,000 PWH) or Ukraine (244,877 PWH) (ECDC 2024). ECDC estimates that 828,519 people are living with HIV in Western Europe (ECDC 2024). Countries in this region with the highest burden of HIV include: France (178,700 PWH), Spain (148,371 PWH), Italy (140,730 PWH), United Kingdom (95,932 PWH), Germany (90,800 PWH), and Portugal (45,532 PWH) (ECDC 2024). An estimated 73,969 PWH live in Central Europe; countries in this subregion with the highest burden of HIV include Slovakia (19,415 PWH), Poland (18,923 PWH), and Romania (18,221 PWH) (ECDC 2024).

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

Globally, certain populations such as men who have sex with men (MSM), persons who inject drugs (PWID), women and sex workers have a higher burden of disease compared with the general population. In the EU/EEA, heterosexual sex was the most reported mode of transmission, accounting for 33.7% of all HIV diagnoses in 2022 and 46.3% of diagnoses where the route of transmission was known (ECDC, 2023). Migrants from Central and Eastern Europe account for 28.2% of the heterosexual transmission followed by 26.4% of migrants from Sub-Saharan Africa. Sex between men also remains a common mode of HIV transmission in this region, accounting for 33.3% of HIV diagnoses in 2022 and 45.8% of diagnoses where the route of transmission was known. Approximately 4.3% of reported HIV diagnoses in 2022 were attributed to injection drug use, and an estimated 1.2% diagnoses were attributed perinatal transmission.

SI.1.2 The main existing treatment options

Treatment of HIV requires use of combination antiretroviral therapy (CAR). 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 tolerability of the treatment on the part of the individual. Treatment guidelines have been developed to guide clinicians in selecting appropriate treatments for patients. The most commonly used guidelines are those developed by the World Health Organization (WHO) [WHO, 2022], the European AIDS Clinical Society (EACS) [EACS, 2023] and the Department of Health and Human Services (DHHS) in the United States of America (USA) [DHHS, 2024]. However, many countries have developed their own national guidelines to reflect the local epidemic.

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, for example, adverse events, consideration of drug-drug interactions for patients requiring concomitant medication due to co-morbidities, drug resistance, a desire to lower pill burden, simplification of dosing and regimen preference. Special populations, such as pregnant women and patients co-infected with tuberculosis or hepatitis B (HBV) or C (HCV) infection may also require different regimens based on their specific situations and a need 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 co-infected patients. Healthcare professionals are encouraged to refer to the guidelines (EACS Guidelines and British HIV Association (BHIVA) Guidelines) in consideration of selecting the most appropriate antiretroviral regimen [EACS, 2023 and BHIVA, 2022).

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

The number of people dying from AIDS-related causes began to decline in the mid-2000s because of increased use of ART and the steady decline in HIV incidence since the peak in 1997. In 2022, an around 630,000 (480,000-880,000)) people died from AIDS-related causes worldwide, compared to 1.3 million (970,000–1.8 million) in in 2010 [UNAIDS, 2023]. Western and Central Europe and North America experienced a 34% decline in AIDS-related deaths since 2010; in contrast, Eastern Europe and Central Asia experienced a 46% increase in AIDS-related mortality since 2010 [UNAIDS, 2023]. In 2022, there were an estimated 13,000

(9300-17,000) AIDS-related deaths in Western and Central Europe and North America, and 48,000 (38,000-58,000) AIDS-related deaths in Eastern Europe and Central Asia. Eastern and Southern Africa experienced a 58% decline in AIDS-related deaths between 2010 and 2022 and West and Central experienced a 49% decline in AIDS-related deaths during the same time. Significant declines occurred in Asia and the Pacific (51%) and Latin America (32%) during the same period [UNAIDS, 2023].

SI.1.4 Important co-morbidities

- Opportunistic infections
- Hepatitis C Virus /Hepatitis B Virus co-infection and liver disease
- Malignancies
- Cardiovascular disease
- Metabolic conditions Type 2 Diabetes mellitus
- Musculoskeletal disorders
- HIV-associated neurocognitive disorders
- Kidney disease
- Aging related complications

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

Key safety findings from non-clinical studies with CAB and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat dose toxicity	
Bone marrow depletion ***In monkeys:*** microscopic changes occurred in the bone marrow with corresponding changes in peripheral leukocyte, reticulocyte and platelet counts in males given 1000 mg/kg/day (mkd) in the 14-day toxicity study. Bone marrow depletion was characterised by a generalised decrease in cellularity of all precursor cells. Subsequent data indicate this finding was most probably related to the overall moribund condition of the animals and not a direct toxic effect of CAB, since it was not observed at lower doses or in other species	Experience to date has not confirmed a risk in humans associated with CAB use at recommended clinical doses; therefore, this effect is not expected to impact the target population.
Hepatology findings: No indications of hepatotoxic potential of CAB were observed in nonclinical studies.	Experience to date has identified a risk in humans. A small number of drug induced liver injury (DILI) cases were observed in Phase II studies at recommended clinical doses.
Cardiovascular effects (including potential for QT interval prolongation) **In monkeys:** a single dose of oral CAB at 1000 mkd in conscious, non-restrained male monkeys produced mild, transient increases in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rates (16 to 23%) during the first 2 h after dosing. No blood pressure or heart rate changes were seen in monkeys after ~ 3 weeks at 500 mkd. There were no adverse effects on the heart (organ weight or histopathology) and no electrocardiogram (ECG) waveform or interval changes.	Experience to date, including a thorough QTc clinical study, has not confirmed the risk in humans associated with CAB use, therefore this finding is not expected to impact target population.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Reproductive Toxicity	
CAB did not show a teratogenic potential or effect on reproductive function. The reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity, or maternal behaviour.	There is no anticipated risk in humans based on the non-clinical study findings. CAB is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.
Developmental toxicity	
Effects of exposure in late stage pregnancy A pre- and post-natal (PPN) study conducted in rats demonstrated delayed onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. Decreases in F1 pup survival and viability resulting in reduced litter sizes during the first 4 days of life at the maximum tested dose of 1000 mkd. In a follow up cross-fostering study, vehicle control or CAB at 1000 mkd was given orally by gavage to mated female rats on Gestation Day 6 through Lactation Day 7. Results from this study produced a similar decrease in pup survival and viability during the first 4 days of life as compared to findings from the first study (87.4% versus 98.9% in control). Further, results suggest that it is likely that the decrease in pup survival during the first 4 days of life is related to gestational exposure to CAB. This is supported by the lack of effects on postnatal deaths among control foster pups exposed to the test article via milk. There was no foetal mortality when rat foetuses were delivered by caesarean. Collectively these data suggested that a delay in the onset of parturition in rats receiving 1000 mkd led to increased foetal mortality (stillbirths) and neonatal deaths in a subset of rats immediately after birth.	The clinical significance in humans of the non-clinical pre- and post-natal findings in rats is unknown. Effects seen in the PPN study were at doses >30 times the systemic exposure at the maximum recommended human dose (exposure data from 26-week rat study) [m1.3].CAB is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.
Juvenile toxicity	
No indications of juvenile toxicity of CAB were observed in non-clinical studies.	Non-clinical data for CAB do not indicate a safety concern for humans.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity	
No indications of a genotoxic potential of CAB were observed in genotoxicity tests (in vitro and in vivo).	Non-clinical data for CAB do not indicate a safety concern for humans.
Carcinogenicity	
Carcinogenicity studies were conducted in CD1 mice and Sprague Dawley rats over 104 weeks. Results indicate there was no CAB-related effect on the distribution of non-neoplastic or neoplastic lesions contributing to death or preterminal euthanasia of animals in the study and no non-neoplastic or neoplastic test item-related macroscopic and microscopic pathology findings. No indication of carcinogenetic potential was observed in tests for CAB.	The non-clinical data for CAB do not indicate a safety concern for humans.
General safety pharmacology:	
There were no key safety findings from safety pharmacology studies for CAB.	Since there were no safety findings from safety pharmacology studies there is no indication of an unacceptable risk for administration of CAB to patients.
Mechanisms for drug interactions	
In vitro, no clinical drug interaction risk was identified for co-administered substrates of cytochrome P450 (CYP) 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 3A4, uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17, permeability glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic cation transporter (OCT) 1, OCT2, organic anion transporting polypeptides (OATP) 1B1, OATP1B3, multidrug and toxin extrusion (MATE) 1, MATE 2-K, multidrug resistance-associated protein (MRP) 2, or MRP4 at a clinical dose of 30 mg CAB.	CAB is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

Key Safety findings (from non-clinical studies)	Relevance to human usage
The route of metabolism for [^{14}C]-CAB in rat, monkey and human hepatocytes was by glucuronidation of CAB. In human liver, kidney and intestinal microsomal incubations, [^{14}C]-CAB was metabolised to a single UGT-dependent metabolite, M1. Data from human liver microsomes and recombinant UGT enzymes suggest that UGT1A1 is the primary enzyme involved in the glucuronidation of CAB in vitro with contribution from UGT1A9.	The following list comprises drugs for which significant decreases in CAB plasma concentrations may occur due to UGT1A1 and/or CYP3A enzyme induction. This could result in loss of virologic response in clinical practice and co-administration is not recommended: • Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin • Antimycobacterials: Rifabutin, rifampin, rifapentine
CAB chelates with polyvalent cations, resulting in decreased absorption; chelation was demonstrated for CAB in vitro.	Antacids containing polyvalent cations are to be administered at least 2 hours before or 4 hours after oral CAB
CAB was shown to be an inhibitor of organic anion transporter (OAT) 1 and OAT3 in vitro.	Less than a mean 1.25-fold increase in exposure of OAT1/3 substrates are predicted based on in vitro data, supporting low risk for clinically significant interaction with OAT1 and OAT3 substrates. No dose adjustment is required when CAB is co-administered with OAT1/3 substrates, including sensitive substrates with narrow therapeutic indices, such as tenofovir disproxil fumarate (TDF) and methotrexate. Consistent with the lack of clinically relevant changes in OAT1/3 substrates predicted by mechanistic static and Physiologically based pharmacokinetic modelling, the renal safety data for oral CAB in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), including the sensitive OAT1/3 substrate TDF, support that CAB is not a clinically relevant inhibitor of OAT1/3.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

During clinical development of CAB (with Rilpivirine), the HIV treatment clinical trials described below have been conducted. Clinical trials with CAB for HIV pre-exposure prophylaxis are not in scope of this RMP.

Adults

The combination of oral CAB (10, 30, or 60 mg once daily) and oral RPV (25 mg once daily) has been administered to HIV-infected subjects in Study LATTE (LAI116482) (Phase IIb). All oral doses of CAB achieved durable suppression of HIV infection with a two-drug (CAB+RPV) maintenance regimen, and CAB was well tolerated across all doses studied. CAB 30 mg once daily was selected for use in studies LATTE-2 (200056), FLAIR (201584, and ATLAS (201585) based on pharmacokinetic, safety and efficacy results of Study LATTE (LAI116482). In Study 200056 (LATTE-2), subjects' HIV-1 RNA suppression was induced with a three-drug antiretroviral regimen consisting of CAB + abacavir/lamivudine (ABC/3TC) fixed dose combination and then switched to a two-drug two-class regimen consisting of CAB long acting (LA) + RPV LA for the maintenance of HIV-1 RNA suppression. The overall objective of this study was to select an intramuscular dosing regimen of CAB+RPV LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to CAB 30 mg plus ABC/3TC orally once daily, in HIV-1 infected antiretroviral-naïve subjects. Subjects in the POLAR (209035) IIb study initiated CAB LA 600 mg + RPV LA 900 mg Q2M after transition from oral CAB 30 mg + RPV 25 mg in the LATTE (LAI116482) study. The CUSTOMIZE (209493) study was a phase IIIb, implementation study, of virologically-suppressed PLHIV receiving oral CAB 30 mg + RPV 25 mg once daily for 4 weeks, then IM CAB LA 600 mg + RPV LA 900 mg at Month 1, followed by IM CAB LA 400 mg + RPV LA 600 mg every month through Month 12. The SOLAR (213500) study is a Phase 3b, switch study designed to demonstrate the non-inferior antiviral activity of CAB LA 600 mg + RPV LA 900 mg administered every 2 months (Q2M) compared to continuing Bictegravir/emtricitabine/tenofovir alafenamide (BIK) administered orally once daily for 12 months. The CARISEL (213199) study is a Phase 3b, open-label, hybrid type 3 trial evaluating implementation strategies for long-acting CAB plus long-acting RPV every 2 months in HIV-1 infected, virologically suppressed adults in select European healthcare settings.

CAB+RPV LA is an effective and well tolerated regimen for the maintenance of HIV-1 suppression, based on the Week 48 data from the two pivotal Phase III trials with CAB+RPV (FLAIR (201584) and ATLAS (201585)). The Phase III trials showed that CAB+RPV LA is non-inferior to daily oral current antiretroviral regimen (CAR) in maintaining virologic suppression in HIV-1 infected subjects. Data from the Phase III/IIIb studies shows a small number of patients with confirmed virologic failure (CVF) that developed drug resistance. The Week 48 data from the Phase IIIb, ATLAS-2M (207966) trial, designed to assess the antiviral activity and safety of CAB+RPV LA dosing once every 4 weeks (Q4W) compared with CAB+RPV LA dosing once every 8 weeks (Q8W) in HIV-1 infected, virologically suppressed, adult subjects showed similar levels of viral suppression on the Q8W arm compared with the Q4W arm.

Adolescents

Adolescents (12-17 years) have been studied in a collaborative study sponsored by the National institute for Health/Division of AIDs (NIH/DAIDS) and supported by ViiV Healthcare, in a Phase I/II multicentre, open-label, non-comparative study, MOCHA (208580). The study 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.

W16 MOCHA Cohort 1

55 HIV-1 infected and virologically suppressed adolescents, aged 12 to <18 years, weighing at least 35 kg were enrolled to one of four subgroups. In cohort 1C, participants (n=30) received oral CAB 30 mg once daily for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 IM injections of CAB LA for Q4W regimen, each separated by 4 weeks (600 mg for the first injection and 400 mg for the second and third injections) or followed by 2 IM injections of CAB LA for Q8W regimen, each separated by 4 weeks (both 600 mg), in addition to cART (Step 2).
In cohort 1R, participants (n=25) received oral RPV 25 mg once daily for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 IM injections of RPV LA for Q4W regimen, each separated by 4 weeks (900 mg for the first injection and 600 mg for the second and third injections) or followed by 2 IM injections of RPV LA for Q8W regimen, each separated by 4 weeks (both 900 mg), in addition to cART (Step 2).

W24 MOCHA Cohort 2

Cohort 2 enrolled eligible participants who had completed Cohort 1 as well as eligible participants who had not been previously enrolled in the study. Cohort 2 participants (n=144) discontinued their pre-study cART regimen and received oral CAB 30 mg + oral RPV 25 mg once daily for 4 to 6 weeks (Step 3) and then CAB LA (600 mg) + RPV LA (900 mg) Q8W through Week 96 (Step 4), with the first 2 injections separated by 4 weeks.

Based on data from the Week 16 (Cohort 1) and Week 24 (Cohort 2) analyses of the MOCHA Study, no new safety concerns were identified in adolescents (aged at least 12 years and weighing 35 kg or more) when compared with the safety profile established in adults. As observed in adults, ISRs were the most frequently reported AEs. No participants discontinued treatment due to ISRs. The safety data for cabotegravir observed in participants in the MOCHA study is consistent with the safety profile in the current product labelling for cabotegravir when used in combination with rilpivirine in adults.

Cumulatively, 3270 individuals up to 18 February 2023 were exposed to CAB and RPV (regardless of formulation or dose) in Phase II and III and IIIb ViiV Healthcare sponsored HIV treatment clinical trials.

Table 2 Duration of Exposure

Summary of Duration of Exposure to Oral Cabotegravir		
Duration of exposure	**Patients (n)**	**Person time (years)**
<4 weeks	122	7.214
4 weeks to <6 months	2563	338.765
6 months to <1 year	37	25.369
1 year to <2 years	22	32.402
2 years to <3 years	55	129.837
3 years to <4 years	12	42.040
4 years to <5 years	2	9.128
≥5 years	117	698.864
Total	2930	1283.619
Summary of Duration of Exposure to Long Acting Cabotegravir		
Duration of exposure	**Patients (n)**	**Person time (years)**
<4 weeks	47	1.358
4 weeks to <6 months	228	58.229
6 months to <1 year	802	639.953
1 year to <2 years	621	918.689
2 years to <3 years	500	1327.748
3 years to <4 years	577	1878.713
4 years to <5 years	257	1084.055
≥5 years	218	1575.959
Total	3250	7484.704

Summary of Duration of Combined Exposure to Long-Acting and Oral Cabotegravir		
Duration of exposure	**Patients (n)**	**Person time (years)**
<4 weeks	45	1.489
4 weeks to <6 months	262	62.018
6 months to <1 year	677	547.773
1 year to <2 years	742	1018.371
2 years to <3 years	445	1133.703
3 years to <4 years	657	2145.602
4 years to <5 years	236	1020.482
>=5y	346	2838.886
Total	3410	8768.323
Data cut off: 18 February 2023		
Note: Person time was calculated based on LAI116482 (LATTE) End of Study, 200056 (LATTE-2) End of Study, 201584 (FLAIR) Week 124, 201585 (ATLAS) Week 96, 207966 (ATLAS-2M) Week 152, 209035 (POLAR) End of Study, 209493 (CUSTOMIZE) End of Study, 208580 (MOCHA) Cohorts 1 and 2 Week 24 sNDA, 213199 (CARISEL) End of Study, and 213500 (SOLAR) End of Study Note: Person time was calculated up to the point of the subject's last dose administered or until 18 FEB 2023 for subjects still on treatment at that time. For injections, exposure can last for up to a year or more after the last injection.		

Table 3 Age Group and Gender

Oral Cabotegravir				
	Patients (n)		Person time (years)	
Age Group	**Male**	**Female**	**Male**	**Female**
<18 years	72	76	8.613	8.706
18-64 years	2160	581	1143.343	118.590
65-74 years	24	15	2.735	1.457
>=75 years	2	0	0.175	0.000
Total	2258	672	1154.867	128.753
Long acting Cabotegravir				
	Patients (n)		**Person time (years)**	
Age Group	**Male**	**Female**	**Male**	**Female**
<18 years)	70	75	63.269	57.520
18 to 64 years	2427	632	5864.520	1398.470
65-74 years	26	18	60.838	37.708
>=75 years	2	0	2.379	0.000
Total	2525	725	5991.006	1493.697
Data cut off: 18 February 2023				
Note: Person time was calculated based on LAI116482 (LATTE) End of Study, 200056 (LATTE-2) End of Study, 201584 (FLAIR) Week 124, 201585 (ATLAS) Week 96, 207966 (ATLAS-2M) Week 152, 209035 (POLAR) End of Study, 209493 (CUSTOMIZE) End of Study, 208580 (MOCHA) Cohorts 1 and 2 Week 24 sNDA, 213199 (CARISEL) End of Study, and 213500 (SOLAR) End of Study. For injections, exposure can last for up to a year or more after the last injection.				

Table 4 Dose

Dose of exposure to Oral Cabotegravir[a]	**Patients (n)**	**Person time (years)**
10 to 60 mg once daily oral (LATTE, LATTE-2) [1]	467	1019.507
30 mg once daily oral lead-in [2,3]	2463	264.112
Total	2930	1283.619
Dose of Exposure Oral 30 mg Cabotegravir + Oral 25 mg Rilpivirine	**Patients (n)**	**Person time (years)**
CAB 30 mg + RPV 25 mg once daily oral (LATTE)	145	557.361
CAB 30 mg + RPV 25 mg once daily oral lead-in [4]	2747	295.121
Total	2892	852.482

Dose of Exposure to Long acting Cabotegravir[b]	Patients (n)	Person time (years)
Up to 800 mg IM LA	3250	7484.704
Total	3250	7484.704
Data cut off: 18 February 2023		
Note: Person time was calculated based on LAI116482 (LATTE) End of Study, 200056 (LATTE-2) End of Study, 201584 (FLAIR) Week 124, 201585 (ATLAS) Week 96, 207966 (ATLAS-2M) Week 152, 209035 (POLAR) End of Study, 209493 (CUSTOMIZE) End of Study, 208580 (MOCHA) Cohorts 1 and 2 Week 24 sNDA, 213199 (CARISEL) End of Study, and 213500 (SOLAR) End of Study [1] For LATTE-2 induction phase and control arm exposure. [2] For CAB this includes FLAIR, ATLAS, ATLAS-2M, CUSTOMIZE, MOCHA studies oral lead-in exposure. [3] For subjects that subsequently take oral bridging after starting LA, their time on oral bridging is also included in their total duration on oral. [4] Exposure from studies LATTE-2, FLAIR, ATLAS, ATLAS-2M, POLAR, CUSTOMIZE, CARISEL and SOLAR. For subjects that subsequently take oral bridging after starting LA, their time on oral bridging is also included in their total duration on oral. [a] Note: Person time was calculated up to the point of the subject's last dose administered or until 18FEB2023. [b] Note Injections-Person time was calculated up to the point of the subject's last dose administered or until 18FEB2023 for subjects still on treatment at that time. For injections, exposure can last for up to a year or more after the last injection.		

Table 5 Ethnic Origin

Ethnic Origin* (Oral Cabotegravir)	Patients (n)	Person time (years)
Black or African American	658	341.766
White	2028	857.645
American Indian or Alaska Native	69	23.833
Arabic	0	0.000
Asian	139	35.362
Native Hawaiian or Other Pacific Islander	5	1.539
Mixed	31	23.474
Missing	0	0.000
Total	2930	1283.619
Ethnic Origin* (Long Acting Cabotegravir)	**Patients (n)**	**Person time (years)**
Black or African American	701	1414.842
White	2274	5501.692

American Indian or Alaska Native	77	188.819
Arabic	0	0.000
Asian	158	287.406
Native Hawaiian or Other Pacific Islander	5	18.579
Mixed	35	73.366
Missing	0	0.000
Total	3250	7484.704
Data cut off: 18 February 2023		
Note: Person time was calculated based on LAI116482 (LATTE) End of Study, 200056 (LATTE-2) End of Study, 201584 (FLAIR) Week 124, 201585 (ATLAS) Week 96, 207966 (ATLAS-2M) Week 152, 209035 (POLAR) End of Study, 209493 (CUSTOMIZE) End of Study, 208580 (MOCHA) Cohorts 1 and 2 Week 24 sNDA, 213199 (CARISEL) End of Study, and 213500 (SOLAR) End of Study. . *Based on US Food & Drug Administration (FDA) style ethnicity presentation		

Table 6 Summary of Patient Characteristics by Treatment Regimen

Summary Group/Category	CAB+RPV [1] (n=3373)	CAR [2] (n=853)
Duration of exposure [3], n (%)		
<4 weeks	40 (1.2%)	5 (0.6%)
4 weeks to <6 months	259 (7.7%)	32 (3.8%)
6 months to <1 year	722 (21.4%)	316 (37.0%)
1 year to <2 years	705 (20.9%)	500 (58.6%)
2 years to <3 years	427 (12.7%)	0
3 years to <4 years	645 (19.1%)	0
4 years to <5 years	243 (7.2%)	0
>=5 years	332 (9.8%)	0
Age category, years, n (%)		
<18 years	144 (4.3%)	0
18 to 64 years	3181 (94.3%)	838 (98.2%)
65-74 years	46 (1.4%)	14 (1.6%)
>=75 years	2 (<0.1%)	1 (0.1%)

Gender, n (%)		
Male	2622 (77.7%)	656 (76.9%)
Female	751 (22.3%)	197 (23.1%)
Racial origin, n (%)		
Black or African American	742 (22.0%)	195 (22.9%)
White	2347 (69.6%)	589 (69.1%)
American Indian or Alaska Native	77 (2.3%)	17 (2.0%)
Arabic	0	0
Asian	165 (4.9%)	40 (4.7%)
Native Hawaiian or Other Pacific Islander	5 (0.1%)	2 (0.2%)
Mixed	37 (1.1%)	10 (1.2%)
Missing	0	0

Data cut off: 18 February 2023

Note:
[1] CAB+RPV includes studies LATTE, LATTE-2, FLAIR, ATLAS, ATLAS-2M, POLAR, CUSTOMIZE, MOCHA, CARISEL, and SOLAR. For LATTE-2, duration of CAB+RPV and patients exposed to CAB+RPV will not include use of CAB+RPV with ABC/3TC for those randomized to stay on CAB/ABC/3TC who did not switch to CAB+RPV LA during the extension phase of the study.

[2] CAR includes studies LATTE, FLAIR, ATLAS, POLAR, and SOLAR.
For FLAIR and ATLAS the duration of CAR and patients exposed to CAR will not include use of CAR prior to randomization (Day 1).

[3] Exposure was calculated based on LATTE End of Study, LATTE-2 End of Study, FLAIR Week 124, ATLAS Week 96, ATLAS-2M Week 152, POLAR End of Study, CUSTOMIZE End of Study, MOCHA Cohorts 1 and 2 Week 24 sNDA, CARISEL End of Study, and SOLAR End of Study. The duration will not account for temporary treatment interruptions.

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

There were no trials conducted specifically in special patient populations (e.g. pregnant or lactating women) as part of the development program for CAB.

Missing information relevant for the approved indication is included in module SVII.

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

All pivotal Phase III and IIIb clinical trials were conducted with the CAB+RPV LA combination regimen, so the exclusion criteria of the pivotal trials apply to the combination regimen and are not CAB LA specific

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Subjects with advanced HCV or requiring treatment for HCV during the first 48 weeks of maintenance therapy	In the Phase III and IIIb trials subjects with HCV with either advanced disease or requiring treatment could confound safety and efficacy results	No	Asymptomatic subjects with stable HCV were allowed to enrol in the Phase II, III and IIIb trials for CAB+RPV 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 study. Treatment with CAB+RPV in these HCV coinfected subjects will be guided by established guidance and medical practice. Limited data are available and do not indicate that these stable co- infected patients have different efficacy and safety outcomes compared to mono infected HIV patients.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Women who are pregnant or plan to become pregnant	Pregnant and breast-feeding women are not routinely enrolled into clinical trials to avoid exposing the foetus to the study medication.	Yes	There are limited data from the use of CAB in pregnant women. While reproductive toxicity testing has not identified a risk for CAB based on nonclinical findings, at recommended clinical doses, there have been no adequate and well controlled clinical studies of CAB in pregnant women.
Breastfeeding women	Breast-feeding women are not routinely enrolled into clinical trials to avoid exposing the breast-fed infant to the study medication.	No	This exclusion criterion is consistent with the proposed indication
Subjects in the clinical trials had to be virologically suppressed with a viral load <50 copies/mL. (subjects with viral load >=50 copies/mL were excluded) (Documented evidence of at least two plasma HIV-1 RNA measurements <50 copies/mL in 12 months prior to screening; one within the 6 to 12-month window and one within 6 months of screening.)	This study entry criterion of excluding patients not virally suppressed ensured that subjects who enrolled into the study were adequately suppressed and represented the population for the chosen indication.	No	This exclusion criterion is consistent with the proposed indication.

Subjects positive for HBV at screening (Hepatitis B virus antigen	HBV surface antigen positivity was an exclusion criterion for Phase II and III trials, due to lack of an ART regimen with a NRTI with HBV activity	No	No conclusions can be made about the safety of CAB in HBV coinfected patients. HIV treatment guidelines recommend NRTI-containing regimens with activity against HBV
Alanine transaminase (ALT) >5 times the upper limit of normal (ULN) Phase III: ALT >3xULN	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study.	No	Treatment with CAB will be guided by established guidance and medical practice
Any verified Grade 4 laboratory abnormality	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Treatment with CAB will be guided by established guidance and medical practice.
Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh Classification	CAB is primarily hepatically metabolized via UGT1A1 with a minor UGT1A9 component. Severe hepatic impairment could impact metabolism of CAB Pharmacokinetic studies investigating the use of CAB+RPV have only been performed in subjects with mild and moderate hepatic impairment (Class A and B).	No	There was no change in CAB steady state drug levels in patients with moderate hepatic impairment in separate single oral dose pharmacokinetic studies, and therefore no expected change in subjects with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of CAB has not been studied. Severe hepatic impairment will be managed through the product Summary of Product Characteristics (SmPC).

Subject has estimated creatinine clearance <50 mL/min via Chronic Kidney disease (CKD)-EPI method	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Renal elimination is not a major component of CAB clearance, therefore a significant effect of severe renal impairment on CAB metabolism is not anticipated. Moderate renal impairment did not have a significant effect on CAB pharmacokinetics. Severe renal impairment (creatinine clearance <30 mL/min and not on renal replacement therapy) had minimal impact on total CAB plasma pharmacokinetics. Patients with mild to moderate renal impairment can therefore take CAB without dose adjustment. In patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease, CAB+RPV should be used with caution and increased monitoring for adverse effects is recommended Treatment with CAB will be guided by established treatment guidelines, and/or medical practice and managed through the product SmPC.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia	To avoid putting the safety of the subject at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Patients with HIV infection receiving CAB+RPV 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 CAB will be guided by established guidance and medical practice.
Evidence of an active Centres for Disease Control and Prevention (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.	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 is exacerbated during the study.	No	This exclusion criterion is consistent with the proposed indication. Treatment with CAB+RPV will be guided by established guidelines and medical practice.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	At the data-cut for the initial submission, CAB had been used in 2233 subjects with HIV infection.	Given that over 2233 subjects have been exposed to CAB at the time of initial submission, then there is a >99% probability that very common (>1 in 10) and common (>1 in 100) adverse events would have been observed. Up to 18 February 2023 3270 participants with HIV infection have been exposed to CAB.
Due to prolonged exposure	There is safety data available for 445 subjects receiving CAB at the recommended dose for 1 to <2 years, approximately 582 subjects receiving CAB for 2 to <5 years and approximately 346 subjects receiving CAB for ≥5 years..	Longer term data from 346 subjects who have been exposed to CAB for ≥5 years, have not identified any long-term adverse effect of CAB to date. These longer term data continue to demonstrate that the combination of CAB+RPV 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 favourable. The long-term safety of CAB will be monitored through routine pharmacovigilance.
Due to cumulative effects	Long-term clinical safety data are now available for 445 subjects receiving CAB at the recommended dose for 1 to <2 years, approximately 582 subjects receiving CAB for 2 to <5 years and approximately 346 subjects receiving CAB for ≥5 years.	There were no new safety signals identified during CAB studies that might have been due to cumulative effects. No specific organ toxicity was detected.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which have a long latency	The assessment of longer-term toxicities seen with CAR, such as bone disorders and lipodystrophy require a considerably extended follow up period. Since the Marketing Authorisation Application for the CAB submission, long-term clinical safety data are now available for approximately 346 subjects who have received CAB at the recommended dose ≥5 years.	No long-term adverse effect of CAB is apparent from clinical studies to date and no AEs with a long latency have been identified. The long-term safety of CAB will be monitored through routine pharmacovigilance

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

Table 7 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant women were excluded from CAB clinical studies. Subjects that became pregnant (intrauterine) were required to discontinue the study medication (and discontinue the study). Clinical experience of CAB use during pregnancy is therefore limited.
Breastfeeding women	Breastfeeding women were excluded from the CAB clinical studies.
Symptomatic/advanced HCV co-infection	Asymptomatic subjects with stable HCV were allowed to enrol in the Phase III and IIIb CAB clinical studies 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 study up to primary endpoint. Beyond this timepoint, subjects in the study were allowed to receive treatment for HCV. During the Phase III studies, subjects co-infected with HCV (n=41) (based on HCV serology alone at Baseline) had similar treatment outcomes as mono-infected HIV subjects.
Patients with moderate to severe hepatic impairment, or unstable liver disease.	Patients with moderate to severe hepatic impairment were excluded from the Phase III and IIIb CAB clinical studies.
Hepatitis B co-infection	Patients with HBV were excluded from CAB clinical studies.
Patients with renal impairment	Subjects in the adult studies with estimated creatinine clearance <50 mL/min/1.73m^2 (CKD-EPI method) indicative of moderate (<60 mL/min) and severe (<30 mL/min) renal impairment, were excluded from CAB clinical studies.
Patients with cardiovascular impairment	Patients with clinically significant cardiovascular disease, were not included in the CAB clinical studies.
Patients with a disease severity different from inclusion criteria in clinical trials	The majority of subjects who enrolled into the Phase III CAB clinical studies were CDC category HIV infection stage 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 Phase III).
Subpopulations carrying relevant genetic polymorphisms	Subjects with genetic polymorphisms were not in general excluded from the CAB clinical studies. In trials where ABC-containing drugs were used, subjects with the major histocompatibility complex HLA-B*5701 allele were given an alternative regimen without ABC.

Paediatrics/Adolescents	Children <18 years of age were not included in the adult Phase II, Phase III and IIIb CAB registrational clinical studies for treatment of HIV. **Adolescents** Since the registrational studies, adolescents have been studied in the Phase I/II multicentre, open-label, non-comparative, MOCHA (208580) study. The study 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. **Paediatrics** The safety and efficacy of children aged less than 12 years (or adolescents) weighing less than 35 kg have not been established and no data are available. The safety, tolerability, acceptability, and pharmacokinetics of CAB + RPV is being studied in an ongoing Phase I/II study in children 2 to <12 years of age, CRAYON (214003).
Elderly	There was no upper age limit for inclusion into trials. There is limited information regarding the use of CAB in subjects 65 years or older. Twenty six (1.4%) subjects on CAB clinical studies were 65 years of age or older at enrolment in the Phase II, III and IIIb programme. No difference in safety profile was observed in this sub-population

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Cabotegravir for HIV treatment received its first marketing authorisation approval in Canada on 18 March 2020. Based on the cumulative post-marketing exposure the benefit-risk profile for CAB, in combination with RPV, for the treatment of HIV-1 infection in its approved patient population remains favourable.

SV.1.1 Method used to calculate exposure

The algorithms used to derive post-approval exposure data are as follows:

- For the film-coated tablet formulation, a standard dose of cabotegravir of 30 mg once daily for 30 days is assumed (presented per course – 30 days = 1 course).

- For the IM injection formulation, a standard dose of 1 (200 mg/ml) vial every 2 months administered at the same time as 1 (300 mg/ml) vial of rilpivirine is assumed (presented as patient years)

Please note: from the post-marketing sales data provided, it is not possible to distinguish between 4-weekly and 8-weekly dosing, since vial sizes are not provided as part of the exposure data.

SV.1.2 Exposure

Based on IQVIA data, an estimated 8088 patients have received 1 course of oral cabotegravir tablets during the period 01 July 2020 to 31 December 2022.

The absolute number of vials of cabotegravir 200 mg/mL sold is 139 530, equivalent to an estimated cumulative exposure of 11 627 patient years. This can be broken down as follows:

- 23 789 vials of cabotegravir 200 mg/mL sold as Vocabria for HIV treatment, equivalent to an estimated exposure of 1982 patient years.

- 100 058 vials of cabotegravir + rilpivirine 200 mg/mL+300 mg/mL sold as Cabenuva for HIV treatment, equivalent to an estimated exposure of 8338 patient years.

- 15 683 vials of cabotegravir 200 mg/mL sold as Apretude for PrEP equivalent to an estimated exposure of 1307 patient years.

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

Potential for misuse for illegal purposes

The Marketing Authorisation Holder does not consider that there is a potential for misuse for illegal purposes with CAB.

The INI class of compounds has no known drug abuse potential. There are no data suggesting that CAB has the potential to lead to illicit use, abuse, or dependency.

No studies to investigate the potential for abuse or dependency with CAB have been performed given that: a) CAB is not centrally active, b) there is evidence that this compound has low blood brain barrier penetration, c) mechanistically, CAB does not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, d) preclinical and clinical data available are not indicative of a potential for drug abuse and e) CAB will be administered in a healthcare setting by Healthcare Professionals (HCPs), which would further reduce any chance for misuse.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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 in the RMP

Not all adverse drug reactions or safety concerns for CAB are considered important risks for inclusion in the list of safety concerns in the RMP. Further information on these and the reason they are not considered important risks for CAB is provided below.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

The majority of the adverse drug reactions that occurred in the Phase III clinical studies were non-serious and Grade 1 or 2 in severity [m 2.5 Section 5.4.1.1]. These adverse drug reactions are included in the SmPC (Section 4.8).

Psychiatric disorders: Depression, Anxiety, Abnormal dreams, Insomnia.

Nervous system disorders: Headache, Dizziness, Somnolence, Vasovagal reactions (in response to injections)

Gastrointestinal disorders: Nausea, Vomiting, Abdominal pain, Flatulence, Diarrhoea.

Skin and subcutaneous tissue disorders: Rash (includes the Medical dictionary for regulatory activities (MedDRA) terms: rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular. rash pruritic)

Musculoskeletal and connective tissue disorders: Myalgia

General disorders and administrative site conditions: Injection site reactions (pain and discomfort, site nodule, induration, swelling, erythema, pruritus, bruising, warmth, haematoma, cellulitis, abscess, anaesthesia, haemorrhage, discolouration), Fatigue, Asthenia, Malaise, Pyrexia (includes the MedDRA terms: body temperature increased, feeling hot).

Investigations: Weight increased, Transaminase increased, Blood bilirubin increased, Lipase elevations.

In addition, the following safety concerns specific to CAB are not considered to lead to important risks for the product and are therefore not included as safety concerns in the RMP:

Drug interactions with strong UGT1A1 inducers:

Co-administration significantly decreases CAB plasma concentrations, increasing the potential for loss of therapeutic effect and development of resistance: Rifampin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine [m.2.7.2 Section 2.5.6]. Based on these findings, co-administration of these compounds with CAB is contra-indicated in the product SmPC [see also Part II: Module SII].

Drug interactions with antacids (polyvalent cations):

Co administration has the potential to decrease oral CAB plasma concentration and has not been studied, this could increase the potential for loss of therapeutic effect and development of resistance [m.2.7.2 Section 2.5.6]. Based on these findings, co-administration of antacid compounds with CAB are recommended at least 2 hours before or 4 hours after oral CAB in the product SmPC [see also Part II: Module SII].

Opportunistic infections

Patients receiving CAB or any other ART may still develop opportunistic infections and other complications of HIV infection. Therefore, the product SmPC states the patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection

While effective viral suppression with ART has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. The product SmPC states that precautions to prevent transmission should be taken in accordance with national guidelines.

Drug Resistance

All antivirals are prone to the selection of resistance in the setting of archived transmitted substitutions and/or incomplete adherence to therapy or low drug exposure for any reason. Cases of confirmed virologic failure with drug resistance were observed in a small number of participants in the CAB development programme but these were uncommon (<1.5% (n=7) in Phase III at Week 48) [m2.5 section 4.6.2.3]. In the Phase IIIb ATLAS-2M study 10 subjects met CVF criteria through Week 48: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm [2019N406358_00]. The impact on the risk-benefit balance is low for the individual patients, provided patients remain in care as alternative treatment options are available if drug resistance or virologic failure occurs and oral standard of care regimens have been successful in achieving re-suppression. Given the low number of CVFs with identified resistance, the likelihood of resistance occurring in clinical practice is low.

Suicidal behaviours

As suicidal behaviours have been seen with other INSTIs, prospective suicidality monitoring was conducted during the course of Phase II and Phase III treatment studies.

Suicidality assessments were collected prospectively during Phase II and Phase III studies using the eC-SSRS (m2.7.4 Section 2.1.6.6). Validated true positive alerts for suicidality assessments occurred at lower incidence in the CAB+RPV group compared with the CAR group during Phase III studies (3 subjects [<1%] in the CAB+RPV group; 6 subjects [1%] in the CAR group). There

were seven serious reports of suicidal ideation and suicidal attempts with treatment with CAB+RPV during Phase II (m2.7.4 Section 2.1.6.6). There were no completed suicides, drug-related serious reports, or withdrawals from treatment with CAB+RPV, during the Phase II, III and IIIb trials.

There is currently insufficient evidence to conclude that there is an association between suicidal ideation and suicidal behaviour with treatment with CAB+RPV to designate it as an important safety concern in the RMP.

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:

Hypersensitivity

Hypersensitivity reactions of the delayed type have been reported with other INSTIs (raltegravir and dolutegravir) and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Administration of cabotegravir oral lead-in was used in clinical studies to help identify patients who may be at risk of a hypersensitivity reaction. Analysis of data from the FLAIR (201584) study at Week 124, and the overall OLI experience in Phase III/IIIB Studies, including FLAIR (201584), ATLAS (201585), and ATLAS 2-M (207966) evaluating safety and efficacy of CAB + RPV was performed. At Week 124 for the FLAIR (201584) study, patients electing to switch (at Week 100) from abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) to CAB + RPV in the Extension Phase, with and without an oral lead-in phase; creating an OLI group and a direct to injection (DTI) group. No cases of confirmed hypersensitivity were identified from this analysis in phase III studies and no safety concern was identified to preclude progression to DTI. No delayed type hypersensitivity reactions reports have been received during the CAB clinical development programme to date. The theoretical risk of hypersensitivity does not impact the overall risk-benefit profile of CAB as while its impact may be severe for an individual patient, considering the absence of reports in clinical development, it is expected to occur uncommonly or rarely.

Other reasons for considering the risks not important:

Potential for Off-label use

Off-label use of CAB is possible as the indication restricts use to a clearly specified HIV infected population, in combination with RPV. Appropriate use of CAB+RPV is described in the SmPC. The risk of inappropriate use is considered low as prescribers are expected to adhere to the directions for use in the SmPC. The scenarios of potential off label use described below will be followed via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. Relevant risk minimisation messages are included in the SmPC.

Off label use as such is not considered an important risk for inclusion in the RMP as the outcomes of off label use scenarios described below are not expected to lead to serious clinical consequences. Clear advice in product labelling, widespread availability of alternatives including fixed dose combinations and treatment guidelines are anticipated to minimise the off-label usage in the following scenarios;

Off label use of tablet dosage form

Section 4.2 of the SmPC had language recommending that CAB should be first administered as an oral medication for 1 month (at least 28 days) in virologically suppressed patients prior to the initiation of CAB injection. While the oral lead-in stage is currently recommended, optional use has been evaluated in the development programme and review of safety data from the FLAIR (201584) Week 124 study analysis showed that initiating the CAB LA + RPV LA regimen with or without OLI (DTI) did not identify any new safety concerns related to omitting the OLI phase. At Week 124, rates of virologic suppression (HIV-1 RNA <50 c/mL) were similar in both DTI (110/111 [99.1%]) and OLI groups (113/121 [93.4%]). The proposed DUS will assess drug usage patterns (Table 10).

Off-label use of tablets in combination with antiretrovirals other than RPV

The use of oral CAB together with other oral antiretrovirals is not indicated in the SmPC and as noted above is not thought to be a likely scenario given the availability of alternative fixed dose oral treatments. During the development programme, oral CAB has been administered in combination with ABC and 3TC during the induction phases of Phase II (LATTE + LATTE-2) studies. There were no concerning safety issues associated with the regimen, and CAB is not thought to present a safety issue if used in this way.

Off-label use as first-line therapy

It is unknown if resistance emergence may be more likely in subjects that are not already virally suppressed at treatment initiation with CAB+RPV. However, Section 4.1 of the SmPC clearly states that CAB injection is indicated, in combination with RPV injection, for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) without resistance to or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class. The treatment naïve population has not been studied in the clinical development programme and CAB+RPV is clearly positioned as a switch regimen.

Use in patients who are not virologically suppressed and unable to fully adhere to treatment regimen

Section 4.2 of the SmPC states that prior to starting CAB, HCPs should carefully select patients who agree to the required injection dosing 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 with missed doses. Section 4.1 of the SmPC states that subjects must be virologically suppressed (HIV-1 RNA <50 copies/mL) when starting treatment. The maintenance of virological suppression may be disrupted for example, in patients who struggle with adherence to oral regimens due to psychiatric disorders or that have gastrointestinal malabsorption issues who start the regimen while not fully suppressed. The issue of non-compliance is addressed in section SVII.3.1.

Off-label use in adolescent population

Section 4.8 of the SmPC states the safety and efficacy of CAB in children and adolescents aged under 18 years have not been established. No data are currently available in the adolescent population, studies are planned as part of the paediatric clinical development. The risk of off-label use in this population is low, as clinicians will be aware of the limitations of data availability in the adolescent population. The availability of well-established treatments

recommended in this population, may minimise the off-label usage in this scenario. The data from a DUS looking into usage patterns will indicate if there is use in adolescents.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk #1: Hepatotoxicity

A risk of elevated transaminases has been observed with other INSTIs including dolutegravir and raltegravir. In Phase I, II, III and IIIb clinical studies, six participants exposed to oral CAB (60 mg n=2; 30 mg n=4) had suspected DILI, one of whom was a healthy volunteer. No participant receiving CAB LA has developed suspected DILI to the date-lock point of this RMP. Administration of CAB oral lead-in was used in clinical studies to help identify patients who may be at risk of hepatotoxicity. Analysis from the FLAIR (201584) study at Week 124, including data from the Phase III/IIIB including studies ATLAS (201585), and ATLAS 2-M (207966), evaluating safety and efficacy of CAB + RPV was performed. Investigators and patients elected to switch (at Week 100) from abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) to CAB + RPV in the Extension Phase, with and without an oral lead-in phase, creating an OLI group and a DTI group. From the FLAIR (201584) Week 124 analysis, overall initiating CAB LA + RPV LA regimen in studies FLAIR (201584), ATLAS (201585), and ATLAS 2-M (207966) with DTI, did not identify any new hepatotoxicity related safety concerns related to omitting the OLI phase.

Risk Benefit Impact: Mild to moderate hepatoxicity, manifested as elevations in aminotransferases, was observed in six subjects exposed to CAB oral during the clinical trial programme, which resolved on cessation of drug treatment. If similar toxicity were to occur in patients receiving CAB LA in clinical practice, this could theoretically progress to more a serious nature and prolong the resolution of signs and symptoms since measurable CAB levels would persist, potentially for several months. Occurrence of DILI would require clinical management of the patient hepatic disorder and adoption of an alternative antiretroviral regimen. In the context of HIV treatment, the risk-benefit impact is considered acceptable given the availability of alternative treatments, and infrequency of DILI in the clinical programme.

Important Potential Risk #2: Medication errors including treatment non-compliance

Factors that could negatively impact therapeutic levels of the treatment leading to potential for treatment failure and/or resistance development include: if the CAB+RPV LA regimen component drugs are not administered correctly; the individual injectable components of the CAB+RPV LA regimen are not administered at the same time, as required; the patient does not receive their repeat injections within the specified window for dosing; the patient does not adhere to their injection visits; or the treatment with CAB+RPV LA is discontinued for any reason without the recipient moving onto another fully suppressive ARV regimen. The SmPC and Instructions for use (IFU) have been developed to minimise the risk of medication errors or lack of compliance with regimen requirements.

Risk-Benefit impact: If the combination regimen is not administered correctly as per the proposed labelling, there is a risk of lower than intended drug doses, increased risk of adverse events, confusion over dosing strategy between Q4W and Q8W, or of monotherapy with either component of the dual regimen being delivered to patients. In turn, this may result in potential loss of viral suppression and/or increase the likelihood of emergence of viral resistance,

especially if the patient discontinues without switching onto another suppressive Antiretroviral (ARV) regimen. In addition, patient non-adherence to their injection visit schedule could also negatively impact the effectiveness of CAB+RPV LA. As the treatment delivery is by healthcare professionals, the likelihood of medication errors is low. While the probability of medication errors such as maladministration, or confusion between available regimens may be higher at the time of initial market availability, it is anticipated the risk will reduce as HCPs become more familiar with the use of the product.

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

Not Applicable.

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

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

Important Identified Risk: Hepatotoxicity

MedDRA Preferred Terms (PT): Hepatitis, non-infectious (Standardised MedDRA Query (SMQ) Narrow Search)

Hepatic failure, fibrosis and cirrhosis and other liver damage (SMQ Narrow Search)

Potential mechanisms:

Idiosyncratic reaction with no mechanism currently identified. To date evidence of hepatotoxicity has only been observed in a small number of subjects exposed to CAB.

Evidence source(s) and strength of evidence:

Clinical trials have shown that transient elevations of liver enzymes (transaminitis) can potentially occur with a CAB-containing regimen for a variety of reasons; these events are uncommon. Clinical study data from the development programme with CAB provide the evidence for this risk (detailed below).

Characterisation of the risk:

Table 8 Phase IIb trials

Study	No. of Subjects Exposed	Subjects who met Liver stopping criteria	
		Total No.	No. of suspected DILI
LAI116482 (LATTE, Phase IIb)	181	4	2

200056 (LATTE-2, Phase IIb)	309	14	2

There have been four cases meeting liver stopping criteria that were compatible with DILI that occurred in subjects on CAB during the Phase IIb clinical trial programme. All four of the suspected DILI cases occurred during oral dosing.

LATTE-2 (200056)

The first subject from 200056 had underlying hepatic steatosis as a possible risk factor and 44 days after receiving oral CAB 30 mg and ABC/3TC developed ALT of 9x ULN, aspartate aminotransferase (AST) 6.4x ULN and bilirubin within normal limits. The subject discontinued ART and the transaminases stabilised after approximately 8 weeks. The second subject had chronic active HCV and grade 3/4 fibrosis and developed ALT of 7x ULN, AST 11x ULN and bilirubin 2x ULN 4 weeks after initiation of oral CAB 30 mg and ABC/3TC. The subject discontinued ART and transaminases stabilised after approximately one week. No alternative cause for the liver stopping criteria was identified for both cases.

LATTE (LAI116482)

This was a dose finding Phase II study in which two subjects receiving CAB 60 mg during the oral induction phase met liver stopping criteria (Grade 4 ALT). Routine chemistries for both subjects revealed rises in ALT values to 12x ULN, which returned to pre-treatment levels approximately 2 to 4 weeks after discontinuing drug. The ALT elevation was considered possibly related to CAB and no definitive alternative etiology for the rise was identified. Both subjects remained asymptomatic and neither subject developed a concomitant elevation in bilirubin, no alternative cause for meeting the liver stopping criteria was identified for either case.

Pharmacokinetic study (205712)

An additional case was identified in this repeat dose pharmacokinetic drug interaction study to identify the potential for drug-drug interaction between oral CAB and rifabutin.

A 50 to 60-year old male developed Grade 3 elevations in liver aminotransferases three weeks after co-administration of oral CAB 30 mg and rifabutin 300 mg ended. Liver workup was unremarkable except for a fatty liver on ultrasound examination, the subject was asymptomatic throughout and the findings were consistent with a mixed hepatocellular and cholestatic type hepatitis. The elevated liver aminotransferases (ALT 8.34x ULN, bilirubin within normal limits) fully resolved after approximately 2-3 weeks off study drugs. The investigator considered that there was a reasonable possibility of a causal relationship to CAB and rifabutin exposure, therefore the corresponding serious adverse event was reported as related to the study medications.

Phase III

During the pivotal Phase III studies (ATLAS and FLAIR) there have been no cases of suspected DILI, or hepatocellular injury attributed to CAB. No DILI cases were noted from the FLAIR (201584) study analysis evaluating safety and efficacy of CAB + RPV at Week 124 for patients electing to switch (at Week 100) to DTI, in consultation with their HCPs. None of these events

in the randomized CAB + RPV group during Maintenance + Extension Phase (Day 1 to Week 124) were considered to represent DILI.

Phase IIIb

During the Phase IIIb trial (ATLAS 2M), 1 case of possibly DILI was observed in a subject receiving oral CAB+RPV, resulting in a transient rise in ALT and AST (ALT 206 U/L [>4x ULN], AST 137 U/L [>3x ULN] with no elevation in bilirubin at week 4a after receiving 28 days of oral CAB+RPV. Investigations were negative for viral hepatitis; syphilis and an autoimmune screen. The oral lead in (OLI) was extended while the subject was investigated for alternative causes of transaminitis. During this time ALT and AST remained elevated and the subject was withdrawn from the study after receiving a total of 11 weeks of oral CAB+RPV. The subject commenced ABC/3TC/dolutegravir and the ALT/AST returned to normal after 12 weeks.

MOCHA (208580)

During the Phase I/II multicentre, open-label, non-comparative study, adolescent MOCHA (208580) study, no AESIs relevant to hepatotoxicity were reported in adolescents (12 to <18 years of age) weighing at least 35 kg in Cohort 1C (CAB only) and Cohort 2 (CAB+RPV).

The risk of hepatotoxicity will be further evaluated in the ongoing Phase III/IIIb clinical studies.

Risk factors and risk groups:

None identified, as reports have been received involving a limited number of subjects receiving CAB in clinical studies, with or without known pre-existing hepatic disease.

Preventability:

Labelling will facilitate appropriate patient selection by physicians. Liver chemistry monitoring as part of routine SOC in HIV patients will facilitate identification of patients with increasing transaminases and prompt further investigation for cause.

The SmPC includes a statement in the warnings and precautions and adverse drug reaction sections that hepatotoxicity, presenting as serum transaminase elevations, has been reported in a limited number of subjects receiving CAB. There is also a recommendation to monitor patients' liver chemistries and to discontinue treatment with CAB should hepatotoxicity be suspected.

Impact on the risk-benefit balance of the product:

The number of cases of suspected drug induced liver injury is very low in the context of overall product exposure and no severe cases have been identified. The risk is considered manageable through routine liver chemistry monitoring and discontinuation of CAB treatment, where necessary. The risk is, therefore, acceptable given the expected benefits to patients of this novel regimen, the seriousness of HIV infection and the need for lifelong treatment.

Public health impact:

To date very few subjects have developed DILI across the CAB clinical development programme, and therefore public health impact is expected to be low. Liver chemistry monitoring is routine standard of care in for HIV patients.

Important Potential Risk: Medication errors including treatment non-compliance

MedDRA terms: Medication errors SMQ

Potential mechanisms:

Initially a two-drug injectable regimen will be novel to HCPs treating HIV patients; entailing a requirement for different initiation and continuation doses as well as an option to use oral lead-in. The dual regimen will be separately packaged and marketed, which could potentially be a risk for administering an incomplete regimen. The requirement for different injection volumes at initiation (3 mL) and continuation (2 mL) for the Q4W schedule, and the differences in volume for the continuation dose for the Q8W schedule compared with the Q4W schedule as well as the requirement to administer both CAB+RPV at the same visit as separate injections could introduce potential risk for inadequate regimen compliance or dosing or administration errors. A switch to a fully suppressive ARV regimen should also take place if discontinuation of CAB+RPV were to occur, to minimise the risk of viral resistance. If the drug or drugs are not administered correctly, the individual components of the regimen are not administered at the same time, as required, or the subject does not receive their repeat injections within the specified window for dosing, this could negatively impact therapeutic levels of the treatment leading to potential treatment failure and/or resistance development. Additionally, patient non- adherence to the injection visit schedule, errors with preparation of the injection, dispensing errors or storage errors could also negatively impact the effectiveness of CAB+RPV.

Evidence source(s) and strength of evidence:

In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on subjects. There is potential for detection of some, but not all administration or dosing errors from the clinical studies and would likewise be the same in clinical practice as it is difficult to readily determine if an incorrect injectable dose has been administered. Overall, the potential risk to subjects due to medication errors is considered to be low, as the efficacy of the CAB+RPV LA regimen has not been affected in most cases observed in the clinical studies to date.

Human factor studies were conducted using commercially representative medicinal product kits including representative drug product vials, to-be-marketed delivery devices and packaging, and to-be-marketed labelling including instructions for use for the initiation and continuation doses of the combination drug regimen (CAB+RPV LA) under simulated use conditions with the objective to provide evidence that the user requirements have been adequately met. The conclusions from the human factor studies were used to create and refine the instructions for use.

The risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen is theoretical and could not be assessed in clinical trials.

Characterisation of the risk:

During the Maintenance Phase, up to week 48 of the Phase III pivotal studies FLAIR (201584) and ATLAS (201585) 14682 injections were administered (Data Source: ISS/ISE Table 3.110).

Medication errors not associated with device malfunction were formally reported and were infrequent occurrences during these studies. These errors were reported to have occurred in 15 subjects, sometimes involving more than one drug, and sometimes involving more than one subject at the same investigative site. For most subjects (n=14), these involved receiving the wrong dose and in one subject this involved receiving the right dose and drug but from the wrong study (Data Source: Study 201584 CSR Listing 66, Study 201585 CSR Listing 2). Of the 14 subjects receiving the wrong dose, eight involved an under dose and six an overdose. In 11 subjects these errors occurred during the first 12 weeks of commencing CAB+RPV LA indicating an initial lack of familiarity with use of the product.

In the FLAIR (201584) study, from Week 48 to Week 96, 2 subjects had syringe device malfunctions; these incidents included luer lock failure, leakage from syringe during dosing, and suspension did not move from needle . None of the device malfunctions resulted in maladministration of study drug. Four subjects had various dosing errors: administered dose □1 mL of study drug and administered study drug from wrong study. Dosing errors and device malfunctions occurred in the randomized CAB + RPV group only.

Only 1 incident of device malfunction occurred during extension Phase from Week 96 to Week 124 analysis; this incident was during a CAB injection, the site staff administered 1 mL and met resistance so they stopped and changed needles and then administered the remaining 1 mL without any issues. The subject received the correct treatment and there were no maladministration issues.

During the ATLAS 2M trial, 1 subject was underdosed (received 2 mL instead of 3 mL) with both CAB+RPV LA . No adverse events were directly attributable to these errors. No evidence of lack of efficacy has been detected as determined by absence of suspected or confirmed virological failure following the occurrence of an error.
There have been no reports of attempts to combine CAB and RPV into a single syringe.

In a controlled clinical trial setting the risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen could not be characterised. Data on the risks from 'real world' use will be gathered via routine pharmacovigilance. The marketing authorisation holder (MAH) will also conduct a drug utilization study (DUS) and a post authorisation efficacy study (PAES), COMBINE 2 to characterise the risk of medication errors including treatment non-compliance.

The Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in adult Patients initiating an ARV regimen of CAB+RPV LA in collaboration with EuroSIDA (DUS), will aim to better understand the patient population receiving CAB + RPV LA containing regimens in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness of this regimen and monitor for resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 48 months after discontinuation. During this 48-month follow up period, the study will collect data on the ARV regimen in patients who switch after CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available. However, the data on resistance testing collected by EuroSIDA may not be comprehensive and resistance testing cannot be mandated across the sites participating in

EuroSIDA cohort within the current framework of data collection. Due to this limitation in the EuroSIDA cohort's ability to provide comprehensive data on HIV subtype and resistance, an additional study will be conducted. Assessment of effectiveness of the routine risk minimisation measures for treatment compliance, such as the compliance with the SmPC recommendations on adherence to the dosing schedule and how to handle treatment discontinuations, will be reported in the PBRER/PSUR. Data will be analysed from the DUS interim and final reports, and cases received via routine pharmacovigilance.

The PAES COMBINE-2 for CAB+RPV LA Regimen: A Prospective Cohort Study to Monitor Adherence, Effectiveness and Resistance, will be in collaboration with the NEAT ID network. The study will also monitor for clinical effectiveness, discontinuations and resistance among adult patients on the CAB+RPV LA regimen. This study will aim to include at least 1000 patients across Europe, and will have mandatory testing for resistance and HIV subtype following virological failure if not already available and monitor for virologic outcomes for 24 months following initiation of the regimen. All patients who discontinue the regimen for any reason, will be followed for 48 months after discontinuation. The study will test for resistance and will monitor for emergence of resistance among those who discontinue CAB+RPV LA regimen and have viral failure while on subsequent ARV regimen.

Together the DUS and COMBINE-2, will provide a large enough study population for a long term assessment of the regimen usage, adherence, clinical effectiveness, discontinuations and emergence of resistance. (See Table 10 and Table 11).

Inadvertent partial intravenous administration with adverse outcomes is known to have occurred during the CAB + RPV development programme through the cut-off dates for this submission. There were also other potential cases without adverse outcomes which were detected by reviewing subject's pharmacokinetic data. A higher than expected peak exposure could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases.

Over 48,000 CAB injections have been administered in the clinical program (Studies FLAIR (201584), ATLAS (201585), LATTE-2 (200056) and ATLAS 2-M (207966)) and no other adverse outcomes are known to have occurred with CAB LA as a result of partial intravenous administration or due to increased exposure in these studies. Symptoms such as feeling lightheaded, numbness or tingling, hard to breathe, chest discomfort, sweating, nausea and/or feeling anxious have occurred after an injection with RPV LA. In these cases, high RPV pharmacokinetic levels have been observed, which may indicate that a partial intravenous injection occurred. Not all patients in whom an accidental intravenous injection was suspected reported such symptoms. The majority of the symptoms resolved within minutes.

Overall, no discernible trends or systematic errors were identified with administration of CAB LA, apart from initial lack of familiarity. There have been rare instances of partial intravenous administration of RPV LA which have resulted in adverse reactions. It is likely that the observed errors represent the experience in a group of HCPs that initially lacked familiarity with the product and injection administration technique. To assess this potential risk associated with medication errors and treatment non-compliance, data from the post-marketing setting will be collected and evaluated via routine pharmacovigilance, as evidence from the controlled clinical study programme is limited.

Additional data will be collected and evaluated by the DUS and the post authorisation efficacy study, COMBINE-2 regarding the consequences of medication errors and treatment non-

compliance impacting clinical effectiveness, development of resistance and other adverse outcomes.

Risk factors and risk groups:

The CAB+RPV regimen will initially be novel to HCPs. The treatment has two or three stages for dosing, depending on whether dosing with an optional OLI is used, or direct initiation of injection dose(s), followed by different continuation injection doses corresponding to the Q4W and Q8W regimens, intramuscular initiation dose, and intramuscular continuation dose, with both CAB and RPV being administered as separate injections. There is a risk of administering an incomplete regimen, potentially resulting in sub-optimal therapeutic levels. Inadvertent partial intravenous administration resulting in a higher than expected peak exposure initially could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases also resulting in sub-optimal therapeutic levels. Treatment with CAB+RPV LA should not be initiated in patients who are not suitably suppressed, or those who may not be adherent to the regimen as this could potentially result in sub-optimal therapeutic levels.

Preventability:

The proposed label is clear concerning the requirement for the combined use and delivery of both CAB and RPV. The packaging for the different CAB and RPV dosing stages will be colour coded to help ensure the correct dosage is given at each visit. The primary colour of the 3 mL CAB dose is orange, and the primary colour of the 2 mL CAB dose is dark grey. The single entity packs will facilitate each injection by providing devices (needle, syringe, vial adapter) for correct administration procedure.

Detailed instructions for use will be co-packaged with CAB and RPV, informed by user risk assessment, which identified critical steps in the dispensing, preparation, and administration of the regimen. The ability to complete the critical steps according to the instructions for use without errors was evaluated through extensive human factors studies. The instructions for use have been developed through an iterative process with the goal of reducing errors. The outer packaging for CAB+RPV injection has been developed to differentiate between initiation and continuation doses.

Treating physicians will be advised to select patients who are committed and able to adhere to the required injection dosing schedule and have been counselled about the importance of adherence to scheduled dosing visits, and the risks of treatment discontinuation without adopting an alternative fully suppressive regimen.

In addition, HIV-infected patients transitioning onto the CAB+RPV regimen will be treatment experienced and already suppressed instead of treatment naïve, and therefore are more likely to understand the importance of adherence for any HIV regimen to be effective. In many countries, regimen implementation tools, such as appointment reminder systems and protocols used by hospitals and clinics, are part of standard healthcare practices.

Impact on the risk-benefit balance of the product:

The frequency of inadequate compliance with the complete drug regimen/maladministration is anticipated to be low in the treatment population and should decrease over time as HCPs become more familiar with the treatment. The HCP will also select patients who agree to the required

injection dosing schedule and have been counselled about the importance of adherence to scheduled dosing visits, to decrease the chance of treatment non-compliance occurring. Therefore, the risk-benefit balance remains positive given the benefits of improved adherence and reduction in pill burden for patients afforded by this regimen.

Public health impact:

There is low anticipated public health impact, however if there is non-compliance there may be a risk of resistance to either or both components of the regimen developing, which could limit treatment options for individuals.

SVII.3.2 Presentation of missing information

Use in Pregnancy

Clinical experience of the use of CAB during pregnancy is limited.

No studies have been conducted with CAB in pregnant women during the clinical development programme and pregnant and breastfeeding women were excluded from these clinical studies. Females of reproductive potential (FRP) are required to use effective contraception methods whilst receiving CAB in clinical studies and throughout long term follow up phases of studies after exposure to CAB LA.

Subjects receiving CAB in ViiV Healthcare sponsored clinical studies who became pregnant (intrauterine) were initially required to discontinue CAB, however, there is no longer such a requirement based on reproductive toxicity studies in animals and the clinical and post-marketing data available to date. Women who are confirmed to be pregnant whilst participating in ViiV Healthcare sponsored CAB studies are now given the option to either continue in the study and continue receiving CAB and RPV, following a benefit/risk discussion with the investigator and providing revised informed consent, or they can choose to discontinue CAB and withdraw. Management of pregnancies are per protocol and all pregnancies will be followed up to outcome. Due to the long acting nature of the CAB injection exposure could occur at the time of conception and throughout the duration of the pregnancy even if injections were stopped as soon as pregnancy was identified.

During the CAB+RPV development program at the data lock point of the submissions for the MAA, out of twelve pregnancies exposed to CAB (four oral only and eight long acting), there was one live birth of a healthy infant and two ongoing pregnancy at the time of database lock. There were three spontaneous abortions and one medical termination for anembryonic pregnancy. The remaining five pregnancies were electively terminated for non-medical reasons.

Population in need of further characterisation:

As clinical experience of the use of CAB as an injectable regimen during pregnancy is not available, it is not possible to define the risk in this patient population. Further information is required to understand the safety profile (i.e. maternal and foetal outcomes) in pregnant women taking CAB.

Further studies are ongoing to collect additional information on the use of CAB during pregnancy (see APR and EPPICC pregnancy study, Table 10 or further information).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 9 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatotoxicity
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in Pregnancy

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities:

Cumulative review of medication error cases in adolescents (i.e, non-adherence to the dosing schedule, incorrect route of administration) to be included in the PBRER.

III.2 Additional pharmacovigilance activities

The pharmacovigilance plan for CAB and CAB-containing products is to implement a post-marketing safety study (PASS) to further quantify the risk of hepatotoxicity and to possibly determine associated risk factors. In addition, the PASS will monitor for CAB discontinuation rates due to adverse events. A DUS will also be conducted to better understand the patient population receiving CAB+RPV LA injectable regimen in routine clinical practice, usage patterns, adherence and post marketing clinical effectiveness of this regimen.

Study short name and title: A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen.

Rationale and study objectives:

Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART therapy, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of patients receiving CAB with or without known pre-existing hepatic disease. Healthcare professional should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

The MAH proposes a five-year post authorization safety study (PASS) to be conducted in a real-world context. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events following initiation of CAB based ARV regimen.

This safety study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

Following the initiation of any ARV regimen containing CAB LA among HIV infected patients, the study will aim to:

1. Characterise the rates and risks of hepatotoxicity by:
- estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
- estimating the incidence of cases of combined ALT and total bilirubin elevations and risk factors for elevations
2. Estimate the number of patients discontinuing CAB based ARV regimen due to any reason and specifically discontinuations due to liver related adverse events

Study design:

A prospective cohort study nested within the EuroSIDA study, using electronic patient medical information from participating clinical sites will be conducted over a period of five years to meet the study objectives. In addition to ALT and total bilirubin, the study will also assess other liver chemistry tests (LCTs) including changes to aspartate aminotransferase (AST), Alkaline phosphatase (ALP) and Albumin levels.

For this non-interventional study, treatment and laboratory testing decisions will be made by the treating physician according to standard practice, taking into account the treatment history, patient characteristics, the approved SmPC for CAB oral and LA formulations, contemporary regimen and local guideline or recommendations.

Study population:

The study population will include HIV positive patients over the age of 18 years, who are new users of CAB based ARV regimens.

Milestones:

A study-specific protocol was developed and submitted by 31 December 2020 for the EMA's review and endorsement. The study started once the protocol was approved by the EMA, and CAB LA was registered and commercially available in the relevant countries and will continue through to at least 2025 or later, for a total of five years of monitoring. Annual reports (interim) with cumulative data will be submitted and a final report will be submitted 12 months after the study completion.

Study short name and title: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Rationale and study objectives:

ViiV Healthcare proposes a five-year DUS to be conducted in a real-world context. This prospective observational cohort study will aim to better understand the patient population receiving CAB LA and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for

resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 48 months after discontinuation. During this 48-month follow up period, the study will collect data on the ARV regimen in individuals who switch after CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available.

The proposed study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

The study will evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors including treatment non-compliance and assess the use of CAB LA and/or RPV LA containing injection regimens according to the SmPC recommendations by addressing the specific study objectives as outlined below. Following the initiation of any ARV regimen containing CAB LA and/or RPV LA among HIV infected patients, the study will aim to assess usage patterns, durability, discontinuation, and virological outcomes among persons first exposure to CAB LA and /or RPV LA containing regimens. The specific aims are to:

1. Describe CAB LA and/or RPV LA containing regimens usage patterns

- Descriptive analysis of study population by baseline demographic and clinical characteristics
- Monitor for use of oral lead-in
- Comparison of treatment groups*
    a. CAB+RPV regimen only
    b. CAB LA monotherapy
    c. CAB LA use in combination with ARVs other than RPV LA
    d. RPV LA monotherapy
    e. RPV LA use in combination with ARVs other than CAB LA
    f. CAB LA+RPV LA+other ARVs
    g. Combined group b-f

2. Assess adherence, durability and discontinuation for persons starting CAB+RPV LA regimen ;

- Proportion of individuals discontinuing the regimens of interest will be assessed.
- Reasons for discontinuation will be assessed.
- Non-adherence to dosing schedule will be assessed by
    a. Estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB + RPV LA containing regimens and mean and median number of injections missed during a 12-month period
    b. Estimating the number of individuals who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections
    c. Estimating the number of individuals who missed one or more consecutive injections without taking daily oral bridging therapy or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe patient characteristics for the individuals that are non-adherent.
- Number of individuals with incorrect route of administration will be described.

3. Assess the clinical effectiveness (i.e. proportion of individuals experiencing virologic failure) among HIV patients who initiate CAB+RPV LA regimen

a. Estimate the proportion of individuals with virologic failure, during the first 6 months after initiation of CAB+RPV LA
b. Estimate the proportion of individuals with virologic failure, 6, 12 and 24 months after initiation of CAB+RPV LA
c. Stratified analyses for 3a and 3b will be conducted for VL at regimen initiation (<50 copies/mL and ≥50 copies/mL).
d. Assessment of VL for PLWH on other regimen combinations (b-f in objective 1) at 6, 12 and 24 months after initiation of the regimen

4. Monitor for resistance and next treatment response among individuals who discontinued CAB+RPV LA, where viral load data are available and resistance testing has been done as part of routine clinical practice

- Describe the ARV regimen individuals are switched to after discontinuation of CAB+RPV LA containing regimens
- Monitor for resistance (where this has been done as part of routine clinical practise) during the 48 months following the switch
- Describe virologic outcomes at 12, 24, 36 and 48 months after discontinuation of CAB+RPV LA containing regimens

5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen

- Assess off-label use as described in objective 1
- Estimate proportion of treatment naive or individuals not suppressed initiating regimen
- Assess non-adherence to the dosing schedule as described in objective 2
- Assess the frequency of discontinuation due to incorrect route of administration

Study design:

A prospective cohort study nested within the EuroSIDA study, using electronic patient medical information from participating clinical sites will be conducted over a period of five years to meet the study objectives.

For this non-interventional study, treatment decisions and resistance testing decisions will be made by the treating physician according to standard practice, taking into account the treatment history, patient characteristics, the approved SmPCs for CAB and RPV oral and LA formulations and for the contemporary regimen and local guidelines or recommendations. All individuals who discontinue the regimen for any reason, will be followed for 48 months after discontinuation.

Study population:

The study population will include HIV infected patients over the age of 18 years, from EuroSIDA clinical sites who are new users of CAB LA and/or RPV LA containing regimens over a period of 5 years. Persons will be eligible for inclusion from the date of starting the treatment regimens after approval and commercial availability of the regimens. Only the first exposure to CAB LA and/or RPV LA containing regimens will be included in analyses.

Milestones:

A study-specific protocol was developed and submitted by 31 December 2020 for EMA's review and endorsement. The study started once the protocol was approved by the EMA, and CAB+RPV LA was registered and commercially available in the relevant countries and will continue through to at least 2026 or later, for a total of five years of monitoring. Annual (interim) reports with cumulative data will be submitted and a final report will be submitted 12 months after the study completion. Please note study considerations above for lag in data from uptake in clinic to availability of data in EuroSIDA.

CAB in Pregnancy studies:

Due to the long-acting nature of the CAB injection, exposure could occur at the time of conception and throughout the duration of the pregnancy even if injections were stopped as soon as pregnancy was identified. Cabotegravir reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity. There is no anticipated risk in humans based on the non-clinical study findings.

No studies have been conducted with CAB in pregnant women. Pregnant and breastfeeding women were excluded from the CAB clinical studies. Women of childbearing potential were required to use highly effective measures to avoid pregnancy. Subjects that became pregnant were required to discontinue the study medication and discontinue the study, regardless of termination status of pregnancy. Clinical experience of CAB use during pregnancy is therefore limited. Thus, the safety of CAB during human pregnancy has not been established. The proposed SmPC states that CAB is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus and additionally prescribers are reminded of long acting exposure following injection.

In addition to routine pharmacovigilance to monitor pregnancies occurring with exposure to CAB, ViiV Healthcare has proposed two studies for post marketing data generation to assess the safety and effectiveness of CAB in pregnancy using data from The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) and The Antiretroviral Pregnancy Registry (APR).

Study short name and title: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Rationale and study objectives:

Data from the EPPICC will assess maternal outcomes (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. The exposure to CAB relative to all gestation periods including conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Study design:

This is a non-interventional study involving analysis of prospectively collected i.e. exposure data collected before the pregnancy outcome is known.

Study population:

EPPICC is an international network of cohort and surveillance studies set up in 2010 and coordinated by Penta Child Health (www.penta-id.org). The collaboration conducts epidemiological research on pregnant women living with HIV and their children (infected and HIV-exposed uninfected), with a focus on scientific and clinical management-related questions requiring a large sample size of patients which the contributing studies cannot answer individually. The safety and effectiveness of CAB in pregnancy will be assessed in real world, using observational data collected in cohort and surveillance studies of pregnant women living with HIV and their infants from European countries within EPPICC.

Participating sites/cohorts in EPPICC will provide coded, anonymised data on pregnant women using CAB-containing ARV, as per detailed standard operating procedure (SOP) for data reporting, including a data specification guidance based on a modified HIV Cohorts Data Exchange Protocol (HICDEP) (www.hicdep.org). Following merger of these individual cohort/study datasets, analyses will be conducted on the pooled dataset to address the study objectives.

Milestones:

A study-specific protocol was developed and submitted by 31 December 2020 for the EMA's review and endorsement. The study started once the protocol was approved by the EMA. Four analyses have been planned: the first interim report was planned for submission when the number of pregnant women exposed to CAB-containing regimen in the cohorts reaches 25, followed by two more interim reports when the study population reaches 100 and 200 pregnancies. A final report will be completed 12 months after the third interim report.

Study short name and title: Antiretroviral Pregnancy Registry (APR)

Rationale and study objectives:

The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure- registration cohort. The APR is a ViiV Healthcare-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. Exposure to CAB relative to all gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Study design:

This is a non-interventional study involving analysis of prospectively collected i.e. exposure data collected before the pregnancy outcome is known.

Study population:

The APR is a voluntary, international, prospective exposure registration cohort that was established in 1989 to monitor and detect any teratogenic effects of ARV drugs used in pregnancy. Annually, the Registry enrols approximately 1300-1700 pregnant women exposed to ARV drugs for the treatment of HIV and HBV infection and prevention of HIV infection. This number includes approximately 1300 or 15% of the 8,700 HIV infected women who give birth to live infants annually in the US and approximately 350 pregnant women from other countries.

Clinicians register pregnant women with prenatal exposures to any ARV before the outcome of pregnancy is known, report data on exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential. Defects are reviewed by a teratologist, and all data are reviewed semi-annually by an independent Advisory Committee. Exposure to ARVs is classified and analysed by the earliest trimester of exposure to each individual ARV medication.

Birth defect prevalence (any pregnancy outcome > 20 weeks of gestation with a defect/live births) is compared to both internal and external comparator groups. The external comparators used are two population-based surveillance systems – Metropolitan Atlanta Congenital Defects Program (MACDP) by the Centres for Disease Control and Prevention (CDC) and the Texas Birth Defects Registry (TBDR). Internal comparators include exposures to other drugs and exposures in the second or third trimester of pregnancy relative to 1st trimester exposures when organogenesis occurs.

Milestones:

A study-specific protocol was developed and submitted by 31 December 2020 for the EMA's review and endorsement. The study started once the protocol was approved by the EMA. ViiV Healthcare, has proposed to conduct in depth interim analyses of non-defect data per schedule shown in the Table 10, in Section III.3. The first interim report will be authored and submitted when the number of pregnant women exposed to a CAB-containing regimen in the registry reaches 25, followed by two more interim reports when the study population reaches 100 and 200 pregnancies. A final report will be completed 12 months after the third report.

III.3 Summary Table of additional Pharmacovigilance activities

Table 10 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA Ongoing	Describe CAB LA and/or RPV LA containing regimens usage patterns Assess adherence, durability and discontinuation for persons starting CAB+ RPV LA regimen Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who are on CAB+RPV regimen Monitor for resistance and next treatment response among individuals who discontinued CAB + RPV LA regimen Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen	Medication errors including treatment non-compliance	Estimated Study completion	31 December 2025 or 5 years following commercial availability of CAB
			Estimated Final report	30 September 2027
			Regular updates	Yearly interim reports presenting the progress and status of the study will be submitted to the EMA.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3- Required additional pharmacovigilance activities				
A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating CAB containing antiretroviral regimen Ongoing	Monitor for hepatotoxicity, Estimate the number of patients discontinuing CAB based ARV regimen due to adverse events, and adverse events related to hepatic events	Hepatotoxicity	1st Interim Report	March 2023
			2nd Interim Report	March 2024
			3rd Interim Report	Estimated – March 2025
			4th Interim Report	Estimated – March, 2026
			Estimated study completion	30 June 2026 or 5 years following commercial availability of CAB
			Estimated Final report	30 June 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
EPPICC: Ongoing	To assess maternal and foetal outcomes following CAB use during pregnancy	Use in pregnancy	Updated Interim Report 1 (25 pregnancies)	Estimated 31 December 2026
			Interim Report2 (100 Pregnancies)	Estimated 31 December 2028
			Interim Report 3 (200 Pregnancies)	Estimated 31 December 2030
			Final report	12 months after third analysis Estimated 31 December 2031
APR Ongoing	Assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy.	Use in pregnancy	Updated Interim Report 1 (25 Pregnancies)	Estimated 31 December 2024
			Interim Report 2 (100 Pregnancies)	Estimated 31 December 2026
			Interim Report 3 (200 Pregnancies)	Estimated 31 December 2028
			Final report	12 months after third analysis Estimated 31 December 2029

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Study short name and title: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance

Table 11 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
COMBINE-2 for CAB+RPV LA Regimen: A Prospective Cohort Study to Monitor, Effectiveness, Adherence and Resistance Ongoing	The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen. The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults 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 will be eligible for inclusion.	Clinical effectiveness of the regimen Development of resistance	Estimated Study completion	30 June 2026 or 5 years following commercial availability of CAB
			Interim Reports	Yearly interim reports presenting the progress and status of the study will be submitted to the EMA.
			Final report	30 September 2026

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 12 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hepatotoxicity	**Routine risk communication:** • SmPC section 4.4, 4.8. • Patient Leaflet (PL) section 2 & 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation for liver chemistry monitoring are included in SmPC section 4.4 **Other routine risk minimization measures beyond the Product Information:** • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV.
Medication errors including treatment non-compliance	**Routine risk communication:** • SmPC section 4.2, 4.4 • PL section 2 & 3 **Other routine risk minimization measures beyond the Product Information:** • Administered by Healthcare Professionals. • Different packaging designs for each phase of treatment.
Use in Pregnancy	**Routine risk communication:** • SmPC section 4.6. • PL section 2 **Other routine risk minimization measures beyond the Product Information:** • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV

V.2. Additional Risk Minimisation Measures

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

V.3. Summary of risk minimisation measures

Table 13 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8. • PL section 2 & 4 • Recommendation for liver chemistry monitoring are included in SmPC section 4.4 • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional Pharmacovigilance activities:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen
Medication errors including treatment non-compliance	**Routine risk minimisation measures:** • SmPC section 4.2, 4.4 • PL section 2 & 3 • Administered by Healthcare Professional. • Different packaging colours and logo for each phase of treatment. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Other pharmacovigilance activities: Cumulative review of adolescent cases of medication errors including treatment non-compliance to be included in PBRER/PSUR. **Additional pharmacovigilance activities:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in Pregnancy	**Routine risk minimisation measures:** • SmPC section 4.6. • PL section 2 • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Antiretroviral Pregnancy Registry (APR) European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Vocabria 30 mg film-coated tablets (cabotegravir)

This is a summary of the risk management plan (RMP) for Vocabria 30 mg film-coated tablets. The RMP details important risks of Vocabria 30 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Vocabria 30 mg film-coated tablets risks and uncertainties (missing information).

Vocabria 30 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vocabria 30 mg film-coated tablets should be used.

This summary of the RMP for Vocabria 30 mg film-coated tablets 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 Vocabria 30 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Vocabria 30 mg film-coated tablets are authorised in combination with rilpivirine tablets for the short-term 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 NNRTI and INI class for:

- oral lead-in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting Vocabria injection plus long acting rilpivirine injection.
- oral therapy for those who will miss planned dosing with Vocabria injection plus rilpivirine injection.

See SmPC for the full indication. It contains cabotegravir as the active substance and it is given by the oral route.

Further information about the evaluation of Vocabria 30 mg film-coated tablets' benefits can be found in Vocabria 30 mg film-coated tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/rmp-summary/vocabria-epar-risk-management-plan_en.pdf

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

Important risks of Vocabria 30 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Vocabria 30 mg film-coated tablets' risks, are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Vocabria 30 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vocabria 30 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vocabria 30 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hepatotoxicity
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in Pregnancy

II.B Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical trials have shown that transient elevations of liver enzymes (transaminitis) can potentially occur with a CAB-containing regimen for a variety of reasons; these events are uncommon. Clinical study data from the development programme with CAB provide the evidence for this risk.
Risk factors and risk groups	None identified, as reports have been received involving a limited number of subjects receiving cabotegravir in clinical studies, with or without known pre-existing hepatic disease
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4, 4.8 PL section 2 & 4 Recommendation for liver chemistry monitoring are included in SmPC sections 4.4 This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **Study short name:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen *See section II.C of this summary for an overview of the post- authorisation development plan.*

Important potential risk: Medication errors including treatment non-compliance	
Evidence for linking the risk to the medicine	In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on subjects. There is potential for detection of some, but not all administration or dosing errors from the clinical studies and would likewise be the same in clinical practice as it is difficult to readily determine if an incorrect injectable dose has been administered. Overall, the potential risk to subjects due to medication errors is considered to be low, as the efficacy of the CAB+RPV regimen has not been affected in most cases observed in the clinical studies to date. Human factor studies were conducted using commercially representative medicinal product kits including representative drug product vials, to-be-marketed delivery devices and packaging, and to-be-marketed labelling including instructions for use for the initiation and continuation doses of the combination drug regimen (CAB+RPV) under simulated use conditions with the objective to provide evidence that the user requirements have been adequately met. The conclusions from the human factor studies were used to create and refine the instructions for use. The risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen is theoretical and could not be assessed in clinical trials.
Risk factors and risk groups	The CAB+RPV regimen will initially be novel to Healthcare Professionals. The treatment has either two or three stages for dosing, if an optional oral lead-in dosing is used, or direct initiation of injection dose(s), followed by different continuation injection doses corresponding to the Q4W and Q8W regimens, intramuscular initiation dose, and intramuscular continuation dose, with both CAB and RPV being administered as separate injections. There is a risk of administering an incomplete regimen, potentially resulting in sub- optimal therapeutic levels. Inadvertent partial intravenous administration resulting in a higher than expected peak exposure initially could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases also resulting in sub-optimal therapeutic levels. Treatment with CAB+RPV LA should not be initiated in patients who are not suitably suppressed, or those who may not be adherent to the regimen as this could potentially result in sub-optimal therapeutic levels.

Important potential risk: Medication errors including treatment non-compliance	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2, 4.4 PL section 2 & 3 Administered by healthcare professionals. Different packaging colours and logo for each phase of treatment. **Additional risk minimisation measures***:* None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **Study short name:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA *See section II.C of this summary for an overview of the post- authorisation development plan.*

Missing information: Use in Pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6. PL section 2 This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **Study short name:** Antiretroviral Pregnancy Registry (APR) **Study short name:** European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) *See section II.C of this summary for an overview of the post- authorisation development plan.*

II.C Post-authorisation development plan

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

Study short name: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Purpose of the study: ViiV Healthcare proposes a five-year DUS to be conducted in a real-world context. This prospective observational cohort study will aim to better understand the adult patient population receiving CAB LA and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 48 months after discontinuation. During this 48-month follow up period, the study will collect data on the ARV regimen in individuals who switch after CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available.

The proposed study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

The study will evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of CAB LA and/or RPV LA containing injection regimens according to their SmPC recommendations by addressing the specific study objectives as outlined below. Following the initiation of any ARV regimen containing CAB LA and/or RPV LA among HIV infected patients, the study will aim to assess usage patterns, durability, discontinuation, and virological outcomes among persons first exposure to CAB LA and /or RPV LA containing regimens. The specific aims are to:

1. Describe CAB LA and/or RPV LA containing regimens usage patterns
    - Descriptive analysis of study population by baseline demographic and clinical characteristics
    - Monitor for use of oral lead-in
    - Comparison of treatment groups*
        a. CAB+RPV LA regimen only
        b. CAB LA monotherapy
        c. CAB LA use in combination with ARVs other than RPV LA
        d. RPV LA monotherapy
        e. RPV LA use in combination with ARVs other than CAB LA
        f. CAB+RPV LA +other ARVs
        g. Combined group b-f

2. Assess adherence, durability and discontinuation for persons starting one of the regimens a-e above;

   - Proportion of patients discontinuing the regimens of interest will be assessed.
   - Reasons for discontinuation will be assessed.
   - Non-adherence to dosing schedule will be assessed by
     a. Estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB LA and/or RPV LA containing regimens and mean and median number of injections missed during a 12-month period
     b. Estimating the number of individuals who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections
     c. Estimating the number of individuals who missed one or more consecutive injections without taking daily oral bridging therapy or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe patient characteristics for the individuals that are non-adherent.
   - Number of individuals with incorrect route of administration will be described.

3. Assess the clinical effectiveness (i.e. proportion of individuals experiencing virologic failure) among HIV patients who initiate CAB+RPV LA regimen
   a. Estimate the proportion of individuals with virologic failure, during the first 6 months after initiation of CAB+RPV LA
   b. Estimate the proportion of individuals with virologic failure, 6, 12 and 24 months after initiation of CAB+RPV LA
   c. Stratified analyses for 3a and 3b will be conducted for VL at regimen initiation (<50 copies/mL and ≥50 copies/mL).
   d. Assessment of VL for PLWH on other regimen combinations (b-f in objective 1) at 6, 12 and 24 months after initiation of the regimen

4. Monitor for resistance and next treatment response among individuals who discontinued CAB+RPV LA, where viral load data are available and resistance testing has been done as part of routine clinical practice
   - Describe the ARV regimen individuals are switched to after discontinuation of CAB+RPV LA containing regimens
   - Monitor for resistance (where this has been done as part of routine clinical practise) during the 48 months following the switch
   - Describe virologic outcomes at 12, 24, 36 and 48 months after discontinuation of CAB+RPV LA containing regimens

5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen
   - Assess off-label use as described in objective 1

- Estimate proportion of treatment naive or individuals not suppressed initiating regimen
- Assess non-adherence to the dosing schedule as described in objective 2
- Assess the frequency of discontinuation due to incorrect route of Administration

Study short name: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance

Purpose of the study: The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen.

The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regime without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class will be eligible for inclusion.

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

Study short name: A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen.

Purpose of the study: Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART therapy, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of patients receiving CAB with or without known pre-existing hepatic disease. Healthcare professional should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

ViiV Healthcare proposes a five-year post authorization safety study (PASS) to be conducted in a real-world context. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events following initiation of CAB based ARV regimen.

This safety study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

Following the initiation of any ARV regimen containing CAB LA among HIV infected patients, the study will aim to:

1. characterise the rates and risks of hepatotoxicity by:

- estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
- estimating the incidence of cases of combined ALT and total bilirubin elevations and risk factors for elevations

2. Estimate the number of patients discontinuing CAB based ARV regimen due to any reason and specifically discontinuations due to liver related adverse events

Study short name: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Purpose of the study: Data from the EPPICC study will assess maternal outcomes (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. The exposure to CAB relative to all gestation period including conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Study short name: Antiretroviral Pregnancy Registry (APR)

Purpose of the study: The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a ViiV Healthcare-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. Exposure to CAB relative to all gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Summary of risk management plan for Vocabria 400 mg prolonged- release suspension for injection (2 ml) (cabotegravir)

This is a summary of the risk management plan (RMP) for Vocabria 400 mg prolonged-release suspension for injection (2 mL). The RMP details important risks of Vocabria 400 mg prolonged-release suspension for injection (2 mL), how these risks can be minimised, and how more information will be obtained about Vocabria 400 mg prolonged-release suspension for injection (2 mL)'s risks and uncertainties (missing information).

Vocabria 400 mg prolonged-release suspension for injection (2 mL)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vocabria 400 mg prolonged-release suspension for injection (2 mL) should be used.

This summary of the RMP for Vocabria 400 mg prolonged-release suspension for injection (2 mL) 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 Vocabria 400 mg prolonged-release suspension for injection (2 mL)'s RMP.

I. The medicine and what it is used for

Vocabria 400 mg prolonged-release suspension for injection (2 mL) is authorised, in combination with rilpivirine 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 NNRTI and INI class (see SmPC for the full indication). It contains cabotegravir as the active substance and it is given by intramuscular injection.

Further information about the evaluation of Vocabria 400 mg prolonged-release suspension for injection (2 mL)'s benefits can be found in Vocabria 400 mg prolonged-release suspension for injection (2 mL)'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/rmp-summary/vocabria-epar-risk-management-plan_en.pdf

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

Important risks of Vocabria 400 mg prolonged-release suspension for injection (2 mL), together with measures to minimise such risks and the proposed studies for learning more about Vocabria 400 mg prolonged-release suspension for injection (2 mL)'s risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the

package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Vocabria 400 mg prolonged-release suspension for injection (2 mL) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vocabria 400 mg prolonged-release suspension for injection (2 mL) are risks that need special risk management activities to further investigate or minimise 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 Vocabria 400 mg prolonged-release suspension for injection (2 mL). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Hepatotoxicity
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in Pregnancy

II.B Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical trials have shown that transient elevations of liver enzymes (transaminitis) can potentially occur with a CAB-containing regimen for a variety of reasons; these events are uncommon. Clinical study data from the development programme with CAB provide the evidence for this risk.
Risk factors and risk groups	None identified, as reports have been received involving a limited number of subjects receiving cabotegravir in clinical studies, with or without known pre-existing hepatic disease.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.4, 4.8 PL section 2 & 4 Recommendation for liver chemistry monitoring are included in SmPC section 4.4 This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: **Study short name:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen *See section II.C of this summary for an overview of the post- authorisation development plan.*

Important potential risk: Medication errors including treatment non-compliance	
Evidence for linking the risk to the medicine	In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on subjects. There is potential for detection of some, but not all administration or dosing errors from the clinical studies and would likewise be the same in clinical practice as it is difficult to readily determine if an incorrect injectable dose has been administered. Overall, the potential risk to subjects due to medication errors is considered to be low, as the efficacy of the CAB+RPV regimen has not been affected in most cases observed in the clinical studies to date. Human factor studies were conducted using commercially representative medicinal product kits including representative drug product vials, to-be-marketed delivery devices and packaging, and to-be-marketed labelling including instructions for use for the initiation and continuation doses of the combination drug regimen (CAB+RPV) under simulated use conditions with the objective to provide evidence that the user requirements have been adequately met. The conclusions from the human factor studies were used to create and refine the instructions for use. The risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen is theoretical and could not be assessed in clinical trials.
Risk factors and risk groups	The CAB+RPV regimen will initially be novel to Healthcare Professionals. The treatment has either two or three stages for dosing; if an optional oral lead-in dosing is used, or direct initiation of injection dose(s), followed by different continuation injection doses corresponding to the Q4W and Q8W regimens, intramuscular initiation dose, and intramuscular continuation dose, with both CAB and RPV being administered as separate injections. There is a risk of administering an incomplete regimen, potentially resulting in sub- optimal therapeutic levels. Inadvertent partial intravenous administration resulting in a higher than expected peak exposure initially could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases, also resulting in sub-optimal therapeutic levels. Treatment with CAB+RPV LA should not be initiated in patients who are not suitably suppressed, or those who may not be adherent to the regimen as this could potentially result in sub-optimal therapeutic levels.

Important potential risk: Medication errors including treatment non-compliance	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2, 4.4 PL section 2 & 3 Administered by Healthcare Professionals. Different packaging colours and logo for each phase of treatment. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **Study short name:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA *See section II.C of this summary for an overview of the post- authorisation development plan.*

Missing information: Use in Pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6. PL section 2 This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV. **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **Study short name:** Antiretroviral Pregnancy Registry (APR) **Study short name:** European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) *See section II.C of this summary for an overview of the post- authorisation development plan.*

II.C Post-authorisation development plan

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

Study short name: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Purpose of the study: ViiV Healthcare proposes a five-year DUS to be conducted in a real-world context. This prospective observational cohort study will aim to better understand the patient population receiving CAB LA and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 48 months after discontinuation. During this 48-month follow up period, the study will collect data on the ARV regimen in the individuals who switches after CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available.

The proposed study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

The study will evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of CAB LA and/or RPV LA containing injection regimens according to the SmPC recommendations by addressing the specific study objectives as outlined below. Following the initiation of any ARV regimen containing CAB LA and/or RPV LA among HIV infected patients, the study will aim to assess usage patterns, durability, discontinuation, and virological outcomes among persons first exposure to CAB LA and /or RPV LA containing regimens. The specific aims are to:

1. Describe CAB LA and/or RPV LA containing regimens usage patterns
    - Descriptive analysis of study population by baseline demographic and clinical characteristics
    - Monitor for use of oral lead-in
    - Comparison of treatment groups*
        a. CAB+RPV LA regimen only
        b. CAB LA monotherapy
        c. CAB LA use in combination with ARVs other than RPV LA
        d. RPV LA monotherapy
        e. RPV LA use in combination with ARVs other than CAB LA
        f. CAB+RPV LA +other ARVs
        g. Combined group b-f

2. Assess adherence, durability and discontinuation for persons starting CAB+RPV LA regimen ;
   - Proportion of individuals discontinuing the regimens of interest will be assessed.
   - Reasons for discontinuation will be assessed.
   - Non-adherence to dosing schedule will be assessed by
     a. Estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB LA and/or RPV LA containing regimens and mean and median number of injections missed during a 12-month period
     b. Estimating the number of individuals who received the injections seven or more days later than their scheduled injection visit and median duration of delayed injections
     c. Estimating the number of individuals who missed one or more consecutive injections without taking daily oral bridging therapy or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe patient characteristics for the individuals that are nonadherent.
   - Number of individuals with incorrect route of administration will be described.

3. Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who initiate CAB+RPV LA regimen
   a. Estimate the proportion of individuals with virologic failure, during the first 6 months after initiation of CAB+RPV LA
   b. Estimate the proportion of patients with virologic failure, 6, 12 and 24 months after initiation of CAB+RPV LA
   c. Stratified analyses for 3a and 3b will be conducted for VL at regimen initiation (<50 copies/mL and ≥50 copies/mL).
   d. Assessment of VL for PLWH on other regimen combinations (b-f in objective 1) at 6, 12 and 24 months after initiation of the regimen

4. Monitor for resistance and next treatment response among individuals who switched off CAB+ RPVLA and/or RPV LA where viral load data are available and resistance testing has been done as part of routine clinical practice
   - Describe the ARV regimen individuals are switched to after discontinuation of CAB+RPV LA containing regimens

   Monitor for resistance (where this has been done as part of routine clinical practise) during the 48 months following the switch
   - Describe virologic outcomes at 12, 24, 36 and 48 months after discontinuation of CAB LA and/or RPV LA containing regimens

5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen
   - Assess off-label use as described in objective 1
   - Estimate proportion of treatment naive or individuals not suppressed initiating regimen
   - Assess non-adherence to the dosing schedule as described in objective 2
   - Assess the frequency of discontinuation due to incorrect route of administration

Study short name: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance

Purpose of the study: The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen.

The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults 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 will be eligible for inclusion.

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

Study short name: A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen.

Purpose of the study: Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART therapy, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of patients receiving CAB with or without known pre-existing hepatic disease. Healthcare professional should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

ViiV Healthcare proposes a five-year post authorization safety study (PASS) to be conducted in a real-world context. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events following initiation of CAB based ARV regimen.

This safety study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

Following the initiation of any ARV regimen containing CAB LA among HIV infected patients, the study will aim to:

1. characterise the rates and risks of hepatotoxicity by:
    - estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
    - estimating the incidence of cases of combined ALT and total bilirubin elevations and risk factors for elevations
2. Estimate the number of patients discontinuing CAB based ARV regimen due to any reason and specifically discontinuations due to liver related adverse events

Study short name: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Purpose of the study: Data from the EPPICC study will assess maternal outcomes (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. The exposure to CAB relative to all gestation period including conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Study short name: Antiretroviral Pregnancy Registry (APR)

Purpose of Study: The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a ViiV Healthcare-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. Exposure to CAB relative to all gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Summary of risk management plan for Vocabria 600 mg prolonged- release suspension for injection (3 ml) (cabotegravir)

This is a summary of the risk management plan (RMP) for Vocabria 600 mg prolonged-release suspension for injection (3 mL). The RMP details important risks of Vocabria 600 mg prolonged-release suspension for injection (3 mL), how these risks can be minimised, and how more information will be obtained about Vocabria 600 mg prolonged-release suspension for injection (3 mL)'s risks and uncertainties (missing information).

Vocabria 600 mg prolonged-release suspension for injection (3 mL)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vocabria 600 mg prolonged-release suspension for injection (3 mL) should be used.

This summary of the RMP for Vocabria 600 mg prolonged-release suspension for injection (3 mL) 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 Vocabria 600 mg prolonged-release suspension for injection (3 mL)'s RMP.

I. The medicine and what it is used for

Vocabria 600 mg prolonged-release suspension for injection (3 mL) is authorised, in combination with rilpivirine 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 NNRTI and INI class (see SmPC for the full indication). It contains cabotegravir as the active substance and it is given by intramuscular injection.

Further information about the evaluation of Vocabria 600 mg prolonged-release suspension for injection (3 mL)'s benefits can be found in Vocabria 600 mg prolonged-release suspension for injection (3 mL)'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/rmp-summary/vocabria-epar-risk-management-plan_en.pdf

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

Important risks of Vocabria 600 mg prolonged-release suspension for injection (3 mL), together with measures to minimise such risks and the proposed studies for learning more about Vocabria 600 mg prolonged-release suspension for injection (3 mL)'s risks, are outlined below.

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Vocabria 600 mg prolonged-release suspension for injection (3 mL) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vocabria 600 mg prolonged-release suspension for injection (3 mL) are risks that need special risk management activities to further investigate or minimise 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 Vocabria 600 mg prolonged-release suspension for injection (3 mL). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Hepatotoxicity
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in Pregnancy

II.B Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical trials have shown that transient elevations of liver enzymes (transaminitis) can potentially occur with a CAB-containing regimen for a variety of reasons; these events are uncommon. Clinical study data from the development programme with CAB provide the evidence for this risk.
Risk factors and risk groups	None identified, as reports have been received involving a limited number of subjects receiving cabotegravir in clinical studies, with or without known pre-existing hepatic disease.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.4, 4.8 PL section 2 & 4 Recommendation for liver chemistry monitoring are included in SmPC section 4.4 This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: **Study short name:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen *See section II.C of this summary for an overview of the post- authorisation development plan.*

Important potential risk: Medication errors including treatment non-compliance	
Evidence for linking the risk to the medicine	In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on subjects. There is potential for detection of some, but not all administration or dosing errors from the clinical studies and would likewise be the same in clinical practice as it is difficult to readily determine if an incorrect injectable dose has been administered. Overall, the potential risk to subjects due to medication errors is considered to be low, as the efficacy of the CAB+RPV regimen has not been affected in most cases observed in the clinical studies to date. Human factor studies were conducted using commercially representative medicinal product kits including representative drug product vials, to-be-marketed delivery devices and packaging, and to-be-marketed labelling including instructions for use for the initiation and continuation doses of the combination drug regimen (CAB+RPV) under simulated use conditions with the objective to provide evidence that the user requirements have been adequately met. The conclusions from the human factor studies were used to create and refine the instructions for use. The risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen is theoretical and could not be assessed in clinical trials.
Risk factors and risk groups	The CAB+RPV regimen will initially be novel to Healthcare Professionals. The treatment has either two or three stages for dosing; if an optional oral lead-in dosing is used, or direct initiation of injection dose(s), followed by different continuation injection doses corresponding to the Q4W and Q8W regimens, intramuscular initiation dose, and intramuscular continuation dose, with both CAB and RPV being administered as separate injections. There is a risk of administering an incomplete regimen, potentially resulting in sub- optimal therapeutic levels. Inadvertent partial intravenous administration resulting in a higher than expected peak exposure initially could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases, also resulting in sub-optimal therapeutic levels. Treatment with CAB+RPV LA should not be initiated in patients who are not suitably suppressed, or those who may not be adherent to the regimen as this could potentially result in sub-optimal therapeutic levels.

Important potential risk: Medication errors including treatment non-compliance	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2, 4.4 PL section 2 & 3 Administered by Healthcare Professionals. Different packaging colours and logo for each phase of treatment. **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	***Additional pharmacovigilance activities:*** **Study short name:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA *See section II.C of this summary for an overview of the post- authorisation development plan.*

Missing information: Use in Pregnancy	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC section 4.6. PL section 2 This is a prescription only medicine. Prescribed by physicians experienced in the treatment of HIV. **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **Study short name:** Antiretroviral Pregnancy Registry (APR) **Study short name:** European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) *See section II.C of this summary for an overview of the post- authorisation development plan.*

II.C Post-authorisation development plan

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

Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Purpose of the study: ViiV Healthcare proposes a five-year DUS to be conducted in a real-world context. This prospective observational cohort study will aim to better understand the patient population receiving CAB LA and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 48 months after discontinuation. During this 48-month follow up period, the study will collect data on the ARV regimen in individuals who switch after CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available

The proposed study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

The study will evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of CAB LA and/or RPV LA containing injection regimens according to the SmPC recommendations by addressing the specific study objectives as outlined below. Following the initiation of any ARV regimen containing CAB LA and/or RPV LA among HIV infected patients, the study will aim to assess usage patterns, durability, discontinuation, and virological outcomes among persons first exposure to CAB LA and /or RPV LA containing regimens. The specific aims are to:

1. Describe CAB LA and/or RPV LA containing regimens usage patterns
    - Descriptive analysis of study population by baseline demographic and clinical characteristics
    - Monitor for use of oral lead-in
    - Comparison of treatment groups*
        a. CAB+RPV LA regimen only
        b. CAB LA monotherapy
        c. CAB LA use in combination with ARVs other than RPV LA
        d. RPV LA monotherapy
        e. RPV LA use in combination with ARVs other than CAB LA
        f. CAB+RPV LA + other ARVs
        g. Combined group b-f

2. Assess adherence, durability and discontinuation for persons starting one of the regimens a-e above;

   - Proportion of individuals discontinuing the regimens of interest will be assessed.
   - Reasons for discontinuation will be assessed.
   - Non-adherence to dosing schedule will be assessed by

     a. Estimating the number of individuals that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB LA and/or RPV LA containing regimens and mean and median number of injections missed during a 12-month period

     b. Estimating the number of individuals who received the injections seven or more days later than their scheduled injection visit and average duration of delayed injections

     c. Estimating the number of individuals who missed one or more consecutive injections without taking daily oral bridging therapy or those who received the injections seven or more days later than their scheduled injection visit (Combined group a OR b) and describe patient characteristics for the individuals that are nonadherent.

   - Number of individuals with incorrect route of administration will be described.

3. Assess the clinical effectiveness (i.e. proportion of individuals experiencing virologic failure) among HIV patients who initiate CAB+RPV LA regimen

   a. Estimate the proportion of individuals with virologic failure, during the first 6 months after initiation of CAB+RPV LA

   b. Estimate the proportion of patients with virologic failure, 6, 12 and 24 months after initiation of CAB+RPV LA

   c. Stratified analyses for 3a and 3b will be conducted for VL at regimen initiation (<50 copies/mL and ≥50 copies/mL).

   d. Assessment of VL for PLWH on other regimen combinations (b-f in objective 1) at 6, 12 and 24 months after initiation of the regimen

4. Monitor for resistance and next treatment response among individuals discontinued CAB + RPV LA where viral load data are available and resistance testing has been done as part of routine clinical practice

   - Describe the ARV regimen individuals are switched to after discontinuation of CAB + RPV LA containing regimens
   - Monitor for resistance (where this has been done as part of routine clinical practise) during the 48 months following the switch
   - Describe virologic outcomes at 24 months after discontinuation of CAB + RPV LA containing regimens

5. Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label

   - Assess off-label use as described in objective 1

- Estimate proportion of treatment naive or individuals not suppressed initiating regimen use of CAB+RPV LA regimen
- Assess non-adherence to the dosing schedule as described in objective 2
- Assess the frequency of discontinuation due to incorrect route of administration

Study short name: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance

Purpose of the study: The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen.

The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults 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 will be eligible for inclusion.

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

Study short name: A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen.

Purpose of study: Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART therapy, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of patients receiving CAB with or without known pre-existing hepatic disease. Healthcare professional should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

The MAH proposes a five-year post authorization safety study (PASS) to be conducted in a real-world context. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events following initiation of CAB based ARV regimen.

This safety study will be conducted through 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. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

Following the initiation of any ARV regimen containing CAB LA among HIV infected patients, the study will aim to:

1. characterise the rates and risks of hepatotoxicity by:
    - estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors

for elevations

- estimating the incidence of cases of combined ALT and total bilirubin elevations and risk factors for elevations

2. Estimate the number of patients discontinuing CAB based ARV regimen due to any reason and specifically discontinuations due to liver related adverse events

Study short name: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Purpose of study: Data from the EPPICC study will assess maternal outcomes (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. The exposure to CAB relative to all gestation period including conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

Study short name: Antiretroviral Pregnancy Registry (APR)

Purpose of study: The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a MAH-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. Exposure to CAB relative to all gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

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

Not applicable.