Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Cabotegravir Pre-Exposure Prophylaxis (PrEP) (Oral tablets and 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	1.2
Data lock point for this RMP	31 December 2023
Date of final sign off	5 November 2024

Rationale for submitting an updated RMP

This RMP update provides supplemental data from the HPTN 083-01 and 084-01 adolescent studies to support the ongoing use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection. Other revisions include updates to the clinical trial exposure and inclusion of the approved protocol for the additional Pharmacovigilance,activities, the Antiretroviral Pregnancy Registry (APR) and EU cohort study.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in the present EU-RMP
PART II, SAFETY SPECIFICATION	SI Epidemiology of the indication(s) and the target population	Updated epidemiology section
PART II, SIII CLINICAL TRIAL EXPOSURE	SIII Clinical trial exposure	Inclusion of updated clinical trial exposure data, from adolescent 083-01 and 084-01 studies
PART II, SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS	SIV.2 Limitations to detect adverse reactions in clinical trial development programmes	Clinical trial exposure related information updated
	SIV.3 Limitation in respect to populations typically under represented in clinical trial development programmes	Inclusion of data from adolescent 083-01, 084-01 and MOCHA studies
PART II, SV POST AUTHORISATION EXPERIENCE	SV1.1 Method used to calculate exposure	Inclusion of updated post marketing exposure
	SV1.2 Exposure	
PART II SVII- DETAILS OF IMPORTANT IDENTIFIED RISKS, AND IMPORTANT POTENTIAL RISKS AND MISSING INFORMATION	SVII 3.1 Presentation of important Identified and Potential Risks	Hepatotoxicity risk updated with adolescent 083-01 and 084-01 studies

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES	III.2 Additional Pharmacovigilance activities	Updates to study numbers
	III.3 Summary Table of additional Pharmacovigilance activities	Study status and milestone information revised
PART VII ANNEXES	Annex 3	Inclusion of approved APR and EU cohort study protocol
	Annex 7	Updated information in references linked to Epidemiology section updates

Other RMP versions under evaluation

Not applicable

Details of the currently approved RMP

Version number	**Approved with procedure**	**Date of approval (opinion date)**
1.0	EMEA/H/C/005756/0000	20 July 2023

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

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
APR	Antiretroviral Pregnancy registry
ART	Antiretroviral therapy
aRMM	Additional Risk Minimization Measure
BRCP	breast cancer resistance protein
CAB	Cabotegravir
CrCl	Creatinine clearance
CYP	Cytochrome
EEA	European Economic Area
EU	European Union
HBV	Hepatitis B virus
HbsAg)	Hepatitis B virus (HBV) surface antigen
HCP	Healthcare professional
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IFU	Instructions for use
IM	Intramuscular
LA	Long acting
LD	Lactation day
OATP	Organic anion transporting polypeptides
OLI	Oral lead-in
OAT	Organic anion transporting
MHRD	Maximum human recommended dose
MSM	Men who have sex with men
PK	Pharmacokinetics
PL	Patient Leaflet
PrEP	Pre Exposure Prophylaxis
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMM	Risk Minimization Measure
RMP	Risk Management Plan
SmPC	Summary of product characteristics
STI	Sexually transmitted infections
TDF	Tenofovir disoproxil fumarate
UGT	Uridine glucuronosyl transferase
UDT	Uridine diphosphate

Trademark Information

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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 Authorization Holder/ Applicant	ViiV Healthcare
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Apretude 30 mg Film-coated tablets, Apretude 600 mg prolonged release suspension for injection (3 mL)
Marketing authorization 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 about its composition: None
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).

Indication(s) in the EEA	Current: Film-coated Tablets: Cabotegravir tablets are indicated in combination with safer sex practices for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adolescents and adults weighing at least 35 kg (see Dosage and Administration and Warnings and Precautions). Cabotegravir tablets may be used as: • oral lead in to assess tolerability of cabotegravir prior to administration of cabotegravir injection. • oral PrEP in individuals who will miss planned dosing with cabotegravir injection. Suspension for Injection: Cabotegravir injections are indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in high-risk adolescents and adults weighing at least 35 kg
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: ***Oral lead-in* (Film-coated Tablets)** When used for oral lead-in, cabotegravir oral tablets are recommended for approximately one month (at least 28 days) prior to the initiation of cabotegravir injection to assess tolerability to cabotegravir. ***Suspension for Injection*** Initiation Injections The recommended initial cabotegravir injection dose in adults is a single 3 mL (600 mg) intramuscular injection. If oral lead-in has been used, the first injection should be planned for the last day of oral lead-in or within 3 days thereafter.

	One month later, a second 3 mL (600 mg) intramuscular injection should be administered. Individuals may be given the second 3 mL (600 mg) initiation injection up to 7 days before or after the scheduled dosing date. Continuation Injections After the second initiation injection, the recommended continuation injection dose in adults is a single 3 mL (600 mg) intramuscular injection administered every 2 months. Individuals may be given injections up to 7 days before or after the scheduled dosing date.
	Proposed: Not Applicable
Pharmaceutical form(s) and strengths	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>600 mg (3 mL) Vial</u> Each vial contains 600 mg cabotegravir in 3 mL. Prolonged-release suspension for injection. White to light pink suspension.
	Proposed (if applicable): 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

Recent data suggest a decline in HIV incidence worldwide. Approximately 1.3 million (95% confidence interval: 1.0 -1.7 million) adults and children were newly infected with HIV in 2022, down from approximately 2.2 million (2.0-2.5 million) new HIV infections in 2010 (UNAIDS, 2023). Steepest declines in incident HIV infections have been among children (0-14 years) and young people (15-24 years); in 2022, an estimated 210,000 (130,000 – 300,000) girls and young women aged 15-24 and an estimated 140,000 (67,000 – 210,000) boys and young men aged 15-24 acquired HIV, representing a 50% and 44% reduction since 2010, respectively (UNAIDS, 2023).

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). 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 Czech Republic (1:1)

PREVALENCE

An estimated 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, 2024a). 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. The vast majority of these people lived in either Russia (1 million PWH) or Ukraine (244,877 PWH) (ECDC, 2024a). An estimated 73,969 PWH live in Central Europe; countries of interest in this subregion include Slovakia (19,415 PWH), Poland (18,923 PWH), and Romania (18,221 PWH) (ECDC, 2024a). ECDC estimates that 828,519 people are living with HIV in Western Europe (ECDC, 2024a). 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 (45,320 PWH) (ECDC, 2024a).

The median HIV prevalence is much higher in key populations in this region than among the general population, including men who have sex with other men, people who inject drugs, people in prisons, and sex workers. A recent review found that the HIV prevalence among these groups in Europe varied by country (Stengaard, 2021). The review found that HIV prevalence among men who have sex with other men ranged from 2.4% (1.1%-5.2%) in Sweden to 29.0% (26.3%-32.0%) in the Netherlands; among people who inject drugs ranged from 0% (0% - 0.2%) in Hungary to 59.5% in Estonia (56.3% - 62.8%); among prisoners ranged from 0.15% (0.05%-0.35%) in Croatia to 15.6% (14.5%-17.1%) in Estonia; among sex workers ranged from 1.1% (0.01%-2.4%) in United Kingdom to 8.5% (6.0%-12.1%) in Portugal (Stengaard, 2021).

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

Any individual can acquire HIV, regardless of sexual orientation, race, ethnicity, gender or age. However, certain groups are at higher risk for HIV acquisition compared to the general population (WHO, 2020). For instance, globally, the risk of HIV acquisition is 28 times higher among men who have sex with men (MSM) compared to heterosexual men; 35 times higher among people who inject drugs compared to people who do not inject drugs; 14 times higher among transgender women than the general population; and 13 times higher among sex workers compared to adult women (UNAIDS, 2022).

In 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). 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 to mother-to-child transmission.

SI.1.2 The main existing treatment options

Comprehensive clinical guidelines have been developed to assist clinicians in identifying people who would benefit from PrEP. Table 2 lists the only currently approved biomedical prophylactic options for HIV prevention in Europe.

Table 2 Currently approved prophylactic drugs used in the prevention of HIV acquisition in the EU

Brand Name	Generic Name
Truvada	Emtricitabine/tenofovir disoproxil fumarate
Descovy	Emtricitabine/tenofovir alafenamide
Apretude	Cabotegravir

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

In the absence of biomedical interventions, the probability of acquiring HIV is dependent on the type of exposure (WHO, 2020). The probabilities of HIV acquisition by the common routes of transmission are as follow:

- Receptive anal intercourse – 1.38%
- Insertive anal intercourse – 0.11%
- Male-to-female vaginal sex – 0.08%
- Female-to-male vaginal sex – 0.04%

These probabilities fluctuate depending on other risk factors, including history of sexually transmitted infections (STIs), viral load of sexual partner, partner's HIV treatment status, and condom use. Prevalence of STIs is particularly high among people eligible and/or on PrEP. Studies have demonstrated high STI prevalence among key populations, such as men who have sex with men (MSM) (Jansen, 2020).

The number of people dying from AIDS-related causes began to decline worldwide in the mid-2000s because of scaled-up antiretroviral (ART) therapy and the steady decline in HIV incidence since the peak in 1997. In 2022, an estimated 630,000 (480,000 – 880,000) people died from AIDS-related causes worldwide, representing a 51% decline in AIDS-related mortality from 2010, when 1.3 million (970,000 – 1.8 million) AIDS-related deaths occurred (UNAIDS, 2022).

During 2022, 767 people were reported to have died because of AIDS- or non-AIDS-related causes in 26 EU/EEA countries (ECDC, 2022). This represented a 44.1% decrease compared with the 1,373 deaths reported for the same countries in 2013. However, because of delays in reporting and underreporting numbers across countries, these numbers should not be interpreted as representative of the true AIDS mortality burden in the Europe. According to a country survey from 2006, only about one third of European countries were able to match their HIV/AIDS registries with their national mortality or vital statistics registries (ECDC, 2023).

SI.1.4 Important co-morbidities

Only specific fluids, such as blood, semen, vaginal secretions, and breast milk, from an HIV-infected person can transmit HIV. These specific fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the blood-stream (from a needle or syringe) for transmission to possibly occur (WHO, 2020).

Primary risk factors for HIV transmission include: unprotected vaginal, anal and oral sex; having another STI, such as chlamydia, gonorrhea, syphilis, or bacterial vaginosis; sharing contaminated needles and syringes when injecting drugs; receiving unsafe injections, blood transfusion, and tissue transplantation (WHO, 2020).

Incidence and prevalence of STIs in the population vulnerable to acquisition of HIV vary widely across Europe, with differences in national surveillance systems and considerable overall underreporting. Chlamydia is the most frequently reported STI in Europe and the number of reported cases is continuously increasing, with currently more than 200,000 new cases reported each year. Many chlamydia infections do not produce symptoms, and the growing number of reported cases is likely to be the result of increased awareness about the disease and intensified testing (ECDC, 2024a). The highest rates of chlamydia are reported among young people aged 20–24 years (accounting for 40% of all reports) (ECDC, 2024b). Gonorrhoea and syphilis are less common but still on the rise. A total of 70,881 cases of gonorrhoea were reported by 28 European countries in 2022 (ECDC, 2024c). The overall crude notification rate was 17.9 cases per 100 000 population. Rates of reported gonorrhoea infection vary considerably across the Europe with higher rates reported in northern Europe. MSM accounted for more than half (60%) of the reported cases in 2022. The overall 2022 notification rate of gonnorhoea in the region increased by 48% compared to 2021 and 59% compared to in 2018 (ECDC, 2024c). The number of syphilis cases has been consistently increased by 70% across Europe since 2020, mostly affected MSM living in urban cases. Overall, more than 35,391 confirmed syphilis cases were reported from 29 European countries in 2022, representing a 34% increase in the crude notification year compared to the year prior and a 41% increase compared to 2018. (ECDC, 2024d).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

Table 3 Key Safety findings (from non-clinical studies)

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 1,000 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	In excess of 6900 participants have received CAB across the treatment and PrEP trials, of which approximately 4000 were on CAB PrEP. Experience to date has not confirmed a risk of bone marrow toxicity in humans associated with CAB use; at recommended clinical doses; therefore, this effect is not expected to impact target population.
Hepatology findings: No indications of hepatotoxic potential of CAB were observed in nonclinical studies.	In excess of 6900 participants have received CAB across the treatment and PrEP trials, of which approximately 4000 were on CAB PrEP. Experience to date has highlighted a small number of suspected DILI cases observed in Phase II/III studies at recommended clinical doses. Further described in SVII.3.1.
Cardiovascular (CV) effects (including potential for QT interval prolongation) In monkeys: a single dose of oral CAB at 1,000 mg/kg/day 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 2h 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 ECG waveform or interval changes.	In excess of 6900 participants have received CAB across the treatment and PrEP trials, of which approximately 4000 were on CAB PrEP. Experience to date has not confirmed a cardiovascular risk in humans associated with CAB use; therefore, this finding is not expected to impact target population.

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.	Pregnancy experience is available from the HPTN084 study up to the data cut off of 05 November 2020. There were 49 confirmed PrEP pregnancies (defined as a first positive pregnancy test followed by a positive confirmatory test result at least 4 weeks later or confirmation by another method (eg, ultrasound, full or pre-term birth, or investigator assessment consistent with active pregnancy). Of which 29 were confirmed CAB PrEP pregnancies and no specific safety findings were highlighted. See Section SVII.3.2 for further information. Similarly experience from 18 pregnancies in CAB treatment clinical trials has not indicated a specific safety concern, albeit with limited numbers. CAB should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (See Section SVII.3.2).
Developmental toxicity	
Effects of exposure in late stage pregnancy A PPN study conducted in rats demonstrated 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 mg/kg/day. In a follow up cross-fostering study, vehicle control or CAB at 1000 mg/kg/day ((>30 times the exposure in humans at the MRHD) was given orally by gavage to mated female rats on Gestation Day (GD) 6 through Lactation Day (LD) LD 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% vs 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. A lower dose of 5 mg/kg/day (approximately 10 times the exposure in humans at the MRHD) cabotegravir was not associated with delayed parturition or neonatal mortality.	Given the exposure ratio, the clinical significance in humans of the non-clinical pre- and postnatal findings in rats is unknown. At the time of the initial submission there were 29 confirmed CAB PrEP pregnancies. CAB should be used during pregnancy and by women planning pregnancy only if the expected benefit justifies the potential risk to the foetus.

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 partition in rats receiving 1000 mg/kg/day led to increased foetal mortality (stillbirths) and neonatal deaths in a subset of rats immediately after birth.	
Juvenile toxicity	
No indications of juvenile toxicity of CAB were observed in non-clinical studies.	The nonclinical data for CAB do not indicate a safety concern for humans.
Genotoxicity	
No indications of a genotoxic potential of CAB were observed in genotoxicity tests (in vitro and in vivo).	The nonclinical data for CAB do not indicate a safety concern for humans.
Carcinogenicity	
Carcinogenicity studies were conducted in CD1 mice and Sprague Drawley 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 were observed in tests for CAB.	The nonclinical data for CAB do not indicate a safety concern for humans.
General safety pharmacology:	
There were no key findings from safety pharmacology studies for CAB.	Since there were no findings from safety pharmacology studies there is no indication of an unacceptable risk for administration of CAB to patients. Data from clinical trials supports the findings from safety pharmacology studies
Mechanisms for drug interactions	
In vitro, no clinical drug interaction risk was identified for co-administered substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 3A4, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17, P-gp, BCRP, BSEP, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE 2-K, MRP2, or MRP4 at a clinical dose of 30 mg CAB. 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	CAB is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters. CAB is primarily metabolised by UGT1A1 with some contribution from UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease CAB plasma concentrations leading

microsomal incubations, [^{14}C]-CAB was metabolized to a single UDPGA-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. CAB chelates with polyvalent cations, resulting in decreased absorption; chelation was demonstrated for CAB in vitro. CAB was shown to be an inhibitor of OAT1 and OAT3 in vitro.	to lack of efficacy and therefore would be contraindicated. The following co-administered drugs for which significant decreases in CAB plasma concentrations may occur due to uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 and/or cytochrome P450 (CYP)3A enzyme induction, which may result in loss of protective efficacy: Rifampicin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine are contraindicated in the SmPC. No dose adjustment is required for CAB PrEP oral tablets when used concomitantly with rifabutin. CAB PrEP LA injections are recommended to be given every month when used concomitantly with rifabutin, as a shorter dosing interval is required. Antacids containing polyvalent cations are to be administered at least 2 hours before or 4 hours after oral CAB 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 (PBPK) modelling, the renal safety data for oral CAB in combination with 2 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

The CAB PrEP clinical development program includes 2 pivotal Phase IIb/III studies, Study 201738 / HPTN 083 (initiated in December 2016, [NCT02720094]) and Study 201739 / HPTN 084 (initiated in November 2017, [NCT03164564]) adult males and females. These studies were conducted by the HIV Prevention Trials Network (HPTN under the sponsorship of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) and in collaboration with ViiV Healthcare. The studies were designed to assess the safety and efficacy of CAB PrEP when compared to the active comparator daily oral TDF/FTC for HIV PrEP in the most key affected populations globally (i.e., MSM and TGW [enrolled in HPTN 083] and cisgender women [enrolled in HPTN 084]).

Two ViiV Healthcare sponsored Phase IIa randomized, placebo-controlled PrEP studies were conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of CAB PrEP: Study 201120 / ÉCLAIR was conducted in HIV-negative, adult men at low risk of acquiring HIV infection and Study 201103 / HPTN 077 was conducted in HIV-negative adult men and women at low risk of acquiring HIV infection. The optimal CAB injection dosing regimen (every 2 months) for the pivotal studies was selected based on these studies.

Adolescents

Studies HPTN 083-01 and HPTN 084-01 are single-arm, open-label, safety, tolerability, and acceptability studies in sexually active, healthy adolescents assigned either male or female sex at birth, respectively. These CAB studies in adolescents were sub-studies to their respective parent protocols for the PrEP indication, in adult males (HPTN 083) and females (HPTN 084), respectively. Cumulatively, 6385 individuals up to 17 September 2023 were exposed to CAB PrEP in Phase II and III and ViiV Healthcare sponsored and supported PrEP clinical trials.

Table 4 Duration of exposure

Cumulative for PrEP indication (person time)		
Duration of exposure to **Oral Cabotegravir**	**Participants (n)**	**Person time (years)**
<4 Weeks	786	44.81
4 Weeks to <6 Weeks	3341	271.50
6 Weeks to <6 Months	84	13.16
6 Months to <1year	4	2.80
1 to <2 years	0	0
2 to <3 years	0	0
3 to <4 years	0	0
4 to <5 years	0	0
>= 5 years	0	0
Total	**4215**	**332.27**

Duration of exposure to Long Acting Cabotegravir	Participants (n)	Person time (years)
<4 Weeks	155	2.543
4 Weeks to <6 Months	536	169.079
6 Months to <1year	982	714.094
1 to <2 years	1792	2551.595
2 to <3 years	461	1106.9879
3 to <4 years	0	0
4 to <5 years	0	0
>= 5 years	0	0
Total	**3926**	**4544.30**

Note: Person time was calculated based on 201120 (ECLAIR) End of Study, 201103 (HPTN-077) End of Study, 201738 (HPTN-083) with data cut-off of May 14, 2020, 201739 (HPTN-084) with data cut-off of November 5, 2020, 213002 (HPTN 083-01) with data cut-off of October 24, 2022 and 213003 (HPTN 084-01) with data cut-off of July 21, 2022.

Note: Person time was calculated up to the point of the participant's last dose administered up to the data cut-off date for ongoing studies. For oral, time on oral calculated for the clinical study report was used. For injections, time from first injections till the last injection administered is used for calculating exposure. Exposure can last for up to a year or more after the last injection.

Duration of exposure for injections does not account for treatment interruptions including pregnancies.

Table 5 Age group and gender at birth

Age group (Oral Cabotegravir)	Participants (n)		Person time (years)	
	M	F	M	F
<18 years	9	550	0.86	5.27
18 to 64 years	2434	1714	190.94	134.97
65-74 years	3	0	0.24	0
>=75	0	0	0	0
Total	2446	1769	192.03	140.24

Age group (Long Acting Cabotegravir)	Participants (n)		Person time (years)	
	M	F	M	F
<18 years	9	53	6.89	27.99
18 to 64 years	2254	1608	2768.80	1740.15
65-74 years	2	0	0.46	0
>=75	0	0	0	0
Total	2265	1661	2776.16	1768.14

Note: Person time was calculated based on 201120 (ECLAIR) End of Study, 201103 (HPTN-077) End of Study, 201738 (HPTN-083) with data cut-off of May 14, 2020, 201739 (HPTN-084) with data cut-off of November 5, 2020, 213002 (HPTN 083-01) with data cut-off of October 24, 2022 and 213003 (HPTN 084-01) with data cut-off of July 21, 2022.

Note: Person time was calculated up to the point of the participant's last dose administered up to the data cut-off date for ongoing studies. For injections, time from first injections till the last injection administered is used for calculating exposure. Exposure can last for up to a year or more after the last injection. Duration of exposure for injections does not account for treatment interruptions including pregnancies.

Table 6 Dose

Dose of exposure (Oral Cabotegravir)	Participants (n)	Person time (years)
30mg once daily oral lead-in	4215	332.27
Total	4215	332.27
	Participants (n)	**Person time (years)**
Dose of exposure (Long Acting Cabotegravir)		
Up to 800 mg IM LA	3926	4544.30
Total	3926	4544.30

Note: Note: Person time was calculated based on 201120 (ECLAIR) End of Study, 201103 (HPTN-077) End of Study, 201738 (HPTN-083) with data cut-off of May 14,2020, and 201739 (HPTN-084) with data cut-off of November 5, 2020, 213002 (HPTN 083-01) with data cut-off of October 24, 2022 and 213003 (HPTN 084-01) with data cut-off of July 21, 2022.

Note: Person time was calculated up to the point of the participant's last dose administered up to the data cut-off date for ongoing studies. For oral, time on oral calculated for the clinical study report was used up to the data cut-off date for ongoing studies. For injections, time from first injections till the last injection administered is used for calculating exposure. Exposure can last for up to a year or more after the last injection. Duration of exposure for injections does not account for treatment interruptions including pregnancies.

Table 7 Ethnic origin

Ethnic origin	Participants (n)	Person time (years)
Oral Cabotegravir		
Black or African American	2335	183.71
White	738	58.64
American Indian or Alaska Native	616	48.19
Arabic	0	0
Asian	427	33.96
Native Hawaiian or Other Pacific Islander	6	0.49
Mixed	78	6.16
Missing	15	1.14
Total	4215	332.27
Long Acting Cabotegravir	**Participants (n)**	**Person time (years)**
Black or African American	2167	2493.04
White	689	832.26
American Indian or Alaska Native	566	551.36

Arabic	0	9
Asian	414	574.85
Native Hawaiian or Other Pacific Islander	6	4.11
Mixed	70	71.90
Missing	14	16.79
Total	3926	4544.30

Note: Note: Person time was calculated based on 201120 (ECLAIR) End of Study, 201103 (HPTN-077) End of Study, 201738 (HPTN-083) with data cut-off of May 14, 2020, 201739 (HPTN-084) with data cut-off of November 5, 2020, 213002 (HPTN 083-01) with data cut-off of October 24, 2022 and 213003 (HPTN 084-01) with data cut-off of July 21, 2022.

Note: Person time was calculated up to the point of the participant's last dose administered up to the data cut-off date for ongoing studies. For oral, time on oral calculated for the clinical study report was used. For injections, time from first injections till the last injection administered is used for calculating exposure. Exposure can last for up to a year or more after

Note: Mixed Race includes race reported as OTHER or MULTIPLE; Missing includes race reported as UNKNOWN.

* Based on US Food & Drug Administration (FDA) style ethnicity presentation.

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

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

Table 8 Exclusion criteria

Criterion for exclusion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Participants with Hepatitis C virus antibody positive at screening	In the CAB PrEP trials participants with HCV could confound and impact on study results.	No	Limited data in HCV infected patients is available from the CAB treatment program [CAB Treatment ISS] No conclusions can be made about the safety of CAB PrEP in hepatitis C co-infected participants. HCV medications are mostly substrates of CYP3A4, BCRP, OATP, and Pgp, and no drug interactions are expected. Therefore, based on this information no specific safety concerns are expected when HCV medications and CAB PrEP are co-administered. Individuals will be managed as per local guidelines.
Women who are pregnant, breast feeding or plan to become pregnant or breastfeed	Pregnant and breast-feeding women are not routinely enrolled into clinical trials to avoid exposing the foetus, or breast-fed infant to the study medication.	Yes	There are limited data from the use of CAB in pregnant women and none available in breastfeeding women. While reproductive toxicity testing has not identified a risk for CAB based on nonclinical findings, at the recommended clinical doses, there have been no adequate and well controlled clinical studies of CAB in pregnant women.

Criterion for exclusion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Participants positive for hepatitis B virus (HBV) surface antigen at screening (+HbsAg)	Hepatitis B surface antigen positivity was an exclusion criterion for Phase 2 and 3 trials	No	No conclusions can be made about the safety of CAB PrEP in hepatitis B co-infected participants. HBV medications are primarily excreted in urine and are substrates of BCRP, Pgp, and OCT, no drug interactions are expected when HBV medications and CAB PrEP are co-administered. Individuals will be managed as per local guidelines.
Alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN) & Total Bilirubin >2.5 times ULN.	To avoid putting the safety of the individual at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study.	No	Clinical and laboratory monitoring should be considered, and CAB should be discontinued if hepatotoxicity is confirmed and individuals managed as clinically indicated.
Any verified Grade 3 laboratory abnormality	To avoid putting the safety of the individual at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition exacerbated during the study	No	Use of CAB PrEP will be guided by established guidance and medical practice. Clinical and laboratory monitoring should be considered, and individuals managed as clinically indicated.

Criterion for exclusion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Participants with severe hepatic impairment (Class C) as determined by Child-Pugh Classification	CAB is primarily hepatically metabolized via uridine diphosphate glycosyltransferase (UGT) 1A1 with a minor UGT1A9 component. Severe hepatic impairment could impact metabolism of CAB	No	There was no change in CAB PK in patients with moderate hepatic impairment in separate single oral dose PK studies, and therefore no expected change in individuals with mild to moderate hepatic impairment. Severe hepatic impairment will be managed through the product SmPC The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of CAB has not been studied and is reflected in the product SmPC.
Participants with estimated creatinine clearance <60 mL/min via Cockcroft-Gault equation	To avoid putting the safety of the participant 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. In participants with moderate renal impairment a significant effect on CAB PK was not seen. Participants with severe renal impairment (creatinine clearance <30 mL/min and not on renal replacement therapy) had minimal impact on total CAB plasma pharmacokinetics. No dosage adjustment is required in individuals with mild to severe renal impairment and not on dialysis.
Malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or	To avoid putting the safety of the individual at risk through participation, and to avoid confounding the	No	Use of CAB PrEP will be guided by medical practice.

Criterion for exclusion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
cervical intraepithelial neoplasia	efficacy and safety analysis if the disease/condition is exacerbated during the study		
Patients with pre-existing physical or mental condition (including substance use disorder)	If, in the judgment of the investigator this could interfere with the participants ability to comply with the dosing schedule and/or protocol evaluations or which could compromise the safety of the participant.	No	Only participants considered likely by the HCP to be able to adhere to the dosing schedule will be started on CAB PrEP.
Coagulopathy (primary or iatrogenic) which would contraindicate IM injection (concomitant anticoagulant or anti-platelet therapy	To avoid putting the safety of the individual at risk through participation,	No	Use of CAB PrEP will be guided by established guidelines for IM injections and medical practice.
Inflammatory skin conditions that compromised the safety of intramuscular (IM) injections	To avoid putting the safety of the individual at risk through participation, and to avoid confounding the efficacy and safety analysis if the disease/condition	No	Use of CAB PrEP will be guided by established guidelines and medical practice.

Criterion for exclusion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	is exacerbated during the study.		

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

Table 9 Limitations to detect adverse reactions in clinical trial development program

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 PrEP had been used in 4151 HIV uninfected participants	The pivotal clinical trials recruited a large number of (4151) participants. No rare events of concern have been detected thus far. Up to 17 September 2023, 6385 participants have been exposed to CAB PrEP
Due to prolonged exposure	There is safety data available for 1792 participants receiving CAB at the recommended dose for 1 to <2 years and approximately 461 participants receiving CAB for 2 to <3 years.	While the exposure of CAB PrEP is limited to 461 participants up to <3 years, there have been no long-term adverse reactions identified to date. The long-term safety of CAB will be monitored through routine pharmacovigilance
Due to cumulative effects	The Marketing Authorisation Application for the CAB submission includes long-term clinical safety data for 1792 participants receiving CAB at the recommended dose for 1 to <2 years	There were no new safety signals identified during CAB PrEP studies that might have been due to cumulative effects. No specific organ toxicity was detected.

	and approximately 461 participants receiving CAB for 2 to <3 years.	
Which have a long latency	The assessment of longer-term toxicities, such as bone disorders and renal tubular dysfunction require a considerably extended follow up period. The Marketing Authorisation Application for the CAB submission includes long-term clinical safety data for 461 participants receiving CAB for 2 to <3 years.	Although information on long-term safety is limited, no long-term adverse effect of CAB is apparent from clinical studies to date and no AEs considered related to CAB 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 program

Table 10 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Pregnant women were excluded from CAB PrEP clinical studies. Participants that became pregnant during CAB PrEP studies (intrauterine) with a confirmed positive pregnancy test conducted at least four weeks later stopped receiving further CAB, CAB LA, or CAB LA placebo. Clinical experience of CAB use during pregnancy is therefore limited.
Breastfeeding women	Breastfeeding women were not included in the PrEP clinical development programme.
Individuals with Hepatitis C virus	Participants who were Hepatitis C virus antibody positive were not enrolled in the Phase II and III trials for CAB PrEP pivotal studies.
Patients with moderate to severe hepatic Impairment, or unstable liver disease.	Participants with moderate to severe hepatic Impairment or patients with unstable liver disease were excluded from the phase III CAB PrEP clinical studies.
Individuals with Hepatitis B infection	Participants who were Hepatitis B virus surface antigen positive were excluded from CAB PrEP clinical studies.

Patients with renal impairment	Participants with severe renal impairment [estimated creatinine clearance (CrCl) ≤60 mL/min (Cockcroft-Gault equation), were excluded from PrEP studies. Renal toxicity management criteria required individuals on the PrEP studies to discontinue or temporarily interrupt treatment.
Patients with cardiovascular impairment	Patients with clinically significant cardiovascular disease, were not included in the CAB PrEP clinical studies.
Subpopulations carrying relevant genetic polymorphisms	Subjects with genetic polymorphisms in general were not excluded from the clinical studies.
Children/Adolescents	Children/Adolescents were not included in the registrational blinded, comparative efficacy studies for CAB PrEP Since the registrational studies, adolescents (below age 18 years of age and body weight ≥35 kg) have been studied in the phase 2b HPTN 083-01 and HPTN 084-01 single-arm, open-label, safety, tolerability, and acceptability studies in sexually active, healthy adolescents assigned either male (HPTN 083-01) or female (HPTN 084-01) sex at birth. Results from HPTN 083-01 and HPTN 084-01 demonstrated an acceptable safety profile for CAB when used as PrEP in adolescents weighing at least 35 kg. Safety data from HPTN 083-01 and HPTN 084-01 PrEP studies in adolescents do not show or indicate any new safety concerns or signals compared with the safety profile of CAB PrEP for adults (based on findings from the adult PrEP studies HPTN 083 and HPTN 084) PrEP and the currently approved product labelling. There was also high overall adherence among participants in HPTN 083-01 and HPTN 084-01. The safety profile in adolescents is further supported by data from the MOCHA (208580) Study, a study conducted in adolescents living with HIV. Based on data from the Week 16 analysis of the MOCHA study in HIV-infected adolescents (aged at least 12 years and weighing ≥35 kg) receiving background combination anti-retroviral therapy, no new safety concerns were identified in adolescents with the addition of oral cabotegravir followed by injectable cabotegravir (n=29) when compared with the safety profile established with cabotegravir in adults.

Elderly	There was no upper age limit for inclusion into CAB PrEP HPTN 083 trial, there was an upper limit of 45 years old for the HPTN 084 trial. There is limited information regarding the use of CAB in the elderly (>50 years old). 24 (1%) of participants were 50 years of age or older at enrolment on the HPTN 083 trial. No difference in safety profile was observed in this population.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorization exposure

Cabotegravir, used as a single agent for PrEP to reduce the risk of sexually acquired HIV-1 infection, received its first approval in the United States (US) on 20 December 2021.

SV.1.1 Method used to calculate exposure

The algorithm used to derive post-marketing exposure data is as follows:

For the IM injection formulation, a standard dose of 1 (200 mg/ml) vial per 2 monthly administration.

Due to the oral cabotegravir tablet being marketed for both HIV-1 treatment and HIV-1 PrEP indications, the exposure of oral cabotegravir PrEP tablets cannot be provided as the sales data is currently combined with the treatment indication.

SV.1.2 Exposure

Cumulative post-marketing exposure to CAB PrEP available up to 31 December 2023 is estimated to be 6564 patient years of exposure.

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 registrational studies HPTN 083 and HPTN 084 were non-serious and Grade 1 or 2 in severity. These adverse drug reactions are included in the SmPC (Section 4.8).

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

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

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

Hepatobiliary disorders: Transaminase increased

Skin and subcutaneous tissue disorders: Rash (includes the Medical dictionary for regulatory activities (MedDRA) preferred 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 tenderness, site nodule, induration, swelling, erythema, pruritus, bruising, warmth, haematoma, abscess, anaesthesia, discolouration), Fatigue, Malaise, Pyrexia (includes the MedDRA preferred terms: body temperature increased, feeling hot).

Investigations: Weight increased, Blood bilirubin increased

In addition, the following safety concerns specific to CAB PrEP are not included as safety concerns in the RMP as outlined below:

Drug interactions with strong UGT1A1 inducers:

Co-administration significantly decreases CAB plasma concentrations, increasing the potential for loss of protective effect: Rifampin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine. 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. 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].

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:

As a result of routine pharmacovigilance activities and following a thorough assessment of the totality of data for CAB, from all sources, for both HIV treatment and for PrEP, including post marketing experience it is considered that there is sufficient evidence to support a causal association for CAB for PrEP and hypersensitivity reactions, including angioedema and urticaria, suicide attempt and suicidal ideation (particularly in patients with a pre-existing history of depression or psychiatric illness). These events were identified from post marketing experience and are included in Section 4.8 of the SmPC. Hypersensitivity and suicide related events are expected to be occurring with a low frequency and manageable in view of the available data and will continue to be monitored through routine pharmacovigilance and any updated information will be managed through the product labelling.

Suicidal behaviours

Suicidal behaviours have been seen with other INSTIs.

The frequency of suicidal behaviour events were low (≤1%) and was generally similar across the CAB and comparator group in both HPTN 083 and HPTN 084 studies.

In HPTN 083, 2 participants in the CAB group experienced SAEs of suicide attempt which were considered by the investigator to be related to study drug; 1 participant had a family history of psychiatric illness (bipolar disorder) and the other had a history of depression which preceded study entry. There were no serious, study drug-related (as determined by the investigator) Suicide Ideation and Behaviour adverse events reported in HPTN 084.

The following information is included in the adverse drug reactions Section 4.8 of the SmPC:

Psychiatric disorders: Suicide attempt; Suicidal ideation (particularly in patients with a pre-existing history of psychiatric illness) (frequency uncommon)

Hypersensitivity

Hypersensitivity reactions have been reported with integrase inhibitors and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. No cases of confirmed hypersensitivity were identified from HPTN 083 and HPTN 084 studies. No delayed type hypersensitivity reactions reports have been received during the CAB PrEP programme to date. CAB for PrEP should be discontinued immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated.

The above information is included in Section 4.4 of the SmPC, with appropriate cross references to the long-acting properties of CAB injection. The following information is included in the adverse drug reactions Section 4.8 of the SmPC:

Immune system disorders: Hypersensitivity (frequency uncommon)

Skin and subcutaneous tissue disorders: angioedema; urticaria (frequency uncommon)

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 during HIV treatment. Clinical trials have shown that transient elevations of liver enzymes (transaminitis) may occur with CAB PrEP for a variety of reasons; these events are uncommon.

Risk Benefit Impact: 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

IMPORTANT IDENTIFIED RISK #2: HIV-1 SEROCONVERSION

If the individual at risk does not: adhere to the CAB PrEP dosing schedule, does not adhere to their injection visits, CAB PrEP LA is discontinued without fully ascertaining the individual's continued level of risk of HIV acquisition and without consideration of an alternative PrEP regimen, plasma levels of CAB may decrease to a level where protection is decreased and HIV infection may occur, or if individuals do not maintain other elements of the prevention strategy including the use of other HIV-1 prevention measures and safer sex practices (e.g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).

Risk-Benefit impact: The number of cases of seroconversion while receiving CAB PrEP is low in the context of product exposure (0.37/100 person-years of exposure). Although the impact to the individual is high, the probability of occurrence is low. The risk is proposed to be managed through routine labelling, counselling and increased awareness of the risk of seroconversion through the CAB PrEP educational materials (including educational guides for both the prescriber and individuals at risk, prescriber checklist and a reminder card for individuals at risk), see Section V.2. The risk-benefit impact is balanced against the expected benefits to individuals at risk of this novel and efficacious PrEP regimen and it's effectiveness at preventing HIV acquisition.

IMPORTANT IDENTIFIED RISK #3: DEVELOPMENT OF RESISTANCE:

- **IN PARTICIPANTS STARTING CAB WITH UNRECOGNIZED OR ACUTE HIV-1 INFECTION**
- **DUE TO BREAKTHROUGH HIV-1 INFECTION WHILE ON CAB OLI OR LA AND DELAYED DIAGNOSIS**
- **POTENTIAL RISK OF HIV-1 ACQUISITION OCCURRING DURING 'PK TAIL' AND DIAGNOSIS IS DELAYED, OR EFFECTIVE ARV IS NOT STARTED TIMELY**

Resistance may develop in individuals starting CAB with unrecognized or acute HIV-1 infection, as the individual is being treated with an incomplete regimen which is not able to fully suppress the viral replication, leading to possible development of INSTI resistance.

While an individual is receiving CAB PrEP OLI or LA, there is a risk that if the participant acquires HIV, there may be a delay in diagnosis due to the potency of CAB, which may suppress HIV viral load to a level below the level of detection of traditional HIV tests. This could result in a delay in identification of seroconversion. The individual would be delayed in starting a fully suppressive ARV regimen and may develop INSTI resistance.

If HIV-1 infection occurs during the 'PK tail' and the diagnosis is delayed and if fully suppressive ARV is not started in a timely fashion the individual would receive inadequate treatment to suppress the viral replication and so may develop INSTI resistance.

Risk-Benefit impact: The impact on the risk-benefit balance of CAB PrEP is low as while its impact may be severe on an individual, this situation is expected to occur infrequently when the CAB PrEP label is adhered to and through increased awareness of this risk communicated in the CAB PrEP educational materials.

IMPORTANT POTENTIAL RISK #4: MEDICATION ERRORS (INCLUDING TREATMENT NON COMPLIANCE):

CAB PrEP as a long acting PrEP formulation may be considered novel and extra care may be required initially to avoid medication errors.

Risk factors that could lead to medication errors include: mistakes in the prescribing, dispensing, storing, preparation and administration of CAB PrEP Moreover, if CAB PrEP is not administered in accordance with the product labelling and if individuals are not compliant with the CAB PrEP regimen e;g. the individual at risk does not receive their repeat injections within the specified window for dosing; the individual at risk does not adhere to their injection visits;

CAB PrEP LA is discontinued without fully ascertaining the individual's continued level of risk of HIV acquisition and without consideration of alternative PrEP regimen.

The SmPC and Instructions for use (IFU) have been carefully developed and will be supplemented by the CAB PrEP educational materials to help increase awareness and minimise the risk of medication errors and lack of compliance with regimen requirements.

Risk-Benefit impact: The impact on the risk-benefit balance of CAB PrEP is low as medication errors including maladministration and non-compliance with the dosing schedule will be infrequent and are anticipated to reduce over time as HCP and individuals at risk become familiar with the regimen and the importance of treatment compliance and adherence.

MISSING INFORMATION #1: USE IN PREGNANCY AND BREASTFEEDING

The safety of CAB during human pregnancy and breastfeeding has not been established. No studies have been conducted with CAB for HIV treatment or PrEP in pregnant and breastfeeding women.

Risk-benefit impact: As clinical experience of the use of CAB as an injectable regimen during pregnancy is limited and not available in breastfeeding, 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 and breastfeeding women taking CAB.

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

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) may occur with CAB PrEP for a variety of reasons; these events are uncommon. Hepatotoxicity (Drug induced liver injury [DILI]) is considered an identified risk for CAB. Clinical study data from the CAB PrEP development programme provide the evidence for this risk.

Characterisation of the risk:	Transient increases in hepatic transaminases have been observed during the CAB PrEP clinical development program and do not necessarily lead to clinical signs or symptoms of hepatic disease; most cases were asymptomatic. The incidence of hepatotoxicity and other potentially associated adverse events (hepatotoxicity AESI) was similar between treatment groups. Adults The HPTN Hepatic Adjudication Committee (HHAC), that consisted of external academic experts was convened by DAIDS, evaluated all randomized study participants who met the liver-related study drug discontinuation criteria defined in the HPTN 083, and 084 study protocols, suggesting a hepatic event. For HPTN 083, a total of 78/4566 participants were reviewed by the HHAC as of 14 May 2020. Of the 78 study participants, 40 receiving CAB discontinued study drug due to liver-related reasons. Of these 40 participants with liver-related study product discontinuations, 14 participants receiving CAB were assessed by the HHAC as 'probable' DILI (n=5) or 'possible' DILI (n=9) due to liver transaminase elevations, the remaining 23 were considered unlikely and 3 were unassessable. These findings were similar to the control group (TDF/FTC), with 38 participants who met liver-related study product discontinuations. Of these, 15 participants receiving TDF/FTC were assessed by the HHAC as 'probable' DILI (n=2) or 'possible' DILI (n=13). The HHAC reviewed data for participants who met the liver discontinuation criteria through the data cut-off date of 5 November 2020. A total of 33/3224 participants were reviewed. Of the 33 participants with liver-related study product discontinuations: 8 participants receiving CAB were assessed by the HHAC as 'probable' DILI (n=1) or 'possible' DILI (n=7) due to liver transaminase elevations. 7 participants receiving TDF/FTC were assessed by the HHAC as 'probable' DILI (n=2) or 'possible' DILI (n=5). No individuals with suspected DILI were observed during 201120 ÉCLAIR and 201103 HPTN 077 studies. Adolescents HPTN 083-01 and HPTN 084-01 were Phase 2b, single-arm, open-label, safety, tolerability, and acceptability studies in sexually active, healthy adolescents assigned either male (HPTN 083-01) or female (HPTN 084-01) sex at birth. There were no reported events of potential hepatotoxicity AESIs in

	Step 1 (oral lead-in) or Step 2 (injection phase) of either HPTN 083-01 or HPTN 084-01. The risk will be further characterized with information gathered from the post-marketing study.
Risk factors and risk groups:	Hepatotoxicity has been reported in a limited number of individuals receiving CAB with or without known pre-existing hepatic disease.
Preventability:	The CAB PrEP label includes a statement in the Warnings and Precautions section that hepatotoxicity has been reported in a limited number of participants receiving CAB. Clinical and laboratory monitoring should be considered, and CAB should be discontinued if hepatotoxicity is confirmed and individuals managed as clinically indicated. Hepatotoxicity is included in the Adverse drug reactions section of the label.
Impact on the risk-benefit balance of the product:	The number of cases of suspected liver injury is low in the context of product exposure and no clinically meaningful severe cases have been identified; all cases on PrEP have been mild (Aithal, 2011). The risk is considered manageable with discontinuation of oral tablets or injections and clinical management, where necessary. In view of the given expected benefits to participants of this novel PrEP regimen the risk is considered tolerable and similar to the alternative treatment (TRUVADA). Liver chemistry is expected to normalize once CAB PrEP is discontinued.
Public health impact:	Data to date have shown that very few subjects (<1%) have developed suspected DILI across the PrEP clinical development programme , and therefore public health impact is expected to be low.

Important identified Risk: HIV-1 seroconversion

Potential mechanisms	If the individual at risk does not adhere to the CAB PrEP dosing schedule, does not adhere to their injection visits, CAB PrEP LA is discontinued without fully ascertaining the individual's continued level of risk of HIV acquisition and without consideration of an alternative PrEP regimen, plasma levels of CAB may decrease to a level where protection is decreased and HIV infection may occur. In addition, if individuals do not use other aspects of the prevention strategy with CAB PrEP, including the use of other HIV-1 prevention measures and safer sex practices (e.g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use) this could also impact the level of protection and increase the risk of HIV-1 seroconversion.
Evidence source(s) and strength of evidence:	During the HPTN 083 trial, there were 13 incident infections on the CAB arm. Four incident infections occurred during the HPTN 084 trial on the CAB arm. Overall, the incidence of HIV-1 infections on CAB was low. However, these occurred in a controlled clinical trial setting; In real world use, there may be more instances where individuals at risk may not fully adhere to the dosing regimen or other prevention strategies.
Characterisation of the risk:	Adult HPTN 083 Of the 13 incident infections on HPTN 083, 5 incident infections occurred while receiving regular CAB PrEP injections of which 4 participants received on-time injections and 1 participant had one injection off-schedule. Although CAB concentrations were >8x PA-IC90 at the first HIV positive visit in all 4 participants, lower CAB concentrations at preceding visits may reflect increased vulnerability to viral acquisition. Plasma CAB concentrations for these 4 participants are comparable to those in the Longitudinal PK analysis group that was pre-selected based on the administration of timely injections with no missed injections through Week 57. Overall, CAB LA PK was similar in participants receiving on-time injections that seroconverted compared with participants in the longitudinal subpopulation that did not seroconvert. Five incident infections occurred between 8 to 30 months after the individuals had stopped CAB PrEP. At these

	timepoints the plasma CAB PK was either non-quantifiable in 3 participants or below the protein adjusted 90% inhibitory concentration (PA-IC90) of 0.166 µg/mL in the remaining 2 participants. Three incident infections occurred during the oral lead in period. One out of the 3 participants had non-quantifiable concentrations during OLI. In 2 of the 3 participants, measurable plasma CAB concentrations observed at the HIV+ visit were consistent with adherent oral dosing <u>HPTN 084</u> Of the 40 incident HIV 1 infections in HPTN 084, 4 occurred in the CAB group (incidence of 0.20 per 100 PY) and 36 occurred in the TDF/FTC group (incidence of 1.85 per 100 PY). Timing for detection of the 4 incident HIV-1 infections in the CAB group is as follows: • 1 seroconversion was detected in a participant who had completed Step 1 but had no recent oral CAB exposure and had not received any CAB injections; this participant was non-adherent to oral CAB based on plasma CAB concentrations and the first HIV-positive visit occurred 7.3 weeks after the end of Step 1; • 1 seroconversion was detected following a prolonged period when the participant was off CAB due to a temporary study-related discontinuation (i.e., due to pregnancy); this participant became pregnant during OLI ~4 weeks post enrollment and was offered open-label TDF/FTC; the first HIV-positive visit for this participant occurred 57 weeks post enrollment and 52 weeks after the last quantifiable plasma CAB concentration. Thus, at the time of seroconversion, this participant had no recent oral CAB exposure and had not received any CAB injections; • 2 seroconversions were detected during Step 2 while the participants were receiving CAB injections. <u>Adolescents</u> HPTN 083-01 Of the 9 adolescents enrolled in HPTN 083-01, no HIV incident infections were identified (data cut off 24 October 2022).

	HPTN 084-01 Of the 55 adolescents enrolled in HPTN 084-01, no HIV incident infections were identified (data cut off 21 July 2022). The risk will be further characterized with information gathered using post-marketing study described in Section III.2
Risk factors and risk groups:	Multiple factors, including individuals who do not adhere to the dosing regimen and other prevention strategies while receiving CAB PrEP may be associated with a risk of seroconversion.
Preventability:	The CAB PrEP labelling together with the CAB PrEP educational materials (comprising of guides for prescribers and individuals at risk, a checklist for prescribers and a reminder card for individuals at risk) will help to increase awareness and reinforce the importance of adherence to the dosing regimen, and the use of other prevention strategies. Labelling will also provide instructions in cases of a delayed or missed dose of CAB PrEP. Individuals will be counselled periodically to strictly adhere to the recommended cabotegravir dosing schedule/appointments in order to reduce the risk of HIV-1 acquisition and the potential for development of resistance, in addition to the importance of other prevention strategies while receiving CAB PrEP.
Impact on the risk-benefit balance of the product:	The number of cases of seroconversion while receiving CAB PrEP is low in the context of product exposure (0.37/100 person-years of exposure). The risk is considered manageable through the use of routine labelling, the dedicated CAB PrEP educational materials for HCPs and individuals at risk, and counselling. The impact on the risk-benefit balance is therefore considered acceptable, when offset against the expected benefits to individuals at risk of this novel and efficacious PrEP regimen.
Public health impact:	Data to date have shown that very few subjects (<1%) have seroconverted due to lack of adherence on the PrEP clinical development programme therefore, the public health impact is expected to be low.

Important identified Risk: Development of resistance

In participants starting CAB with unrecognized or acute HIV-1 infection

Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis

Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely

Potential mechanisms	There are 3 potential mechanisms for of the development of drug resistance: Resistance may develop in individuals starting CAB with unrecognized or acute HIV-1 infection, as the individual is being treated with an incomplete regimen which is not able to fully suppress the viral replication, leading to possible development of INSTI resistance. While an individual is receiving CAB PrEP OLI or LA, there is a risk that if the participant acquires HIV, there may be a delay in diagnosis due to the potency of CAB, which may suppress HIV viral load to a level below the level of detection of traditional HIV tests. This could result in a delay in identification of seroconversion. The individual would be delayed in transferring to fully suppressive ARV and may develop INSTI resistance. If HIV-1 infection occurs during the 'PK tail' and the diagnosis is delayed and if fully suppressive ARV is not started in a timely fashion the individual would receive inadequate treatment to suppress the viral replication and so may develop INSTI resistance.
Evidence source(s) and strength of evidence:	HPTN 083: There were 4 prevalent/baseline HIV infections on HPTN 083, where HIV infected participants were started on CAB PrEP. Of the 4 participants, 1 participant developed INSTI resistance. There were 7 participants with incident infections on HPTN 083, 3 during the OLI period and 4 during in time injections. Of these incident infections 4/7 participants showed INSTI resistance. There were 5 incident infections in participants that occurred ≥6 months after the last dose of CAB PrEP (during the PK tail), none of these participants showed INSTI resistance.

	HPTN 084 Four (0.25%) HIV incident infections occurred in the CAB group and 36 (1.85%) in the TDF/FTC group. Two infections occurred in women with no recent oral CAB exposure and no injections and two occurred during the injection phase of the study. HIV genotyping results were available for 3 of the 4 CAB group participants. No major INSTI resistance mutations were detected. One of the 3 participants had an integrase mutation at the first viremic visit (L74I). This mutation is considered to be a polymorphism and was also detected in several participants in the TDF/FTC group.
Characterisation of the risk:	Adults HPTN 083 There were 4 prevalent/baseline HIV infections on HPTN 083, where participants were started on CAB PrEP, despite being HIV infected. One of the participants developed INSTI resistance 8.6 weeks after starting CAB PrEP. Three incident HIV infections occurred during the oral lead-in phase. Two of these 3 participants had INSTI resistance mutations. The mutations detected have been previously observed with CAB therapy and were detected 8-11 weeks after starting CAB PrEP. Four incident HIV infections occurred despite on-time CAB injections. Of the 4 infections, 2 of the participants had INSTI resistance. Five incident HIV infections occurred in participants with no recent CAB exposure; 3 of those participants had at least 1 CAB injection (cases B1, B3 and B4). INSTI resistance was not observed in the 5 participants. In all 5 cases that had INSTI resistance, a delay in HIV diagnosis at the study site and/or a delay in ARV initiation may have provided an opportunity for selection of INSTI-resistant variants. HPTN 084 HIV genotyping results were available for 3 of the 4 CAB participants. No major INSTI resistance mutations were detected. One of the 3 participants had an integrase mutation

	at the first viremic visit (L74I). This mutation is considered to be a polymorphism and was also detected in several participants in the TDF/FTC group. Adolescents In the adolescent studies HPTN-083-01 (data cut off 24 October 2022) and HPTN-084-01 (data cut off 21 July 2022), no incident HIV infections were reported.
Risk factors and risk groups:	In some settings, a clinic may not have access to a diagnostic HIV test with a level of sensitivity to detect HIV infections early during the acute period of infection. Delay in confirmation of an individual's positive HIV status may increase the risk of resistance development as the individual will not be transferred to a fully suppressive ARV regimen. A delay in HIV diagnosis with a delay in fully suppressive ARV initiation may provide an opportunity for selection of INSTI-resistant variants. Incomplete adherence to PrEP or other preventative strategies is a possible risk factor for HIV infection and subsequent development of drug resistance. Individuals who may be at risk of non adherence to the prespecified visits and injection schedule or who may stop CAB PrEP, or miss scheduled appointments, without informing their physician or do not follow other preventative strategies may not be suited to LA injection for HIV prevention.
Preventability:	The CAB PrEP labelling together with the CAB PrEP educational materials (comprising of guides for prescribers and individuals at risk, and a checklist for prescribers and a reminder card for individuals at risk) will help to increase awareness and minimise the risk of development of resistance. The SmPC for CAB PrEP contains guidance information in the Warning and Precautions section with respect to the risk of HIV infection and subsequent development of resistance either before, during administration of CAB, or following discontinuation of CAB PrEP. Further resistance information is also detailed in the Pharmacodynamics 'resistance in vivo' sections of the label. Individuals will be clinically reassessed for the risk of HIV acquisition and tested to confirm HIV negative status at each injection visit. Individuals who are suspected or confirmed with HIV-1 should immediately begin ART.

	CAB PrEP should be administered in accordance with the recommended dosage and administration in the prescribing information, and in conjunction with HIV-1 prevention measures and safer sex practices (e.g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use). Treating HCPs will be advised to select individuals who are committed and able to adhere to the treatment schedule. Individuals wanting to discontinue CAB PrEP for any reason should discuss their options based on their continued level of risk of HIV acquisition with their HCP. Alternative forms of non long-acting PrEP should be considered following discontinuation of CAB for those individuals at continued risk of HIV acquisition and initiated within 2 months of the final CAB PrEP injection.
Impact on the risk-benefit balance of the product:	The impact on the risk-benefit balance of CAB PrEP is low as while its impact may be severe on an individual, this situation is expected to occur infrequently. Moreover, the risk is anticipated to be further mitigated by the availability of information in the CAB PrEP label and through the dedicated educational materials for both the prescribers and individuals at risk for the development of drug resistance. In all cases of INSTI resistance occurring on the HPTN 083 trial, a fully suppressive ARV regimen was able to be constructed to treat those participants.
Public health impact:	CAB PrEP is one component of a comprehensive HIV prevention strategy incorporating emphasis on safer sex practices and regular HIV testing. If individuals acquire HIV and develop resistance to CAB, physicians will take the appropriate measures to manage them, and should be able to initiate treatment with a fully suppressive ART regimen. The public health impact is therefore considered low.

Important Potential risk: Medication errors (including treatment non-compliance)

Potential mechanisms	CAB PrEP as a long acting PrEP formulation may be considered novel and extra care may be required initially to avoid medication errors, which includes mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine. If CAB PrEP is not administered correctly in accordance with the product labelling and if individuals are not compliant with the CAB PrEP regimen, this could also negatively impact the effectiveness of CAB PrEP. This could include, e.g. if the individual at risk does not receive their repeat injections within the specified window for dosing, the individual at risk does not adhere to their injection visits, CAB PrEP LA is discontinued without fully ascertaining the individual's continued level of risk of HIV acquisition and without consideration of an alternative non-long acting PrEP regimen. These factors could negatively impact how efficacious CAB is leading to potential HIV seroconversion and/or development of resistance.
Evidence source(s) and strength of evidence:	In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on individuals. Some reports of medication errors have been reported during post marketing use, but overall, the potential risk to individuals due to medication errors is considered to be low, 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. Whilst Cab PrEP is a monotherapy, human factor studies have provided some experience for Cab PrEP and helped to guide and refine the CAB PrEP instructions for use.
Characterisation of the risk:	A small number of reports of dispensing errors occurred during the pivotal HPTN 083 and 084 studies which included delays in dosing, some dosing errors such as incorrect dosing volume administered and incorrect use of needle size. No adverse events were reported as a consequence of these dosing errors in HPTN 083 and adverse events reported in HPTN 084 did not highlight any cases of HIV seroconversion, drug resistance or an issue of lack of efficacy. One year after first marketing of CAB PrEP, a few (n=11) post-marketing cases of medication errors (including improper administration, vial leakage, underdosing, incorrect storage of product) have been reported. These cases were

	generally, poorly documented. No cases of HIV seroconversion or resistance were reported as a result of the reported medication errors. Some post-marketing cases have been received describing non-adherence by individuals, e.g. resulting in dosing outside the dosing window/schedule and/or individuals missing their injection visit. In the majority of these cases no adverse events were reported as a consequence of the non-adherence and no seroconversion or drug resistance were reported as a result of these reported medication errors. In the HPTN 083-01 and 084-01 adolescent studies there was high adherence overall among participants. With limited evidence from controlled clinical trials, data on medication errors will be collected from the post-marketing setting and evaluated via routine pharmacovigilance. This risk will be further characterized with information gathered in the EU post-marketing study described in Section III.2 .
Risk factors and risk groups:	CAB PrEP is an injectable, long-acting formulation and there is a risk that if CAB Prep is not administered in accordance with label, the individual could be underdosed or if an individual misses their dose this could potentially result in CAB PrEP being less effective. Individuals who may be at risk of nonadherence to the prespecified visits and injection schedule or who may stop CAB PrEP, or miss scheduled appointments, without informing their HCP, or do not follow other preventative strategies may not be suited to LA injection for HIV prevention.
Preventability:	The CAB PrEP labelling together with the CAB PrEP educational materials (comprising of guides for prescribers and individuals at risk, and a checklist for prescribers and a reminder card for individuals at risk) will help to provide guidance and reminders of the risk of medication errors, including noncompliance. The SmPC and the Instructions for Use in the SmPC for CAB PrEP have been developed, taking into consideration the Applicant's CAB for HIV treatment experience, with storage, preparation and dispensing instructions comprehensively detailed. Storage of CAB PrEP does not require any special conditions, but can be stored if desired under-standard refrigeration conditions, reducing any further complexity or risk of storage errors.
Impact on the risk-benefit balance of the product:	CAB PrEP is a monotherapy, the frequency of inadequate compliance with CAB PrEP /maladministration is anticipated

	to be low and is likely to be further mitigated by clear guidance information in the label and the CAB PrEP educational materials which will reinforce the importance of treatment compliance and adherence to the dosing schedule/regimen. Prescribers will carefully select motivated and suitable individuals 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. The risk-benefit balance remains positive given the benefits of improved adherence and reduction in pill burden for patients afforded the option of long acting PrEP.
Public health impact:	The label and the CAB PrEP educational materials will help to provide awareness of CAB PrEP adherence to minimise medication errors and treatment non-compliance. Therefore, the public health impact of this risk is expected to be low.

SVII.3.2 Presentation of the missing information

Use in Pregnancy and breastfeeding

Use in Pregnancy

Evidence Source:

The safety of CAB during human pregnancy has not been established. No studies have been conducted with CAB for HIV treatment or PrEP in pregnant and breastfeeding women. Clinical experience of CAB use during pregnancy is therefore limited. In post marketing, individuals will be informed that CAB should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. As CAB has been detected in systemic circulation for up to 12 months or longer after an injection, consideration should be given to the potential for foetal exposure during pregnancy.

At the time of the data cut-off for the initial submission (05 November 2020) there were 49 confirmed (defined as a first positive pregnancy test followed by a positive confirmatory test result at least 4 weeks later or confirmation by another method) pregnancies from HPTN 084. Of these, there were 29 confirmed pregnancies for CAB PrEP. Outcomes of confirmed pregnancies occurred at similar frequencies across treatment groups.

Population in need of further characterization:

Further information is required to understand the safety profile (i.e. maternal and foetal outcomes) in pregnant women taking CAB.

Women who are confirmed to be pregnant whilst in CAB PrEP studies are given the option to either continue in the study and receive long acting CAB PrEP following a benefit/risk discussion with the investigator and a revised informed consent taken or can withdraw. Management of pregnancies are per protocol and all pregnancies will be followed up to outcome. In addition to routine pharmacovigilance activities to monitor pregnancies from all sources occurring with exposure to CAB PrEP, the MAH has proposed a study which is planned to collect additional information on the use of CAB PrEP during pregnancy (see Section III.2 and III.3 , Table 12 for further information).

Anticipated risk/consequence of the missing information:

Due to the LA nature of the CAB injection, exposure could occur at the time of conception and throughout the time of the pregnancy even if injections were stopped as soon as pregnancy was identified. As clinical experience of the use of CAB as an injectable regimen during pregnancy is limited, it is not possible to define the risk in this patient population.

Use in breastfeeding

In lactating rats that received 1000 mg/kg/day 10 days postpartum, CAB was detected in milk. It is expected that CAB will be secreted into human milk based on animal data, although this has not been confirmed in humans. Due to the long acting nature of the CAB injections, CAB may be present in human milk for up to 12 months or longer after the last CAB injection.

It is recommended that women breast-feed only if the expected benefit justifies the potential risk to the infant.

It is challenging to gather data in a sufficient number of breastfeeding women and therefore, where possible the MAH will analyse data from relevant studies conducted globally (either sponsored or supported) where data in breastfeeding becomes available. The MAH will monitor use in breastfeeding women through routine pharmacovigilance activities, from all available sources (spontaneous, clinical trial and postmarketing surveillance) as appropriate. As part of routine pharmacovigilance, a targeted follow up questionnaire for breastfeeding will be used to collect further information from post-marketing reports of use in breastfeeding women where applicable.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 11 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatotoxicity
	HIV-1 seroconversion
	Development of resistance: • In participants starting CAB with unrecognized or acute HIV-1 infection • Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis • Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in pregnancy and breastfeeding

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

III.1 Routine pharmacovigilance activities

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

Specific adverse reaction follow-up questionnaires for:

HIV-1 seroconversion and Development of Resistance

HIV Infection targeted follow up questionnaire will gather information on the participants HIV testing method, HIV status, presence of resistance mutations, symptoms of HIV seroconversion and the patient's adherence to the CAB PrEP regimen to gather information on the above safety concerns.

Breastfeeding

The targeted follow up questionnaire will support the collection of further information from post-marketing reports of drug exposure during breastfeeding.

Other forms of routine pharmacovigilance activities for safety concerns: None

III.2 Additional pharmacovigilance activities

As part of additional PV activities, to better understand the population receiving CAB PrEP, usage patterns, monitoring for seroconversion, resistance, hepatotoxicity, medication errors (including treatment non- compliance (due to nonadherence)) and to obtain information in pregnancy in the post-marketing setting, the below studies are planned.

PASS SHORT NAME SUMMARY

STUDY SHORT NAME AND TITLE:

Study 221935 CAB LA PrEP EU Cohort Study, to Assess Adherence and Effectiveness, and Monitor for Hepatotoxicity and Resistance

RATIONALE AND STUDY OBJECTIVES:

This 5-year prospective, non-interventional study will aim to better understand the population receiving CAB LA for PrEP in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness and monitor for resistance among seroconverted individuals.

Specific Aims:

1. CAB LA PrEP usage pattern: Describe the population initiating CAB LA PrEP by age, sex, BMI and other variables, geographic region, history of previous PrEP use and use of CAB oral lead in prior to initiating injections

2. Adherence: Monitor for adherence by assessing the frequency of delayed and missed injections without oral PrEP and to estimate the frequency of discontinuations

3. Effectiveness: Monitor for incidence of seroconversion while on CAB PrEP and describe the timing of seroconversion
   a. Infected during Oral Lead In
   b. Breakthrough infections while adhering to CAB LA PrEP regimen

4. Safety: Monitor for occurrence of hepatotoxicity following CAB LA injections

5. Resistance: incidence of and risk for developing resistance among individuals in the following groups

   a. CAB LA PrEP started when the individual had acute undiagnosed HIV infection & subsequent emergence of resistance while on CAB monotherapy
   b. CAB LA PrEP discontinued, without subsequent oral PrEP & potential risk of HIV seroconversion and viral resistance during CAB LA PK tail
   c. Breakthrough infections while adhering to CAB LA PrEP and development of resistance during treatment for HIV infection

STUDY DESIGN:

This will be a 5-year long prospective EU cohort study of individuals weighing ≥35 kgs, initiating CAB LA PrEP, in real world clinical setting.

STUDY POPULATION

All CAB LA PrEP users will be followed for at least 3 years

All seroconverters will be followed for 12 months and their virologic suppression and emergence of resistance to antiretrovirals (ARVs) & cross resistance to other integrase inhibitors will be monitored

Participants discontinuing the CAB LA PrEP will be monitored for 12 months for seroconversion and additional 12 months if seroconverted to monitor for ARV effectiveness & potential emergence of resistance

Individuals initiating CAB LA PrEP will be eligible for inclusion from the date of starting the injections, once CAB LA PrEP is approved and commercially available in the EU

Testing for seroconversion & resistance: Testing frequency for HIV seroconversion and resistance if needed, will be per guidelines for LA PrEP and the SmPC

Milestones:

A study protocol was submitted for EMA's review following CAB PrEP approval in the EU. Annual interim reports with cumulative data will be submitted during the conduct of the 5 year study. A final study report will be submitted 6 months after the data collection ends (See Section III.3).

STUDY SHORT NAME AND TITLE:

Study 215325: The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy

Study Rationale and Objectives:

The APR is an international registry that monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure registration cohort. The registry's primary objective is to monitor for birth defects among ARV exposed pregnancies both for treatment of HIV and prevention of HIV. The registry has been monitoring pregnancies with prenatal exposure to ARVs used for PrEP since the approval of ARVs used in oral PrEP.

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 foetal outcomes (premature births and low birth weight) following CAB LA PrEP use during pregnancy. Exposure to CAB LA PrEP relative to 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 data i.e. ARV exposure data collected before the pregnancy outcome is known.

Study population:

The APR is a voluntary, prospective exposure registration cohort of pregnancies exposed to ARV drugs. Annually, the Registry enrolls approximately 1300-1700 pregnant women exposed to ARV drugs for the treatment of HIV and HBV infection and prevention of HIV infection.

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 viewed 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 submitted after CAB PrEP approval in the EU. A registry interim report is prepared semi-annually summarizing data on birth defects. These data from the interim reports will be presented in the CAB PSURs/PBRERs. Additionally, we propose to conduct in depth analyses of non-defect pregnancy outcomes, the first analyses will be conducted when the number of pregnant women exposed to CAB in the registry reaches 25, followed by two more interim analyses when the study population reaches 100 and 200 pregnancies. A final report will be completed 12 months after the third report (See III.3).

III.3 Summary Table of additional Pharmacovigilance activities

Table 12 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 authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				
CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance Ongoing	This 5-year prospective, non-interventional study will aim to better understand the population receiving CAB LA for PrEP in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness and seroconversion, discontinuations, and monitor for resistance among seroconverted individuals.	Hepatotoxicity HIV-1 seroconversion Development of resistance: • In participants starting CAB with unrecognized or acute HIV-1 infection • Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis • Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely Medication errors including treatment non-compliance	Final report	Estimated June 2030

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy Ongoing	The APR is an international registry that monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure registration cohort. The registry's primary objective is to monitor for birth defects among ARV exposed pregnancies. The registry has been monitoring pregnancies with prenatal exposure to ARVs used for PrEP since the approval of ARVs used in oral PrEP. 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 foetal outcomes (premature births and low birth weight) following CAB	Use in pregnancy	Interim Report 1 (25 pregnancies)	Estimated - December 2024
			Interim Report 2 (100 Pregnancies)	Estimated – December, 2026
			Interim Report 3 (200 Pregnancies)	Estimated – December, 2028
			Final report	Estimated – December, 2029

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	LA PrEP use during pregnancy. Exposure to CAB LA PrEP relative to 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 IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

Table 13 Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study (Status)	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				

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

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 14 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization 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 minimisation measures beyond the Product Information:** This is a prescription only medicine.
HIV-1 Seroconversion	**Routine risk communication:** • SmPC section 4.4 • PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Individuals should be re-confirmed to be HIV-negative at each injection visit **Other routine risk minimisation measures beyond the Product Information**: This is a prescription only medicine

Development of resistance: In participants starting CAB with unrecognized or acute HIV-1 infection Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed or effective ARV is not started timely	**Routine risk communication:** • SmPC section 4.4, 4.8 • PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Individuals should be re-confirmed to be HIV-negative at each injection visit **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine.
Medication errors including treatment non-compliance	**Routine risk communication** • SmPC section 4.2, 4.4 • PL section 2 & 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine.
Use in Pregnancy and breastfeeding	**Routine risk communication:** • SmPC section 4.6. • PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None

	Other routine risk minimization measures beyond the Product Information: This is a prescription only medicine

V.2. Additional Risk Minimization Measures

The key messages from the educational materials listed below are provided in ANNEX 6.

The education materials comprise of the following:

Guide for prescribers
Guide for individuals at risk
Prescribers' Checklist
Reminder Card for individuals at risk

Objectives:

The objectives of the educational materials are to enhance the information in the label to mitigate the risks of HIV seroconversion, development of resistance and medication errors including treatment noncompliance, in individuals taking CAB PrEP by increasing awareness of these risks and providing guidance information for prescribers and individuals at risk.

Rationale for the additional risk minimisation activity:

Guides for prescriber and individuals at risk
The educational guides for prescribers and individuals at risk will help to increase awareness and guidance around the risks of HIV seroconversion and the development of resistance, in line with the label. It is imperative that prescribers and individuals at risk are reminded that CAB PrEP has to be part of an overall HIV-1 infection prevention strategy, including the use of other HIV-1 prevention measures. CAB PrEP should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative. There is a potential risk of developing resistance to cabotegravir if an individual acquires HIV-1 either before, while taking CAB PrEP, or following discontinuation of CAB PrEP, as CAB PrEP alone does not constitute a complete regimen for treatment of HIV. It is essential to clinically re-assess individuals for the risk of HIV-1 acquisition and to test to confirm HIV-1 negative status at each injection visit. Individuals should be counselled periodically to strictly adhere to the recommended dosing schedule (appointments) in order to reduce the risk of HIV-1 acquisition and the potential development of resistance. Moreover, alternative forms of non long-acting PrEP should be considered following discontinuation of CAB PrEP injection for those individuals that continue to be at risk of HIV acquisition.

Prescriber Checklist.
There are different considerations to be made for individuals at risk by the prescriber prior to, at the start of, during ongoing therapy and on discontinuing CAB PrEP therapy. The checklist is intended to facilitate consultation between the prescriber and individual during CAB PrEP injection visits, to ensure a consistent approach to evaluating, counselling and follow up of individuals to mitigate the risks of HIV-1 acquisition and development of resistance.

Reminder Card for individuals at risk
The reminder card will provide an additional opportunity to reinforce and remind the individuals at risk of the date of their next injection visit and the significance of adherence to their CAB PrEP appointment and dosing schedule. The format of the reminder card will be determined at a national level, in line with local regulations.

Target audience and planned distribution path:

Following approval of the EU RMP and prior to launch, the Applicant will follow local processes in each member state where CAB PrEP is anticipated to launch to ensure implementation of the education materials for prescribers and individuals at risk. This will include submission of the educational materials to the national competent authority together with the proposed tools to be used and a local communication and distribution plan for the pre-determined target audience, as required.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance

Routine pharmacovigilance will include ongoing monitoring of HIV seroconversion and drug resistance from all sources (spontaneous, clinical trials, post-marketing surveillance).

Additional Pharmacovigilance

Monitoring adherence and effectiveness of CAB PrEP in the following study:

- CAB LA PrEP EU Cohort Study, to Assess Adherence and Effectiveness, and Monitor for Hepatotoxicity and Resistance (See Section III.2).

V.3 Summary of risk minimization measures

Table 15 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization 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. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance
HIV-1 Seroconversion	Routine risk minimisation measures: • SmPC section 4.1, 4.4 • PL section 2 • Individuals should be re-confirmed to be HIV-negative at each injection visit • This is a prescription only medicine. Additional risk minimization measures CAB PrEP Educational materials (including prescribers and individuals at risk guides, prescribers' checklist and a	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: HIV infection targeted follow-up questionnaire Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance

Safety concern	Risk minimization measures	Pharmacovigilance activities
	reminder card for individuals at risk)	
Development of resistance: In participants starting CAB with unrecognized or acute HIV-1 infection Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed or effective ARV is not started timely	Routine risk minimisation measures: • SmPC section 4.1, 4.4 • PL section 2 • Individuals should be re-confirmed to be HIV-negative at each injection visit • This is a prescription only medicine. Additional risk minimisation measures CAB PrEP Educational materials (including prescriber and individuals at risk guides, prescribers' checklist and a reminder card for individuals at risk)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: HIV infection targeted follow-up questionnaire Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance
Medication errors including treatment non-compliance	Routine risk minimisation measures: • SmPC section 4.2, 4.4 • PL section 2 & 3 • This is a prescription only medicine. Additional risk minimisation measures: CAB PrEP Educational materials (including prescriber and individuals at risk guides, prescribers' checklist and a reminder card for individuals at risk)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in Pregnancy and breastfeeding	Routine risk minimisation measures: • SmPC section 4.6 • PL section 2 • This is a prescription only medicine. Additional risk minimisation measures None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Use in breastfeeding targeted follow-up questionnaire Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR APRETUDE 30 MG FILM-COATED TABLETS (CABOTEGRAVIR)

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

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

This summary of the RMP for Apretude 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 Apretude 30 mg Film-coated tablets RMP.

I. The medicine and what it is used for

Apretude 30 mg Film-coated tablets is authorised in combination with safer sex practices for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg.

Cabotegravir tablets may be used as:

- oral lead in to assess tolerability of cabotegravir prior to administration of cabotegravir injection.
- oral PrEP in individuals who will miss planned dosing with cabotegravir injection.

It contains cabotegravir as the active substance and it is given by oral route.

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

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

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

Important risks of Apretude, together with measures to minimise such risks and the proposed studies for learning more about Apretude '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 the case of Apretude, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of Apretude, 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 Apretude. 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
	HIV-1 seroconversion
	Development of resistance: • In participants starting CAB with unrecognized or acute HIV-1 infection • Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis • Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely

Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in pregnancy and breastfeeding

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) may occur with CAB PrEP for a variety of reasons; these events are uncommon. Hepatotoxicity (Drug induced liver injury [DILI]) is considered an identified risk for CAB. Clinical study data from the CAB PrEP development programme provide the evidence for this risk as detailed below
Risk factors and risk groups	Hepatotoxicity has been reported in a limited number of individuals receiving CAB 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. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: HIV-1 Seroconversion	
Evidence for linking the risk to the medicine	Adult HPTN 083 and 084 During the HPTN 083 trial, there were 13 incident infections on the CAB arm. Four incident infections occurred during the HPTN 084 trial on the CAB arm. The numbers of incident infections on CAB were low, and those due to possible non-adherence even lower still. However, these occurred in a controlled clinical trial setting; In real world use, there may be more instances where individuals at risk may not fully adhere to the dosing regimen or other prevention strategies. Adolescent HPTN 083-01 and 084-01 In the HPTN-083-01 (data cut off 24 October 2022) and HPTN-084-01 (data cut off 21 July 2022) studies, no incident HIV infections were reported.
Risk factors and risk groups	Multiple factors, including individuals who do not adhere to the dosing regimen and other prevention strategies while receiving CAB PrEP may be associated with a risk of seroconversion.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.1, 4.4 • PL section 1, 2 • Individuals should be re-confirmed to be HIV-negative at each injection visit • This is a prescription only medicine. Additional risk minimisation measures: CAB PrEP educational materials (including Prescribers and Individuals at risk guides, Prescribers' checklist and a Reminder card for individuals at risk)

Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Development of resistance: In participants starting CAB with unrecognized or acute HIV-1 infection Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed or effective ARV is not started timely	
Evidence for linking the risk to the medicine	Adults HPTN 083 There were 4 prevalent/baseline HIV infections on HPTN 083, where HIV infected participants were started on CAB PrEP. Of the 4 participants, 1 participant developed INSTI resistance. There were 7 participants with incident infections on HPTN 083, 3 during the OLI period and 4 during in time injections. Of these incident infections 4/7 participants showed INSTI resistance. There were 5 incident infections in participants that occurred ≥6 months after the last dose of CAB PrEP (during the PK tail), none of these participants showed INSTI resistance. <u>HPTN 084</u> Four (0.25%) HIV incident infections occurred in the CAB group and 36 (1.85%) in the TDF/FTC group. Two infections occurred in women with no recent oral CAB exposure and no injections and two occurred during the injection phase of the study. HIV genotyping results were available for 3 of the 4 CAB group participants. No major INSTI resistance mutations were detected. One of the 3 participants had an integrase mutation at the first viremic visit (L74I). This mutation is considered to be a polymorphism and was also detected in several participants in the TDF/FTC group. Adolescents HPTN 083-01 and 084-01 In the HPTN-083-01 (data cut off 24 October 2022) and HPTN-084-01 (data cut off 21 July 2022) studies, no incident HIV infections were reported.
Risk factors and risk groups	In some settings, a clinic may not have access to a diagnostic HIV test with a level of sensitivity to detect HIV infections early during the acute period of infection. Delay in confirmation of an individual's positive HIV status may increase the risk of resistance development

	as the individual will not be transferred to a fully suppressive ARV regimen. A delay in HIV diagnosis with a delay in fully suppressive ARV initiation may provide an opportunity for selection of INSTI-resistant variants. Incomplete adherence to PrEP or other preventative strategies is a possible risk factor for HIV infection and subsequent development of drug resistance. Individuals who may be at risk of adherence to the prespecified visits and injection schedule or who may stop CAB PrEP, or miss scheduled appointments, without informing their physician or do not follow other preventative strategies may not be suited to LA injection for HIV prevention.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.1, 4.4 • PL section 1, 2 • Individuals should be re-confirmed to be HIV-negative at each injection visit • This is a prescription only medicine. Additional risk minimisation measures CAB PrEP educational materials (including Prescribers and Individuals at risk guides, Prescribers' checklist and a Reminder card for individuals at risk)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance 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	CAB PrEP as a long acting PrEP formulation may be considered novel and extra care may be required initially to avoid medication errors, which includes mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine. If CAB PrEP is not administered correctly in accordance with the product labelling and if individuals are not compliant with CAB PrEP adherence this could also negatively impact the effectiveness of CAB PrEP. This could include, e.g. if the individual at risk does not receive their repeat injections within the specified window for dosing, the individual at risk does not adhere to their injection visits, CAB PrEP LA is discontinued without fully ascertaining the individual's continued level of risk of HIV acquisition and without consideration of alternative PrEP options as required. These factors could negatively impact how effective CAB is leading to potentially HIV seroconversion and/or development of resistance. <u>Clinical trials</u> A few reports of dispensing errors occurred during the pivotal HPTN 083 and 084 studies which included delays in dosing, some dosing errors such as incorrect dosing volume administered and incorrect use of needle size. No adverse events were reported as a consequence of these dosing errors in HPTN 083 and adverse events reported in HPTN 084 did not highlight any cases of HIV seroconversion, drug resistance or an issue of lack of efficacy. <u>Post-marketing use</u> A small number (n=11) of cases of medication errors (including improper administration, vial leakage, underdosing, incorrect storage of product) have been reported one year after first marketing of CAB PrEP. These cases were generally, poorly documented. No cases of HIV seroconversion or resistance were reported as a result of the reported medication errors. Some post-marketing cases have been received describing non-adherence by individuals, e.g. dosing outside the dosing window/schedule and/or individuals missing their injection visit. In the majority of these cases no adverse events were reported as a consequence of the non-adherence and no seroconversion or drug resistance were reported as a result of these reported medication errors.

Risk factors and risk groups	CAB PrEP is a long acting formulation and there is a risk that if CAB PrEP is not administered following the label correctly, the individual could be underdosed, or if an individual misses their injection dose, this could make CAB PrEP less effective. Individuals who may be at risk of non-adherence to the prespecified visits, injection schedule, miss scheduled appointments or who may stop CAB PrEP, without informing their HCP or do not follow other preventative strategies may not be suited to LA injection for HIV prevention.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2, 4.4 • PL section 2 and 3 • This is a prescription only medicine. Additional risk minimisation measures: CAB PrEP educational materials (including Prescribers and Individuals at risk guides, Prescribers' checklist and a Reminder card for individuals at risk)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance *See section II.C of this summary for an overview of the post-authorisation development plan*
Missing information: Use in Pregnancy and breast feeding	
Evidence for linking the risk to the medicine	The safety of CAB during human pregnancy and breastfeeding has not been established. No studies have been conducted with CAB for HIV treatment or PrEP in pregnant and breastfeeding women. Clinical experience of CAB use during pregnancy is limited and is not available in breastfeeding. At the time of the data cut-off in the initial submission (05 November 2020) there were 49 confirmed (defined as a first positive pregnancy test followed by a positive confirmatory test result at least 4 weeks later or confirmation by another method) pregnancies from HPTN 084. Of these, there were 29 confirmed pregnancies for CAB PrEP.

	Outcomes of confirmed pregnancies occurred at similar frequencies across treatment groups.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.6 • PL section 2 • This is a prescription only medicine. Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorization development plan

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

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

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

Study short name and title:
CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance

Purpose of the Study:
This 5-year prospective, non-interventional study will aim to better understand the population receiving CAB LA for PrEP in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness and seroconversion, discontinuations, hepatotoxicity and monitor for resistance among seroconverted individuals.

Study short name and title:
The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy

Purpose of the Study:
The APR is an international registry that monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure registration cohort. The registry's primary objective is to monitor for birth defects among ARV

exposed pregnancies. The registry has been monitoring pregnancies with prenatal exposure to ARVs used for PrEP since the approval of ARVs used in oral PrEP.

Summary of risk management plan for APRETUDE 600 mg prolonged release suspension for injection (3 mL)

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

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

This summary of the RMP for Apretude 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 Apretude 600 mg prolonged release suspension for injection (3 mL) RMP.

I. The medicine and what it is used for

Apretude 600 mg prolonged release suspension for injection (3 mL) is proposed for PrEP in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg. It contains cabotegravir as the active substance and it is given by intramuscular injection.

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

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

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

Important risks of Apretude, together with measures to minimise such risks and the proposed studies for learning more about Apretude'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 the case of Apretude, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of Apretude, 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 Apretude. 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
	HIV-1 seroconversion
	Development of resistance: • In participants starting CAB with unrecognized or acute HIV-1 infection • Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in pregnancy and breastfeeding

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) may occur with CAB PrEP for a variety of reasons; these events are uncommon. Hepatotoxicity (Drug induced liver injury [DILI]) is considered an identified risk for CAB. Clinical study data from the CAB PrEP development programme provide the evidence for this risk as detailed below
Risk factors and risk groups	Hepatotoxicity has been reported in a limited number of individuals receiving CAB 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. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: HIV-1 Seroconversion	
Evidence for linking the risk to the medicine	Adult HPTN 083 and 084 During the HPTN 083 trial, there were 13 incident infections on the CAB arm. Four incident infections occurred during the HPTN 084 trial on the CAB arm. The numbers of incident infections on CAB were low, and those due to possible non-adherence even lower still. However, these occurred in a controlled clinical trial setting; In real world use, there may be more

	instances where individuals at risk may not fully adhere to the dosing regimen or other prevention strategies. Adolescents HPTN 083-01 and 084-01 In the HPTN-083-01 (data cut off 24 October 2022) and HPTN-084-01 (data cut off 21 July 2022) studies, no incident HIV infections were reported.
Risk factors and risk groups	Multiple factors, including individuals who do not adhere to the dosing regimen and other prevention strategies while receiving CAB PrEP may be associated with a risk of seroconversion.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.1, 4.4 • PL section 1, 2 • Individuals should be re-confirmed to be HIV-negative at each injection visit • This is a prescription only medicine. Additional risk minimisation measures: CAB PrEP educational materials (including Prescribers and Individuals at risk guide, Prescribers' checklist and a Reminder card for individuals at risk)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Development of resistance:	
In participants starting CAB with unrecognized or acute HIV-1 infection Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed or effective ARV is not started timely	
Evidence for linking the risk to the medicine	Adult HPTN 083 and 084 There were 4 prevalent/baseline HIV infections on HPTN 083, where HIV infected participants were started on CAB PrEP. Of the 4 participants, 1 participant developed INSTI resistance. There were 7 participants with incident infections on HPTN 083, 3 during the OLI period and 4 during in time injections. Of these incident infections 4/7 participants showed INSTI resistance. There were 5 incident infections in participants that occurred ≥6 months after the last dose of CAB PrEP (during the PK tail), none of these participants showed INSTI resistance. <u>HPTN 084</u> Four (0.25%) HIV incident infections occurred in the CAB group and 36 (1.85%) in the TDF/FTC group. Two infections occurred in women with no recent oral CAB exposure and no injections and two occurred during the injection phase of the study. HIV genotyping results were available for 3 of the 4 CAB group participants. No major INSTI resistance mutations were detected. One of the 3 participants had an integrase mutation at the first viremic visit (L74I). This mutation is considered to be a polymorphism and was also detected in several participants in the TDF/FTC group. Adolescents HPTN 083-01 and 084-01 In the HPTN-083-01 (data cut off 24 October 2022) and HPTN-084-01 (data cut off 21 July 2022) studies, no incident HIV infections were reported.
Risk factors and risk groups	In some settings, a clinic may not have access to a diagnostic HIV test with a level of sensitivity to detect HIV infections early during the acute period of infection. Delay in confirmation of an individual's positive HIV status may

	increase the risk of resistance development as the individual will not be transferred to a fully suppressive ARV regimen. A delay in HIV diagnosis with a delay in fully suppressive ARV initiation may provide an opportunity for selection of INSTI-resistant variants. Incomplete adherence to PrEP or other preventative strategies is a possible risk factor for HIV infection and subsequent development of drug resistance. Individuals who may be at risk of adherence to the prespecified visits and injection schedule or who may stop CAB PrEP, or miss scheduled appointments, without informing their physician or do not follow other preventative strategies may not be suited to LA injection for HIV prevention.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.1, 4.4 • PL section 1, 2 • Individuals should be re-confirmed to be HIV-negative at each injection visit • This is a prescription only medicine. Additional risk minimisation measures CAB PrEP educational materials (including Prescribers and Individuals at risk guide, Prescribers' checklist and a Reminder card for individuals at risk)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance 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	CAB PrEP as a long acting PrEP formulation may be considered novel and extra care may be required initially to avoid medication errors, which includes mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine. If CAB PrEP is not administered correctly in accordance with the product labelling and if individuals are not compliant with CAB PrEP adherence this could also negatively impact the effectiveness of CAB PrEP. This could include, e.g. if the individual at risk does not receive their repeat injections within the specified window for dosing, the individual at risk does not adhere to their injection visits, CAB PrEP LA is discontinued without fully ascertaining the individual's continued level of risk of HIV acquisition and without consideration of alternative PrEP options as required. These factors could negatively impact how effective CAB is leading to potentially HIV seroconversion and/or development of resistance. <u>Clinical trials</u> A few reports of dispensing errors occurred during the pivotal HPTN 083 and 084 studies which included delays in dosing, some dosing errors such as incorrect dosing volume administered and incorrect use of needle size. No adverse events were reported as a consequence of these dosing errors in HPTN 083 and adverse events reported in HPTN 084 did not highlight any cases of HIV seroconversion, drug resistance or an issue of lack of efficacy. <u>Post-marketing use</u> A small number (n=11) of cases of medication errors (including improper administration, vial leakage, underdosing, incorrect storage of product) have been reported one year after first marketing of CAB PrEP. These cases were generally, poorly documented. No cases of HIV seroconversion or resistance were reported as a result of the reported medication errors. Some post-marketing cases have been received describing non-adherence by individuals, e.g. dosing outside the dosing window/schedule and/or individuals missing their injection visit. In the majority of these cases no adverse events were reported as a consequence of the non-adherence and no seroconversion or drug resistance were reported as a result of these reported medication errors.
Risk factors and risk groups	CAB PrEP is a long acting formulation and there is a risk that if CAB PrEP is not administered following the label correctly, the individual could be underdosed, or if an individual misses their injection dose, this could make CAB PrEP less effective. Individuals who may be at risk of non-adherence to the prespecified visits, injection schedule, miss scheduled appointments or who may stop CAB

	PrEP, without informing their HCP or do not follow other preventative strategies may not be suited to LA injection for HIV prevention.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.2, 4.4 • PL section 2 and 3 • This is a prescription only medicine. Additional risk minimisation measures: CAB PrEP educational materials (including Prescribers and Individuals at risk guide, Prescribers' checklist and a Reminder card for individuals at risk)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance See section II.C of this summary for an overview of the post-authorisation development plan

Missing information: Use in Pregnancy and breastfeeding	
Evidence for linking the risk to the medicine	The safety of CAB during human pregnancy and breastfeeding has not been established. No studies have been conducted with CAB for HIV treatment or PrEP in pregnant and breastfeeding women. Clinical experience of CAB use during pregnancy is limited and not available in breastfeeding. Due to the LA nature of the CAB injection, exposure could occur at the time of conception and throughout the time of the pregnancy even if injections were stopped as soon as pregnancy was identified. In post marketing, individuals will be informed that CAB should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. As CAB has been detected in systemic circulation for up to 12 months or longer after an injection, consideration should be given to the potential for foetal exposure during pregnancy. At the time of the data cut-off of the initial submission (05 November 2020) there were 49 confirmed (defined as a first positive pregnancy test followed by a positive confirmatory test result at least 4 weeks later or confirmation by another method) pregnancies from HPTN 084. Of these, there were 29 confirmed pregnancies for CAB PrEP. Outcomes of confirmed pregnancies occurred at similar frequencies across treatment groups.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.6 • PL section 2 • This is a prescription only medicine. Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR) 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

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

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

Study short name and title:
CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance

Purpose of the Study:
This 5-year prospective, non-interventional study will aim to better understand the population receiving CAB LA for PrEP in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness and seroconversion, discontinuations, hepatotoxicity and monitor for resistance among seroconverted individuals.

Study short name and title:
The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy

Purpose of the Study:
The APR is an international registry that monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure registration cohort. The registry's primary objective is to monitor for birth defects among ARV exposed pregnancies. The registry has been monitoring pregnancies with prenatal exposure to ARVs used for PrEP since the approval of ARVs used in oral PrEP.

PART VII: ANNEXES

LIST OF ANNEXES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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- Use in breastfeeding**:** For the Safety concern **(**missing information) breastfeeding

GSK CASE NUMBER:

Follow-up Questionnaire

HIV INFECTION ON ORAL CAB for PrEP OR long-acting CAB for PREP

Patient Initials:	**Patient Age:**	**Patient Gender:**

Description of the Event

Please provide the date of HIV diagnosis (DD/MM/YY):
_____

Height: _____ **(state units *e.g.*, ft/inches)**

Weight: _____ **(state units *e.g.*, lbs)** **Is the patient obese as per WHO criteria?** ☐ **Yes** ☐ **No**

When was ORAL CAB started (DD/MM/YY): _____ **OR** ☐ **Not Applicable**
When was CAB LA started (DD/MM/YY): _____

State HIV (HIV-1 or HIV-2)/Subtype/clade (e.g., A1/A6): _____ **OR** ☐**Not known**

Was the individual at risk tested for HIV before CABOTEGRAVIR was administered? ☐ **Yes** ☐ **No**

What type of test was used to detect HIV? ☐**Ag/Ab** ☐**HIV RNA**
Please state test results (detectable viral load, Antigen-Antibody): _____

Date of test (DD/MM/YY): _____

Was an RNA test/Viral load measured? ☐ **Yes** ☐ **No**
If yes, please provide qualitative/quantitative result: _____
Date of test (DD/MM/YY): _____

Was a confirmatory test taken? ☐ **Yes** ☐ **No**
If yes, what type of test was used? _____

Were any resistance associated mutations identified? ☐ **Pending** ☐ **Yes** ☐ **No**
If yes, please provide the genotype/phenotype: _____
Date of test (DD/MM/YY): _____

If the individual received CAB LA injections, state needle length used: _____ **(e.g., cm/inches)**

Please provide a detailed account of the event:

Did the patient have acute seroconversion symptoms? If yes, what were they?

What risk activity(ies) was the patient engaging in: ☐ **MSM,** ☐ **IVDU,** ☐**MSW,** ☐**WSM**

If individual was on *oral* Cabotegravir at the time of a positive test, was the patient adherent to the regimen? ☐ **Yes** ☐ **No**

If no, please provide reason: _____

Was the individual on Cabotegravir injections at the time of a positive test? ☐ **Yes** ☐ **No**

If *yes*, did the patient receive injections on time? ☐ **Yes** ☐ **No**

If *no* to CAB Injections, please provide reason (e.g., including any delays): _____

Please provide the dates of the last 4 injections

Injection number (i.e 1st, 2nd)	Date of injection (DD/MM/YY)	Injection administered within window. (Y/N)

Please provide the date of the last dose of Cabotegravir (DD/MM/YY): _____

Was the individual on any concomitant medications or supplements (prescribed/non-prescribed/illicit) ☐ **Yes** ☐ **No**

If yes, please state; names of the products used, length of use and whether they were taken when the patient was on Cabotegravir: _____

Was the patient started on ART? ☐ **Yes** ☐ **No**

If yes, please state the regimen:_____

Diagnostic Tests:

Were any other relevant laboratory investigations, diagnostic tests or clinical investigations performed? For example; CD4 Count, STI Screen etc ☐ **Yes** ☐ **No**

If yes, please specify and give results (or provide a copy):

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GSK

TARGETED FOLLOW UP QUESTIONNAIRE
CABOTEGRAVIR
USE IN BREASTFEEDING

Mother: age, sex at birth, initials: **Mother's weight at time of reporting (are they obese if weight unknown):**	**Child: age, sex, initials and weight at time of report:**	**GSK CASE No:**

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event

	Yes	No
Was there an adverse event reported for the infant/neonate while breastfeeding?	☐	☐
If YES, please provide details: Date Start (DD/MM/YY): Date Stop (DD/MM/YY): Outcome: Was any treatment administered? If YES, please provide details: Please provide the age of the infant(s)/neonate(s):	☐	☐
Were there any concerns with the infant/neonate's health during pregnancy, birth, and/or in the postpartum period? If YES, please provide details:	☐	☐
Was the infant/neonate born prematurely (i.e., <37 completed weeks)? If YES, please state how many weeks + days gestation were they born: Please provide the birthweight of the child:	☐	☐
Has the infant/neonate been receiving any medications for any other underlying condition? If YES, please provide the names and dates of these: Date Start (DD/MM/YY): Date Stop (DD/MM/YY):	☐	☐
Was there an adverse event reported for the mother while breastfeeding? If YES, please provide details: Date Start (DD/MM/YY): Date Stop (DD/MM/YY): Outcome:	☐	☐
Were there any concerns with the mother's health before or during pregnancy, during birth, and/or in the postpartum period? If YES, please provide details:	☐	☐

When was ORAL cabotegravir (CAB) started (DD/MM/YY): _____ OR Not Applicable
When was CAB LA (long acting injectable) started (DD/MM/YY):
Please provide the last date of administration of CAB LA? (DD/MM/YY):
OR Not Applicable

Was CAB LA stopped? ☐ ☐
If YES, please provide stop date (DD/MM/YY):
If CAB LA has been stopped, is the mother on an alternative form of PrEP? ☐ ☐

If YES, please provide details including start/stop dates:

Please provide the date of last menstrual period (DD/MM/YY): _____or estimated date of conception (DD/MM/YY):
Was CAB used during pregnancy? ☐ ☐
If NO, please provide date of last injection (DD/MM/YY):
If YES, please provide
Date Start (DD/MM/YY):
Date Stop (DD/MM/YY):

Was CAB started during breastfeeding? OR ☐ ☐
Was CAB therapy started prior to breastfeeding and continued? ☐ ☐
If YES, please provide
Date Start (DD/MM/YY):
Date Stop (DD/MM/YY): OR Not Applicable:

Breastfeeding and newborn development

	Yes	No
Is the mother currently breastfeeding?	☐	☐
If YES, please provide date started breastfeeding: (DD/MM/YY):		
If NO, please state stop date of breast feeding (DD/MM/YY):		
Were there any problems with breastfeeding?	☐	☐
If YES, please provide more information:		
Is the mother using formula milk?	☐	☐
If YES, please provide the reason why		
Date Start (DD/MM/YY):		
Date Stop (DD/MM/YY):		
How often is the mother breastfeeding? Please provide frequency:		
Is the newborn maintaining or gaining weight as expected?	☐	☐
If NO, please provide more detail:		
Is the neonate achieving its developmental milestones?	☐	☐
If NO, please provide further information:		

History:

	Yes	No
Please provide relevant past medical history for the mother:		
Was the mother on any concomitant medications or supplements (prescribed/non-prescribed/illicit) whilst breastfeeding? If YES, please state; names of the products used, length of use and whether they were taken when the patient was on CAB:	☐	☐
Was the mother on any concomitant medications or supplements (prescribed/non-prescribed/illicit) during the pregnancy? If YES, please state; names of the products used, length of use and whether they were taken when the patient was on CAB:	☐	☐
Is the mother still HIV Negative at the time of reporting?	☐	☐
If NO, • Was the patient started on ART? If YES, please provide details:	☐	☐
• Is the neonate/infant still HIV negative at the time of reporting? If NO, please provide details:	☐	☐

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Prior to the launch of Apretude in a Member State, the Marketing Authorization Holder (MAH) must agree the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

To supplement routine risk minimisation activities, the educational materials are aimed at mitigating the risks of HIV seroconversion, the development of resistance and medication errors, including treatment noncompliance in individuals taking Apretude by increasing awareness of these risks and providing guidance information for prescribers and individuals at risk.

The MAH shall ensure that in each Member State where Apretude is marketed, all healthcare professionals and individuals at risk who are expected to prescribe and/or use Apretude have access to/are provided with the following educational package, which comprises of the following:

- Guide for prescribers
- Guide for individuals at risk
- Prescribers' checklist
- Reminder Card for individuals at risk

Key messages of the additional risk minimization measures for Apretude for Pre Exposure Prophylaxis (PrEP) are outlined below.

Guide for prescribers shall contain the following elements:

- Details on use of Apretude for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
- Reminder that Apretude should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative.
- Individuals should be re-confirmed to be HIV-negative at each injection visit while taking Apretude for pre-exposure prophylaxis.
- If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, HIV-1 status should be reconfirmed.
- Details on the potential risk of developing resistance to Apretude if an individual acquires HIV-1 either before, or while taking Apretude, or following discontinuation of Apretude.
- Importance of commencing antiretroviral therapy (ART) in instances of HIV-1 acquisition in individuals who are suspected or confirmed with a diagnosis of HIV-1.
- Apretude does not constitute a complete ART regimen for the treatment of HIV 1 and HIV resistance mutations have emerged in individuals with undetected HIV 1 infection who were only taking Apretude.

- Consideration of alternative forms of non-long-acting PrEP following discontinuation of Apretude injection for those individuals that remain at risk of HIV acquisition, which should be initiated within 2 months of the final Apretude injection.
- Importance of counselling individuals at risk periodically to strictly adhere to the recommended Apretude dosing schedule/appointments to reduce the risk of HIV-1 acquisition and the potential development of resistance.

Prescriber checklist shall provide reminders for evaluations and counselling at initial and follow up visit, including:

- Test to re-confirm HIV-1 negative status at each injection visit to minimise the risk of developing resistance to Apretude.
- To reconfirm HIV-1 status, if clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected.
- To commence antiretroviral therapy (ART) in instances of HIV-1 acquisition in individuals who are suspected or confirmed with a diagnosis of HIV-1.
- To discuss and reiterate the importance of adherence to the recommended Apretude dosing schedule/appointments to reduce the risk of HIV-1 acquisition and the potential development of resistance.
- To summarise and restate that Apretude for pre-exposure prophylaxis is part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
- To consider alternative forms of non-long-acting PrEP following discontinuation of Apretude injection for those individuals that remain at risk of HIV-1 acquisition, which should be initiated within 2 months of the final Apretude injection.

Guide for Individuals at risk shall contain the following elements:

Important information individuals at risk need to know before, while taking and after stopping Apretude including:

- Requirements that Apretude for pre-exposure prophylaxis is part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
- Reminder that Apretude should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative.
- Individuals should be re-confirmed to be HIV-negative at each injection visit while taking Apretude for pre-exposure prophylaxis.
- Importance of informing physician if recent (< 1 month) exposures to HIV-1 are suspected.
- Apretude alone does not constitute a complete regimen for the treatment of HIV.-1.
- Ensure strict adherence to dosing regimen/appointment to reduce the risk of HIV 1 acquisition and the potential development of resistance.

- Consideration of alternative forms of non long-acting PrEP following discontinuation of Apretude if they remain at risk of HIV-1 acquisition.

Reminder card for Individuals at risk shall contain the following elements:

- The date of the individuals next Apretude injection visit
- Reminder of the importance of strict adherence to dosing regimen/appointment to reduce the risk of HIV-1 acquisition and the potential development of resistance.
- Reminder that Apretude pre-exposure prophylaxis is part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).