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	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.
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 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	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.
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 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 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 (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 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	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.
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 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	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.
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 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 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 (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 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.