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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

APRETUDE

International non-proprietary name: cabotegravir

Procedure No. EMEA/H/C/005756/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Quality

BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
CPP	Critical process parameter
CQA	Critical quality attribute
CTAB	Cetyltrimethylammonium bromide
DoE	Design of experiments
EC	European Commission
GC	Gas chromatography
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma optical emission spectroscopy
IM	Intramuscular
IPC	In-process control
IR	Infrared
KF	Karl Fischer titration
LLDPE	Linear low-density polyethylene
MAH	Marketing Authorisation holder
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
PAR	Proven acceptable range
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PSD	Particle size distribution
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative humidity
SmPC	Summary of product characteristics
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
UV	Ultraviolet
XRPD	X-ray powder diffraction

Non-Clinical

ART	Antiretroviral therapy
AUC	Area under the curve
BDC	Bile duct-cannulated
CAB	Cabotegravir
C_{max}	Maximum observed concentration
FC	Fold change
FDC	Fixed-dose combination
GI	Gastrointestinal
HIV	Human immunodeficiency virus
IM	Intramuscular
INSTI	Integrase strand transfer inhibitor
ISR	Injection site reactions
KLH	Keyhole limpet hemocyanin
LA	Long acting
M1	Cabotegravir glucuronide or GSK3388352
MC4	Melanocortin 4
MRHD	Maximum recommended human dose
NMR	Nuclear magnetic resonance
NNRTI	Non-nucleoside reverse transcriptase inhibitor

NOAEL	No observed adverse effect level
NOEL	No observed effect level
OLI	Oral Lead In
$PAIC_{90}$	Protein-adjusted 90% inhibitory concentration
PBMC	Peripheral bone marrow cells
PBPK	Physiologically-based pharmacokinetics
PICs	Pre-integration complexes
PK	Pharmacokinetics
PND	Postnatal day
PO	Per os (oral)
PPN	Peri- and postnatal
PopPK	Population-based pharmacokinetics
PrEP	Pre-exposure prophylaxis
RPV	Rilpivirine
SC	Subcutaneous
TDAR	T cell dependent antibody response

Clinical

µg	Microgram
µm	Micrometer
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-tau)	Area under the concentration-time curve from time 0 to the end of the dosing interval
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
c/mL	Copies per milliliter
CAB	Cabotegravir, GSK1265744
CAB PrEP	Cabotegravir oral tablets and long-acting injectable, extended release suspension for injection used for pre-exposure prophylaxis of HIV infection
CAB LA	Cabotegravir long-acting injectable, extended release suspension for injection
cART	Combination antiretroviral therapy
CD	Cluster of differentiation cells
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent clearance following oral and LA dosing
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
Ctau	Trough plasma concentrations at the end of the dosing
DAIDS/NIAID	Division of Acquired Immunodeficiency Syndrome/US National Institute of Allergy and Infectious Diseases
ddQTcF	Individual time-matched GSK1265744 treatment groups -placebo QTcF in change from Baseline difference
DILI	Drug-induced liver injury
DSMB	Data and Safety Monitoring Board
DTG	Dolutegravir
DTI	Direct to Injection
EAC	Endpoint adjudication committee
ECG	Electrocardiogram
eCRF	Electronic case report form

ESA	East and Southern Africa
EU	European Union
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
FTC	Emtricitabine
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCP	Health care provider
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HHAC	HPTN Hepatic Adjudication Committee
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HPLC-MS/MS	High performance liquid chromatography tandem mass spectrometric method
HPTN	HIV Prevention Trials Network
HR	Hazard ratio
HSR	Hypersensitivity reaction
IM	Intramuscular
INSTI	Integrase strand transfer inhibitor
iPREX	Pre-exposure Prophylaxis Initiative
ISR	Local injection site reaction
ISS	Integrated Summary of Safety
Janssen	Janssen Sciences Ireland UC
kg	Kilogram
L	Liter
LA	Long-acting injectable, extended release suspension for injection, or prolonged release suspension for injection
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified intent-to-treat
mL	Milliliter
mm	Millimeter
mmol	Millimole
msec	Millisecond
MSM	Men who have sex with men
NCEP	National Cholesterol Education Program
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OBSP	On blinded study product
OLI	Oral lead-in
PA-IC90	Protein-adjusted 90% inhibitory concentration
PD	Pharmacodynamic
Pgp	P-glycoprotein
PI	Prediction interval
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PrEP	Pre-exposure prophylaxis
PT	Preferred term
PY	Person years
Q12h	Every 12 hours
Q12W	Every 12 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QTcB	Heart Rate-corrected QT Interval
QTcF	QT Interval Corrected using Fridericia's Formula
RAL	Raltegravir
RNA	Ribonucleic acid
RPV	Rilpivirine (TMC278)
RPV LA	Rilpivirine long-acting injectable

SAE	Serious adverse event
SHIV	Simian/human immunodeficiency virus
SIV	Simian immunodeficiency virus
SMSQ	Study Medication Satisfaction Questionnaire
SOC	System organ class
STI	Sexually transmitted infection
t1/2	Terminal phase half-life
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TGW	Transgender women who have sex with men
tmax	Time to reach Cmax
TQT	Thorough QT
UGT1A1	UDP-glucuronosyltransferase 1A1
UGT1A9	UDP-glucuronosyltransferase 1A9
ULN	Upper limit of normal
US	United States
USP	United States pharmacopeia
Vc/F	Apparent volume of the central compartment
VOICE	Vaginal and Oral Interventions to Control the Epidemic
Vp/F	Apparent peripheral compartment volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ViiV Healthcare B.V. submitted on 24 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Apretude, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 11 July 2022.

The applicant applied for the following indication:

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 at-risk individuals weighing at least 35 kg (see sections 4.2 and 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

This application is submitted as a multiple of Vocabria authorised on 17/12/2020 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0102/2022 on the agreement of a paediatric investigation plan (PIP), which has been linked to EMA Decision P/0272/2014 in accordance with Regulation (EC) No 1901/2006.

At the time of submission of the application, the PIP P/0272/2014 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 September 2014	EMEA/H/SA/2517/2/2014/III	Dieter Deforce, Mair Powell
28 January 2016	EMEA/H/SA/2517/2/FU/1/2015/III	Dieter Deforce, Mair Powell
26 January 2017	EMEA/H/SA/2517/3/2016/I	Mair Powell, Peter Mol

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- *The proposed starting materials and approach to certain specific impurities*
- *The dissolution method, the proposed reporting limit for leachables data, microbiological control strategy, for the injectable suspension.*
- *Appropriateness of the dissolution method for tablets*
- *The overall non-clinical program*
- *The proposed drug interaction study plan, including CYP studies and oral contraceptive study.*
- *The dose determination, proposal not to conduct ADME, renal and hepatic impairment studies with the CAB LA formulation, the inclusion of an oral lead-in period and plans to manage the PK tail when CAB LA is discontinued.*
- *The overall approach for collection of safety data and proposal to include safety data from the treatment studies to support the PrEP indication.*
- *The proposed Risk Management Plan*
- *The overall phase 2/3 clinical program, possibility for adaptive study designs, choice of comparator, possibility of an open label design, and the management of pregnancy*
- *The possibility of a conditional marketing authorisation*

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Maria Grazia Evandri

The application was received by the EMA on	24 June 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 January 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2023
The Co-Rapporteur's Critique was circulated to all PRAC and CHMP members on	1 February 2023

The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	10 February 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 May 2023
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	12 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	19 May 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 June 2023 and 20 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	7 July 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	14 July 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Apretude on	20 July 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for is: Apretude is indicated 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 (see sections 4.2 and 5.1).

2.1.2. Epidemiology

The HIV pandemic remains a public health emergency with an estimated annual 1.5 million incident infections worldwide in 2020 [UNAIDS, 2021a]. Although the annual number of infections has been decreasing on a global scale with a 30% decline since 2010, new infections continue to occur despite

advances in the development of ART for HIV treatment and data demonstrating that individuals with undetectable HIV-1 viral load do not transmit virus to uninfected partners [Cohen, 2016; UNAIDS, 2021b].

In 2020, the largest proportion of newly diagnosed HIV infections occurred in East and Southern Africa (ESA) with 730,000 incident infections, which accounted for 42.9% of all new infections, followed by Asia and Central Pacific and West and Central Africa, which accounted for 17.7% and 14.1% of total new infections, respectively. Although the geographic regions listed above accounted for the majority of new HIV infections in 2020, they also reported significant declines in HIV incidence in the last decade [UNAIDS, 2021c].

However, HIV incidence has increased steadily over the past decade in 3 regions: Eastern Europe and Central Asia, Latin America, and the Middle East and North Africa, which accounted for 10%, 7.1%, and 1.1% of new HIV infections in 2020, respectively.

Populations disproportionately affected by the ongoing HIV pandemic vary by region. Sixty two percent of incident HIV infections in 2019 were among specific subsets of the population at elevated risk for HIV acquisition, including sex workers, persons who inject drugs, prisoners, transgender people, and MSM and their sexual partners [UNAIDS, 2020].

Ten percent of total HIV incident infections occurred among people who inject drugs, a population that accounted for a disproportionately large share of new infections in eastern Europe and Central Asia (48%) and in the Middle East and North Africa (43%). 2% of new infections in 2019 occurred among TGW [UNAIDS, 2021c].

In the US, where approximately 38,000 new infections are diagnosed per year, MSM accounted for 69% of newly diagnosed infections in 2018 [CDC, 2020].

Sub-Saharan Africa, particularly ESA, continues to carry the greatest HIV burden in the world. Cisgender women accounted for 48% of all newly diagnosed HIV infections among adults over 15 years of age in 2019; however, this figure was as high as 58% in West and Central Africa and 61% in ESA (compared to 21% in West/Central Europe and North Africa) [UNAIDS, 2021c].

Outside of sub-Saharan Africa, men represented more than half of newly diagnosed HIV infections in 2019, from 57% in the Caribbean to 79% in West/Central Europe and North America [UNAIDS, 2021c]. Also in 2019, almost a quarter (23%) of new infections globally occurred among MSM. This population accounted for a large proportion of total HIV infections in Asia and Central Pacific (44%), Latin America (44%), and West/Central Europe and North America (64%) [UNAIDS, 2020].

2.1.3. Aetiology and pathogenesis

HIV can be transmitted via the exchange of a variety of body fluids from infected people, such as blood, breast milk, semen and vaginal secretions. HIV can also be transmitted from a mother to her child during pregnancy, delivery and breastfeeding.

Behaviours and conditions that put individuals at greater risk of contracting HIV include:

- -having condomless anal or vaginal sex;
- -having another sexually transmitted infection (STI) such as syphilis, herpes, chlamydia, gonorrhoea and bacterial vaginosis;
- -engaging in harmful use of alcohol and drugs in the context of sexual behaviour;

- -sharing contaminated needles, syringes and other injecting equipment and drug solutions when injecting drugs;
- -receiving unsafe injections, blood transfusions and tissue transplantation, and medical procedures that involve unsterile cutting or piercing; and
- -experiencing accidental needle stick injuries, including among health workers.

Individuals can reduce the risk of HIV infection by limiting exposure to risk factors. Key approaches for HIV prevention, which are often used in combination, include:

- -male and female condom use;
- -prevention, testing and counselling for HIV and STIs;
- -use of antiretroviral drugs (ARVs) for prevention (oral PrEP and long acting products), the dapivirine vaginal ring;
- -harm reduction for people who inject and use drugs; and
- -elimination of mother-to-child transmission (MTCT) of HIV.

HIV is not transmitted if a person's sexual partner is on effective ART and virally suppressed, so increasing access to testing and supporting linkage to ART is an important component of HIV prevention.

2.1.4. Clinical presentation, diagnosis

The intended benefit of PrEP is the prevention of HIV infection. The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months after being infected, many are unaware of their status until the later stages. In the first few weeks after initial infection, people may experience no symptoms or an influenza-like illness including fever, headache, rash or sore throat.

As the infection progressively weakens the immune system, they can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea and cough. Without treatment, they could also develop severe illnesses such as tuberculosis (TB), cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma.

HIV can be diagnosed through rapid diagnostic tests that provide same-day results. This greatly facilitates early diagnosis and linkage with treatment and care. People can also use HIV self-tests to test themselves. However, no single test can provide a full HIV positive diagnosis; confirmatory testing is required, conducted by a qualified and trained health or community worker at a community centre or clinic.

Most widely-used HIV diagnostic tests detect antibodies produced by the person as part of their immune response to fight HIV. In most cases, people develop antibodies to HIV within 28 days of infection. During this time, people experience the so-called window period – when HIV antibodies have not been produced in high enough levels to be detected by standard tests and when they may have had no signs of HIV infection, but also when they may transmit HIV to others. After infection without treatment and viral suppression, an individual may transmit HIV transmission to a sexual or drug-sharing partner or for pregnant women to their infant during pregnancy, delivery or the breastfeeding period.

2.1.5. Management

PrEP is a key component of the overall strategy to reduce the number of new HIV infections in the US as outlined in the Department of Health and Human Services Ending the HIV Epidemic [HHS, 2019], the US National HIV/AIDS Strategies initiatives [ONAP, 2015], and the WHO Policy Brief on expanding recommendations for oral PrEP for HIV infection [WHO, 2015].

The current standard of care for HIV PrEP in the EU includes the tenofovir-based, fixed dose antiretroviral combination regimen, TDF/FTC, to be orally administered daily:

-TDF/FTC was approved for HIV-1 PrEP by the US FDA in July 2012 and subsequently approved in other countries, including the EU and Canada. TDF/FTC is indicated for use in at-risk adults and adolescents (≥35 kg) to reduce the risk of sexually acquired HIV-1, when used in combination with safer sex practices.

However, the use of daily oral tenofovir-based PrEP regimens for PrEP has limitations. Oral PrEP efficacy requires adherence to daily dosing regimen.

In a systematic review of randomized clinical trials of oral PrEP versus placebo or no oral PrEP, adherence rate of >70% to oral PrEP was associated with 73% effectiveness in the reduction of new HIV-1 infections, while adherences between >40% to <70% or <40% were associated with effectiveness rates of 49% and 7%, respectively [Chou, 2019].

Clinical trials have demonstrated that oral PrEP efficacy is strongly correlated with adherence in key population groups including:

- -MSM and TGW: Of the 22 HIV infections in the DISCOVER study, 5 were likely infected at study entry; excluding these 5 participants, 15 out of 17 (88%) had low (i.e., taking <2 doses/week) or undetectable tenofovir diphosphate concentrations in dried blood spots on the day of HIV diagnosis [Mayer, 2020]. In the iPrEX study, low drug exposure was associated with the majority of incident HIV infections; of the 34 participants with incident HIV infection in the TDF/FTC group, at least 1 study drug component was detected in any plasma or cell specimen from 3 participants [Grant, 2010].
- Cisgender women: The FEM-PrEP study was stopped early due to lack of efficacy attributable to low drug adherence; less than 40% of the HIV-uninfected women in the TDF/FTC group had evidence of recent pill use at visits that were matched to the HIV-infection window for women with seroconversion [Van Damme, 2012]. Similarly, all tenofovir-based regimens assessed in the VOICE trial failed to significantly reduce the risk of HIV acquisition, and the lack of efficacy was associated with low adherence as assessed by measurement of tenofovir levels in plasma [Marrazzo, 2015].

Among 15 EU countries that were able to report gender- and transmission-disaggregated data on PrEP utilization, over 90% of current PrEP users identified as MSM as of March 2019, and it has been estimated that approximately 500,000 MSM who would be very likely to use PrEP are unable to access it [ECDC, 2019; Hayes, 2019]. In Europe, PrEP is available through free public health services in only a select number of countries (e.g., Bosnia and Herzegovina [only Sarajevo], Croatia, Denmark, France, the Netherlands, Moldova, Portugal, and Ukraine) [Moseholm, 2020]. More commonly, PrEP is available in European countries through healthcare providers or online purchasing but not reimbursed (e.g., Austria, Belgium, Czech Republic, Finland, Germany, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, and the United Kingdom), with PrEP users assuming financial responsibility. In a number of European countries, PrEP is available only through demonstration projects, clinical trials, or private sources such as online purchasing (e.g., Bulgaria, Cyprus, Greece, Romania, and Spain) [Balayan, 2021; Moseholm, 2020].

Although women represent approximately a third of new HIV infections in Europe, PrEP services have focused mostly on MSM in this region. In a recent study of 34 European countries, data showed that although oral PrEP was available in 30 of the countries, only 6 countries had specific PrEP recommendations for women [Moseholm, 2020]. Moreover, the adherence challenges to oral TDF/FTC PrEP in cisgender women who participated in oral PrEP studies have been described above.

Alternatives to daily oral PrEP

Apart from daily oral TDF/FTC the following PrEP regimens have been studied or approved:

Individuals who are not at ongoing risk for HIV infection can consider using “on demand” (also known as “intermittent,” “non-daily,” or “event-driven”) PrEP, in which an oral tenofovir-based regimen is only administered near the time of sex [CDC, 2021c]. This option may help to address some of the challenges associated with adherence to a daily dosing regimen, but efficacy is presumed to be limited to only those individuals who are not at continuous high risk. On-demand PrEP has only been evaluated in MSM, and no clinical studies have been conducted in cisgender women or TGW. Furthermore, this type of use is not currently included in the TDF/FTC prescribing information or in the CDC guidelines for PrEP, which still recommends daily PrEP for those at risk for HIV.

The dapivirine vaginal ring may provide a long-acting option for HIV-uninfected women for PrEP to reduce the risk of HIV-1 infection via vaginal intercourse in combination with safer sex practices when oral PrEP is not used, cannot be used, or is not available. The dapivirine vaginal ring 25 mg was assessed by the EMA as part of its coordinated efforts with the WHO to evaluate medicines not intended for use in the EU and was provided with a positive opinion on 23 July 2020. Two clinical studies, The Ring Study and ASPIRE, demonstrated a 27-31% risk reduction of HIV acquisition among women who used the dapivirine ring [Nel, 2016; Baeten, 2016]. Both clinical studies were followed by open-label extension studies, DREAM and HOPE, which illustrated an increase in use of the vaginal ring and a slightly higher risk reduction of approximately 50% (39% - 62%) [Nel, 2021; Baeten, 2021]. As a result, the WHO updated its clinical guidelines to include a conditional recommendation that the dapivirine vaginal ring can be offered as an additional prevention choice for women as a part of combination prevention strategy [WHO, 2021]. This PrEP agent is comprised of a silicone ring that is inserted into the vagina and slowly releases the NNRTI dapivirine; the ring must be replaced every 4 weeks [EMA, 2020]. Although the prolonged drug exposure associated with every month dosing regimen may improve adherence, some of the associated risks of the inserted vaginal ring – including urinary tract infection, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain – may impose some limitations on acceptability. In addition, this PrEP regimen is only an option for women.

2.2. About the product

Cabotegravir is an integrase inhibitor of HIV-1. Cabotegravir inhibits 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.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented in 2 different formats: a 200 mg/ml prolonged release suspension containing 600 mg cabotegravir as active substance and a film-coated tablet containing 30 mg cabotegravir (as sodium salt) as active substance.

Other ingredients are:

Prolonged release suspension: mannitol (E421), polysorbate 20 (E432), macrogol (E1521), water for injections.

Film-coated tablets:

Tablet core: lactose monohydrate, microcrystalline cellulose (E460), hypromellose (E464), sodium starch glycolate, magnesium stearate.

Tablet coating: hypromellose (E464), titanium dioxide (E171), macrogol (E1521).

The prolonged release suspension is available in brown 3 mL type I glass vials, with bromobutyl rubber stoppers and grey aluminium overseals with orange plastic flip-caps as described in section 6.5 of the SmPC.

The film-coated tablets are available in white HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures, with polyethylene faced induction heat seal liners as described in section 6.5 of the SmPC.

2.3.2. Active Substance - Cabotegravir

2.3.2.1. General information

The chemical name of cabotegravir is (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide. It corresponds to the molecular formula $C_{19}H_{17}F_2N_3O_5$, its relative molecular mass is 405.35 and it has the structure shown in Figure 1.

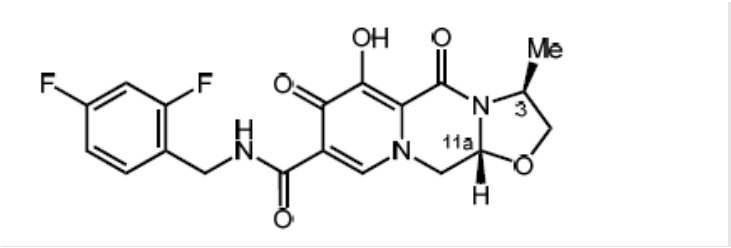


Figure 1: cabotegravir structure

Cabotegravir appears as a white to almost white non-hygroscopic crystalline hygroscopic powder. It is practically insoluble below pH 9 and slightly soluble above pH 10 in aqueous media. It has two pKa, pKa1 = 7.7 (measured), OH group and pKa2 =11.1 (calculated), NH group.

The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectrometry, mass spectrometry (MS), IR spectrometry, elemental analysis and single crystal X-ray crystallography.

Cabotegravir possesses two stereogenic centers and is the isomer with the 3*S*, 11a*R* configuration. The absolute stereochemistry of the active substance has been confirmed by single crystal X-ray crystallography.

Cabotegravir exhibits polymorphism and four solid state forms have been identified, of which only two are relevant to the commercial manufacturing process: Form 1 and Form 2. Form 1 was confirmed as

the most thermodynamically stable form at ambient conditions and is consistently produced by the proposed commercial manufacturing process.

2.3.2.2. Manufacture, characterisation and process controls

Cabotegravir is synthesized in 5 synthetic steps using well defined starting materials with acceptable specifications. The final crystallization step ensures the desired polymorphic form is produced.

A science and risk-based approach was applied in development of the commercial manufacturing process for cabotegravir consistent with ICH Q11 for the development and manufacture of active substances. Based on the Quality Target Product Profile (QTPP) defined for the prolonged release suspension, the Critical Quality Attributes (CQAs) of the active substance have been identified. Based on the CQAs for the active substance, every stage of the manufacturing process has been evaluated and optimized by a quality by design (QbD) approach and the use of Design of experiments (DoE). Design spaces, supported by multivariate experimentation, have been defined for all stages of the commercial manufacturing process. In combination with the input specifications, the design spaces represent the control strategy for cabotegravir. Critical Process Parameters (CPPs) and their target values or ranges are identified, as well as non-critical process parameters. The CPP ranges are within the ranges studied in the DoEs.

Sufficient information was presented for the verification of the proposed DSs at commercial scale. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Potential and actual impurities were well discussed with regards to their origin and characterised.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Rationale for impurity specifications in starting materials and intermediates is based on fate and purge studies.

The active substance packaging is described. The materials comply with EU Commission Regulation No 10/2011 for food contact use. The polyethylene used in the manufacture of the bags meets the compositional requirements of Ph. Eur. Section 3.1.3 Polyolefins. The antistatic additive used in the manufacture of the bags is not listed under Ph. Eur. 3.1.3. However, the manufactured bag material has been tested to, and found to comply with the test requirements of Ph. Eur. 3.1.3.

2.3.2.3. Specification

The active substance specification includes tests for description (visual), identification (IR), solid state form (XRPD), cabotegravir content (HPLC), impurities (HPLC), enantiomer content (chiral HPLC), diastereomer content (chiral HPLC), residual solvents (GC), water content (KF), bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.).

The proposed specification is acceptable. The proposed limits are in line with the relevant guidelines and the provided batch analyses. The limits for specified and unspecified impurities comply with ICH Q3A and for residual solvents with Q3C and are justified through fate and purge studies. The provided justification for the parameters included in the specification and those parameters not included in the specification is acceptable.

There are two mutagenic impurities identified during development which have the potential to be present in active substance. Based on batch data, these mutagenic impurities would not be present in

active substance above 30% of the TTC-based acceptable limit of 16 µg/g. Consequently, neither of these mutagenic impurities are included on the active substance specification.

A risk assessment according to ICH Q3D has been conducted and the proposed controls for elemental impurities are justified.

The analytical procedures have been sufficiently described. Non-compendial analytical methods have been successful validated according to ICH guidance. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data were provided for three production-scale batches of cabotegravir, which were manufactured according to the proposed commercial method at the commercial site and tested by the proposed commercial methods. In addition, as well as several representative batches used in non-clinical and clinical studies that support the specifications and show process consistency.

2.3.2.4. Stability

Stability data have been provided for four pilot scale batches stored under long term conditions (30 °C/75% RH) for up to 60 months and under accelerated conditions (40 °C/75% RH) for up to 6 months. Although higher humidity than recommended in ICH Q1A(R2) was used for the long-term stability studies at 30 °C, no objection is made as the higher humidity is seen as more likely to cause degradation. The batches were stored in the proposed commercial packaging.

Stability batches were tested for description, assay, impurities, water content, solid state, diastereomer and enantiomer content. The methods are the same used for release except for the method for the determination of enantiomer content. The different method for enantiomer content has been described and fully validated and was shown to be equivalent to the method used for release testing.

No trends were observed in any of the provided stability batches under any of the stability conditions. Although control of the storage temperature is not required, the proposed storage condition “Store up to 30 °C” is considered acceptable.

In addition to ICH stability studies, stress studies (50 °C, 40 °C/75% RH, photostability, and freeze-thaw cycles) were performed for one pilot batch up to three months. Photostability was conducted on a pilot batch, according to ICH Q1B. No significant changes were observed and the results demonstrate chemical and physical stability of cabotegravir under these storage conditions.

Forced degradation studies have been performed on cabotegravir to identify potential degradation products. Cabotegravir was chemically stable in the solid state under all stressing conditions used in the forced degradation study. There was no significant increase in the total degradation products under any solid-state stress condition. Significant degradation was only observed in solution under acidic, basic and oxidative conditions. However, the degradation pathways observed under solution phase conditions are formed under forcing conditions that are not representative of those that a solid active substance will experience during manufacture or storage. The results from the forced degradation studies demonstrate that the HPLC methods for assay, impurities, diastereomer and enantiomer content are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable in the proposed container. Based on the available stability data the proposed retest period of 60 months with storage condition “Store up to 30 °C” is acceptable.

2.3.3. Active Substance - Cabotegravir sodium

2.3.3.1. General information

The chemical name of cabotegravir sodium is sodium (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide. It corresponds to the molecular formula $C_{19}H_{16}F_2N_3NaO_5$, its relative molecular mass is 427.33 and it has the structure shown in Figure 2.

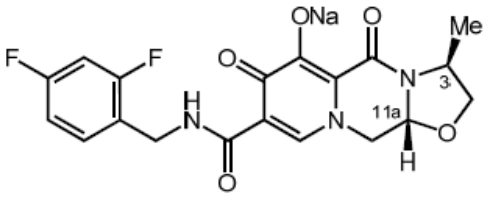


Figure 2: cabotegravir sodium structure

Cabotegravir sodium appears as a white to almost white non-hygroscopic crystalline solid hygroscopic powder. It is practically insoluble below pH 9 and slightly soluble above pH 10 in aqueous media.

The structure of the active substance (AS) was elucidated by a combination of ^{1}H and ^{13}C NMR spectrometry, MS, IR spectrometry, inductively coupled plasma optical emission spectroscopy, elemental analysis and single crystal X-ray crystallography.

Cabotegravir sodium possesses two stereogenic centres and is the isomer with the 3*S*, 11a*R* configuration. The absolute stereochemistry of the active substance is confirmed by single crystal X-ray crystallography.

Cabotegravir sodium exhibits polymorphism. Two solid state forms that are relevant to the commercial manufacturing process have been identified, Form 4 and Form 3. Form 4 was confirmed as the most thermodynamically stable form under ambient conditions and is consistently produced by the proposed commercial manufacturing process. Solid state form is not impacted by micronization. A test for solid state form is included in the active substance specification.

2.3.3.2. Manufacture, characterisation and process controls

Cabotegravir sodium is manufactured using the same process as for cabotegravir but with the addition of salt formation and micronization steps.

Both micronized and non-micronized cabotegravir sodium packaging material has been described. These are the same packaging materials as used for cabotegravir.

2.3.3.3. Specification

The active substance specification includes appropriate tests and limits for description (visual), identification (IR), solid state form (XRPD), cabotegravir sodium content (assay by HPLC), sodium content (ICP-OES), impurities (HPLC), enantiomer content (chiral HPLC), diastereomer content (chiral HPLC), residual solvents (GC), water content (KF), and particle size (laser diffraction).

The proposed specification is acceptable. The proposed limits are in line with the relevant guidelines and the provided batch analyses. The limits for specified and unspecified impurities comply with ICH Q3A and for residual solvents to Q3C and are justified through fate and purge studies. The provided

justification for the parameters included in the specification and those parameters not included in the specification is acceptable.

The analytical procedures have been sufficiently described. Non-compendial analytical methods have been successful validated according to ICH guidance. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data were provided for three full scale and five pilot batches of micronized cabotegravir sodium, which were manufactured according to the proposed commercial method by the proposed manufacturer and micronized at each of the three proposed commercial micronization sites. In addition, data from another 4 batches of cabotegravir sodium (micronized), manufactured using a process representative of that intended for commercial manufacture and synthesized at the commercial site of manufacture have been provided. These batches are representative of the quality of the active substance that was used in clinical trials including the phase 3 study. Batches were tested by the proposed commercial methods or validated clinical release methods. All batches complied with the proposed specifications and confirm the consistency of the manufacturing process.

2.3.3.4. Stability

Stability data for cabotegravir sodium (micronized) have been provided for five pilot scale batches stored under long term conditions (30 °C / 75% RH) for up to 60 months and under accelerated conditions (40 °C / 75% RH) for up to 6 months. The batches were stored in the intended commercial packaging. One batch of micronized material was also stored at 5 ± 3 °C and 50 °C, both without humidity control. In addition, one pilot batch of non-micronized material was stored at 30 °C / 75% RH (60 months), 40 °C/75% RH (6 months), 5 ± 3 °C and 50 °C, the latter two studies without humidity control. Although higher humidity than recommended in ICH Q1A(R2) was used for the long-term stability studies at 30 °C, no objection is made as the higher humidity is seen as more likely to cause degradation.

Stability batches were tested for description, assay, impurities, enantiomer and diastereomer content, water content (non-micronized cabotegravir sodium only), particle size (tested for information only for non-micronized cabotegravir sodium) and solid-state form. The used methods are the same as for release except for the methods for the determination of enantiomer content and impurities. These different methods have been described and fully validated and were shown to be equivalent to the methods used for release. No significant changes or trends were observed under any of the storage conditions.

A photostability study was conducted, according to ICH Q1B, on two pilot batches of cabotegravir sodium (one micronized and one non-micronized). Based on the provided results, cabotegravir sodium requires protection from light.

A freeze/thaw study was also performed in which samples were stored for two repeated cycles consisting of 7 days at -20 °C followed by 7 days at 30 °C. No significant changes were observed and the results demonstrate chemical and physical stability of cabotegravir under these storage conditions.

Forced degradation studies were performed on cabotegravir sodium to identify potential degradation products that might be formed in active substance. Cabotegravir was chemically stable in the solid state under all stress conditions used in the forced degradation study. There was no significant increase in the total degradation products under any solid-state stress conditions. Significant degradation was only observed in solution under acidic, basic and oxidative conditions. However, the degradation pathways observed under solution phase conditions are formed under forcing conditions that are not representative of those that a solid active substance will experience during manufacture or

storage. The results from the forced degradation studies demonstrate that the HPLC methods for assay, impurities, diastereomer and enantiomer content are stability indicating.

Based on the available stability data the proposed retest period of 60 months with storage conditions “store up to 30 °C” and “protect from light” is acceptable.

2.3.4. Finished Medicinal Product - prolonged-release suspension for injection

2.3.4.1. Description of the product and pharmaceutical development

The finished product is a prolonged release suspension for injection containing 200 mg/mL cabotegravir free acid, intended for intramuscular (IM) injection. It is a white to light pink, free flowing suspension. Each sterile, single-use glass vial of Cabotegravir Injectable Suspension is intended to provide a dose of 600 mg. No dilution is required prior to IM administration.

The objective of the pharmaceutical development was a suspension for injection, for long-acting drug delivery, stable, easily re-dispersible, at a sufficient drug load to minimize injection volume for intramuscular administration.

The QTPP, and CQAs of the finished product have been established and discussed. Cabotegravir free acid was chosen due to its low aqueous solubility in order to achieve the desired pharmacokinetic performance. Cabotegravir free acid low aqueous solubility, long systemic half-life and the controlled particle size of the suspension allow for a finished product with long-acting drug delivery and permit high drug loading, which in turn minimizes injection volume required to achieve the desired exposure.

The formulation development studies to ensure the desired finished product attributes are described. All excipients are widely used materials in pharmaceutical formulation and are described in Ph. Eur., with a long story of safe utilisation by injectable administration. Their choice was duly discussed and justified. The list of excipients is included in section 6.1 of the SmPC.

The development of dissolution method has been elaborated and justified.

The development of the manufacturing process has been described in sufficient detail.

The overfill of vials by 0.4 ml is justified since it ensures that the required dose can be extracted from the vial and administered.

In-use stability of the Cabotegravir injectable suspension withdrawn into a sterile syringe has been demonstrated for 2 hours at room temperature. This is reflected in the in-use shelf-life stated in the SmPC section 6.3.

The primary packaging is a brown 3 mL type I glass vial, with bromobutyl rubber stopper and a grey aluminium overseal with an orange plastic flip-cap. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.4.2. Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: gamma irradiation of cabotegravir, compounding of excipients and subsequently, cabotegravir, wet milling, filling into vials and stoppering, and finally, terminal sterilisation. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 production scale batches including the terminal sterilization step. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form.

Data to support the assurance of sterility of finished product and to justify parametric release rather than end product sterility testing has been presented.

2.3.4.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form and consist of tests for description (visual), identification (HPLC, UV), cabotegravir content (HPLC), uniformity of dosage units (Ph. Eur.), impurities (HPLC), extractable volume, particulate contamination (Ph. Eur.), pH (Ph. Eur.), particle size (laser diffraction), dissolution (Ph. Eur., HPLC), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). The tests and limits for both sets of specification are adequately justified in line with applicable guidance.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that no elemental impurity controls are needed in the finished product specification.

A thorough risk evaluation concerning the potential presence of nitrosamine impurities in the finished product has been submitted following a CHMP Major Objection. The risk evaluation considered all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 4 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The product is released to the market based on the release specifications, through traditional final product release testing for all parameters except for sterility where parametric release has been justified.

2.3.4.4. Stability of the product

Stability data from 4 production scale batches of finished product stored for up to 36 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Data are also available from batches stored under refrigerated conditions (5±3 ºC) for up to 36 months. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were stored in both upright and inverted format.

Samples were tested according to the shelf-life specifications. The analytical procedures used are stability indicating. No significant changes or trends to any of the measured parameters were observed. Nonetheless, given that the suspension for injection is packaged to be in direct contact with the rubber stopper, a risk of contamination by particles from the rubber stopper cannot be excluded. It is therefore recommended by the CHMP to include the control of the particulate matter contamination (visible particles and sub-visible particles) in the post-approval stability protocol.

Samples were also exposed to heat (50 ºC) and freeze thaw conditions. The product is stable at high temperature but out of specification results were seen for description, assay and particle size in the frozen samples.

In addition, the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is photostable.

Based on available stability data, the proposed shelf-life of 36 months without specific storage conditions (other than “do not freeze” as stated in the SmPC section 6.3) is acceptable.

2.3.4.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.5. Finished Medicinal Product – film-coated tablets

2.3.5.1. Description of the product and pharmaceutical development

The finished product is an immediate release film coated tablet for oral administration, containing cabotegravir sodium equivalent to 30 mg of cabotegravir free acid. The tablets are white film-coated, oval-shaped tablets, debossed with ‘SV CTV’ on one side.

A science and risk-based approach, applying QbD and quality risk management (QRM) principles in accordance with ICH Q8, Q9, Q10, was used to develop the film coated tablets.

The QTPP, has established the desired quality characteristics of the finished product. The finished product CQAs have been identified and an understanding of the impact of the attributes of the active substance, excipients, container closure system and in-process materials, as well as the process parameters of the manufacturing process on finished product quality were established.

The active substance for the cabotegravir tablets is the sodium salt of cabotegravir which is micronized to meet the QTPP. Cabotegravir sodium is a BCS 2 compound The sodium salt has higher solubility than the free acid form ensuring oral bioavailability and appropriate pharmacokinetics. Particle size distribution (PSD) was studied in a human pharmacokinetics study that showed that micronized cabotegravir sodium gave an increased AUC and Cmax when compared to non-micronised substance.

All chosen excipients are widely used in solid oral products and the levels chosen for this product are within typical ranges used for tablets. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The choice and optimization of active substance crystalline form, particle size limits, the excipients, their function and quantity were sufficiently justified and explained.

The finished product CQAs and the input materials attributes or process parameters that determine the CQAs are identified. A risk assessment has been conducted and the relationship between process parameters and intermediate and finished product CQAs was established. Process development has

been conducted at commercial scale. The granulation unit operation has been identified to impact the CQAs. Based on the DoE, a design space was established for this step.

The development of the dissolution method has been well described. The method is considered suitable since it can differentiate between clinically bio-equivalent and non-bioequivalent batches.

The primary packaging consists of opaque, white HDPE bottles with polypropylene child resistant closures, with a polyethylene faced induction heat seal liners. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.5.2. Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: blending of cabotegravir sodium with intra-granular excipients, wet granulation, milling and drying, blending with extra-granular excipients, compression, and film-coating. The process is considered to be a standard manufacturing process.

Traditional 3-batch process validation has not been performed. Continuous process validation principles from the CHMP finished product process validation guideline are employed which actively monitor the validity of the design space. The approach is adequately documented in the process validation scheme. The results of qualification studies for the CQAs are presented and acceptable.

2.3.5.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description (visual), identification (HPLC, UV), uniformity of dosage units (HPLC, Ph. Eur.), cabotegravir content (HPLC), impurities (HPLC), dissolution (Ph. Eur., UV) and microbiological limit tests (Ph. Eur.).

The proposed specifications are set based on the requirements of ICH Q6A and Ph. Eur. The justifications provided are agreed. The limits for impurities are in line with ICH Q3B. The specifications are sufficiently justified and together with the manufacturing process control ensure the finished product quality attributes will be consistently met.

A risk assessment for elemental impurities has been conducted in accordance with ICH Q3D Option 2b, to evaluate the potential for elemental impurities to be present in the finished product and the relevant discussion has been provided. No elemental impurities were identified to be present at a level of greater than 30% of the PDE limit for oral administration. Based on this, no tests for elemental impurities are included in the finished product specification.

A risk assessment, in line with the “Questions and answers on Information on nitrosamines for marketing authorisation holders” and the “Information on nitrosamines for marketing authorisation holders” published on the EMA website, have been presented for both the finished product manufacturing process and the active substance with respect to potential formation of nitrosamine impurities. The outcome of the risk assessment confirms that there is no risk for nitrosamine impurities formation.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 7 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

2.3.5.4. Stability of the product

Stability data from three commercial scale batches of finished product manufactured by the proposed commercial process at the proposed site and stored for up to 48 months under long term conditions (5 ºC, 25 ºC / 60% RH and 30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. These batches were packed in the primary packaging proposed for marketing. Samples were tested according to the release specifications and using the same test methods. In addition, water content was tested according to the Karl Fisher method (Ph. Eur. 2.5.32). No significant changes in description, content, drug related-impurities, dissolution and microbial limit test were observed, and all results comply with specification. A small increase in the water content was observed under accelerated conditions only which had no impact on other product CQAs.

In addition, studies have been performed on one full-scale batch under various stressed conditions: 50 ºC/ ambient humidity and a freeze/thaw cycle (-20 ºC/30 ºC). No significant changes to any measured parameters were observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photostable.

Forced degradation studies were performed on one full-scale batch under three conditions: 80 °C for 14 days, 80 °C/ 75 % RH for 14 days and UV-Vis light exposure (ICH Q1B conditions). No increase in degradation products above the ICH Q3B limit was observed and mass balance was always achieved. No significant changes other measured parameters were observed.

In-use stability studies were presented at the initial timepoint and after storage at the long-term storage condition for 49 months. The in-use stability studies were performed on one of the primary stability batches. No significant changes in description, assay, impurities and dissolution were observed. An increase in water content was observed, however this is not associated with any change in physical or chemical stability and has no impact on any other CQAs.

Based on available stability data, the proposed shelf-life of 60 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.3.5.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other excipients derived from animal or human origin have been used.

2.3.6. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished products has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that

the product should have a satisfactory and uniform performance in clinical use. The major objection relating to the potential presence of nitrosamines was resolved by submission of a more thorough risk evaluation.

The applicant has applied QbD principles in the development of the active substances and finished products and their manufacturing processes. Design spaces have been proposed for several steps in the manufacture of the active substance and for the granulation step in tablet manufacture. The design spaces have been adequately verified.

2.3.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.8. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation concerning the prolonged-release suspension for injection formulation:

- The MAH is recommended to include the control of the particulate matter contamination (visible particles and sub-visible particles) in the post-approval stability protocol.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Cabotegravir (GSK1265744 or CAB) inhibits 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. CAB is a potent in vitro inhibitor of HIV integrase and inhibits the integrase catalysed viral DNA strand transfer with IC50 values in the nanomolar range (3.0 to 13 nM).

The antiviral mechanism of CAB on HIV replication was investigated using quantitative PCR, in vitro passage, and direct binding dissociation studies. CAB demonstrated equivalent potency against 2 nonnucleoside inhibitor resistant, 2 nucleoside inhibitor resistant and 2 protease inhibitor resistant HIV-1 mutant clones (one with 3 and one with 6 mutations) compared with the wild type strain. In addition, passage studies with CAB selected mutations within the integrase enzyme; some of those mutations recreated as site-direct mutant HIV virus conferred moderate levels of CAB resistance when compared to wild type virus.

The critical review of primary pharmacodynamic studies is reported in the clinical section.

2.4.2.2. Secondary pharmacodynamic studies

The secondary pharmacology potential of CAB was evaluated for possible interactions with 16 enzyme assays and 65 physiological receptor and ion channel and transporter binding sites and 12 isolated tissue assays. CAB at 10 µM higher than free clinical Cmax following oral lead in (0.1 uM) did not significantly affect (defined as ≥50%) 80 of the 81 in vitro assays. The only effect greater than 50% was a 53% inhibition of binding in the melanocortin (MC4) receptor binding assay. The potential to antagonise MC4R was also observed for another integrase inhibitor dolutegravir (Tivicay) at a concentration equal to the clinical Cmax. The MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in the MC4R is associated with monogenic obesity. However, no dose-related significant effects occurred on body weight and food consumption in the repeat dose toxicity studies in the rat (up to 26 weeks) and monkey (up to 39 weeks), indicating the lack of apparent biological activity at the MC4 receptor. Additionally, no selective association of radioactivity with melanin was observed after single oral administration of [14C]-CAB to partially pigmented Lister-Hooded (see PK section). Notwithstanding, no findings associated with MC4R agonism or antagonism have been observed in toxicity studies with CAB, and there were no clinically significant patterns of changes in vital signs (weight, heart rate, systolic and diastolic blood pressure) across the clinical studies. Additionally, variations in weight or appetite were generally not reported or reported as uncommon adverse drug reactions in any of the clinical studies and were generally similar between CAB and comparators.

2.4.2.3. Safety pharmacology programme

CAB at 7.14 µg/mL (the maximum concentration limited by solubility), corresponding approx. to the clinical oral lead in Cmax 20 uM, caused no inhibition of hERG channel tail current in HEK-293 cells stably transfected with hERG cDNA. In conscious telemetered male monkeys, a CAB oral dose of 1000 mg/kg (Cmax of 67 µg/mL; AUC0-24 1051 µg.h/mL) produced a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 hours after dosing. No ECG waveform or interval changes were associated with these pressure and heart rate changes and no effects occurred at doses of 8 and 25 mg/kg (Cmax 20.8 µg/mL; AUC0-24 233 µg.h/mL).

In addition, no ECG changes occurred in male or female monkeys given up to 1000 mg/kg/day for at least 14 consecutive days. In a thorough QTc study (mass balance study in healthy subjects) oral dose of CAB supratherapeutic dose of 150 mg q 12 h x 3 doses had no significant effect on cardiac repolarization (see clinical section).

No respiratory effects occurred in conscious telemetered male rats in safety pharmacology studies at oral doses up to 300 mg/kg (Cmax of 35.8 µg/mL; AUC0-24 708 µg.h/mL). No neurobehavioral effects occurred in male rats on day 5 of the 14-day oral toxicity study at doses up to 300 mg/kg (Cmax of 35.8 µg/mL; AUC0-24 708 µg.h/mL).

Overall, the exposure margins of oral CAB in safety pharmacology studies were in the range of 0-8 fold compared the clinical total Cmax reached with oral lead in administration.

2.4.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamics drug-drug interaction studies have been conducted.

The critical review of clinical studies conducted with CAB in combination with other antivirals is reported in the clinical section.

2.4.3. Pharmacokinetics

Studies have been performed to characterize the absorption, pharmacokinetics, distribution, metabolism and excretion of cabotegravir. In vivo studies were primarily conducted by the oral route and by the subcutaneous/ intramuscular routes, as these are the proposed therapeutic routes for CAB in humans. Also, the intravenous route was used experimentally to assess the pharmacokinetics and bioavailability. In vitro investigations have also been conducted to determine the binding of CAB to plasma proteins, its association with red blood cells, its metabolism by or interaction with cytochrome P450 isoenzymes, and the potential interaction with various transporters. These studies have been conducted in compliance with Company Divisional Standard Operating Procedures and Policies and in general accordance with the principles of Good Laboratory Practice (GLP). Analysis in support of the pivotal repeated dose toxicity studies, whole body autoradiography studies and excretion studies was performed in full compliance with GLP regulations and were conducted in an Organization for Economic and Cooperation and Development (OECD) member country in accordance with the OECD Test Guidelines.

The species and strains used in the present studies reflected those employed in the toxicological testing of CAB, to enable meaningful assessment of the exposure levels in the toxicity studies and provide confidence in the conclusions drawn regarding the safety of CAB in humans. The species and strains used were CD-1 mice, Sprague Dawley rats, partially pigmented Lister-Hooded rats, Dutch belted rabbits, beagle dogs and cynomolgus monkeys.

The Applicant submitted a new PK study in minipig dated 31 May 2021: 2021N472397_00; GSK1265744: Investigation of the Systemic Exposure of GSK1265744 in the Male Gottingen Minipig Following Intramuscular Administration at a Dose Level of 1 mg/kg. The minipig PK study was only conducted to investigate a potentially new animal model to study additional injectable formulations for CAB.

Methods of analysis

CAB quantified by high performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) in plasma samples of mouse, rat, rabbit and monkey. The metabolic profiling of CAB was conducted by using chromatographic separation with radiometric detection and identification of metabolites performed by using LC-MS; nuclear magnetic resonance (NMR) methods were used to confirm structures not confirmed by mass spectrometric methods. The bioanalytical methods are considered adequate.

Absorption

Following single IV administration of CAB to dogs and monkeys, the plasma clearance (<2% of hepatic plasma flow) and steady-state volume of distribution (<0.35 L/kg) were low, with half-life values of 4 to 6 hours. The sampling regimen in the rat was insufficient to characterize the pharmacokinetic parameters; however, the CAB concentration time profile was indicative of a lower clearance and longer half-life than in dogs and monkeys.

In rats and monkeys given a single SC or IM injection, CAB was slowly released from the injection site with a mean apparent plasma half-life ranging from 12 to 29 days (SC) or from 8 to 12 days (IM). The mean half-life of CAB was 76 hours following a single IM dose (1 mg/kg) to minipig.

Following oral administration as a solution, the oral bioavailability of CAB was good (44 to 83%) and consistent with its high passive permeability. However, when administered as a suspension, or in solid dosage forms, the bioavailability appeared limited by dissolution rate or solubility which resulted in a less than proportional increase in systemic exposure of CAB relative to dose. In mice, rats and

monkeys, no consistent notable (>2-fold) difference in oral systemic exposure between sexes was observed.

Distribution

CAB has high passive membrane permeability, is highly protein bound and is widely distributed and crosses the placental barrier. The glucuronide metabolite of CAB (also referred to as CAB glucuronide, M1 or GSK3388352) exhibited low plasma protein binding.

The protein binding of CAB in rat, dog, monkey and human plasma and serum was high (>99%). CAB is a substrate for Pgp and BCRP, but due to its high permeability, no alteration in absorption would be expected by co-administration of either Pgp or BCRP inhibitors. After single oral administration of [^{14}C]-CAB to partially pigmented Lister-Hooded rats, radioactivity was slowly absorbed and then largely confined to the systemic circulation albeit widely distributed to other tissues. Radiolabelled drug-related material was minimally associated with cellular components of blood. Elimination of radioactivity was slow with most tissues containing low but quantifiable radioactivity at 28 days. Association of radioactivity to the melanin-containing tissues in the eye and skin was not observed.

Metabolism

In general, the metabolism of CAB in the nonclinical species reflects that observed in humans, with CAB being the principal component circulating in plasma. The major metabolite of CAB in all species was CAB glucuronide, which was formed primarily by UGT1A1 (with some involvement from UGT1A9) and was eliminated in the urine and bile. Additional studies in human (IM, SC and PO) confirmed that the metabolism and excretion of CAB is independent of route of administration. Metabolic conversion of CAB to its stereoisomers was not detected in rat, dog, monkey, or human hepatocytes, or in human plasma following repeat oral administration for 14 days.

The metabolism of CAB has not been investigated in the rabbit, but it has been investigated in the rat, the other species used for embryofoetal development investigations, and the pathways of biotransformation (predominately glucuronidation as indicated by CAB glucuronide in urine and bile) were the same as those observed in human. Although there were no disproportionate CAB metabolites identified that needed characterization, it is generally understood that when characterization of metabolite toxicity is warranted for effects on embryo-foetal development, a toxicity study in one species is considered sufficient (EMA/CHMP/ICH/507008/2011). It is acknowledged the lack of disproportionate CAB metabolites regarding human PK, and therefore the metabolism of CAB has sufficiently been investigated in rat and does not require further characterisation in the rabbit.

Elimination

Across all species, elimination of drug-related material occurred predominantly via the faeces (58.5 to 94.5% of the dose). In rodents, absorbed radioactivity as determined by the amount of drug-related material recovered in the urine and bile (limited to approx. 2% dose), was predominantly secreted into the bile while renal excretion was minimal. In monkeys, the absorbed radioactivity (approximately 30% dose) was eliminated via both the biliary and renal routes.

In vitro data indicates that circulating CAB permeates passively into hepatocytes and is metabolized to CAB glucuronide which undergoes both biliary and sinusoidal excretion. Biliary excretion of CAB glucuronide is mediated by MRP2, while hepatic basolateral excretion into sinusoidal blood was via both MRP3 and MRP4. Circulating CAB glucuronide undergoes efficient renal clearance, where uptake into the proximal tubule is mediated by OAT3 and subsequent secretion into urine by MRP2 and MRP4, which would explain the minimal systemic exposure of CAB glucuronide in human.

Pharmacokinetic drug interactions

No clinical drug interaction risk was identified for co-administered substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17, Pgp, BCRP, BSEP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE 2-K, MRP2 or MRP4 at a clinical oral dose of 30 mg CAB. An additional in vitro study confirmed that CAB is not an inducer of CYP1A2 or CYP2B6 at concentrations from 0.03 to 30 uM in cryopreserved cultured human hepatocytes from three individual donors, incubated for 48 hr.

As CAB is metabolized by UGT1A1 and a clinical study has confirmed a drug interaction with the UGT1A1 inducer rifampin, the co-administration of CAB with strong inducers of UGT is contraindicated. This potential drug interaction is stated in the SmPC.

There was no observed PK interaction between CAB and RPV when co-administered IM to rats or monkeys.

In a folate receptor α assay, CAB demonstrated 36.7% inhibition at 25.8 µM. The applicant presented resounding data showing that CAB is not a clinical inhibitor of folate transport pathways, and it was not predicted to elicit clinical decreases in maternal and foetal folate levels. However, according to Foster et al., 2022 (https://doi.org/10.3390/ph15121533), more investigation and comprehensive data are needed to understand the PK, placental passage, and safety of CAB in pregnancy to confirm or refute the potential safety signal of neural tube birth defects observed in infants born to women receiving dolutegravir-based ART periconception. This is particularly relevant for PrEP indication. Currently, the statement in section 4.6,

> "Apretude injection is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus. Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for foetal exposure during pregnancy (see section 4.4)"

is adequate from a (non-)clinical point of view.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No GLP-compliant single dose oral toxicity studies have been performed. Single dose toxicity studies included one GLP-compliant study in rats with administration of cabotegravir by subcutaneous or intramuscular injection at doses of up to 100 and 75 mg/kg, respectively. Additional studies comprised a set of 9 non-GLP studies with administration of cabotegravir by the oral route (mouse and cynomolgus monkey) or subcutaneous or intramuscular injections (rat, cynomolgus monkey) or with administration of cabotegravir in combination with rilpivirine (rat, intramuscular). In the non-GLP studies, the dose levels administered by the oral, subcutaneous and intramuscular routes were up to 2000, 50 and 35 mg/kg, respectively. Dose levels of cabotegravir and rilpivirine employed in the study with the combination were of 10 and 60 mg/kg, respectively.

None of the studies revealed cabotegravir-related mortality. In the intramuscular/subcutaneous GLP-compliant study, effects (erythema and oedema) were observed at the injection sites. In the two studies with oral administration (both non-GLP) effects included the observation of decreased activity and irregular breathing shortly after dosing in one mouse (out of 15) treated with 2000 mg/kg. No adverse effects were observed in cynomolgus monkey given oral doses up to 1000 mg/kg.

2.4.4.2. Repeat dose toxicity

Repeated dose toxicity studies included 9 studies with daily oral administration and one study with weekly or monthly administration by subcutaneous or intramuscular injection. The studies with oral administration were conducted in mice, rats and cynomolgus monkeys treated during up 13, 26 and 39 weeks, respectively. The study with subcutaneous or intramuscular injection was a 13-week study conducted in rats. All studies except for a 7-day study in cynomolgus monkeys were GLP-compliant. Endpoints evaluated in the non-GLP study were limited to clinical observations, toxicokinetics, body weights, haematology and clinical chemistry. In the GLP-compliant studies, in addition to conventional endpoints commonly evaluated in repeated dose toxicity studies, the following were included: stage-dependent evaluation of spermatogenesis (2-week in mice, 2 and 4-week in rats, 4-week in monkeys), neurobehavioral assessment and hepatic P450 isoform evaluation (both in 2-week in rats), electron microscopy and viral serology (both in 4-week in cynomolgus monkeys).

The test species were justified as the rodent and non-rodent species with the highest systemic exposure. All selected species are considered relevant from a metabolite perspective.

Cabotegravir was generally well tolerated without adverse effects in the oral repeat-dose toxicity studies in mice, rats and monkeys. In the 2-week toxicity study in monkeys, a high mortality was observed in males given 1000 mg/kg/day, which was associated with GI effects. The effects on the GI tract are considered due to local irritation of the compound as opposed to a systemic effect. The 39-week study in monkeys revealed ocular findings in two monkeys - slight vascular inflammation was noted unilaterally near the optic nerve of a single monkey dosed with 500 mg/kg/day and inflammation and swelling of the optic nerve head with peripapillary oedema and diffuse corneal opacity was observed in a single animal dosed with 50 mg/kg/day. The applicant considers these ocular events as incidental.

At the end of the longest-term toxicity studies in rats and cynomolgus monkeys (26-week with administration of up to 1000 mg/kg/day and 39-week with administration of up to 500 mg/kg/day, respectively), systemic exposures (AUC_{0-24}) at the maximum tested dose (also the NOAEL) were 3203 and 4781 µg·hr/mL in male and female rats, respectively, and 542 and 552 µg·hr/mL in male and female cynomolgus monkeys, respectively. These AUC are, approximately, 22 to 32-fold, in rats, and 4-fold, in monkeys, the clinical AUC exposure in patients treated with oral doses of 30 mg/day.

In the study with subcutaneous or intramuscular administration - with weekly subcutaneous doses of 100 mg/kg, monthly subcutaneous doses of up to 100 mg/kg and monthly intramuscular doses of up to 75 mg/kg - four high dose rats treated monthly were euthanized due to deteriorating conditions or found dead. The cause of moribundity or death in these animals was not linked to any underlying pathology findings, as none of these animals had explanatory pathology findings distinct from survivors. Therefore, these deaths were considered unlikely treatment-related. Besides dose-proportional signs of redness, swelling and inflammation following subcutaneous and intramuscular injections at all dose levels, no additional adverse effects were noted.

At the end of study, systemic exposures ($AUC_{1440-2160h}$ and $AUC_{2016-2184h}$ for monthly and weekly administrations, respectively) at the maximum tested dose (also the NOAEL) given weekly subcutaneously, monthly subcutaneously and monthly intramuscularly were the following in rat males and females (M/F): 22291/34315, 70494/116602 and 78051/107080 µg·hr/mL, respectively. According to the provided calculations of margins of exposure, at the NOAEL, the AUC values in males/females after monthly administration by subcutaneous and intramuscular injections were, approximately, 37.46/61.96 and 41.47/56.90-fold, respectively, the clinical AUC_{0-t} value in patients given a dose of 600 mg every 2 months by intramuscular injection.

Table 1: Estimated Margins of CAB Relative to Clinical Exposure Following Administration of CAB Injectable Suspension

Species	Dose (mg/kg)	Sex	Route of administration	Cmax (µg/mL)[a,b]	AUC (µg.h/mL)[a,c]	2X AUC (µg.h/mL)[f]	Animal to human ratio for AUC[g]
Rat (Single dose)	5	M	SC	8.36	4346	8692	2.31
		F	SC	9,04	5367	10734	2.85
	30	M	SC	38.7	19978	39956	10.62
		F	SC	36.9	19218	38436	10.21
	100[d] (NOAEL)	M	SC	98.3	47912	95824	25.46
		F	SC	104	51104	102208	27.15
	2.5	M	IM	12.6	4321	8642	2.30
		F	IM	14.2	4525	9050	2.40
	10	M	IM	32.4	15926	31852	8.46
		F	IM	40.6	16464	32928	8.75
	75 (NOAEL)	M	IM	105	60071	120142	31.92
		F	IM	124	64765	129530	34.41
Rat (3-month)	5	M	SC monthly	19.2	11204	22408	5.95
		F	SC monthly	26.8	15238	30476	8.10
	30	M	SC monthly	84.8	48082	96164	25.55
		F	SC monthly	96.8	55956	111912	29.73
	100 (NOAEL)	M	SC monthly	137	70494	140988	37.46
		F	SC monthly	195	116602	233204	61.96
	2.5	M	IM monthly	16.9	7031	14062	3.74
		F	IM monthly	15.9	5500	11000	2.92
	10	M	IM monthly	49.6	26001	52002	13.82
		F	IM monthly	55.2	24934	49868	13.25
	75 (NOAEL)	M	IM monthly	135	78051	156102	41.47
		F	IM monthly	181	107080	214160	56.90
	100 (NOAEL)	M	SC weekly	166	22291	NA	NA
		F	SC weekly	226	34315	NA	NA

Human[e]	600 mg Every 2 months	M/F	IM	4.0	3764	NA	NA

Key: n=3 animals/sex/dose, except where noted. NOAELs are in bold text

a. Results are reported as means.

b. For rat 3-month, C_{max} reported as overall study C_{max}.

c. For rat single dose, AUC reported as AUC_{0-720}, AUC through 30 days (morning of Day 31). For rat 3-month, AUC for SC or IM monthly groups reported for the 3rd monthly interval, $AUC_{1440-2160h}$. For rat 3-month, AUC for SC weekly groups is reported as AUC during Week 13 (from predose on Day 85 to Day 92), $AUC_{2016-2184}$.

d. n = 2 males for AUC0-t in the 100 mg/kg dose group due to unscheduled death on Day 39.

e. Geometric mean exposure (Cmax and AUC0-t) at steady state. Data Source: GSK Document Number 2018N384611_01 Table 17 and GSK Document Number 2019N421460_00 Table 14 [see m2.7.2 section 3.1.5].

f. 2X AUC is calculated by doubling the AUC for the rat AUC monthly exposure.

g. Animal to human exposure margins are based on 2X once monthly animal AUC values (to estimate 2 month exposures) compared to every 2 month clinical dosing exposure $AUC_{0-2\ month}$ values.

2.4.4.3. Genotoxicity and carcinogenicity

CAB was negative in a complete set of in vitro and in vivo genotoxicity assays. CAB has demonstrated a lack of carcinogenic potential in conventional oral 2-year studies in mouse and rats.

2.4.4.4. Reproductive and developmental toxicity

Reproductive toxicity studies included studies to evaluate potential effects on fertility (rat), embryo-foetal development (rat, rabbit) and pre-postnatal development (rat). All studies employed the oral route of administration and, excepted for a dose range finding study in rabbits and two follow-up investigative pre- postnatal studies in rats, all were GLP-compliant.

Potential adverse effects of cabotegravir on fertility were investigated in a dedicated study in male rats, and in a combined fertility and embryo-foetal development study in female rats. No cabotegravir-related effects on male or female fertility were observed at oral doses up to 1000 mg/kg/day, the maximum tested dose. Based on toxicokinetic data from the 26-week oral repeated dose toxicity study in rats, this dose is estimated to correspond to a systemic exposure level (AUC_{0-24}) at least 20-fold higher than that reached in patients treated at the oral recommended dose of 30 mg/day.

Potential adverse effects of cabotegravir on embryo-foetal development were investigated in a combined fertility and embryo-foetal development study in female rats and in two dedicated studies in rabbits, one dose range finding and the other pivotal. The combined study in rats and the pivotal study in rabbits had cabotegravir administered at a dose of up to 1000 and 2000 mg/kg/day, respectively.

In rats, there was no evidence of a treatment-related increased incidence of foetal anomalies at any dose level. Based on a decrease in foetal weights at the high dose level, the developmental NOAEL was determined at 5 mg/kg/day. Based on toxicokinetic data from the 26-week oral repeated dose toxicity

study in rats, at this dose, maternal exposure levels (AUC_{0-24}) are estimated to be approximately 14-fold those reached in patients treated orally at 30 mg/day.

In rabbits, the absence of treatment-related effect on embryo-foetal development is claimed at all dose levels. Systemic exposure at the maximum tested dose, also the maximum feasible dose, was very low, 0.66-fold that in patients treated with 30 mg/day. The maximum tested dose induced some maternal toxicity based mostly on a transient decrease in body weight gain.

Studies on pre-postnatal development comprised three studies in rats, one pivotal and two follow-up investigative studies - a study on the cause of the increased F_1 offspring postnatal deaths, namely, on its dependency on exposure in utero and/or during lactation, and a study on toxicokinetics.

In the initial PPND study, rats were treated from GD6 to LD20 at oral doses of 0.5, 5 or 1000 mg/kg/day. At the high dose level, treatment-related decreases in F_1 pup survival and viability were observed (increased number of stillborn pups and neonatal mortality from PND1 to PND4); it resulted in reduced litter sizes during the first 4 days of life. Postnatal development of pups surviving on PND4 was not shown to be affected by treatment.

The NOAEL for perinatal mortality was set at 5 mg/kg/day. Based on the exposure levels observed in the 26-week repeat-dose toxicity study in rats, systemic exposure at 5 mg/kg/day is estimated to be 12.75-14.27-fold that expected in patients treated orally with 30 mg/day.

The follow-up PPND study on causality confirmed these adverse findings and cross-fostering experiments showed that perinatal mortality was attributable to gestational, but not to lactational, exposure to cabotegravir and was not related to decreased maternal care. In both studies, the duration of gestation at 1000 mg/kg/day was longer than that of controls but remained within the historical control range. There was also no treatment-related effect on the average pup delivery time in any study (a finding which could account for increased stillbirth or neonatal mortality). The follow-up PPND study showed that the proportion of stillbirths on GD23 (i.e., pups born from dams with delayed onset of parturition) was 3.5-fold higher in the treated group than in the control group (1.3% vs. 4.6%; or 2/152 vs. 22/478) and was above the historical control data. It is also noted that stillbirths were not reported on GD22 in the control group (0/305 pups) whereas it affected 2/99 pups (2%) exposed in utero to cabotegravir born on that day. Moreover, the number of pups born on GD23 and dead on PND1 prior to cross-fostering was clearly increased in the treated (17) vs. control (0) group. Therefore, an effect of treatment on perinatal mortality cannot be excluded.

The additional investigative toxicokinetic study indicates that exposure levels of both maternal animals and pups were similar at GD20 when dams were treated on GD20 only or from GD6 up the GD20.

No juvenile animal studies have been conducted.

2.4.4.5. Local Tolerance

CAB could be considered to be non-irritant and non-sensitizer.

2.4.4.6. Other toxicity studies

CAB could be considered to be non-immunosuppressive. Effect in anti-KLH IgG antibody observed in males was considered as minimal and not observed in females.

Based on the absence of any relevant signals in the repeat dose toxicity studies, no dependence study was performed. This is acceptable.

No discussion was provided by the Applicant regarding the potential phototoxicity of cabotegravir. Nevertheless, it is known that CAB absorbs mainly at 257nm, and could be considered as non-phototoxic.

Data generated in standard and/or impurity-spiked repeat-dose toxicology studies are considered sufficient to qualify the proposed specifications for the CAB- impurities and degradation products. The control strategy for the genotoxic or potentially genotoxic impurities are considered generally as adequate but only a Summary of the 'Evaluation of Cabotegravir and Cabotegravir sodium Synthesis and Degradation Impurities (Actual and Potential) for Potential Mutagenicity' was provided in section 3.2.S.2.6. of each drug substance. The analysis of the Free base and free acid structures was performed using Derek Nexus version v6.0 (KB 2018 1.1), Lhasa Ltd.; Leadscope version 2.2.1 (Salmonella version 3, E. Coli-Sal 102 version 1), Leadscope Inc.

2.4.5. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment for Apretude (Cabotegravir sodium) was submitted following with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 2006 and the Questions and answers on Guideline on the environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016) document.

ERA report structure and requirements fulfilled the relevant EU guidelines. The studies were conducted according to appropriate OECD test guidelines and under GLP conditions. The species used for testing are species recommended in the OECD test guidelines. Protocols of the ecotoxicological studies were sufficiently detailed to confirm compliance and references made to OECD tests were appropriate.

A comprehensible, concise and detailed ERA report for the active substance, consisted of Phase I and Phase II assessments. All the relevant information required was given, and environmental impact was assessed based on the scientific discussion of the results obtained.

The main results for Phase I and II assessment and the analysis of the results are reported in the following table.

Table 2: for the assessment report providing relevant endpoints of the environmental risk assessment of human pharmaceuticals.
Summary of main study results

Substance (INN/Invented Name): Cabotegravir sodium			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD 107	Log Dow (pH 5) = 1.64 Log Dow (pH 7) = 1.62 Log Dow (pH 9) = 0.96	Potential PBT N < 4.5 action limit
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}	Lod Dow pH 5, 7, 9 1.64, 1.62 and 0.96	not B < phase II trigger 3
	BCF	Lod Dow < pH 4.5	not B
Persistence	DT50 or ready biodegradability OECD 302C	Not readily biodegradable DT50 is not calculable NER (100d): >80% NER max: 92.8-101.7%	vP

Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT				
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.15	µg/L			> 0.01 threshold (Y) Phase II environmental fate and effects is required
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	Koc soil= <10000			Bromsgrove soil; Drayton soil; Elmton soil. 3 soils and 2 activate sewage sludges
Ready Biodegradability Test	OECD 302C	Not Inherently Biodegradable			Not readily biodegradable. Evaluate P criterion: An OECD 308 study should be performed
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	% shifting to sediment >10% DT50 is not calculable NER (100d): >80% NER max: 92.8-101.7%			Distributes to the sediment with more than 10% of the applied dose associated with the sediment at or after Day 14.
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/Species	OECD 201	NOErC ErC10 NOEyC EyC10	0.077 0.16 0.022 0.023	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC immobility NOEC reproduction NOEC length EC10 length	0.71 0.33 0.092 0.25	mg/L	*Dapnia Magna*
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC hatching NOEC larval survival, length, weight EC10 weight	2.00 0.95 1.90	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	15	mg/L	3h/20ºC
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	1000	mg/kg	*Chironomus riparius, o.c. 2.1%*

The applicant provided an ERA Phase 1. Log Pow values were experimentally determined at pH 5, 7 and 9, according to OECD 107 (Test Partition Coefficient (n-octanol/water): Shake Flask Method). The log Pow values of 1.64, 1.62 and 0.96 are clearly below 4.5, the action limit for further screening of persistence, bioaccumulation and toxicity (PBT). Therefore, Cabotegravir is not considered a PBT substance.

The Applicant calculated the PECsurfacewater in compliance with the guideline on ERA EMEA/CHMP/SWP/4447/00 corr. 2, 2006. The PECsurfacewater exceeds the action limit of 0.01 mg/L, so a Phase II environmental fate and effects analysis is required, according to the Guideline EMEA/CHMP/SWP/4447/00 corr 2, 2006.

Phase II is focused on obtaining data related to chronic ecotoxicological effects, biodegradation, potential for sorption to soil or sludge, and potential for partitioning to sediment of Cabotegravir. The data from studies on aquatic species and sludge organisms are used to derive predicted no-effect concentrations (PNEC) for relevant environmental compartments according to the Guidance EMEA/CHMP/SWP/4447/00 Corr 2, 2006. The fate data can be used to assess transport within the environment and potential depletion mechanisms and may be used to derive predicted environmental concentrations. The more relevant methods were used and the results were discussed.

Cabotegravir is not lipophilic at environmentally relevant pH and is unlikely to bioconcentrate in exposed aquatic organisms. A moderately high water/sludge distribution coefficient (Koc) suggests it will partition to the terrestrial environment to some extent but not to a degree that warrants a terrestrial risk assessment. It is not readily nor inherently biodegradable and is not expected to be extensively mineralized. Although this substance is considered to be persistent it is expected to be relatively immobile in the aquatic and terrestrial environment due to its adsorption/desorption characteristics in soil and sediment.
In Phase II Tier A, environmental fate studies were performed in accordance with relevant OECD guidelines. The PEC is compared to an acceptable environmental concentration, the Predicted No Effect Concentration (PNEC) and no risk was identified in Tier A. PEC/PNEC ratios for surface water and groundwater were < 1, and for the $PEC_{surfacewater}/PNEC_{micro\text{-}organisms}$ was < 0.1. Therefore, no further evaluation was deemed necessary. Based on these results, Cabotegravir is not expected to pose a risk to surface water, groundwater or wastewater treatment facilities.

PEC/PNEC for surfacewater, groundwater, micro-organisms were below the action limits, indicate that the environmentally relevant residues of Cabotegravir are of low risk for all compartments. Therefore, no risk for the environment is to be expected.

As the water/sediment study (OECD 308) demonstrated significant shifting of the drug substance to the sediment (more than 10% at 14 days is present in sediment), effects on sediment dwelling organism were investigated. The study on sediment toxicity of Cabotegravir was performed on the larvae Chironomus riparius according to OECD 218.

In Phase II Tier B, sediment toxicity of Cabotegravir on the midge larvae Chironomus riparius was evaluated according to OECD 218. The PEC/PNEC ratio for sediment was < 1. Therefore, Cabotegravir is unlikely to pose a risk to sediment dwelling organisms and no further testing is necessary.

The SmPC and PL contain sufficient information regarding precautionary and safety measures taken to reduce the risk to the environment.

Conclusion

The Applicant provided an environmental risk assessment (ERA) for cabotegravir in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr. 2, 2006). Considering the above data, Cabotegravir is not expected to pose a risk to the environment. From the results of ERA studies, no significant environmental safety issues were identified.

Since no environmental concerns are apparent, it is assumed that Cabotegravir is unlikely to represent a risk for the environment following its prescribed usage.

2.4.6. Discussion on non-clinical aspects

CAB inhibits 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. CAB is a potent in vitro inhibitor of HIV integrase and inhibits the integrase catalysed viral DNA strand transfer with IC50 values in the nanomolar range (3.0 to 13 nM). The antiviral activity is provided in clinical pharmacology section.

CAB at 10 µM did not significantly affect (defined as ≥50%) 80 of the 81 in vitro assays for possible interactions with isolated or tissue enzymes, physiological receptor, ion channel and transporter. The only effect greater than 50% was a 53% inhibition of binding to the human recombinant melanocortin (MC4) receptor seen at a concentration (20 uM) higher than clinical unbound Cmax following oral lead in (0.1 uM). The MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in the MC4R is associated with monogenic obesity. The potential to antagonise MC4R was also observed for another integrase inhibitor dolutegravir (Tivicay) at a concentration equal to the clinical Cmax. Notwithstanding, no findings associated with MC4R agonism or antagonism have been observed in toxicity studies with CAB, and there were no clinically significant patterns of changes in vital signs (weight, heart rate, systolic and diastolic blood pressure) across the clinical studies. Additionally, variations in weight or appetite were generally not reported or reported as uncommon adverse drug reactions in any of the clinical studies and were generally similar between CAB and comparators.

In safety pharmacology core battery assays, no respiratory effects nor neurobehavioral effects occurred in rats dosed orally with cabotegravir, at multiple s of clinical Cmax for oral lead in administration.

CAB at 7.14 µg/mL (the maximum concentration limited by solubility), equivalent to 17.61 µM approx. the human Cmax for oral lead in administration, caused no inhibition of hERG channel tail current in HEK-293 cells stably transfected with hERG cDNA. In conscious telemetered male monkeys, a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 hours after oral cabotegravir dosing, was observed. However, in a thorough QTc study (mass balance study in healthy subjects) oral dose of CAB supratherapeutic dose of 150 mg q 12 h x 3 doses had no significant effect on cardiac repolarization.

PK studies were carried out in animal species and strains used in the toxicological testing of CAB, to enable meaningful assessment of the exposure levels in the toxicity studies and provide confidence in the conclusions drawn regarding the safety of CAB in humans. The species and strains used were CD-1 mice, Sprague Dawley rats, partially pigmented Lister-Hooded rats, Dutch belted rabbits, beagle dogs and cynomolgus monkeys.

Following single IV administration of CAB to dogs and monkeys, the CAB concentration time profile was indicative of a lower clearance and longer half-life.

In rats and monkeys given a single SC or IM injection, CAB was slowly released from the injection site with a mean apparent plasma half-life ranging from 12 to 29 days (SC) or from 8 to 12 days (IM). Following oral administration as a solution, the oral bioavailability of CAB in mice, rats and monkeys was good (44 to 83%) and consistent with its high passive permeability. However, when administered as a suspension, or in solid dosage forms, the bioavailability appeared limited by dissolution rate or solubility which resulted in a less than proportional increase in systemic exposure of CAB relative to dose. CAB has high passive membrane permeability. The protein binding of CAB in rat, dog, monkey and human plasma and serum was high (>99%). After oral administration of [^{14}C]-CAB to rats, radioactivity was slowly absorbed and then largely confined to the systemic circulation albeit widely distributed to other tissues. Radiolabelled drug-related material was minimally associated with cellular

components of blood. Elimination of radioactivity was slow with most tissues containing low but quantifiable radioactivity at 28 days. Association of radioactivity to the melanin-containing tissues in the eye and skin was not observed.

In general, the metabolism of CAB in the nonclinical species reflects that observed in humans, with CAB being the principal component circulating in plasma. The major metabolite of CAB in all species was CAB glucuronide, which was formed primarily by UGT1A1 (with some involvement from UGT1A9) and was eliminated in the urine and bile. Additional studies in human (IM, SC and PO) confirmed that the metabolism and excretion of CAB is independent of route of administration. Metabolic conversion of CAB to its stereoisomers was not detected in rat, dog, monkey or human hepatocytes, or in human plasma following repeat oral administration for 14 days.

Across all species, elimination of drug-related material occurred predominantly via the faeces (58.5 to 94.5% of the dose). No clinical drug interaction risk was identified for co-administered substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17, Pgp, BCRP, BSEP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE 2-K, MRP2 or MRP4 at a clinical oral dose of 30 mg CAB. As CAB is metabolized by UGT1A1 and a clinical study has confirmed a drug interaction with the UGT1A1 inducer rifampin, the co-administration of CAB with strong inducers of UGT is contraindicated. This potential drug interaction is stated in the SmPC.

Additionally, an in vitro study that included CAB was conducted to assess integrase inhibitors as potential inhibitors of human folate transport pathways. In vitro, CAB did not inhibit proton-coupled folate transport or reduce folate carrier activity up to the highest concentration tested (100 μM). In the folate receptor α assay, CAB demonstrated 36.7% inhibition at 25.8 μM; the in vitro concentration is approx. 200-fold higher than the clinical unbound Cmax for oral lead in. The applicant presented resounding data showing that CAB is not a clinical inhibitor of folate transport pathways, and it was not predicted to elicit clinical decreases in maternal and foetal folate levels. However, according to Foster et al., 2022 (https://doi.org/10.3390/ph15121533), more investigation and comprehensive data are needed to understand the PK, placental passage, and safety of CAB in pregnancy in order to confirm or refute the potential safety signal of neural tube birth defects observed in infants born to women receiving dolutegravir-based ART periconception. This is particularly relevant for PrEP indication. Currently, the statement in section 4.6 “Apretude injection is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus. Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for foetal exposure during pregnancy (see section 4.4)” seems adequate from a (non-)clinical point of view.

Repeated dose toxicity studies included 9 studies with daily oral (mice, rats and cynomolgus monkeys) administration up 13, 26 and 39 weeks, and one 13-week study conducted in rats dosed with weekly or monthly administration by subcutaneous or intramuscular injection.

Cabotegravir was generally well tolerated without adverse effects in the oral repeat-dose toxicity studies in mice, rats and monkeys.

The 39-week study in monkeys revealed ocular findings in two monkeys - slight vascular inflammation was noted unilaterally near the optic nerve of a single monkey dosed with 500 mg/kg/day and inflammation and swelling of the optic nerve head with peripapillary oedema and diffuse corneal opacity was observed in a single animal dosed with 50 mg/kg/day. Both ocular findings were considered incidental.

At the end of the longest-term toxicity studies in rats and cynomolgus monkeys (26-week and 39-week, AUC were, approximately, 22 to 32-fold, in rats, and 4-fold, in monkeys, the clinical AUC exposure in patients treated with oral doses of 30 mg/day.

In the rat study with subcutaneous or intramuscular administration - with weekly subcutaneous doses, monthly subcutaneous doses and monthly intramuscular doses - four high dose animals treated monthly were euthanized due to deteriorating conditions or found dead. The cause of moribundity or death in these animals was not linked to any underlying pathology findings, as none of these animals had explanatory pathology findings distinct from survivors. Therefore, these deaths were considered unlikely treatment related.

CAB was negative in a complete set of in vitro and in vivo genotoxicity assays. CAB has demonstrated a lack of carcinogenic potential in conventional oral 2-year studies in mouse and rats.

Reproductive toxicity studies included studies to evaluate potential effects on fertility (rat), embryo-foetal development (rat, rabbit) and pre-postnatal development (rat). All studies employed the oral route of administration.

No cabotegravir-related effects on male or female fertility were observed at oral doses at least 20-fold higher than that reached in humans treated at the oral recommended dose of 30 mg/day.

In rats, there was no evidence of a treatment-related increased incidence of foetal anomalies at exposure approx. 14-fold those reached in humans treated orally at 30 mg/day.

In rabbits, no treatment-related increase in post-implantation loss nor treatment-related increase in foetal malformations was observed at 0.66-fold the exposure in humans treated with 30 mg/day. The maximum tested dose induced some maternal toxicity based mostly on a transient decrease in body weight gain.

Studies on pre-postnatal development comprised three studies in rats, one pivotal and two follow-up investigative studies - a study on the cause of the increased F1 offspring postnatal deaths, namely, on its dependency on exposure in utero and/or during lactation, and a study on toxicokinetics.

In the initial PPND study, treatment-related decreases in F1 pup survival and viability were observed (increased number of stillborn pups and neonatal mortality from PND1 to PND4) at the high dose (1000 mg/kg/day). At the NOAEL, systemic exposure was estimated to be 12.75-14.27-fold the exposure expected in humans treated orally with 30 mg/day.

The follow-up PPND study on causality confirmed these adverse findings and cross-fostering experiments showed that perinatal mortality was attributable to gestational, but not to lactational, exposure to cabotegravir and was not related to decreased maternal care. The follow-up PPND study showed that the proportion of stillbirths on GD23 (i.e., pups born from dams with delayed onset of maturation) was 3.5-fold higher in the treated group than in the control group (1.3% vs. 4.6%; or 2/152 vs. 22/478), and was above the historical control data. It is also noted that stillbirths were not reported on GD22 in the control group (0/305 pups) whereas it affected 2/99 pups (2%) exposed in utero to cabotegravir born on that day. Moreover, the number of pups born on GD23 and dead on PND1 prior to cross-fostering was clearly increased in the treated (17) vs. control (0) group. Therefore, an effect of treatment on perinatal mortality cannot be excluded.

No juvenile animal studies have been conducted. This is acceptable, even if the intended target patients' population for Apretude is not limited to adults. No non-clinical studies are included in the agreed Paediatric Investigations Plan.

CAB could be considered to be non-immunosuppressive. Effect in anti-KLH IgG antibody observed in males was considered as minimal and not observed in females.

Based on the absence of any relevant signals in the repeat dose toxicity studies, no dependence study was performed. This is acceptable.

No discussion was provided by the Applicant regarding the potential phototoxicity of cabotegravir. Nevertheless, it is known that CAB absorbs mainly at 257nm, and could be considered as non-phototoxic.

Data generated in standard and/or impurity-spiked repeat-dose toxicology studies are considered sufficient to qualify the proposed specifications for the CAB- impurities and degradation products. The control strategy for the genotoxic or potentially genotoxic impurities are considered as adequate. Notwithstanding, only a Summary of the 'Evaluation of Cabotegravir and Cabotegravir sodium Synthesis and Degradation Impurities (Actual and Potential) for Potential Mutagenicity' was provided in section 3.2.S.2.6. of each drug substance.

Considering the above data, cabotegravir is not expected to pose a risk to the environment. From the results of ERA studies, no significant environmental safety issues were identified.

2.4.7. Conclusion on the non-clinical aspects

The overall nonclinical program including the data from CAB studies is considered adequate to support the efficacy and safety CAB in the PrEP proposed indication.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Study Design	Population	Treatment Details	Key Conclusions
Pivotal – CAB PrEP				
201738 (HPTN 083)	Phase IIb/III, randomized, multicenter, double-blind, double dummy, non-inferiority study	MSM or TGW who are HIV-uninfected and at high risk for HIV acquisition, ≥18 years of age	**Step 1: OLI Phase** **Arm A – Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for up to 5 weeks **Arm B – Daily oral TDF/FTC** (300 mg/200 mg FDC tablets) and oral CAB placebo for up to 5 weeks **Step 2[a]: Injection Phase** dosing at 2 time points Q4W and then Q8W thereafter **Arm A – CAB LA** (a single [3 mL] 600 mg IM injection and daily oral TDF/FTC placebo **Arm B – Daily oral TDF/FTC** (300/200 mg FDC tablets) and IM placebo (matching vehicle [Intralipid 20% fat emulsion infusion], identical volume as active injectable product in Arm A) **Step 3[b]: Follow-up Phase** **Both arms: Open-label daily oral TDF/FTC** no later than 8 weeks after the last injection (in order to cover the PK tail for Arm A participants), for up to 48 weeks	CAB PrEP demonstrated superior efficacy when compared to daily oral TDF/FTC (HR 0.340, two-sided p=0.0005). 39 HIV incident infections occurred in the TDF/FTC group (incidence rate 1.22/100 PY) and 13 incident infections occurred in the CAB group (incidence rate 0.40/100 PY). The HR in the CAB versus TDF/FTC groups is 0.340 (bias-corrected point estimate; 95% adjusted CI 0.18-0.62), an approximate 66% reduction in the rate of incident infections relative to the active comparator daily oral TDF/FTC. CAB LA was well-tolerated with a safety profile comparable to daily oral TDF/FTC (excluding ISRs). ISRs occurred in 82% of CAB LA participants with 80% reporting the ISRs as mild or moderate. 47 (2.2%) of CAB LA participants discontinued study drug due to an injection-related AE. ≥Grade 2 AEs reported in >5% of participants were comparable between the study groups. The most common (in >10% participants) AEs (listed by PT) in the CAB group were ISRs (injection site pain, injection site nodule, and injection site induration), creatinine renal clearance decreased, blood creatine phosphokinase increased, blood creatinine increased, nasopharyngitis, headache, diarrhoea, anal chlamydia infection, upper respiratory tract infection, lipase increased, proctitis gonococcal, blood glucose increased, and pyrexia. The percentage of participants reporting any AE was similar in the CAB group compared with the TDF/FTC group. The 2 AE terms reported in the highest proportion of participants in both treatment groups were creatinine renal clearance decreased (CAB group: 69%; TDF/FTC group: 73%) and injection site pain (CAB group: 75%; TDF/FTC group: 30%). There were no differences in Grade 3 or higher event rates between CAB LA and oral TDF/FTC. 10 deaths were reported during Steps 1 and 2 (CAB: 4; TDF/FTC: 6), of which 1 was considered drug-related by the investigator (cardiac disorder in the TDF/FTC group).

Study	Study Design	Population	Treatment Details	Key Conclusions
201739 (HPTN 084)	Phase III, randomized, multicenter, double-blind, double dummy, open-label, superiority study	Cisgender women at high risk of HIV acquisition, age 18 to 45 years	**Step 1: OLI Phase** **Arm A – Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for up to 5 weeks plus an HIV prevention package **Arm B – Daily oral TDF/FTC** (300/200 mg FDC tablets) and oral CAB placebo for up to 5 weeks plus an HIV prevention package **Step 2[c]: Injection Phase** dosing at 2 time points Q4W and then Q8W thereafter **Arm A – CAB LA** (a single [3 mL] 600 mg IM injection and daily oral TDF/FTC placebo plus an HIV prevention package **Arm B – Daily oral TDF/FTC** (300/200 mg FDC tablets) and IM placebo (matching vehicle [Intralipid 20% fat emulsion infusion], identical volume as active injectable product in Arm A) plus an HIV prevention package **Step 3[b]: Follow-up Phase** **Arm A – Daily oral TDF/FTC** will be provided no later than 8 weeks after the last injection, for up to 48 weeks plus an HIV prevention package. Arm A participants will then transition to locally available HIV prevention services, including services for pre-exposure prophylaxis, if available. **Arm B – Daily oral TDF/FTC** will be offered plus an HIV prevention package.	CAB PrEP demonstrated superior efficacy when compared to daily oral TDF/FTC (p<0.0001). 36 HIV incident infections occurred in the TDF/FTC group (incidence rate 1.85/100 PY) and 4 HIV incident infections occurred in the CAB group (incidence rate 0.20/100 PY). Comparing the incidence between the groups yields an HR of 0.11 (95% CI 0.04 to 0.31), demonstrating an 89% reduction in the rate of incident infections for CAB relative to the active comparator daily oral TDF/FTC. Overall, there were no notable differences between groups in the proportions of participants who reported any AE (CAB: 96%; TDF/FTC: 96%). Creatinine renal clearance decreased was the most commonly reported AE among participants in both groups (CAB: 72%; TDF/FTC: 74%). The majority of participants in both groups had an AE with a maximum intensity of Grade 2 (CAB: 76%; TDF/FTC: 75%). Overall, injections of CAB PrEP were generally well-tolerated in this population of cisgender women. ISRs were reported more frequently in the CAB group (38%) compared with the TDF/FTC group (11%); these were generally mild. There were 3 deaths reported (all in the CAB group), and none were considered related to study drug. In both groups, 2% of participants reported having 1 or more pregnancy (CAB: 38 participants reported 40 pregnancies; TDF/FTC: 34 participants reported 37 pregnancies), and pregnancy outcomes were similar between the groups.
Supportive – CAB PrEP				
201120 (ÉCLAIR)	Phase IIa, randomized, double-blind, placebo controlled	Healthy male participants at low risk of acquiring HIV, age 18 to 65 years	Randomized 5:1 (Arm 1: Arm 2) **Arm 1**: Daily oral CAB (30 mg tablets) for 4 weeks, followed by a 1 week washout period to establish safety and tolerability, followed by IM injections of 800 mg (two 2-mL injections) of CAB LA at 3 time points at 12 week intervals: Week 5, Week 17, and Week 29 **Arm 2**: Daily oral matching placebo and IM 0.9% saline injections of matched placebo on the same schedule as Arm 1	Safety results demonstrated that oral CAB 30 mg once daily and IM CAB 800 mg Q12W were well-tolerated in the Oral and Injection Phases, respectively, with few AEs leading to withdrawal. During the Injection Phase, Grade 2 through Grade 4 AEs occurred more frequently in the CAB group compared to placebo, driven by ISRs including a statistically significant difference in injection site pain. Few subjects developed ≥Grade 2 laboratory abnormalities. Elevations in laboratory parameters of special interest were primarily Grade 1.

Study	Study Design	Population	Treatment Details	Key Conclusions
				PK results revealed that PK parameters following CAB injection were not as predicted and were driven by a faster absorption rate from the depot injection site. PK results suggested that an 800 mg dose of CAB LA Q12W may be insufficient to provide adequate protective efficacy from HIV infection in males at higher risk of acquiring HIV in future efficacy trials.
201103 (HPTN 077)	Phase IIa, multi-site, double-blind, 2-arm, randomized, placebo-controlled trial of the safety, tolerability, and acceptability of CAB LA	HIV-uninfected men and women at low risk for acquiring HIV infection, ages 18 to 65	**Cohort 1** **Arm 1:** (OLI) Daily oral CAB (30 mg tablets) for 4 weeks (to assess safety and tolerability prior to receiving CAB LA), followed by a 1-week Washout Period, followed by IM gluteal injections of 800 mg of CAB LA (2 sequential 400 mg gluteal injections) at 3 time points at 12-week intervals (Week 5, Week 17, and Week 29) **Arm 2:** Daily oral placebo and IM 0.9% saline injections of matched placebo on the same schedule as Arm 1 **Cohort 2** **Arm 1:** (OLI) Daily oral CAB (30 mg tablets) for 4 weeks, followed by a 1-week Washout Period, followed by IM gluteal injections of 600 mg of CAB LA (one 600 mg gluteal injection) at 5 time points at 4- and 8-week intervals (Week 5, Week 9, Week 17, Week 25, and Week 33) **Arm 2:** Daily oral placebo and IM 0.9% saline injections of matched placebo on the same schedule as Arm 1	CAB LA was well-tolerated with few AEs leading to withdrawal. During the Injection Phase, Grade 2 through Grade 4 AEs occurred at a similar rate between the CAB and placebo groups with ISRs being the only AEs that occurred more frequently in the CAB group. ISRs were generally mild with injection site pain as the most frequently reported ISR (90% of participants in the CAB group); ISRs resulted in <1% of withdrawals. Few participants in the CAB group developed ≥Grade 2 laboratory abnormalities. No significant change in weight was observed over 41 weeks between the groups. The CAB LA 800 mg Q12W dose did not achieve target trough concentrations in male participants. However, the CAB LA 600 mg Q8W dose did achieve target trough concentrations in both male and female participants.
Supportive - Adolescents				
208580	Phase I/II, multi-centre, open-label, non-comparative study	HIV-1 infected children and adolescents, 12 to <18 years of age and weighing ≥35 kg, who are	**Cohort 1** **Cohort 1C:** CAB (30 mg tablets) once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART followed by 3 IM injections of CAB LA Q4W (600 mg first injection, 400 mg second and third injections) in addition to cART **Cohort 1R:** RPV (25 mg tablets) once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART followed by 3 IM injections of RPV LA Q4W (900 mg first injection, 600 mg second and third injections) in addition to cART	8 participants in Cohort 1C provided systemic CAB exposure data through Week 16 following oral dosing and Q4W IM administration. The observed PK profiles after Q4W IM CAB LA met the desired exposure targets for CAB (oral and IM administration). The CAB PK data observed in the 8 participants was compared against a priori model predictions, and the PopPK model adequately captured the observed concentration-versus-time profiles. CAB concentrations were similar between the adolescent participants and adult participants from the CAB development program given the Q4W CAB regimen.

Study	Study Design	Population	Treatment Details	Key Conclusions
		virologically suppressed	**Cohort 2**[d]: CAB (30 mg tablets) + RPV (25 mg tablets) once daily orally for at least 4 weeks (up to a maximum of 6 weeks) followed by IM injections of CAB LA + RPV LA Q4W for 92 weeks (for CAB LA 600 mg first injection and 400 mg subsequent injections; for RPV LA 900 mg first injection, 600 mg subsequent injections).	The CAB PopPK model was deemed appropriate and able to reliably describe and predict CAB PK in adolescents and, therefore, used to predict CAB systemic exposure following CAB Q4W and Q8W dosing regimens. The simulated CAB concentration time profiles following CAB Q4W and Q8W dosing regimens were predicted to stay above the Phase III benchmark of 0.65 μg/mL in ≥95% of the virtual adolescent population throughout the dosing intervals and to be highly comparable to the observed adult exposures. Additionally, the median predicted CAB concentrations after Q4W and Q8W dosing regimen were below the safety threshold of 22.5 μg/mL. As CAB PK was similar in healthy and HIV-infected adults administered the Q8W CAB regimen, no differences are expected in CAB PK between adolescents evaluated in Study 208580 and adolescents who will receive CAB PrEP. The Cohort 1 Week 16 interim analysis safety data observed in adolescents receiving CAB did not identify any new safety concerns or new safety signals in comparison with the safety profile established with adults in the CAB Treatment program.

Note: CAB Treatment studies are provided in m2.7.2 Appendix Table 1 and m2.7.4 Appendix Table 1.

a. At the time the study was initiated, Step 2 was to continue until the required number of endpoints was reached. Each participant was to receive a maximum of 3 years of blinded study medication.
b. Participants may choose to discontinue oral TDF/FTC at this stage. Arm B participants then will transition to locally-available HIV prevention services, including services for pre-exposure prophylaxis, if available.
c. At the time the study was initiated, Step 2 was to continue until the required number of endpoints (114) was reached, estimated to be 81 weeks after enrolling the last participant.
d. No participants were enrolled in Cohort 2 at the time of the interim analysis.

Moreover, two HIV-1 PrEP sub-studies in sexually active, HIV-1-uninfected adolescent males (HPTN 083-01) and females (HPTN 084-01) have been completed. These are safety, tolerability and acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males - A Sub-study of HPTN 083 and women- A Sub-study of HPTN 084.

Two Phase I clinical pharmacology studies (Study 206898 and Study 201767) were not included in the tables above as they were completed after the pooled analysis was conducted. Further details on these studies are provided in Clinical pharmacology.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Cabotegravir (CAB, GSK1265744) is an HIV-1 INSTI. CAB, as 1 component of a dual antiretroviral maintenance therapy regimen in combination with the long-acting formulation of rilpivirine, has been approved in several countries/regions for the treatment of HIV-1 infection in adults (in EU it is approved with the name Vocabria). The current application concerns the use of CAB for risk reduction of sexually acquired HIV-1 infection. To this aim, CAB is to be administered as CAB LA injection 600 mg 1 month apart, followed by 1 injection 600 mg every 2 months with an optional OLI of CAB 30 mg once daily given orally for 1 month. CAB tablets may be used as Oral lead-in (OLI) to assess tolerability of CAB prior to administration of CAB LA and as oral PrEP in individuals who will miss planned dosing with CAB LA injection.

Study HPTN 083 was a Phase IIb/III, multi-site, double-blind, 2-arm, randomized (1:1), controlled non-inferiority study in HIV-uninfected cisgender MSM and TGW where plasma samples were collected sparsely at several moments during the clinical study. This data is used for describing the PK of the target population.

Study HPTN 084 was a Phase 3 double blind safety and efficacy study of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women. This data is used for describing the PK of the target population. Again, plasma samples were collected sparsely at several moments during the clinical study. This data is also used for describing the PK of the target population.

Study 201767 was a Phase I, multicompartmental pharmacokinetic study of cabotegravir long acting in healthy adult volunteers. Samples were collected to determine the PK concentrations of CAB LA administration in blood plasma and in Vaginal tissue, Cervical tissue, and Cervicovaginal fluid in healthy women and in Rectal tissue and Rectal fluid in healthy men and women following a single 600 mg IM dose. Study design, population handling and bioanalysis are acceptable. Plasma CAB PK was consistent with prior studies and CAB concentrations in tissue and fluid were proportional to plasma over time.

Study 208580 was a Phase I/II study of the safety, acceptability, tolerability, and pharmacokinetics of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed HIV-infected children and adolescents. Plasma samples were collected in a mix of rich and sparse collections at different time periods to both describe the PK in the population and test the attainment of an exposure similar to the adult population.

Study 206898 was an open label, Phase I study to evaluate the PK, safety, tolerability and acceptability of long-acting injections of the HIV integrase inhibitor, cabotegravir in HIV uninfected Chinese men. Plasma samples were collected in a mix of rich and sparse collections at different time periods to evaluate the plasma PK of CAB following repeat oral administration (Day 1 to Week 4) and CAB LA IM injections throughout the Injection Phase (Weeks 5 to 41).

Analytical methods

Method validations are provided and can be considered acceptable. The bioanalytical methods used to measure concentrations of CAB in several human tissues were selective, accurate, and reproducible. All methods were appropriately validated, both prior and during studies.

Pharmacokinetic data analysis

The PK of CAB following PO and IM administration was adequately characterized by PopPK analysis based on data from healthy subjects and HIV-1-infected subjects. A 2-compartment model with first-order oral and IM absorption and elimination best described the plasma CAB PK profile, both after single and repeated dosing.

All parameters could be estimated with adequate precision, as measured by a RSE <20% for fixed effects (except for needle length on KA2, with an RSE of 36.2%) and a RSE <25% for random effects. The prediction-corrected VPC demonstrated that the final model adequately described the time course of plasma CAB concentration and its associated variability after oral and IM dosing and can be considered as fit-for purpose. The causes of the high (> 30%) shrinkage values on KA1, V2/F and F1 should be due to the flip-flop and long absorption half-life that limits the correct characterization of the absorption process.

The model characterized the 'flip-flop' (absorption-rate limited) nature of CAB PK following IM injection. The PopPK estimate of plasma CAB half-life after oral dosing was 36.5 hours and after IM dosing was 6.4 weeks for the overall population (5.6 weeks for males and 11.5 weeks for females). The bioavailability of oral CAB relative to long-acting injection CAB (F1) was estimated to be 76%.

External validation of the Population Pharmacokinetic Model was made with High-Risk Participants of study 083 and 084 and the pcVPC (stratified by sex at birth, gender identity subgroup and race) suggest that the final PopPK model was able to reliably describe and predict CAB PK from Studies HPTN 083 and HPTN 084.

Regarding the Adolescent participants in study 208580, the data collected in this study was also used as an external validation of the Population Pharmacokinetic Model as well as for an additional age covariate analysis (study 2021N462341). From the pcVPC, showing that CAB PopPK model (updated by fixing the exponent to 0.75 for body weight on clearances and fixing the exponent to 1 for body weight on volumes) adequately captured the observed concentration-versus-time points and trends within the 90% PI (5th and 95th percentiles) of the simulated values, it can be concluded that the CAB PopPK model can adequately describe and predict CAB PK behaviour of the adolescents in Study 208580. This was further supported by the fact that the additional age covariate analysis resulted in a final model identical to the previously developed one (without the adolescent data). Also, the re-estimated parameters with the adolescent data were essentially the same as in the original model.

Absorption

After IM administration, a tmax of 7 days and a flip-flop kinetic process was observed. After oral administration, a fast absorption with a tmax of 3h was observed.

No absolute BA was determined due to the impossibility to administered CAB by IV route. The absolute bioavailability of oral CAB is, however, predicted to be high based on the high passive permeability of CAB, a high relative bioavailability of oral vs IM, and minimal impact of food on plasma CAB absorption rate. Since in Study LAI117008 approximately 26.8% of the radioactivity was eliminated in urine after a single oral dose of marked Cabotegravir, it can be inferred that absolute bioavailability is at least 26.8%.

Along with information on solubility, the suggested BCS classification for Cabotegravir in BCS class II is acceptable from a PK standpoint.

Bioequivalence

No bioequivalence studies have been part of this clinical pharmacology program, some relative bioavailability studies have been performed.

Study LAI116815 led to selection of the 200 nm nanomilled formulation for LA IM injections.

In study ITZ111682, the oral tablet resulted in a lower exposure than the solution, by 0.6 to 0.7 fold, and Tmax was shorter for the solution.

In Study LAI116585, both free acid candidate oral formulations provided relative bioavailability of at least 50% to that of the current sodium salt. The AUC of the nanomilled and micronized formulations were approximately 12% and 48% lower than those of the sodium salt tablet formulation, respectively. These data suggested that switching to a free acid oral formulation is viable.

In Study LAI117020, neither new formulation met the criteria for progression into Phase 3.

In study 201741, both test formulations made with micronized drug substance met the preestablished acceptance criteria. Neither of the test formulations made with unmicronized drug substance met the acceptance criteria. Since a smaller tablet is desirable for ease of administration, the tablet formulation with the core tablet weight of 500 mg, utilizing micronized GSK1265744B drug substance was selected for progression into phase 3 studies.

Overall, decisions on change and choice of formulations were well detailed and justified.

Influence of food

In study LAI117020, food did not affect 744 PK following administration of the test micronized tablet.

In study ITZ111682, the presence of food increased GSK1265744 AUC(0-inf) and C24 by 15% and had no effect on Cmax for the tablet formulation when compared to tablets administered in the fasted state.

In study 205696, bioavailability was increased by 4-17% by a high fat meal.

It is agreed that the effect of food on CAB is small and clinically irrelevant, therefore oral CAB can be taken without regard to meals. No special recommendations on the oral administration regarding food are provided in the SmPC, which is acceptable.

Distribution

Protein binding was high with an unbound fraction of 0.1-0.2% in healthy subjects, in HIV-1-infected subjects and in subjects with severe renal impairment. In subjects with moderate hepatic impairment, the unbound fraction, which causes the pharmacological effect, was 1.5- to 3-fold higher (0.3%) than in subjects with normal liver function. In vitro, the unbound fraction around clinical Cmax was higher (0.6%). CAB did not preferentially distribute into red blood cells.

CAB is a substrate of P-gp and BCRP but it also shows high passive permeability.

Following administration of oral tablets, the mean apparent oral volume of distribution (Vz/F) in plasma in healthy subjects was about 12-13 L. Using population PK modelling, the estimated Vc/F was 5.3 L and estimated Vp/F was 2.4 L. These volume estimates, along with the assumption of high bioavailability, indicate some distribution beyond the plasma volume to the extracellular fluids.

CAB concentrations in plasma and mucosal tissues at sites of sexual transmission were evaluated in study 201767 following a single IM dose of CAB LA 600 mg through Week 12. CAB was detected in all tissues and fluids potentially relevant to sexual transmission. Tissue and plasma CAB concentrations were strongly correlated (r >0.9) and proportional (tissue concentrations~10% to 20% of plasma concentrations over time), whereas correlations were weak between time-matched fluid and plasma concentrations likely due to the relatively high variability in fluid concentrations.

Elimination

Excretion has been well evaluated and described with the 14C study. Following administration of a single dose [14C]-CAB 30 mg to healthy subjects, 59% of the dose was recovered in faeces and 27% in urine. CAB accounted for 47% of the dose in faeces and was not detected in urine. The major metabolite of CAB, CAB glucuronide, represented most of the radioactivity recovered in urine. CAB glucuronide was found to be a substrate of active renal transporters OAT3, MRP2 and MRP4 indicating active renal clearance; it is unknown however to what extent CAB glucuronide was also excreted in bile.

In vitro metabolism was investigated using pooled human liver, kidney and intestinal microsomal fractions and recombinant UGT enzymes. UGT reaction phenotyping in human liver microsomes indicates that UGT1A performs approximately 2/3 of metabolism and UGT1A9 approximately 1/3. UGT1A3, 1A4, 1A6, 2B4, 2B7 and 2B15 were not involved.

In vivo, the main pathway of metabolism is glucuronidation in metabolite M1. However, in human plasma, CAB was the major circulating component, representing 81-100% of radioactivity in plasma following an oral dose and >99% of IM administered drug-related material. CAB-glucuronide (M1) was a minor component in plasma (<5%).

In urine, M1 was the major component, representing 75 - >85% of drug related material following oral administration and >90% following IM administration. CAB in urine comprised <10%. Minor metabolites found in urine were M2 (product of glucose conjugation), M3 (formed by oxidation, fluorine loss, and cysteine conjugation) and M4 (formed by pentose conjugation), which were found at <5%, <1% and <1% of drug related material respectively. The data indicate active elimination of CAB glucuronide.

In faeces, CAB was the only quantified component, representing 83% of radioactivity and 47% of the radio-labelled oral dose. As mentioned above, this is expected to contain deconjugated metabolite as well as unabsorbed CAB.

CAB and M1 were both detected in bile of humans.

No significant conversion was observed of CAB to any of its stereoisomers was observed.

Based on the in vitro transporter data, CAB glucuronide is a substrate of OATP1B1, OATP1B3, OAT3, MRP2, MRP3 and MRP4, but not of P-gp, BCRP, OAT1 and OAT4. As none of the metabolites are pharmacologically active and no metabolites were quantified in pooled plasma samples, PK of metabolites was not further studied.

UGTA1 activity polymorphism will impact Cabotegravir PK, but in proportions not expected to have clinical impact (mean values of Ctau, AUCtau, and Cmax ~1.5, 1.4 and 1.3-fold higher in subject with low relative to normal predicted activity). This conclusion is acceptable.

Dose proportionality and time dependency

Overall, the data indicate consistently that AUC and Cmax are dose proportional to slightly less than dose proportional over the clinical dose ranges following oral and IM administration.

The time to achieve steady state is governed by half-life and is prolonged with an LA regimen; however, efficacious concentrations are achieved following the initial IM injection. For the Q8W regimen, the loading dose achieves concentrations consistent with steady state 4 weeks following the initiation injection.

Steady-state plasma CAB concentrations are achieved by Day 7 following once daily administration of oral CAB in HIV-1-infected participants, consistent with the approximate 2.5-fold accumulation and a t1/2 of approximately 41 hours.

Overall, PK of cabotegravir appears to be time independent.

Intra- and inter-individual variability

Moderate between-subject variability in plasma CAB PK was observed following repeat-dose administration of CAB both orally and IM. Higher between-subject variability in plasma CAB PK was observed with single dose administration of CAB LA.

Within-subject variability in plasma CAB PK was low following administration of oral CAB. No WSCV is available for the IM administration.

In general, the between-subject variability in CAB PK upon repeated monthly IM injection seems to be somewhat lower than upon once daily oral dosing and variability in HIV-1 subjects was only slightly higher than in healthy subjects.

Pharmacokinetics in target population

PK in target population was evaluated in HIV-Uninfected Women (Study HPTN 084 - 201739) and HIV-Uninfected cisgender MSM and TGW (Study HPTN 083 – 201738).

Observation of different studies, as well as population PK analysis (2021N484575), showed that HIV infected patients presented PK profiles similar to healthy subjects. Plasma CAB exposure following administration of CAB LA Q8W regimen is similar between healthy, HIV-1-infected, and high-risk participants based on results of cross-study comparisons. Overall, high-risk participants appear to have a PK behaviour similar to the previous studied populations of healthy and HIV infected patients.

Special populations

Impaired renal function

The clinical study and the population PK analysis (study 2018N384611) led to the same conclusion that CAB can be administered without dose adjustment in subjects with mild to severe renal impairment (not on renal replacement therapy). Severe RI had minimal impact on plasma CAB Cmax and AUC(0-inf). The total exposures to CAB were similar in subjects with severe renal impairment (CLcr <30 mL/min) compared with healthy, matched control subjects.

CAB has not been studied in subjects with End-Stage Renal Disease (ESRD) on renal replacement therapy. CAB is not expected to be cleared by renal replacement therapies, such as haemodialysis or peritoneal dialysis, due to CAB's high protein binding and because absorption is slow from the CAB LA IM depot site, such that minimal drug would be available to dialysis.

Impaired hepatic function

Both population PK analysis (study 2018N384611) and a dedicated clinical study show that CAB may be taken without dose adjustment in subjects with mild to moderate hepatic impairment. Moderate hepatic impairment had minimal impact on plasma CAB Cmax and AUC(0-inf). The total plasma concentration exposure was only slightly reduced and the unbound plasma concentration slightly increased. Given that plasma CAB Cmax is lower following LA administration, subjects with mild or moderate hepatic impairment would be expected to have lower unbound Cmax than observed following oral dosing.

Gender

No specific studies have been performed investigating gender effect. From the popPK analysis (study 2018N384611) it may be concluded that females had 50.9% lower ka2 compared with males. As a result, due to the absorption rate-limited PK, CAB LA has a longer apparent t½ for females of 11.5 weeks as compared to the apparent t1/2 of 5.6 weeks for males. The slower IM absorption in certain females may be due to differences in body composition. From the PopPK simulations, median CAB Cmin after the first injection was lower in females than males by 31%. Median Cmin at steady state was higher in females than males by 9%.

Observed CAB LA plasma concentrations in high-risk participants from Study HPTN 083 (male gender at birth) and Study HPTN 084 (female gender at birth) are similar to male participants and female participants in healthy and HIV-infected participants.

In conclusion, there was an effect of gender but small enough to not justify any dose modification.

Race

No specific studies have been performed investigating race effect. From the popPK analysis it may be concluded that race does not seem to influence CAB PK. Also, Observed CAB LA plasma concentrations in high-risk participants from Study HPTN 083 and Study HPTN 084 (Race: White, Black or African American, Asian, Other) are similar to healthy, low-risk participants (HPTN 077), and HIV-infected participants (Study 207966).

Study 206898 was conducted to determine CAB PK profile in Chinese healthy subjects when administered orally (30 mg/day for 28 days) or followed by i.m. (600mg once every 4 weeks for a total of 2 dosing and 1 every 8 weeks) as monotherapy. The study was not powered to detect any effect of race on CAB PK, however through an indirect comparison with study 201103 (whose Cohort 2 is comparable in posology scheme, subjects' age and low risk for acquiring HIV infection), which included non-Asian healthy subjects, such influence could be likely excluded because of the similarity of PK profile.

Also, popPK study 2021N467204 was to provide additional evidence on the effect of race (North East Asian vs not- NEA participants) on CAB PK profile in terms of KA, Cl, F. Results confirm that PK parameters that are specific to the CAB LA formulation [i.e., absorption rate constant for LA CAB (Ka2) and relative bioavailability oral-LA i.m. (F1)] were similar between NEA and Not-NEA. Due to lower body weight and clearance for NEA, a higher CAB exposure following repeated i.m. administration is expected in such population with respect to not-NEA subjects. A post-hoc PK analysis suggested that such higher CAB plasma concentration does not exceed the safety threshold of 22 µg/mL, thus no dose adjustment is foreseen in Asian population.

Weight

No specific studies have been performed investigating weight effect. The popPK analysis 2021N484575 analysed CAB PK in participants who were <50 kg at enrolment versus participants ≥50 kg. Plasma CAB concentrations appeared to trend higher in participants <50 kg.

Table 3: Geometric Mean with 95% CI of Post-hoc Estimates of CAB Exposure by Weight in Adult and Adolescent Population

Dosing Interval	Weight Subgroup	N	$AUC_{(0\text{-}tau)}$ (µg × h/mL)	Cmax (µg/mL)	Ctau (µg/mL)	T_{max} [a] Unit [b]
30 mg PO QD Steady State [c]	< 50 kg	42	222.8 (205.7, 241.3)	12.06 (11.24, 12.94)	7.17 (6.53, 7.87)	2.0 (1.5, 3.0)
	≥ 50 kg	2641	146.5 (144.9, 148.1)	7.97 (7.89, 8.06)	4.68 (4.63, 4.74)	2.0 (1.0, 8.0)
CAB LA Initiation Injection [d]	< 50 kg	42	2469.1 (2146.2, 2840.7)	7.33 (6.69, 8.04)	2.52 (2.22, 2.85)	0.0 (0.0, 4.0)
	≥ 50 kg	2641	1454.4 (1428.1, 1481.3)	4.75 (4.70, 4.81)	1.51 (1.48, 1.53)	0.0 (0.0, 4.0)
CAB LA Q8W [e] Steady State [f]	< 50 kg	42	5688.3 (5246.2, 6167.7)	6.18 (5.61, 6.81)	2.36 (2.08, 2.67)	6.0 (5.0, 8.0)
	≥ 50 kg	2641	3724.5 (3685.8, 3763.6)	3.85 (3.80, 3.90)	1.69 (1.66, 1.71)	6.0 (4.0, 10.0)

$AUC_{(0\text{-}tau)}$ = area under concentration-versus-time curve from time 0 to the end of the dosing interval; Ctau = plasma concentration at the end of the dosing interval; Cmax = maximum plasma concentration; CAB = cabotegravir; CI = confidence interval; LA = acting-acting; N= number of participants; PK = pharmacokinetic(s); PO = oral; Q8W = once every 8 weeks; QD = daily; T_{max} = time to reach maximum plasma concentration.

Notes:
a) Median (minimum, maximum).
b) Unit = hr for CAB PO; Unit = day for CAB LA.
c) Following the 28th QD PO dose.
d) Cmax and T_{max} following the initiation injection are determined by the final oral dose and the initiation injection.
e) Q8W CAB LA dosing regimen: CAB PO dose of 30 mg QD for 4 weeks, and then 600 mg CAB LA IM (initiation injection) at 24 hours after the final CAB PO dose, followed by 600 mg CAB LA IM (maintenance dose) Q8W starting at 4 weeks after the initiation injection.
f) Following the 6th CAB LA injection (dosing interval: 36-44 weeks after the initiation injection).

Elderly

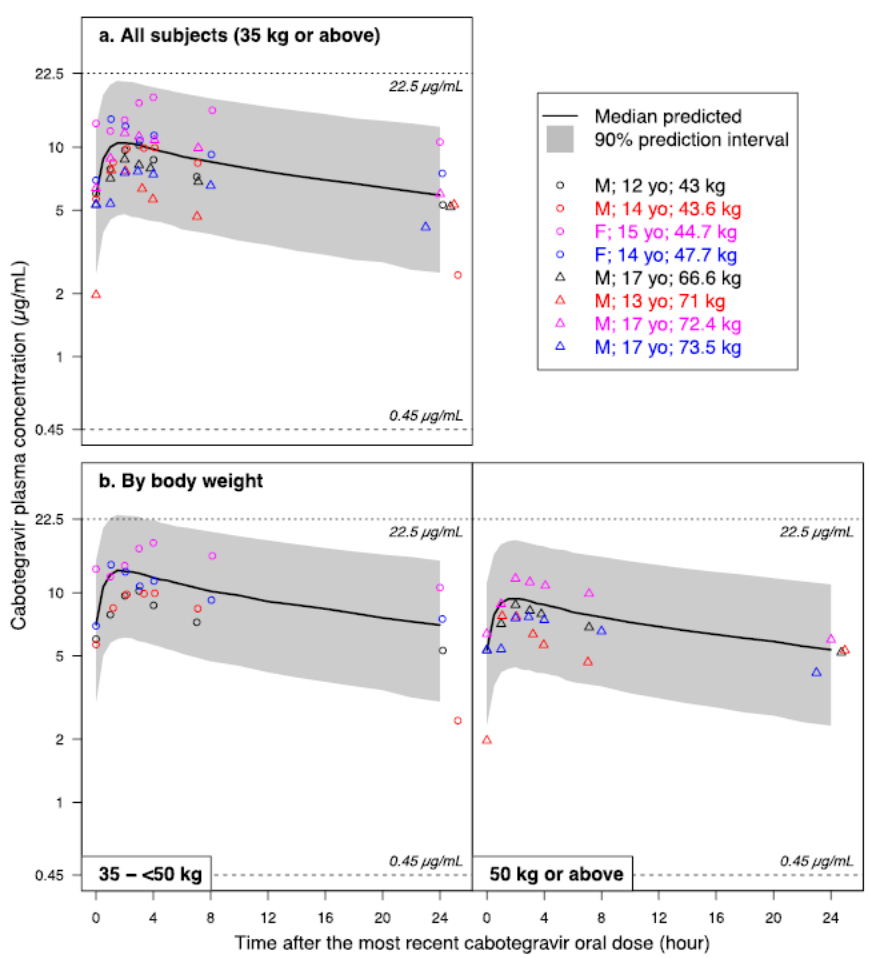
No specific studies have been performed investigating age effect. From the popPK analysis (study 2018N384611) it may be concluded that age had no effect on CAB PK within the age range studied. However, only a limited number of subjects had >65 years (n=35). No clinically relevant difference in PK was observed in high-risk participants from Study HPTN 083 and Study HPTN 084 aged 18 to 24 years and ≥25 years.

Children

PK data from 8 adolescents with HIV infection was evaluated by means of the already developed popPK for the adult population. From this, it could be concluded that the combined population PK analysis with both adolescent and adult PK data confirmed no impact of age on the PK of cabotegravir. Also, the developed model could be used to predict the exposure in adolescents ≥35kg body weight. Finally, HIV status had no impact on cabotegravir PK. As CAB PK was similar in healthy and HIV-infected adults administered Q8W CAB regimen, no differences are expected in CAB PK between adolescents evaluated in Study 208580 and adolescents who will receive CAB PrEP.

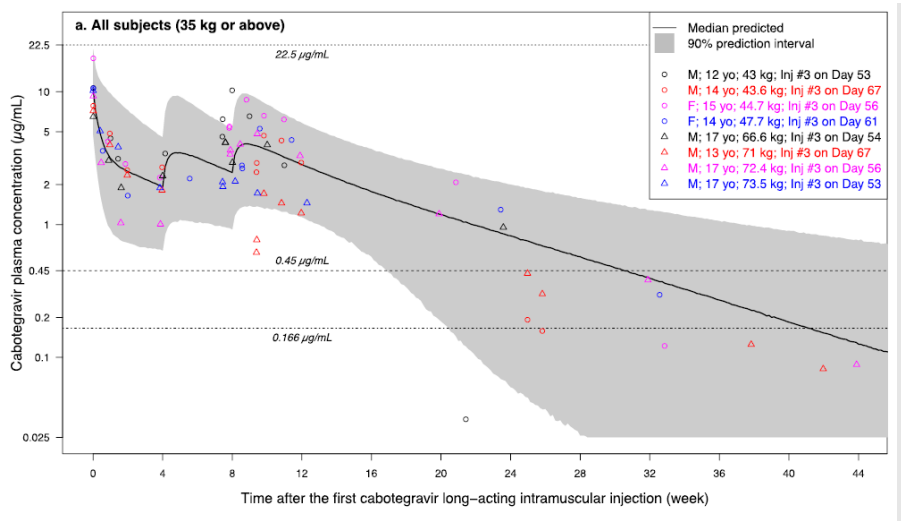
It should be noted that study 208580 design foreseen the enrolment of a different study population compared to the target population of the sought indication, i.e. study 208580 enrolled HIV infected patients instead healthy subjects which would be the target of the indication of prevention of HIV infection. Also, the dosage foreseen in the study is different, i.e. CAB (Cohort 1C) – CAB 30 mg once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 IM injections of CAB LA, each separated by 4 weeks (600 mg for the first injection and 400 mg for the second and third injections), in addition to cART (Step 2). The Applicant was considered compliant with PIP approved final decision (EMEA-C-001418-PIP02-15-M03): “The analysis of the combined PopPK model with the inclusion of both adolescent and adult PK data confirmed no impact of age on CAB PK parameters indicating a good precision of the final model (final111) PopPK model built without

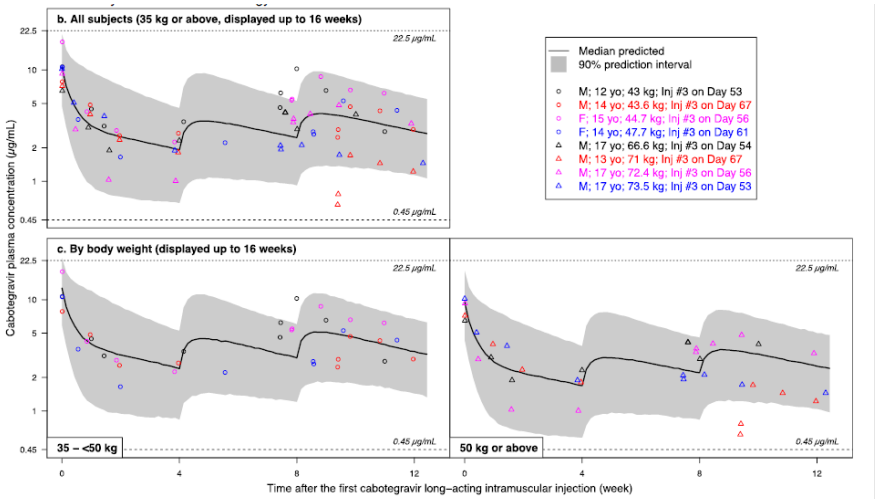
the adolescent data. Therefore, this final model has been used for the prediction of the exposures in adolescents receiving the adult Q8W dosing regimen.
The PopPK analyses demonstrated that the same adult Q8W regimen in adolescents will result in systemic exposures comparable to those in adults and within safety and treatment-based efficacy thresholds. Therefore, the remaining 7 adolescents from the cohort 1 can be waived as the pop PK model seems to have a good precision to predict the Q8W dosing regimen without requiring PK data in adolescents at this regimen."
However, a certain degree in exposure variability has been observed, partially due to the low number of adolescents observed subjects. It is also noted that, during the CAB oral phase, about the 5% of the subjects weighting 35 < 50 kg could reach plasma concentration slightly above 22.5 µg/mL, which is highest exposure observed in clinical studies not associated with any toxicity. Also, in the simulations made in the popPK study 2021N462341, it is showed that both at the oral administration phase and that after the CAB LA Initiation Injection, there is the risk of having Cmax values above the safety value of 22.5 µg/mL which represents the geometric median of Cmax observed at the supratherapeutic dose of oral CAB in TQT study and was not associated with any toxicity. (see figures below).



Data Source: 208580 GSK Document Number 2021N462341_01 Figure 6
The individual participants in Study 208580 are listed in the legend as: Gender (M = male; F = female); Age (yo = years old); Body weight (kg). The individuals are ordered by ascending body weight.
Reference line of 0.45 µg/mL = 5th percentile of the observed CAB trough concentration following the initiation injection in Phase III Studies 201584 and 201585.

Reference line of 22.5 µg/mL = geometric mean of Cmax observed at the supratherapeutic dose of oral CAB 150 mg (3 doses in total, twice daily) in the thorough QT/QTc (TQT) study LAI117009, which is not associated with any toxicity but is the highest exposure observed in clinical studies.





Data Source: 208580 GSK Document Number 2021N462341_01 Figure 7.
The individual participants in Study 208580 are listed in the legend as: Gender (M = male; F = female); Age (yo = years old); Body weight (kg); Time (day) of the third injection (Inj = injection) relative to the first injection (D = Day). The individuals are ordered by ascending body weight.
Reference line of 0.45 µg/mL = 5th percentile of the observed CAB trough concentration following the initiation injection in Phase III Studies 201584 and 201585.

Figure 3: Comparison between Observed and Simulated CAB oral PK in adolescents.

DDI

In Vitro

In study RH2007/00181, no results were provided for the positive controls and all substrates used were different from examples mentioned in the Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2). This was however a preliminary study. In this study, low inhibition potential was shown for CAB on CYP1A2, 2C9 and 2C19 (IC50 12.5- >33 µM, 15 and 13 µM respectively) in pooled human liver microsomes. No inhibition potential (IC50 >33 µM) was shown on CYP2D6 and 3A4.

In study 2012N151766, no inhibition potential (IC50 >100 µM) was shown for CAB on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 in human liver microsomes. Some inhibition was shown on CYP3A4/5. Direct inhibition was observed only at high concentrations (IC50 84 µM). Metabolism-dependent inhibition was observed with IC50 of 41 µM.

Based on the observed in vitro IC50 values, it is unlikely that cabotegravir is an inhibitor of CYP at clinically relevant systemic concentrations following PO and IM administration. In addition, it is unlikely that cabotegravir is an inhibitor of CYP at clinically relevant portal vein and intestinal concentrations following PO administration.

The clinical consequence of such a feature has been clarified through results observed in the clinical DDI study LAI116815 assessing the effect of CAB on midazolam (a probe CYP3A4 substrate) pharmacokinetics.

CAB inhibited UGT1A3 and UGT1A9, with IC50 values of 12 µM and 46 µM, respectively. CAB may alter the exposure of UGT1A3 substrate (e.g., naproxen) at therapeutic concentrations while IC50 for UGT1A9 is higher than the worst concentrations expected at the hepatic level. Therefore, the risk of clinically relevant DDI related to inhibition of UGT1A9 is unlikely whereas UGT1A3 inhibition by CAB cannot be ruled out. The ability for CAB to be involved in DDI through UGT1A3 inhibition has been also assessed using a mechanistic approach (see thereafter). The predicted AUC ratio is <1.25, hence no meaningful DDI expected.

At the highest concentration tested, 100 µM, CAB inhibited UGT1A1 by 15% (in human liver microsomes) to 33% (with recombinant UGT1A1) and UGT2B17 by 24%. This is not expected to be clinically relevant.

Based on the in vitro induction data, it is unlikely that cabotegravir is an inducer via AhR, CAR and PXR at maximal intestinal, portal vein and systemic concentrations after oral administration and at maximal systemic concentrations after IM administration.

CAB did not inhibit P-gp, BCRP, MRP2, MRP4, OATP1B1, OATP1B3, OCT1, OCT2, BSEP, MATE1, and MATE2-K at clinically relevant concentrations (maximal intestinal concentrations for P-gp and BCRP, maximal portal vein concentrations for OCT1, OATP1B1 and OATP1B3 and maximal systemic concentrations for all transporters).

CAB inhibited OAT1 and OAT3 with IC50 values of 0.812 µM and 0.411 µM, which indicates that inhibition of these transporters in vivo cannot be excluded (IC50 value is lower than the maximal systemic concentration following PO and IM administration). PBPK modelling predicted that exposure to several OAT1/OAT3 substrates would not increase more than 25% when used in combination with CAB. However, CAB will be used chronically and remains in the body for a long time. Considering this and the fact that IC50 values for OAT1 and OAT3 inhibition were approximately 10-fold below the estimated maximal concentration of 50-fold unbound Cmax as mentioned in the Guideline on the investigation of drug interactions, the results from the PBPK modelling can be considered supportive, but not sufficient to replace a clinical study regarding the inhibition of OAT1/OAT3 by CAB. As such, a SmPC wording of caution for OAT1/3 substrates is presented in part 4.5.

CAB glucuronide did not inhibit P-gp, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OCT2 and MATE2-K up to 300 µM. CAB glucuronide inhibited human MRP4 and MATE1 by 39.7% and 55.7% at 300 µM, which is not expected to be clinically relevant. CAB glucuronide inhibited OAT1 and OAT3 with IC50 of 73.4 µM and 36.5 µM, respectively. This may be at least partly due to the presence of CAB in the tested batch.

CAB did not inhibit PCFT and RFC up to 100 µM. CAB inhibited the folate receptor α by 37% at 26 µM. However, this is not considered clinically relevant.

In Silico

PBPK predictions in AUC and Cmax for OAT1/OAT3 inhibition and for UGT inhibition/induction were within 30% of values observed in studies from published literature. The predicted decrease in AUC0 inf

for CAB due to the UGT1A1 inhibitor rifampicin was comparable to the decrease observed in clinical study LAI117010 (48% predicted vs 59% observed).

The simulations predicted a mean increase of ≤ 25% in systemic exposure for the tested OAT1/OAT3 substrates with oral cabotegravir.

The simulations predicted a mean increase of ≤ 11% in systemic exposure of CAB in combination with the UGT1A1 inhibitor atazanavir and the UGT1A9 inhibitor mefenamic acid. However, considering the limits from the PBPK modelling and simulations, a word of caution was included in the SmPC, part 4.5.

CAB post-hoc PK exposure (AUC, Cmax, Ctau and Tmax) following CAB Q8W regimen in all participants in the combined dataset were compared across subgroups in PopPK 2021N484575. CAB post-hoc estimates of exposure (geometric mean with 95% CI or median with 5th and 95th percentiles) were similar across contraceptive methods in females in Studies 201103 and 201739.

In vivo

No significant interaction was observed between CAB and rilpivirine.

Decrease of CAB exposure can be expected when orally administered CAB is co-administered with polyvalent cation-containing products. The Applicant expects that the exposure will not decrease below the 10 mg oral CAB exposure. A warning is included in the SmPC to administer antacids at least 2 h before and 4 h after oral CAB. The recommendation to administer antacids containing polyvalent cations at least 2 hours before, or 4 hours after, oral CAB doses is aligned with instructions for co-administration in Phase 3 studies.

Rifampin/rifampicin, which is a strong inducer via PXR (including UGT1A1), reduced CAB AUC(0-inf) by approximately 2.5-fold (59%) and C24 by 2-fold (50%). Rifampin had no effect of the Cmax. The reduction is clinically relevant. Dosing recommendations for co-administration with rifampicin have not been established. Co-administration of CAB with rifampicin and other strong UGT1A1 inducers is contra-indicated, which is agreed.

Rifabutin reduced CAB AUC(0-tau), Cmax, and Ctau by 21%, 17%, and 8%, respectively.

Etravirine had no effect on AUC(0-tau) and Cmax of CAB. Cmin was slightly decreased (by 14%), which is however not considered clinically relevant.

The Applicant concludes that it is not necessary to perform DDI studies with UGT inhibitors based on the pharmacogenetics analysis, in which in subjects with low UGT1A1 activity exposure to CAB was shown to increase by approximately 1.5-fold.

CAB did not significantly affect the PK of ethinyl estradiol and levonorgestrel. CAB can be co-administered with oral contraceptives without clinical consequences.

CAB increased AUC(0-t) and Cmax of midazolam by 10% and 9% respectively. This is not clinically relevant, indicating that CAB does not significantly inhibit or induce CYP3A enzymes.

Exposure relevant for safety evaluation

The recommended initial CAB injection dose in adults is a single 3 mL (600 mg) IM injection. If OLI has been used, the first injection should be planned for the last day of OLI or within 3 days thereafter. One month later, a second 3 mL (600 mg) IM 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. Plasma CAB PK parameters for the proposed regimens are summarized in the table below.

Table 4: PK parameters following CAB orally once daily and initiation and every 2 months continuation intramuscular injections.

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial Injection[d]	600 mg IM Initial Dose	1591 (714, 3245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Every 2-Month Injection[e]	600 mg IM Every 2-month	3764 (2431, 5857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

Data Source: GSK Document Number 2018N384611_01 Table 17; GSK Document Number 2019N421460_00, Table 14

a. PK parameter values were based on individual post-hoc estimates from population PK models for patients in Phase III treatment studies of HIV treatment studies.
b. tau is dosing interval: 24 hours for oral administration; 1 month for monthly and 2 months for every 2 months for IM injections of extended-release injectable suspension.
c. OLI PK parameter values represent steady state.
d. Initial injection Cmax values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the AUC(0-tau) and Ctau values reflect the initial injection. When administered without OLI to HIV infected recipients (n = 110), the observed CAB geometric mean (5th, 95th percentile) Cmax (1-week post-initial injection) was 1.89 µg/mL (0.438, 5.69) and Ctau was 1.43 µg/mL (0.403, 3.90).
e. PK parameter values represent steady state.

2.5.2.2. Pharmacodynamics

A significant part of the clinical pharmacology program is based on the cabotegravir development for the treatment of HIV-1 infection. The Committee's assessment has been focused on the studies most relevant for the indication intended for Apretude.

Mechanism of action

CAB inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Of note, the chemical structure of CAB is very close to dolutegravir.

CAB is a potent in vitro inhibitor of HIV integrase and inhibits the integrase catalysed viral DNA strand transfer with IC50 values in the nanomolar range (3.0 to 13 nM).

Primary and Secondary pharmacology

The susceptibility of 13 clinically diverse HIV-1 subtype B isolates to integrase inhibition by CAB was tested. The mean IC50 for viral replication of the clinical isolate based viruses was 1.3 nM (range 1.0 to 1.6 nM).

Table 5: Activity of CAB against a panel of HIV-1 subtypes B clinical isolates

Virus	EC_{50} (nM)
ASJM 108	1.5
ASM 34	1.4
ASM 42	1.3
NIH 57	1.5
NIH 660	1.0
NIH 657	1.4
NIH 714	1.4
NIH 727	1.3
CV 110	1.1
CV 154	1.2
CV 163	1.2
CV 243	1.1
CV 281	1.1
HIV-1 IIIB	1.1
HXB2	1.6
NL4-3	1.4
Isolate mean	1.3
Isolate Median	1.3
Isolate standard deviation	0.2
Isolate range	1.0-1.6
Laboratory virus mean	1.4
Laboratory virus median	1.4
Laboratory virus standard deviation	0.2
Laboratory virus range	1.1-1.6

Data Source: GlaxoSmithKline Document Number RH2007/00092/01 Table 1

CAB was highly active with broad activity against all HIV-1 (geometric mean EC50 of 0.26 nM and range of 0.02 to 1.06 nM) and HIV-2 (geometric mean EC50 of 0.12 nM and range of 0.10 to 0.14 nM) isolates tested). In the monocyte-derived macrophage assays using 4 Subtype B isolates, the geometric mean EC50 was 0.92 nM and values ranged from 0.29 to 1.64 nM.

Table 6: Mean activity of CAB against broad subtypes and HIV-2 in PBMCs and Subtype B isolates in macrophages.

Virus	Mean EC_{50} (nM)
Subtype A	0.31
Subtype B	0.17
Subtype C	0.14
Subtype D	0.38
Subtype E	0.30
Subtype F	0.10
Subtype G	0.22
Group O	0.64
HIV-2	0.12
Subtype B in Macrophages	0.92

Data Source: GlaxoSmithKline Document Number RH2008/00133/00 Table 3, Table 4, Table 5, Table 7, and Table 8

CAB was evaluated for antiviral activity against a panel of 11 non-HIV viruses. In general, CAB did not exhibit significant antiviral activity in this panel. Some activity was observed against rhinovirus (EC50 = 12.6 µM).

Resistance

Analysis of resistance to CAB was assessed by co-culturing MT-2 cells with Molt-4 cells persistently infected with HIV-1 strain IIIB.

The following IN mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of CAB: Q146L (FC range 1.3-4.6), S153Y alone and in combination (FC range 2.8-8.4), S153F (FC range 6.3-6.4), and I162M (FC=2.8).

Table 7 Passage with HIV III B

Days of Culture	Amino Acid Substitution	CAB Fold Change
14	T124A	1.2-1.9
28	T124A	1.4-5.5
42	T124A	<0.88-4.0
56	T124A	1.1-4.6
	Q146L	3.3
	S153Y	4.7
	T124A, S153Y	6.4
70	T124A	1.1-3.8
	Q146L	1.3
	S153Y	2.8-3.0
	T124A, S153Y	3.6
84	T124A	1.3-5.7
	Q146L	2.9
	S153Y	4.3-5.1
	T124A, S153Y	8.4
	T124A, I162M	2.8
98	T124A	1.3-5.2
	Q146L	3.9
	S153Y	4.7-6.0
	T124A, S153Y	6.3
112	T124A	1.1-7.4
	Q146L	4.6
	S153Y	5.1-5.6
	T124A, S153Y	6.6

Data Source: E-265744-EB-002-R GSK Document RH2007/00210/00 Table 1

Isolation from Wild Type NL-432 and Site Directed Mutant INI Resistant HIV-1 Strain NL432 was performed. Starting with mutants at IN position 148 (H, K, or R), the following additional mutations emerged after passaging with CAB: G56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I. CAB FC for various combinations of these mutations with Q148H/K/R ranged from 2.2 to 410, relative to that observed for NL432.

Table 8: Passage of NL-432 and single mutans with CAB

Initial Virus / Single Mutant	CAB Initial Conc. / Final Conc (nM)	Days of Culture	Amino Acid Substitution	CAB Fold Change of Passaged Virus Pools
NL-432	6.4 / 160	56	No mutation	0.85-1.3
	32	56	No replication	
	160	56	No replication	
Q148K	6.4 / 160	14	Q148K	
		28	E138K, Q148K	
		42	E138K, Q148K	
		56	E138K, Q148K	89-260
	32 / 160	14	E138K, Q148K	
		28	E138K, Q148K	
		42	E138K, Q148K	
		56	E138K, Q148K	53-190
			V72I, E138K, Q148K	410
	160	56	No replication	
Q148R	6.4 / 160	14	Q148R	
		28	Q148R E138K, Q148R	
		42	L74M, Q148R E138K, Q148R	-
		56	L74M, Q148R	
			E138K, Q148R	3.0-11
	32	56	No replication	
	160	56	No replication	

Initial Virus / Single Mutant	CAB Initial Conc. / Final Conc (nM)	Days of Culture	Amino Acid Substitution	CAB Fold Change of Passaged Virus Pools
Q148H	6.4 / 160	14	G140S, Q148H	
		28	G140S, Q148H	
		42	G140S, Q148H E138K, G140S, Q148H L74M, V75A, G140S, Q148H	2.0 17 21 - 160
	32 / 160	28	G140S, Q148H	
		42	G140S, Q148H G140S G148H, G149A C56S, G140S, G148H, G149A	
		56	T122N, G140S, Q148H G140S, Q148H, M154I G56S, G140S, Q148H, G149A	16 2.2 55 - 130
	160	56	No replication	
N155H	6.4 / 6.4	14	N155H	
		28	N155H	
		42	N155H	
		56	N155H	1.1 – 2.0
	32		No replication	
	160		No replication	
E92Q	6.4 / 6.4	14	E92Q	
		28	E92Q	
		42	E92Q	
		56	E92Q	0.52 – 0.77
	32		No replication	
	160		No replication	

Data Source: S-265744-EB-010-R GSK Document Number 2013N166665_00 Table 1

Comparative susceptibilities to CAB, DTG and RAL were obtained from 42 RAL resistant site directed HIV-1 mutants.

CAB showed anti-HIV activity (susceptibility) with fold change (FC) <5 against 22 of 25 INI-resistant mutant viruses with single mutations; for DTG there were 24/25 mutant viruses with FC <5. While both CAB and DTG had >5-FC with G118R, only CAB had >5 FC with Q148K and Q148R. F121Y and T124A caused no increase in FC for either CAB or DTG. N155H resulted in 1.7 FC to CAB and 0.99 FC to DTG.

Among the multiple mutants, the highest FC for CAB was observed with mutants containing Q148K (FC E138A, Q148K = 81) or Q148R (FC G140C, Q148R = 22).

The occurrence of incident HIV infections in the pivotal trials was analysed and characterized.

In the Pivotal Study 201738 / HPTN 083, 51 HIV incident infections had been identified: 12/3211 PY (incidence rate 0.37/100 PY) in the CAB group and 39/3193 PY (incidence rate 1.22/100 PY) in the TDF/FTC group. Four (4) incident infections occurred while the participant was receiving active CAB LA injections. Based on this, the bias-adjusted HR (95% CI) is 0.31 (0.16, 0.58).

3 participants in the CAB group acquired integrase mutations: 2 participants, who became infected during the OLI Phase, and another participant. 3 additional CAB participants with HIV infection had NNRTI resistance and 1 had NRTI resistance.

In the Pivotal Study 201739 / HPTN 084, 40 HIV incident infections had been identified: 4 (0.20/100PY) in the CAB group and 36 (1.85/100PY) in the TDF/FTC group. One of these 4 infections was determined to be a prevalent infection following the primary analysis. In the CAB group, the incident rate was 0.15/100 PY and the TDF/FTC group was 1.85/100 PY. Based on this, the bias adjusted HR (95% CI) is 0.10 (0.04, 0.27).

In the CAB group:

- 2 HIV infections occurred in women with no recent oral CAB exposure and no injections:
    - 1 in a participant who had completed Step 1; this participant was non-adherent to oral CAB based on plasma CAB concentrations, and the first HIV-positive visit occurred 7.4 weeks after the end of Step 1
    - 1 in a participant who was off CAB due to a temporary study-related discontinuation [i.e., due to becoming pregnant during OLI ~4 weeks post enrolment] and for whom the first HIV-positive visit occurred 52 weeks after the last quantifiable plasma CAB concentration).
- 2 HIV infections occurred during the injection phase of the study (i.e., during Step 2).

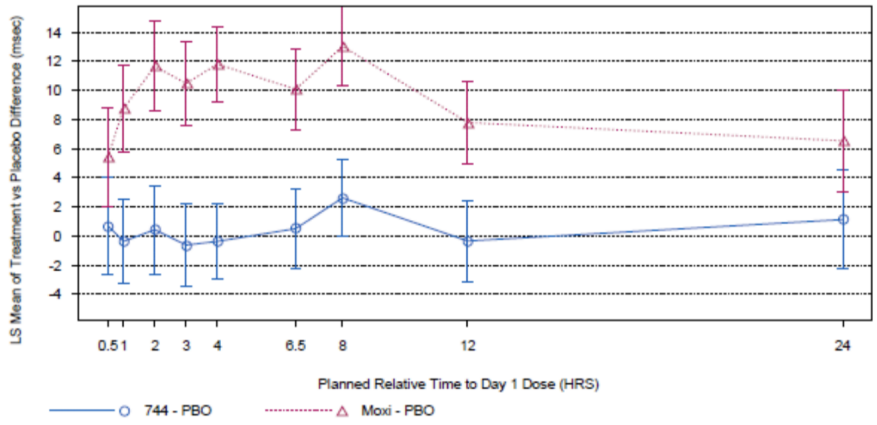
HIV genotyping results were available for 3 of the 4 CAB participants (1 did not have a viremic sample). 1 of the 3 participants had an integrase mutation at the first viremic visit (L74I); this mutation is considered to be a polymorphism and was also detected in several participants in the TDF/FTC group.

HIV genotyping results were obtained for 33 of the 36 incident infections in the TDF/FTC group. 1 participant had both NRTI and NNRTI mutations. Eight other participants had NNRTI mutations alone. INSTI mutations/polymorphisms were detected in 10 samples.

Secondary Pharmacodynamics

In a Thorough QTc Study (LAI117009) CAB had no significant effect on cardiac repolarization at a supratherapeutic dose of 150 mg q 12 h x 3 doses.

The geometric mean CAB Cmax achieved in this study was approximately 3-fold higher than that of the standard clinical dose of 30 mg once daily at steady state and approximately 6-fold higher than that of the Q4W regimen at steady state.



Data Source: LAI117009 GSK Document Number 2014N208600_00 CSR Figure 2.1
Note: Three participants were excluded from analysis due to missing time points
Treatments:
CAB = 3 doses of CAB 150mg (5 x 30 mg tablets) q12 h.
PBO = 3 doses of CAB placebo (5 tablets) q12 h.
Moxifloxacin = A single dose of moxifloxacin 400 mg (1 x 400 mg tablet).

Figure 4: Plot of Least Squares Mean of Treatment Difference (CAB or Moxifloxacim) from Placebo for QTcF Change from Baseline (90% Cis) Following Oral CAB or Placebo Q12h (PD Population)

Therefore, in combination with non-clinical studies, this data supports the lack of effect of CAB in QT prolongation.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

The main PK characteristics of Cabotegravir have been sufficiently well described based on data collected in healthy subjects and patient with HIV-1 infection. These include a flip-flop kinetics after IM administration with a Tmax of 7 days. After oral administration, a relative BE (oral/IM) of 0.76 and a Tmax of 3h was observed. No relevant food effect was observed. There is some distribution beyond plasma, but with low extent. Plasma protein is high (99.9% bound) with a B/P ratio of 0.52. Distribution of CAB in the mucosal tissues at sites of sexual transmission were strongly correlated and proportional to the plasma concentrations (tissue concentrations~10% to 20% of plasma concentrations over time). Elimination is mainly by metabolism, by UGT1A1 and UGT1A9 (minor) phase II reactions.

The clinical studies and the population PK analysis led to the same conclusion that CAB can be administered without dose adjustment in subjects with mild to severe renal impairment (not on renal replacement therapy). Both population PK analysis and a dedicated clinical study show that CAB may be taken without dose adjustment in subjects with mild to moderate hepatic impairment.

Gender and race seem to have no clinically relevant impact on the PK of CAB after IM dosing.

However, plasma CAB concentrations appeared to trend higher in participants <50 kg.

Considering the proposed indication includes subjects weighting at least 35 kg, the applicant was requested to present data divided into narrower weight group; also, the number of subjects included in each group should be specified, in order to better analyse the impact of body weight in cabotegravir

exposure at both the oral lead-in phase and at steady state. Based on the applicant's response, the exposure of CAB was shown higher for the <50 kg population. However, only AUC in these participants seem to be slightly above the observed values in the clinical trials. Both Cmax and Cmin values are contained within the previously observed values. No trends or safety concerns were identified for adult individuals weighing <50 kg suggesting a difference in safety profile or worse safety outcomes. This may indicate that the AUC is not a relevant marker in this respect.

Of major relevance for the current use of Cabotegravir for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg, similar plasma CAB exposure between healthy, HIV-1-infected, and high-risk participants has been observed. In fact, the Cabotegravir PopPK model was able to reliably describe and predict CAB PK from Studies HPTN 083 and HPTN 084 although this population was not used in the model building procedures. Also, PK data for Cabotegravir in adolescents with HIV-infection (> 12 years and >35kg) is like healthy and HIV-adults and, again, the previously developed popPK model could be used to both describe and predict the exposure in adolescents ≥35kg body weight. These conclusions support the extrapolation of data generated in healthy participants, such as drug and food interactions, renal and hepatic impairment, and the TQT study to these two target populations.

However, a certain degree in exposure variability has been observed, partially due to the low number of adolescents observed subjects. It is also noted that, during the CAB oral phase, about the 5% of the subjects weighting 35 < 50 kg could reach plasma concentration slightly above 22.5 µg/mL, which is highest exposure observed in clinical studies not associated with any toxicity. The Applicant, using PopPK simulations, confirmed that subjects with <50kg are predicted to have Cmax that may exceed the 22.5ug/mL, both at the OLI phase or after the CAB initiation injection. The applicant clarified that the Cmax limit of 22.5 µg/mL was, in fact, the geometric mean Cmax for participants (n=40) in Study LAI117009, the dedicated TQT study which did not identify significant safety risks. In this study, the Cmax in LAI117009 ranged from 16.9 to 39.2 ug/mL. None of the simulated subjects did result in values above the 39.2 ug/mL observed value. There is no clearly defined PK/PD model for CAB, but a Cmax below 22.5 (39.2) ug/mL has been shown to be safe, and it is hypothesized that a Cmin above 0.664 ug/mL is required for efficacy. On the other side, the predicted 5th percentile of Ctau is just around the efficacy level and, thus, dose reduction would not be appropriate without a significant change in the interval of administration itself. Information was included in the SmPC stating that, although the exact time from initiation of Apretude for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown, based on model-predicted data, cabotegravir concentrations considered having significant antiviral activity (> 4x Protein Adjusted-IC90 i.e., 0.65 ug/mL) are reached and maintained shortly after the initiation of oral lead-in and, in case of no oral lead in is used, within 7 days after the first injection.

Based on in vitro chelation studies, decrease of CAB exposure can be expected when orally administered CAB is co-administered with polyvalent cation-containing products such as antacids and also mineral supplements. The Applicant expects that the exposure will not decrease below the 10 mg oral CAB exposure. A warning is included in the SmPC to administer antacids at least 2 h before and 4 h after oral CAB. In clinical studies, no significant effect was observed of rilpivirine on CAB. No clinically relevant effect of the weak/moderate UGT inducer etravirine was observed on CAB. The weak/moderate UGT inducer rifabutin reduced CAB AUC(0-tau), Cmax, and Ctau by 21%, 17%, and 8%, respectively. Rifampicin, as a strong UGT1A1 inducer, reduced CAB AUC(0-inf) by 2.5-fold (59%) and C24 by 2-fold (50%). Co-administration of CAB with rifampicin and other strong UGT1A1 inducers is contra-indicated, which is agreed. No clinical studies were performed with UGT inhibitors. The Applicant concludes that it is not necessary to perform DDI studies with UGT inhibitors based on the pharmacogenetics analysis in which in subjects with low UGT1A1 activity exposure to CAB was shown to increase by approximately 1.5-fold. In vitro studies indicate no clinically relevant induction of

CYP1A2 (induction via AhR), 2B6 (induction via CAR) and 3A4 (induction via PXR) by CAB. In vitro studies indicate no clinically relevant inhibition of cytochrome P450. In vitro studies indicate no clinically relevant inhibition of UGT except UGT1A3 in case of oral administration. In case of oral administration, inhibition of UGT1A3 in the intestine cannot be excluded. In vitro studies indicate no clinically relevant inhibition of P-gp, BCRP, MRP2, MRP4, OATP1B1, OATP1B3, OCT1, OCT2, BSEP, MATE1, and MATE2-K. Based on in vitro studies, inhibition of OAT1 and OAT3 by CAB cannot be excluded. PBPK modelling predicted an increase of CAB exposure of maximally 25%. However, considering the low IC50 values found in the in vitro study and the fact that use of CAB/RPV in combination with OAT1/OAT3 substrates is very likely to occur a word of caution was included in the SmPC. Clinical DDI studies were performed with orally administered CAB. In clinical studies, CAB had no significant effect on rilpivirine, ethinyl estradiol and levonorgestrel and CYP3A substrate midazolam. In vitro studies indicate that CAB glucuronide does not inhibit MDR1, BCRP, BSEP, MRP2, MRP4, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K to a clinically relevant extent. Inhibition of OAT1 and OAT3 was observed.

Pharmacodynamics

A significant part of the clinical pharmacology program is based on the development of cabotegravir for the treatment of HIV-1 infection. The focus of the following assessment is more focus on the studies most relevant for the indication intended for Apretude, the pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents.

CAB is a potent in vitro inhibitor of HIV integrase and inhibits the integrase catalysed viral DNA strand transfer with IC50 values in the nanomolar range (3.0 to 13 nM).

The susceptibility of 13 clinically diverse HIV-1 subtype B isolates to integrase inhibition by CAB was tested. The mean IC50 for viral replication of the clinical isolate based viruses was 1.3 nM (range 1.0 to 1.6 nM). CAB was highly active with broad activity against all HIV-1 and HIV-2 isolates tested.

CAB was evaluated for antiviral activity against a panel of 11 non-HIV viruses. In general, CAB did not exhibit significant antiviral activity in this panel although some activity was observed against rhinovirus.

HIV-infected adolescents (Age 12-<18 years and ≥35 kg) were administered with CAB 30 mg once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART, followed by 3 intramuscular (IM) injections of CAB LA, each separated by 4 weeks (600 mg for the first injection and 400 mg for the second and third injections), in addition to cART.

Eight enrolled participants were assigned to Cohort 1C comprising of 6 males and 2 females, with a mean (range) age of 14.9 (12 - 17) years.

All participants were virologically suppressed to <50 c/mL at Week 16, and there were no incidents of confirmed virologic failure through the Cohort 1 Week 16 interim analysis. Thus, no resistance data are available for summary.

The observed PK and safety data from this study support the acceptability of the use of the adult CAB monthly dosing regimen in adolescents.

In HIV-1-infected participants who were naïve or off all ART for at least 12 weeks, oral CAB monotherapy regimens of 5 mg once daily and 30 mg once daily achieved mean decreases in plasma HIV-1 RNA of >2.1 log10 c/mL on Day 11 with geometric mean CAB Ctau of 0.57 µg/mL (3.43x PA-IC90) for CAB 5 mg once daily and 3.28 µg/mL (19.8x PA-IC90) for CAB 30 mg once daily. There was no clear relationship between plasma CAB PK parameters and reduction in plasma HIV-1 RNA

concentrations due to the strong antiviral response observed for the two oral CAB monotherapy regimens of 5 mg once daily and 30 mg once daily.

In healthy participants, in study HPTN 083, geometric mean plasma CAB concentrations 1-week and 4-weeks post- initial injection were 2.90 µg/mL (>4x PA-IC90) and 1.86 µg/mL (>4x PA-IC90), respectively, in participants who did not acquire HIV infection. At steady state (Week 49), geometric mean CAB plasma concentrations were 1.72 µg/mL, (>4x PA-IC90). PK in cisgender women in HPTN 084 were similar to those observed in MSM and TGW in HPTN 083. In Study 201767, CAB concentrations after a single 600 mg IM injection were measured in plasma and in cervical, vaginal, and rectal tissues and in cervical and rectal fluid. Tissue and plasma CAB concentrations were strongly correlated and proportional (tissue concentrations ~10% to 20% of plasma concentrations) over time. The clinical relevance of tissue or fluid concentrations is uncertain in the setting of HIV prevention. However, the plasma PK data from HPTN 083 suggests that pre-dose tissue concentrations >1x PA-IC90 (0.166 g/mL) would be expected in tissues at sites of sexual transmission for PrEP based on the distribution into mucosal tissues observed in Study 201767.

Analysis of resistance to CAB resulted in the identification of the following mutations: Q146L, S153Y, S153F and I162M. Starting with mutants at IN position 148 (H, K, or R), the following additional mutations emerged after passaging with CAB: G56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I. CAB FC for various combinations of these mutations with Q148H/K/R ranged from 2.2 to 410, relative to that observed for NL432.

Comparative susceptibilities to CAB, DTG and RAL showed anti-HIV activity (susceptibility) with fold change (FC) <5 against 22 of 25 INI-resistant mutant viruses with single mutations; for DTG there were 24/25 mutant viruses with FC <5. While both CAB and DTG had >5-FC with G118R, only CAB had >5 FC with Q148K and Q148R.

Among the multiple mutants, the highest FC for CAB was observed with mutants containing Q148K or Q148R.

Clinical trial isolates from seroconversion in previously healthy participants revealed INSTI mutations/polymorphisms (V151I, L74I, E138K, G140S, Q148R, E157Q, G140A), as well as NNRTI and NRTI associated mutations.

Although no direct clear exposure-response relationship exists, the doses selected lead to plasma CAB concentrations >4x PA-IC90 (1-week and 4-weeks post-injection and at steady-state at 49-weeks). Tissue and plasma CAB concentrations were strongly correlated and proportional (tissue concentrations ~10% to 20% of plasma concentrations) over time.

2.5.4. Conclusions on clinical pharmacology

Pharmacokinetics

The population PK analysis with both adolescent and adult PK data seems to allow extrapolation of PK in uninfected adolescents, showing no significant differences in PK parameters.

Pharmacodynamics

The overall clinical pharmacodynamics program is considered adequate to support the use of CAB in the proposed indication.

2.5.5. Clinical efficacy

The clinical development program consists of 2 randomized pivotal studies (Phase IIb/III study 201738/HPTN 083 and Phase III study 201739/HPTN 084) supported by 2 randomized, placebo-controlled studies (study 201120 ÉCLAIR and study 201103/HPTN 077).

The discussed indication is:

Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

Study Identifier / Sponsor	No. Study Centers; Locations	Study Start; Enrollments Status and Date; Total Enrollment / Target Enrollment	Study Objectives	Study Design	Population; Key Inclusion Criteria	Treatment Details	No. of Subjects by Group Entered/ Completed	Gender M/F[a]; Mean Age (Range)	Primary Endpoint(s)
Pivotal Studies									
201738 (HPTN 083) DAIDS/ NIAID/NIH	43 centers; Argentina 2, Brazil 4, Peru 5, US 27, South Africa 1, Thailand 3, Vietnam 1	19-DEC-2016; Ongoing (unblinded following 14-MAY-2020 DSMB review); 4570 (4566 treated)/ 5000	**Primary:** -To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2) -To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC. **Secondary:** HIV incidence, change in hazard of HIV acquisition, changes in renal function,	Phase IIb/III, randomized, multicenter, double-blind, double dummy, non-inferiority study	MSM or TGW who are HIV-uninfected and at high risk for HIV acquisition, ≥18 years of age	**Step 1: OLI Phase** **Arm A – Daily oral CAB for up to 5 weeks** (30 mg tablets) and oral TDF/FTC placebo **Arm B – Daily oral TDF/FTC for up to 5 weeks** (300 mg/200 mg FDC tablets) and oral CAB placebo **Step 2[b]: Injection Phase** / dosing at 2 time points 4 weeks apart (Q4W) and every 8 weeks (Q8W) thereafter **Arm A – CAB LA** (600 mg as a single [3mL] intramuscular [IM] injection and daily oral TDF/FTC placebo. **Arm B – Daily oral TDF/FTC** (300/200 mg FDC tablets) and IM placebo	**Arm A (CAB group)**: 2283 (2282 treated)/ 28 **Arm B (TDF/FTC group):** 2287 (2284 treated)/ 49	4570 M; **Arm A (CAB group)**: 28.0 yrs (18, 69) **Arm B (TDF/FTC group):** 28.2 yrs (18, 69)	**Efficacy:** Number of documented incident HIV infections in Steps 1 and 2 **Safety:** Grade 2 or higher clinical and laboratory adverse events

Study Identifier / Sponsor	No. Study Centers; Locations	Study Start; Enrollments Status and Date; Total Enrollment / Target Enrollment	Study Objectives	Study Design	Population; Key Inclusion Criteria	Treatment Details	No. of Subjects by Group Entered/ Completed	Gender M/F[a]; Mean Age (Range)	Primary Endpoint(s)
			liver function, and bone mineral density, rates of HIV drug resistance in participants who acquire HIV infection, acceptability, changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids			(matching vehicle [Intralipid 20% fat emulsion infusion], identical volume as active injectable product in Arm A). **Step 3 [d]: Follow-up Phase Both arms: Open-label daily oral TDF/FTC** no later than 8 weeks after the last injection (in order to cover the PK tail for Arm A participants), for up to 48 weeks.			
201739 (HPTN 084) DAIDS/ NIAID/NIH	20 centers; Botswana 1, Kenya 1, Malawi 2, South Africa 7, eSwatini (formerly Swaziland) 1, Uganda 3, Zimbabwe 5	27-NOV-2017; Ongoing (unblinded following 05-NOV-2020 DSMB review); 3224 / 3200	**Primary:** -To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).	Phase III, randomized, multicenter, double-blind, double dummy, open-label, superiority study	Cisgender women who are HIV-uninfected, sexually active, with a modified VOICE risk score ≥5, 18-45 years of age	**Step 1: OLI Phase** **Arm A – Daily oral CAB** (30 mg tablets) and TDF/FTC placebo tablets for up to 5 weeks plus an HIV prevention package. **Arm B – Daily oral TDF/FTC** (300/200 mg FDC tablets) and CAB placebo for up to 5 weeks plus an HIV prevention package. **Step 2[c]: Injection Phase**	**Arm A (CAB group)**: 1614/ 4 **Arm B (TDF/FTC group)**: 1610/ 37[e]	3219 F; **Arm A (CAB group)**: 26.0 yrs (18, 44) **Arm B (TDF/FTC group)**: 26.0 yrs (18, 45),	**Efficacy:** Number of documented incident HIV infections in Steps 1 and 2 **Safety:** Grade 2 or higher clinical and laboratory adverse events

Study Identifier / Sponsor	No. Study Centers; Locations	Study Start; Enrollments Status and Date; Total Enrollment / Target Enrollment	Study Objectives	Study Design	Population; Key Inclusion Criteria	Treatment Details	No. of Subjects by Group Entered/ Completed	Gender M/F[a]; Mean Age (Range)	Primary Endpoint(s)
			-To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).			dosing at 2 time points 4 weeks apart (Q4W) and every 8 weeks (Q8W) thereafter **Arm A – CAB LA** (a single [3 mL] 600 mg IM injection and daily oral placebo plus an HIV prevention package. **Arm B – Daily oral TDF/FTC** (300/200 mg FDC tablets) and IM placebo (matching vehicle [Intralipid 20% fat emulsion], identical volume as active injectable product in Arm A) plus an HIV prevention package. **Step 3 [d]: Follow-up Phase** **Arm A – Daily TDF/FTC** will be provided no later than 8 weeks after the last injection, for up to 48 weeks plus an HIV prevention package. Arm A participants will then transition to locally available HIV prevention services, including services for pre-exposure prophylaxis, if available. **Arm B – Daily**			

a. The data provided for "Gender" in this table represent sex at birth, not necessarily a participant's gender identity.
b. At the time the study was initiated, Step 2 was to continue until the required number of endpoints was reached. Each participant was to receive a maximum of 3 years of blinded study medication.
c. At the time the study was initiated, Step 2 was to continue until the required number of endpoints (114) was reached, estimated to be 81 weeks after enrolling the last participant.
d. Participants may choose to discontinue oral TDF/FTC at this stage. Arm B participants then will transition to locally-available HIV prevention services, including services for pre-exposure prophylaxis, if available.
e. There was one case in the TDF/FTC group that was reviewed by the EAC and for which the EAC concluded that HIV status could not be determined based on the available data. This case was not included in analyses of participants with HIV infection because it was not confirmed as an infection by the EAC.

It is known that two HIV-1 PrEP sub-studies in sexually active, HIV-1-uninfected adolescent males (HPTN 083-01) and females (HPTN 084-01) have been completed. These are safety, tolerability and

acceptability studies of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males - A Sub-study of HPTN 083 and women- A Sub-study of HPTN 084.

2.5.5.1. Dose response studies

The Cabotegravir dose rationale was based on maintaining Cabotegravir dose concentrations 4 times greater that the in vitro protein-adjusted 90% inhibitory concentration (PA-IC90) value of 0.166 µg/mL (i.e., 0.664 µg/mL), a concentration range shown to have significant antiviral activity in vitro and in Phase IIa monotherapy studies used for the approval of the use of Cabotegravir in HIV-1 infected participants (in combination with rilpivirine).

CAB 30 mg once daily has been used as OLI in supportive PrEP studies HPTN 077 and Study 201120. similar CAB concentrations were observed at the end of OLI after 30 mg once daily as observed in Study LAI116482. As such, this oral dose was selected for use as OLI in the CAB PrEP Phase III studies.

From the data presented the timing to achieve 4x PA-IC90 of 0.664 µg/mL was similar in population on CAB submitted to OLI and the ones in the DTI group.

According with the data presented and the safety profile of CAB OLI can be optional (this can be of value in population with low adherence (oral or other), but the OLI CAB should continue to be optional to the provider and/or individual), according with the applicant.

The Injection Phase of the dosing regimen used in the pivotal studies HPTN 083 and HPTN 084 is initiated by 2 injections (single 600 mg, 3 mL IM) administered 4 weeks apart, with subsequent injections administered Q8W. This is the same dose used for HIV1 treatment in combination with rilpivirine.

In Phase IIa HPTN 077 LA 800 mg IM Q12W (i.e., Cohort 1) in healthy male and female participants, was amended to enrol a second cohort (i.e., Cohort 2) with dosing of CAB LA 600 mg IM at 2 time points 4 weeks apart and Q8W thereafter for 3 injection visits. In HPTN 077, male participants in Cohort 1 did not consistently achieve target trough concentrations therefore, a regimen of CAB LA 800 mg Q12W may not maintain sufficient exposures in all participants, particularly in males. CAB LA 600 mg Q8W achieved target trough concentrations in both male and female participants in Cohort 2 in HPTN 077.

Study 208580 evaluated the use of the adult Q4W CAB regimen in HIV-infected adolescents (age 12 years to <18 years and >=35 kg) and provided PK and safety data that were considered supportive of the proposed indication for the use of the adult CAB PrEP regimen in individuals weighing at least 35 kg. The same dosing used for HIV1 treatment in adolescents.

The CAB PopPK model that includes body size parameters was utilized to extrapolate exposures and propose the dose for adolescents weighing at least 35 kg in Study 208580.Please refer to the PK and safety section for more detail.

2.5.5.2. Main studies

Study 201738 / HPTN 083

Title: A Phase IIb/III Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who have Sex with Men.

Figure 5 illustrates the study design and randomization scheme of HPTN 083.

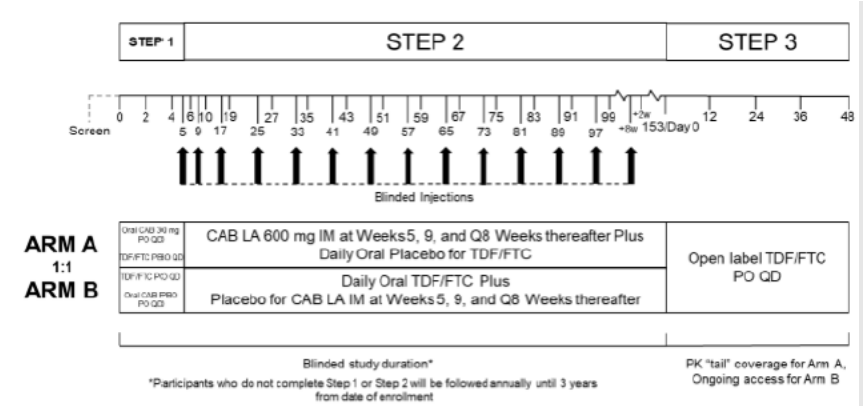


Figure 5: Study 201738 / HPTN 083 Study Design

Study 201739 / HPTN 084

Title: *A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV Uninfected Women*

Figure 6 illustrates the study design and randomization scheme of HPTN 084.

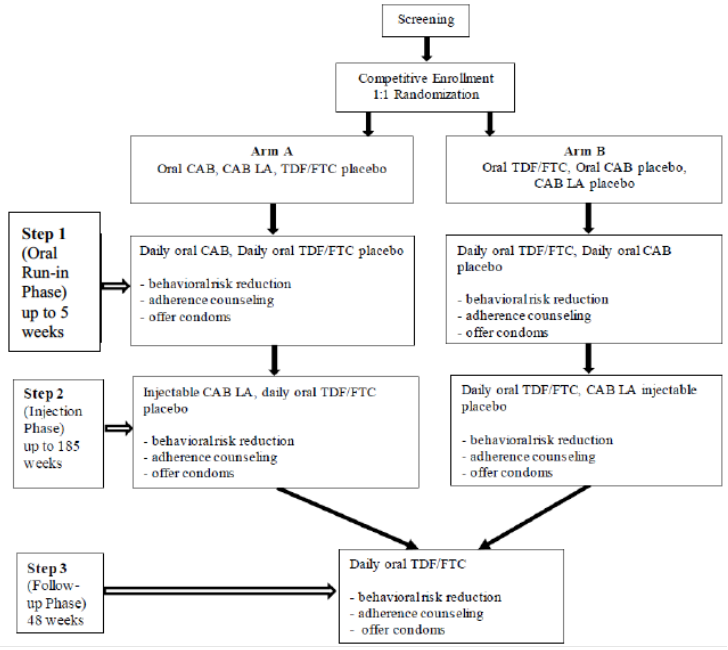


Figure 6: Study 201739 / HPTN 084 Study Design

Due to meeting pre-specified stopping criteria for superiority of CAB LA to TDF/FTC, the blinded, randomized portion of the study was stopped early.

Pregnancies

Regardless of the randomization assignment or point in the study, all pregnant participants were to be placed on open-label TDF/FTC at the first positive pregnancy test visit and if confirmed for the duration of the pregnancy and breastfeeding. No participant with a positive pregnancy test was to be administered CAB, CAB LA, or CAB LA placebo. Once pregnancy outcome was reached, if the

participant was not breastfeeding, or once the participant finished breastfeeding, she could resume unblinded study product and visits according to the SOE.

The main difference in the two pivotal studies above is the population included MSM and TGW in HTPN 083 and women in HTPN 084. The design between both is similar, but, of note HTPN 084 is a superiority study and HTPN083 is a non-inferiority study. Both use as comparator TDF/FTC.

Methods

Study Participants

Main Inclusion criteria

In both studies the main inclusion criteria was to have an HIV negative test. The in- and exclusion criteria reflect a population above 18 years old, sexually active, that should benefit from PrEP, MSM and TGW (HTPN083) or born female (HTPN084) with an exclusion in both studies of AgHBs positive patients, which is acceptable taking into account the comparator used.

Regarding the risk of acquiring HIV infection the inclusion criteria were:

Study 083

At high risk for sexually acquiring HIV infection based on self-report of at least one of the following:

-Any condomless receptive anal intercourse in the 6 months prior to Enrolment (condomless anal intercourse within monogamous HIV seronegative concordant relationship does not meet this criterion)

-More than 5 partners in the 6 months prior to Enrolment (regardless of condom use and HIV serostatus, as reported by the enrolee)

-Any stimulant drug use in the 6 months prior to Enrolment

-Rectal or urethral gonorrhoea or chlamydia or incident syphilis in the 6 months prior to Enrolment

-SexPro score of ≤16 (US sites only)

Study 084

-Sexually active (i.e., vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening)

-Score of ≥5 using a modified VOICE risk score* [Balkus, 2016]

*NOTE: Protocol Version 1.0 (02-Mar-2017) permitted enrolment of women who scored >2 using a modified VOICE Risk Score. Protocol Version 1.0 was updated on 06 November 2019 to allow enrolment of women who scored ≥5 using a modified VOICE risk score to target women at higher risk of HIV acquisition.

Some population groups that could benefit from PrEP with cabotegravir were excluded from the clinical trials, mainly those with an active or recent use of illicit intravenous drugs, hepatitis C positive, and pregnant women.

For the blinded phase of the HPTN 083 and 084 studies, HIV testing was performed at study sites following testing algorithms. The testing algorithm at the screening (Figure 11.1 from the SPP manual), Enrolment (Figure 11.2 from the SPP manual), and follow-up visits (Figure 11.1 from the SPP manual), included a rapid HIV test that was cleared by the United States (US) Food and Drug Administration (FDA) and a laboratory-based antigen-Ab (Ag/Ab) test. In addition, an HIV viral load was performed

within 14 days before Enrolment. The participant was not eligible for study Enrolment if any of the HIV tests from the Screening visit, the HIV RNA test performed prior to the Enrolment visit, or the rapid HIV test from the Enrolment visit was reactive or positive.

In these cases, HIV status was determined based on local testing guidelines. After Enrolment, if the rapid HIV test or the Ag/Ab test was reactive, an HIV RNA test was performed. The first site-positive visit was defined as the first visit near the time of HIV diagnosis at when a reactive or positive HIV test was obtained at a study site (Marzinke 2021).

Samples from all cases where a reactive or positive HIV test result was obtained at study sites were analysed retrospectively at the HPTN Laboratory Center to determine HIV status. Assays used included: qualitative RNA test: Aptima HIV-1 RNA Qualitative Assay; HIV-1 Viral Load: Abbott RealTime HIV-1 Viral Load Assay; Ag/Ab test: Architect HIV Ag/Ab Combo assay; confirmatory Ab test: Geenius HIV 1/2 Supplemental Assay. This testing was performed at the first visit where a reactive or positive test result was obtained at the study site. If a reactive qualitative RNA test result was obtained, back testing was performed with the same assay at prior study visits until a non-reactive result was obtained. The HPTN Laboratory Center classified participants as HIV Positive if they had a positive qualitative RNA test or a positive confirmatory Ab test (Marzinke 2021; Eshleman 2022).

HIV test results from study sites and the HPTN Laboratory Center were reviewed by an External Independent Endpoint Adjudication Committee for all cases where at least one reactive or positive HIV test was obtained at the study site. The adjudication committee decided on HIV status and identified the first HIV-positive visit based on the available data. Confirmation of HIV infection by the adjudication committee required a positive RNA test, a positive confirmatory Ab test, or a positive HIV DNA test with a result above the lower limit of quantification (Marzinke 2021; Eshleman 2022).

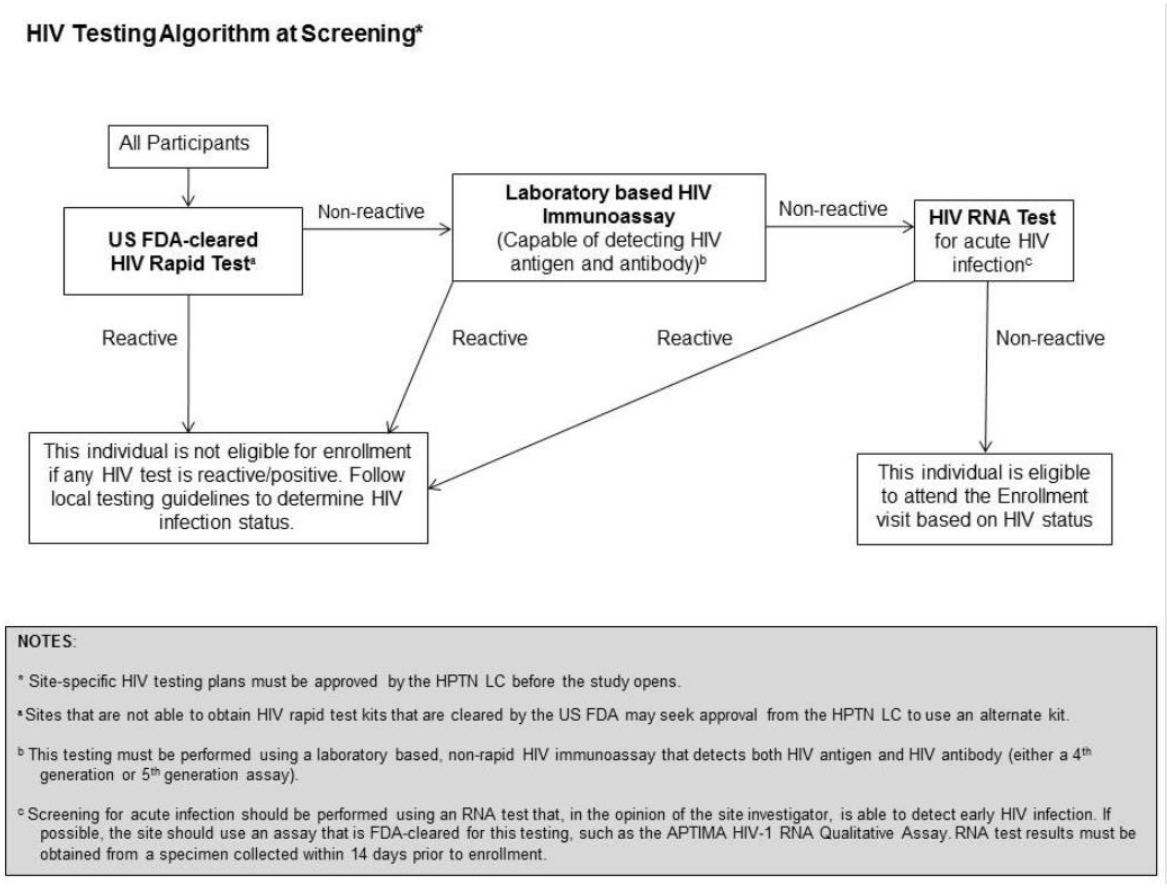


Figure 7: HIV testing algorithm at the screening visit

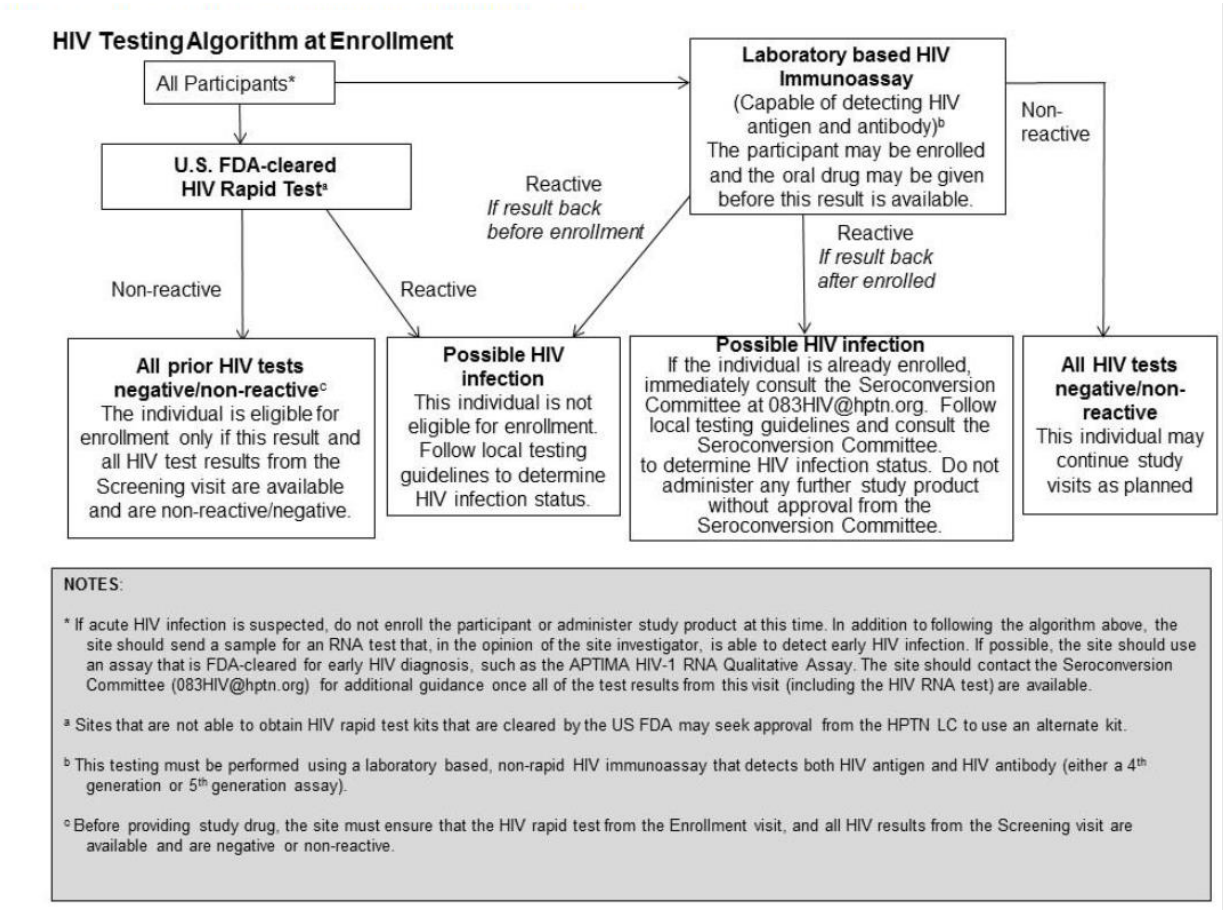


Figure 8: HIV testing algorithm at the Enrolment visit

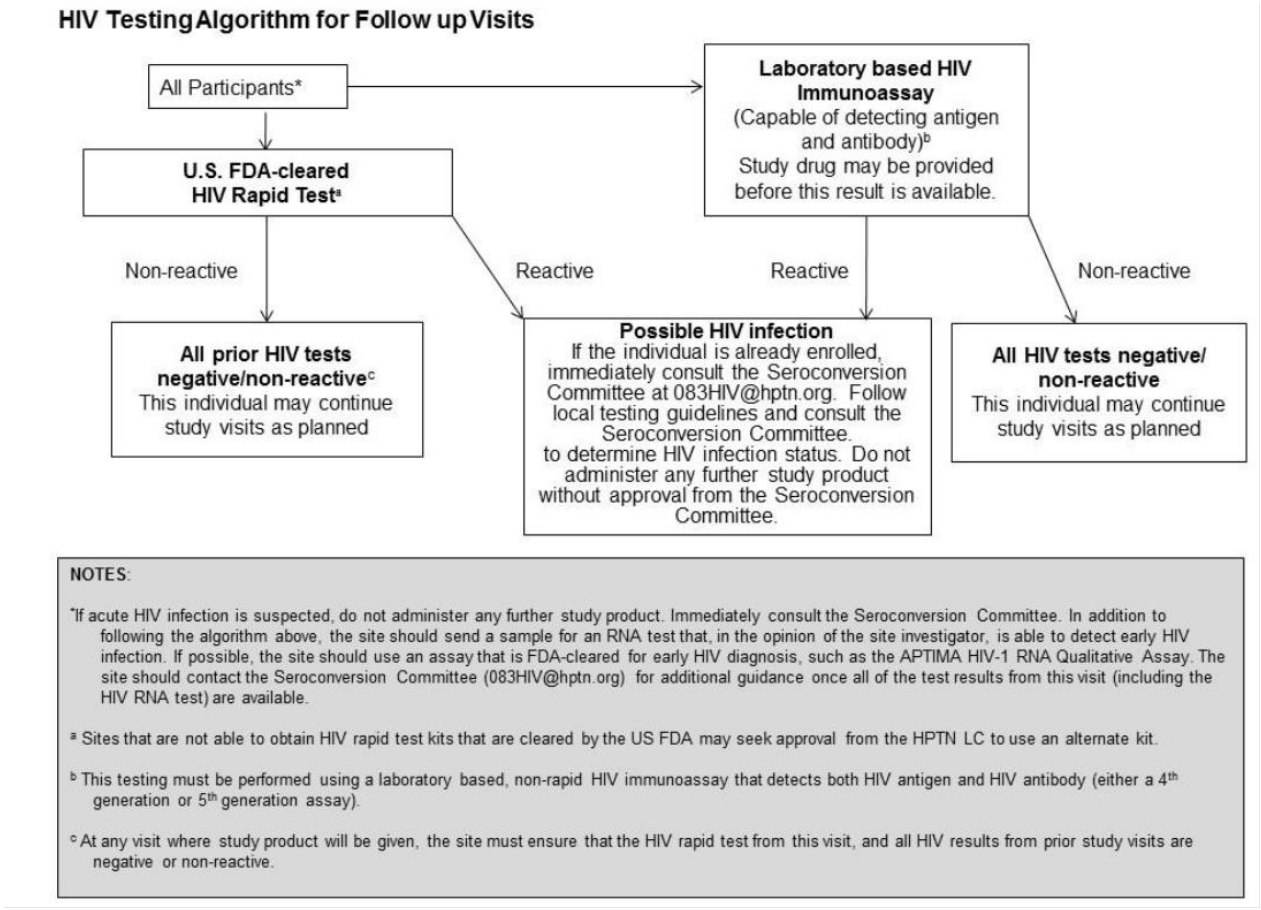


Figure 9: HIV testing algorithm at the follow up visit

Treatments

In both studies the CAB oral, CAB LA and TDF/FTC used were the same that the already approved for the treatment of HIV 1 infection.

Regarding the blinding process, all study site staff, apart from the site Pharmacist of Record or their designee, were blinded to the random assignments. All study products were stored in the pharmacy according to the temperatures noted above. Intralipid 20% suspension was chosen as the matching 'placebo' as it is similar in colour, opacity, and consistency to CAB LA suspension. The unblinded site pharmacist prepared the injections in the pharmacy. Syringes were covered with an overlay by the Pharmacist of Record prior to dispensing to the study clinic as an extra precaution to maintain the blind. The injections were labelled in a blinded fashion as "CAB LA 600 mg or Placebo for CAB LA", including the volume (3 mL), route (IM), participant's ID, date and time of preparation, and date and time of expiration. The active or placebo injections were then delivered to the clinic for administration. The person responsible for administering the injections was blinded to the study intervention.

Objectives

- Study 201738/HTPN 083

This was a non-inferiority study designed to evaluate the safety and efficacy of CAB LA for PrEP in HIV uninfected cisgender men and TGW who have sex with men (MSM and TGW).

Primary

- To compare HIV incidence among participants randomized to oral CAB/CAB LA(oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2).
- To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC (Steps 1 and 2).

- Study 201739/HTPN 084

This was a superiority study designed to evaluate the safety and efficacy of CAB LA for PrEP in HIV uninfected women.

Primary Objectives

- Efficacy: To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).
- Safety: To evaluate the relative safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2).

The objectives of both the studies are considered relevant and appropriate. The main objectives are the same in the two studies.

Outcomes/endpoints

The primary endpoints are equal for both studies:

Efficacy endpoint: Number of documented incident HIV infections in Steps 1 and 2

Safety endpoint: Grade 2 or higher clinical and laboratory adverse events

They match the objectives of the studies and are acceptable. There are some minor differences in other than the primary endpoints in relation with the population studied.

Sample size

Sample size in Study HPTN 083 was calculated based on the NIM; the NIM was well justified.

Standard methods for sample size calculation were applied in Study HTPN 084, interim analysis was carefully planned and stopping rules were defined using a robust method.

Randomisation and blinding (masking)

The central randomisation with 1:1 ratio to study and control treatment and the proposed stratification factors study HTPN083 are acceptable; randomization was stratified by study site, and permuted blocks design was used to ensure balanced treatment assignments within study site. Block size was 8, 10, or 12, with 8 blocks per stratum. The same is true to study HTPN 084.

Study 201738/HTPN 083 and Study 201739/HTPN 084 were double blind and active controlled (*Tenofovir Disoproxil Fumarate/Emtricitabine)*

Statistical methods

Standard statistical analysis methods were applied in both HPTN 083 and HPTN 084.

In both studies, the absolute efficacy of PrEP has been a function of the level of risk in the treated population and of the adherence to prophylaxis. Thus, assay sensitivity could not have been ascertained. It should be noted that defining an appropriate NI-margin was raised as a major concern by the SAWP/CHMP in Scientific advice (EMEA/H/SA/2517/2/FU/1/2015/III).

Analysis followed the SAP proposed analysis for the primary outcome. Stopping rules for the Interim analysis were calculated using a robust and valid method.

Results

Participant flow

- Study 201738/HTPN 083

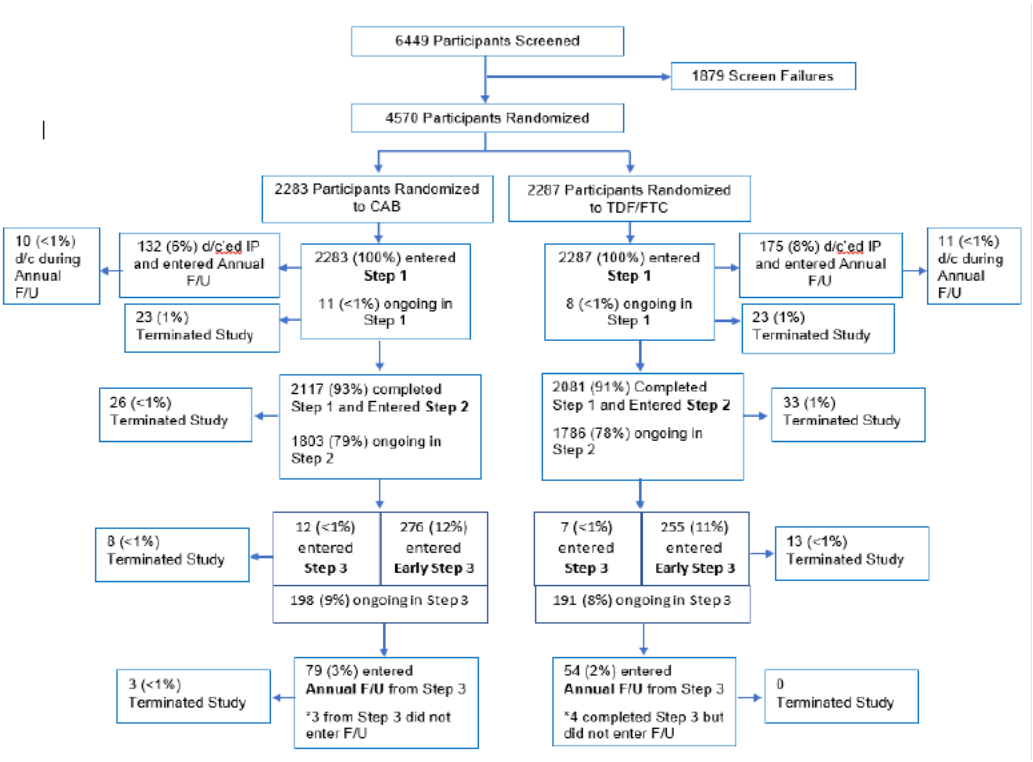


Figure 10: Participant disposition

There were 1879 screen failures, of those 231 were HIV infected, but 342 were not enrolled due to the opinion of the study investigator. The main reason for not providing details of the study investigator´s opinion for not enrolling a participant, was that that information was not requested and now it is impossible to obtain. At this point that information cannot be obtained; it was important to ascertain if any “investigator opinion” could influence the data/utilization of Cabotegravir in PrEP in a real-life setting.

Reasons for treatment discontinuation were similar between both groups, with the exception of the ones related with the injectable treatment.

- Study 201739/HTPN 084

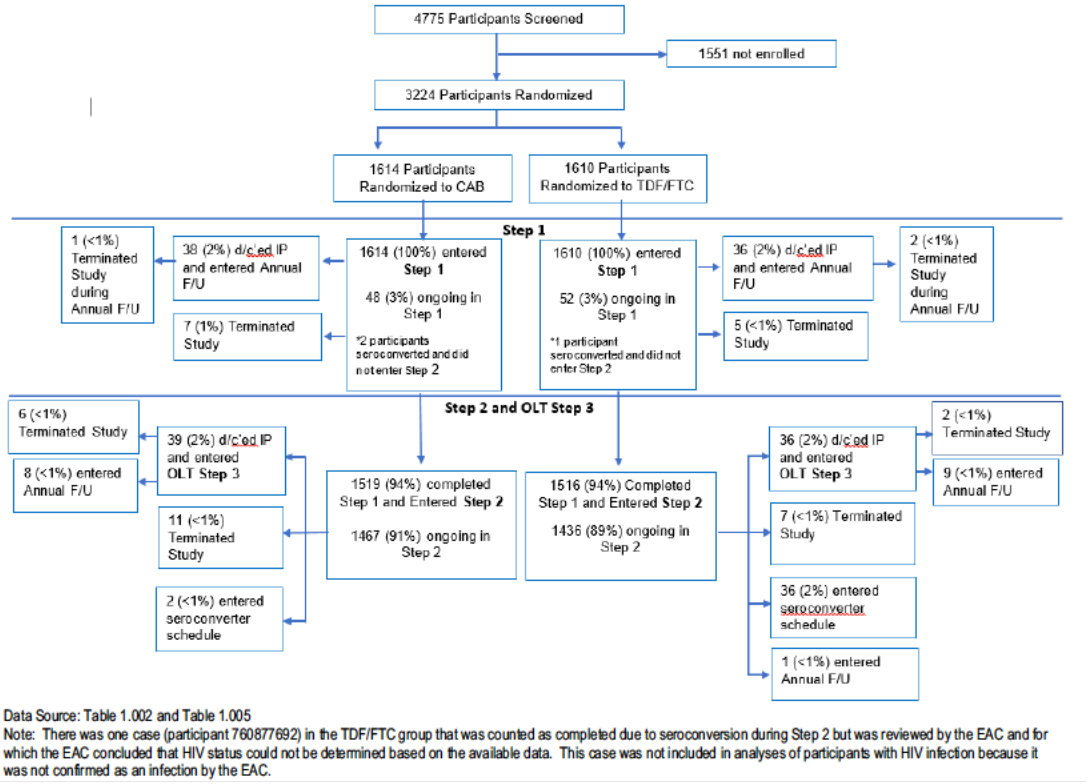


Figure 11: Participant disposition

There were 1551 screen failures, of those 205 were HIV infected, but 297 (27%) were not enrolled due to a medical condition that in the opinion of the study investigator would interfere with the conduct of the study. The main reason for not providing details of the medical conditions that, in the opinion of the investigator, would interfere with the conduct of the study was that that information was not requested and now it is impossible to obtain. As stated previously, at this point, that information cannot be obtained; it was important to ascertain if any “investigator opinion” could influence the data/utilization of Cabotegravir in PrEP in a real-life setting.

Reasons for treatment discontinuation were similar between both groups.

Recruitment

- Study 201738/HTPN 083

This was a multicentre study conducted at 43 HPTN-affiliated centers in: United States (27 centers), Peru (5 centers), Brazil (4 centers), Argentina (2 centers), Thailand (3 centers), Vietnam (1 centre), and South Africa (1 centre). The first participant was enrolled on 19 December 2016.

- Study 201739/HTPN 084

This was a multicentre study conducted at 20 centers in SSA: Botswana, Kenya, Malawi, South Africa, eSwatini [formerly Swaziland], Uganda, and Zimbabwe. The first participant was enrolled on 27 November 2017.

Of note, no European patient was included in both studies. In HTPN084 only women from SSA were included.

Conduct of the study

Protocol amendments

The protocol deviations reported in both studies were similar in both study arms and did not seem to impact in the studies efficacy results reported.

In HTPN083, one DAIDS Clinical Research site failed to follow the study algorithm concerning HIV testing, required to be performed within 14 days of enrolment. This deviation was present in 20 subjects that were tested based on stored samples and were all negative. Although no alteration to the analysis resulted from the deviation this must be considered a major deviation.

In HPTN084, the Applicant confirmed that the under-dosing that took place at a site that was not related to any HIV infection. No HIV infections were seen at this site in the HPTN 084 study.

Although the Implementation of non-IRB-Approved Consent Form and Participant Letter in the Tsepamo study (HTPN 084) was a protocol deviation it did not seem to have an impact in the final results.

Baseline data

Baseline characteristics were well balanced between the two arms of the studies. HTPN 083 only including MSM and TGW and HTPN084 only including cis women.

Baseline STIs were also similar between the two arms in both studies.

In HPTN 083, inclusion/exclusion assessment was done as part of eligibility prior to enrolment and was entirely separate from the demographics questionnaire assessed subsequently - the latter of which people may have refused to answer. Age and identity were confirmed for every participant at every visit per DAIDS (sponsor) policy. Four participants preferred not to answer the demographic questionnaire, but site staff requested demographic information for inclusion consideration.

In both clinical studies none of the subjects included was below 18 years of age.

In Study HTPN 083 the majority of subjects were < 30 years old (with a median age of 26 years), MSM and with a SexPro Score ≤ 16.

In study 084 the majority were < 35 years women with a median age of 25 years, black, a MBI < 30 Kg/m2 and had a screening modified VOICE risk score of ≥5. Just over half of participants had a main or primary partner.

Therefore, the majority of subjects in both studies were at higher risk of HIV acquisition.

Numbers analysed

- Study 201738/HTPN 083

Table 9: Summary of Disposition (Randomized Population) – Study 201738/HTPN 083

	CAB (N=2283) n (%)	TDF/FTC (N=2287) n (%)
Randomized Treatment Status		
Ongoing[a]	1814 (79)	1794 (78)
Completed[b]	28 (1)	49 (2)
Completed due to Seroconversion	16 (<1)	42 (2)
Discontinued from Randomized Treatment[e]	406 (18)	401 (18)
Terminated from study during randomized treatment phase without discontinuation from randomized treatment	35 (2)	43 (2)
Study Status		
Ongoing[c]	2210 (97)	2203 (96)
Completed[d]	6 (<1)	6 (<1)
Terminated from the Study[f]	67 (3)	78 (3)

Data Source: 201738 CSR Table 1.001

a. Ongoing indicates the participant has not entered Step 3 follow-up phase of the study, has not discontinued study drug or terminated study, and has not seroconverted.
b. Completed the randomized treatment is defined as when a participant seroconverts (per Site results) prior to starting Step 3 follow-up or enters Step 3 after reaching the Week 145 visit without study drug discontinuation or study termination.
c. Ongoing in the study indicates the participant has not terminated the study.
d. Completed the study indicates a participant has seroconverted or has entered Step 3 after reaching Week 145 visit and was subsequently followed for 48 weeks in Step 3 without prior study drug discontinuation or study termination or has entered Step 3 after discontinuation of study drug and was subsequently followed for 48 weeks and was followed for a total of 3 years from enrollment.
e. Includes participants with suspected infections that were not subsequently EAC confirmed. One participant in the TDF/FTC group discontinued blinded oral study drug at Visit 29 but per Clinical Management Committee recommendation the site continued to administer injections from Visit 37 to Week 129 and before discontinuing all blinded treatment. End of injections is recorded as Visit 37 to Week 129. Specimen collection and AE records are included from Visit 43 to Week 153.
f. Excludes participants who completed the study.

- Study 201739/HTPN 084

Table 10: Summary of Disposition (Randomized Population) – Studay 201739/HTPN 084

	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Study Status		
Ongoing[a]	1586 (98)	1586 (99)
Completed[b]	3 (<1)	7 (<1)
Terminated from the Study[c]	25 (2)	17 (1)
Randomized Treatment Status		
Ongoing[d]	1515 (94)	1488 (92)
Completed[e]	4 (<1)	37 (2)[f]
Completed due to Seroconversion	4 (<1)	37 (2)[f]
Discontinued from Randomized Treatment[g]	81 (5)	73 (5)
Terminated from study during randomized treatment phase without discontinuation from randomized treatment	14 (<1)	12 (<1)

Data Source: 201739 CSR Table 1.001

a. Participant has not terminated or completed the study.
b. Any seroconverters (per site results or EAC) in Step 1 and seroconverters in Step 2 who have completed 48 weeks of follow-up.
c. Excludes participants who completed the study.
d. Participant has not discontinued study drug or terminated the study.
e. Participant seroconverted (per site results or EAC) during Step 1 and Step 2.
f. There was one case in the TDF/FTC group that was reviewed by the EAC and for which the EAC concluded that HIV status could not be determined based on the available data. This case was not included in analyses of participants with HIV infection because it was not confirmed as an infection by the EAC.
g. Includes participants with suspected infections that were not subsequently EAC confirmed.

Outcomes and estimation

HTPN083

Primary efficacy endpoint

52 HIV infections had occurred in both groups combined.

13 infections occurred in the CAB group:

-3 in OLI phase

-5 while the patient was receiving CAB LA injections

-5 following periods when the patient was off CAB (oral or LA), probably due to non-adherence or study discontinuation

-1 already infected at baseline

39 infections occurred in the TDF/FTC group and 37/39 where related to non-adherence (based in PK assessments in DBS samples).

At blinded study termination, 52 HIV-1 incident infections were identified, 13 in the CAB group, for an incidence of 0.40 per 100 PY, and 39 in the TDF/FTC group, for an incidence of 1.22 per 100 PY.

Following the primary analysis, extended retrospective virologic testing was performed to better characterise the timing of HIV infections. As a result, one of the 13 incident infections on cabotegravir was determined to be a prevalent infection. Therefore, in the CAB group, there were 12 incident HIV-1 infections/3211 PY (for an incidence of 0.37 per 100 PY); and in the TDF/FTC group, there were 39 incident HIV-1 infections/3193 PY (for an incidence of 1.22 per 100 PY). Based on this, the revised bias adjusted HR (95% CI) is 0.31 (0.16 to 0.58).

Consistent with the outcome of the HPTN 083 primary analysis, this supportive analysis with OBSP censoring demonstrated that treatment with CAB LA was superior (p=0.0008) to treatment with oral TDF/FTC for the prevention of HIV-1 acquisition, according with the applicant. The HR of 0.164 (95% CI: 0.06 to 0.47) indicates an 83.6% reduction in the incidence of HIV-1 infections for the CAB group compared with the TDF/FTC group while participants remained on blinded injection study product.

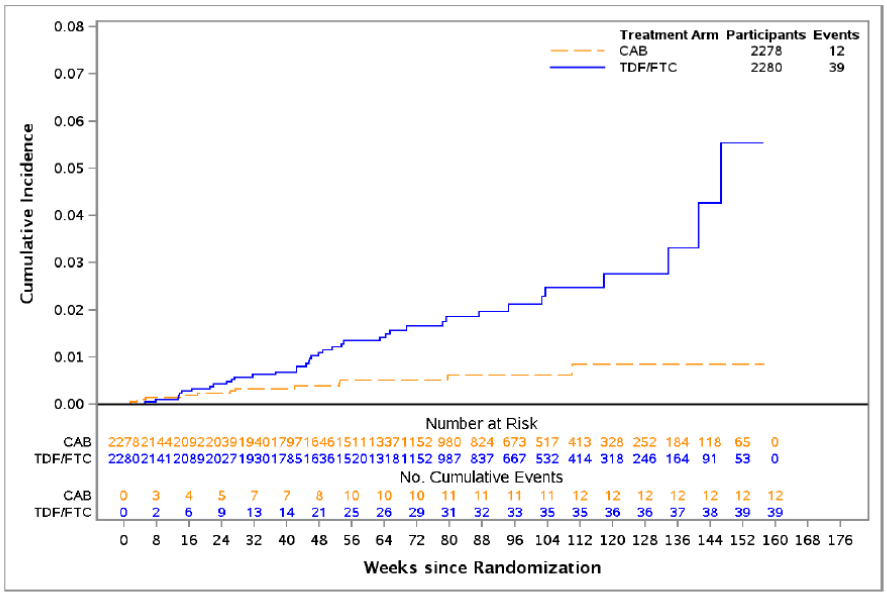


Figure 12: Kaplan Meier plot to Display the Cumulative Rates of Acquired HIV-infections by Arm

Secondary efficacy analyses

Incident HIV-1 infections in Step 2 Only

In this analysis, the HR of 0.210 (95% CI: 0.10 to 0.45) indicates a 79.0% reduction in the incidence of HIV-1 infections for the CAB group compared with the TDF/FTC group during Step 2 of the study, when the active drug received by participants was either IM injections of CAB LA every 2 months or oral TDF/FTC once daily.

Resistance mutations to study products (including but not limited to K65R, M184V/L, Q148R) among seroconverters

HIV genotyping results were obtained for 12 of the 15 CAB cases (1 failed analysis and 2 had no viremic visits). Three participants in the CAB group had integrase resistance mutations. One participant is from Latin America, has HIV subtype B infection, and had integrase mutations L74I and Q148R at the first viremic visit. Another participant also from Latin America, has HIV subtype B infection, and had integrase mutations E138A and Q148R at the first viremic visit. One of the 5 participants with HIV infections despite on-time CAB injections had integrase mutations G140A and Q148R. This participant is from Africa and has HIV subtype C infection.

3 of the participants who acquired HIV infection had a major INSTI mutation Q148R (2 subtype B while on oral CAB, 1 subtype C while on LA CAB with no record of non-adherence).

Three additional CAB participants with HIV infection had NNRTI resistance at the first viremic visit; one of those participants also had NRTI resistance.

None of the 3 participants with Baseline infections had resistance. Twelve participants with incident infection had resistance at the first viremic visit; 7 had NNRTI resistance only, 1 had NRTI resistance only, 1 had a single PI resistance mutation only, and 3 had NNRTI and NRTI resistance.

The 4 participants with NRTI resistance (including 3 who had multi-class resistance) included 3 with M184V/I and 1 with K65R. These mutations could have been selected by TDF/FTC.

HTPN084

Primary efficacy endpoint

For HPTN 084, results of the primary efficacy endpoint analyses demonstrated that the PrEP regimen of every 2 months injections of CAB LA was superior ($p<0.0001$) to the daily oral regimen of TDF/FTC in preventing acquisition of HIV-1 infection based on the rate of incident HIV-1 infections in Steps 1 and 2. At blinded study termination, 40 HIV-1 incident infections were identified, 4 in the CAB group, for an incidence of 0.20 per 100 PY, and 36 in the TDF/FTC group, for an incidence of 1.85 per 100 PY. Of the 4 incident HIV-1 infections reported for the CAB group in the primary analysis, timing for detection is as follows:

- 1 seroconversion due to non-adherence.

-1 seroconversion was detected 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 Enrolment and was offered open-label TDF/FTC; the first HIV-positive visit for this participant occurred 57 weeks post Enrolment 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.

For the TDF/FTC group, seroconversion events were largely due to low adherence to the daily PrEP regimen based on PK findings.

One of the 4 incident infections was determined to be a prevalent infection following the primary analysis. Therefore, in the CAB group, the incident rate was 0.15/100 PY and the TDF/FTC group was 1.85/100 PY. Based on this, the bias adjusted HR (95% CI) is 0.10 (0.04, 0.27).

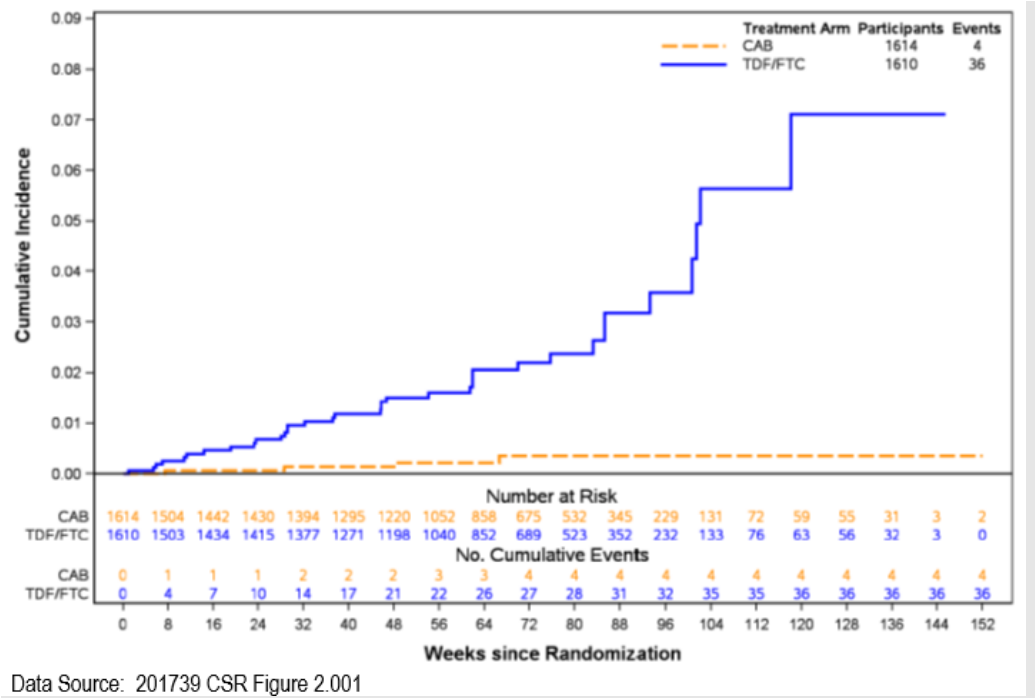


Figure 13: Cumulative Rates of Acquired HIV-1 Infenctions by Group (mITT Population) – 201739 /HPTN 084

Secondary efficacy analyses

Secondary analysis to compare HIV incidence among participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3) was not performed as no participants had reached Step 3 at the time of the analysis and was therefore no different from the primary analysis.

Incident HIV-1 infections in Step 2 Only

This secondary analysis, demonstrated that treatment with the CAB regimen was superior ($p<0.0001$) to treatment with the TDF/FTC regimen for the prevention of HIV-1 acquisition in Step 2 of the clinical study. In this analysis, the HR of 0.06 (95% CI: 0.01, 0.24) indicates a 94% reduction in the incidence of HIV-1 infections for the CAB group compared with the TDF/FTC group during Step 2 of the study (i.e., during the Blinded Injection Phase, when the active drug was either IM injections of CAB LA every 2 months or oral TDF/FTC once daily).

Resistance mutations to study products (including but not limited to K65R, M184V/L, Q148R) among seroconverters

HIV genotyping results were available for 3 of the 4 CAB participants (one did not have a viremic sample). One of the 3 participants had an integrase mutation at the first viremic visit (L74I). None had a major INSTI mutation.

Results were obtained for 33 of the 36 incident infections in the TDF/FTC group (2 failed testing; 1 had no viremic sample). One participant had a major NRTI mutation (M184V); this participant also had NNRTI resistance with the K103N mutation.

Eight other participants had NNRTI resistance only (6 had K103N, alone or with E138A or P225H; 1 had K101E alone; 1 had E138A alone). INSTI mutations/polymorphisms were detected in 10 samples (L74I, L74M, T97A, V151I, E157Q, G193E). For the participant with dual-class (NRTI+NNRTI)

resistance, the first viremic visit was the same as the first site positive visit (at Step 2, Week 17; 33 days after the first HIV positive visit). This participant was classified as non-adherent to TDF/FTC PrEP based on plasma TFV and DBS TFV-DP concentrations at time of the first HIV positive visit.

Ongoing data HTPN083 and HTPN084

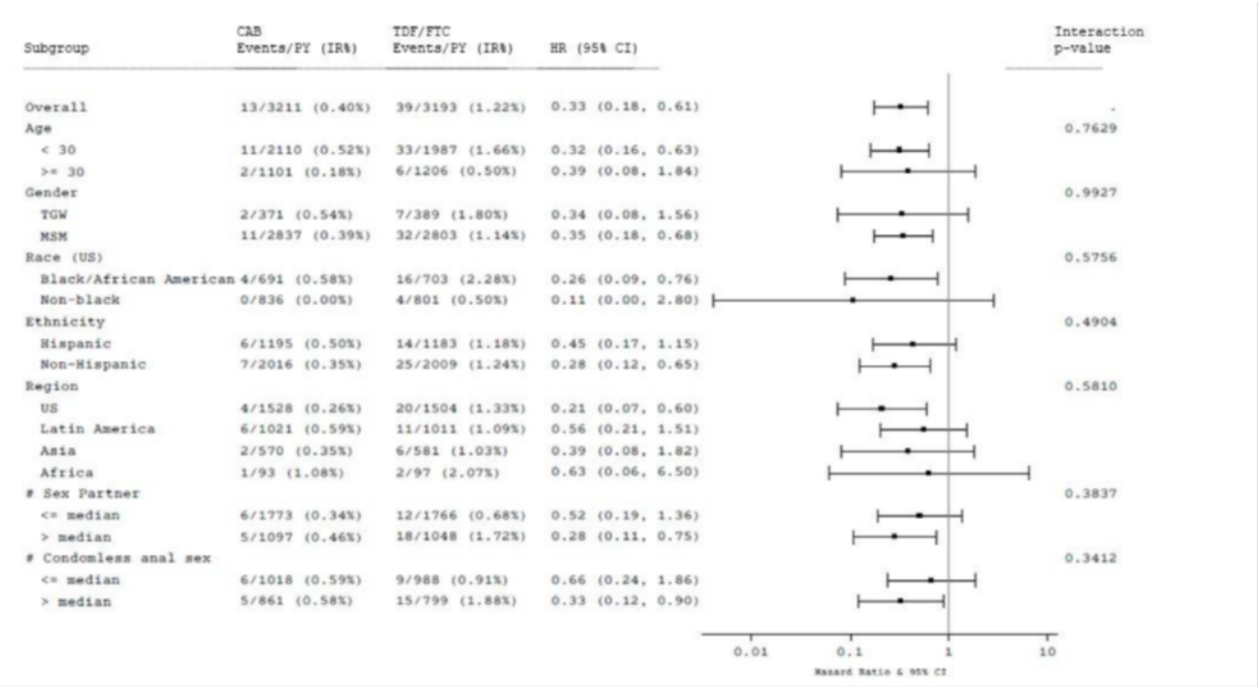
Although no new efficacy issues arise from the data presented, it is noted that during the additional follow-up:

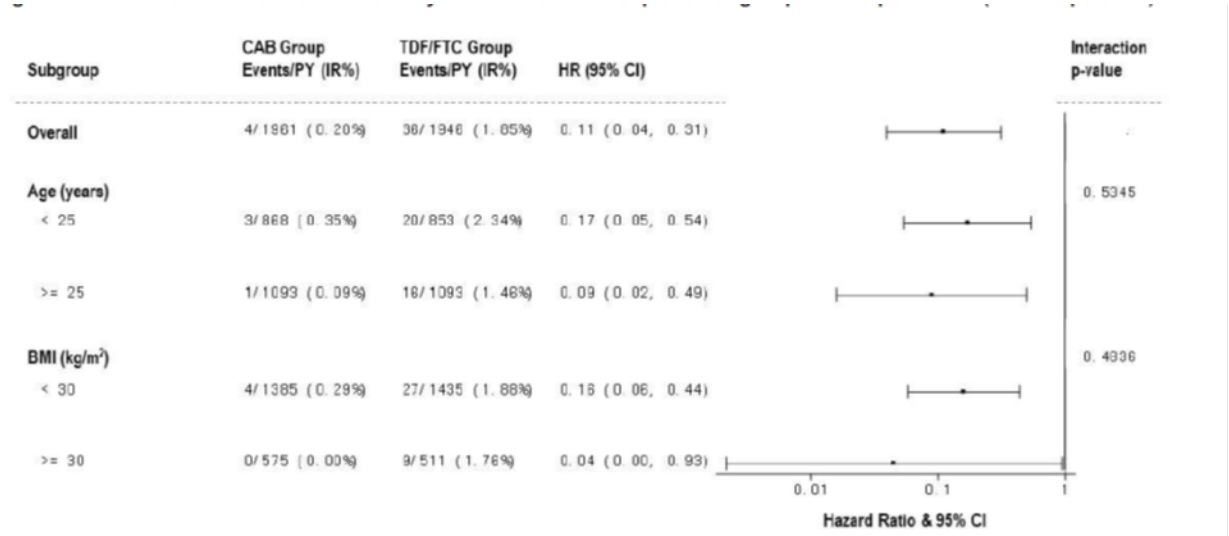
- 46 subjects developed incident HIV infection in the preplanned analysis period (13 CAB, 33 TDF/FTC, 4 during the blinded phase and 42 after unblinding);
- Risk reduction for CAB-LA vs. FTC/TDF remained similar in blinded and unblinded phases;
- HIV incidence was higher in both arms in the unblinded phase, likely attributable to decreased TDF/FTC adherence, reduced CAB injection coverage, and increased relative contributions to overall person-time from high-incidence region;
- No new safety concerns were identified.

Further, additional data on early detection of HIV infection and INSTI resistance in the blinded phase of HPTN 083 presented at CROI 2022 were provided. The findings supported the language in the US package insert and recent guidance from the US CDC for HIV testing in the setting of CAB-LA PrEP. The author concluded that earlier detection of HIV infection using an HIV RNA assay in the setting of CAB-LA PrEP would allow for earlier ART initiation, potentially reducing the risk of INSTI resistance. She also concluded that in the context of proven high efficacy, CAB-LA should also be considered for HIV PrEP in settings where HIV RNA screening is not readily available.

Ancillary analyses

HTPN083





Data Source: Figure 2.003

Note: The hazard ratios and plots are generated from separate Cox proportional hazards models for each subgroup, with treatment arm as the main effect and stratified by site. The p-values for each subgroup are from a type III test of the interaction term in a Cox proportional hazards model on the entire population with treatment arm and subgroup as main effect and a treatment arm by subgroup interaction.

Note: The hazard ratios were calculated using Firth's method.

Note: Efficacy analyses using the mITT Population include data from Steps 1 and 2 as well as from participants who discontinued study product altogether and moved to annual follow-up in Step 1 or 2 (see Table 2 and Section 4.8.3, respectively, for descriptions of the study steps and the analysis populations).

Figure 14: Forest Plot with Hazard Ratio by Randomization Group and Subgroups for Steps 1 and 2 (mITT Population)

An additional (non-pre-specified) subgroup analysis was conducted for the mITT Population of HPTN 083 in participants <25 years old (i.e., ≥18 to <25 years). Findings from this analysis were consistent with the overall primary endpoint comparison for this study and showed, descriptively, that for this <25 years age group, those who were randomized to a PrEP regimen containing CAB LA had a lower rate of incident HIV-1 infections compared with those randomized to the TDF/FTC group (see table below.)

Table 11: Summary of Cox Proportional Hazards Regression Model for Time-to-Infection for Participants <25 years of Age in Step 1 and 2 - (mITT Population) – Study 201738 / HPTN 083

	CAB	TDF/FTC	Hazard Ratio (95% CI)[a]
mITT Population			
n	929	911	
Number of participants infected	9	25	0.352 (0.16, 0.76)
Person-years	1207	1182	
Incidence rate (per 100 PY)	0.75	2.12	
95% CI for incidence rate[b] (per 100 PY)	0.34, 1.42	1.37, 3.12	

Data Source: <25 Yrs Subgroup 201738 Table 2.101.

a. HR <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The unadjusted hazard ratio is based on a Cox proportional hazards model stratified by region.

b. The 95% CI for incidence rate is calculated using the exact Poisson method.

A subgroup analysis was conducted for the mITT Population of HPTN 084 in participants <25 years old (i.e., ≥18 to <25 years of age). Findings from this analysis were consistent with the overall primary endpoint comparison for this study and showed, descriptively, that for this <25 years age group, those who were randomized to a PrEP regimen containing CAB LA had a lower rate of incident HIV-1 infections compared with those randomized to the TDF/FTC group (see table below).

Table 12: Summary of Cox Proportional Hazards Regression Model for Time to- Infection for Participants <25 Years of Age (mITT Population) –Study 201739 / HPTN 084

	CAB	TDF/FTC	Hazard Ratio (95% CI)[a]
mITT Population[b]			
n	800	794	
Number of participants infected	3	20	0.15 (0.04, 0.50)
Person-years	868	853	
Incidence rate (per 100 PY)	0.35	2.34	
95% CI for incidence rate[c] (per 100 PY)	0.07, 1.01	1.43, 3.62	

Data Source: 201739 CSR Table 2.101

a. HR <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by site.
b. Efficacy analyses using the mITT Population include data from Steps 1 and 2 as well as from participants who discontinued study product altogether and moved to annual follow-up in Step 1 or 2.
c. The 95% CI for incidence rate is calculated using the exact Poisson method.

In summary, no relation was found between subgroups and HIV infection in both clinical studies, in HPTN 083 based on region, age, race, ethnicity, gender identity, and Baseline risk factor and HTPN 084 based on age and BMI. The same was true for patients <25 years of age.

Patient-Reported Outcomes

Regarding Patient-Reported Outcomes, the Study Medication Satisfaction Questionnaire (SMSQ) used in HPTN 083 to evaluate participant-reported tolerability of and satisfaction with the study drugs in Study 083 showed a similar (≥60) median satisfaction scores for participants in CAB and TDF/FTC groups which were consistent across all visits. However, it was noted that for injections, the scores were slightly higher in TDF/FTC group compared to CAB group across all visits.

In HPTN 084 a similar proportion of participants in both study groups reported no pain or discomfort with the oral study medication (CAB group: 56%; TDF/FTC group: 52%). In contrast, there were fewer participants who reported no pain or discomfort with the injection with small proportional differences by treatment group (CAB group: 43%; TDF/FTC group: 52%). Similar patterns of treatment satisfaction were noted for participants <25 years of age between treatment groups and across study visits

- Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13: Summary of efficacy for Study 201738 (HPTN 083)

Title: A Phase IIb/III Double Blind Safety and Efficacy Study of Injectable Cabotegravir (CAB) Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men	
Study identifier	Study 201738 (HPTN 083); NCT02720094
Design	This study was a Phase IIb/III, multi-site, double-blind, two-arm, randomized (1:1), controlled non-inferiority study in HIV-uninfected cisgender men and transgender women who have sex with men (MSM and TGW). Participants were randomized to the CAB or TDF/FTC group on Day 1. Participants in the CAB group received daily oral active CAB (30 mg tablet) and oral placebo TDF/FTC for 4 weeks (up to 5◦weeks allowed for any delays in testing results) during Step 1 (Oral Lead-in [OLI] Phase), followed by active CAB LA (Cabotegravir long-acting injectable, extended release suspension for injection) injections (600 mg IM injection at 2 timepoints 4 weeks apart and then Q8W thereafter) and daily oral placebo TDF/FTC during Step 2 (Injection Phase). Participants in the TDF/FTC group received daily oral active TDF/FTC (300 mg/200 mg FDC [Fixed-dose combination] tablets) and oral placebo CAB for 4 weeks (up to 5◦weeks allowed for any delays in testing results) during Step 1 (OLI Phase), followed by daily oral active TDF/FTC (300 mg/200 mg FDC tablets) and IM placebo injections during Step 2 (Injection Phase). Participants in each group received placebo on the same dosing schedule and with matching vehicle as the drug in the other group. At Week 153, participants in both groups received open-label daily oral TDF/FTC for 48 weeks (Step 3). The population included adult (age 18 years or older) cisgender MSM and TGW who have sex with men who were HIV-negative and at high risk of sexual acquisition of HIV infection.
	Duration of Step 1 (OLI Phase): For 4 weeks (up to 5 weeks allowed for any delays in testing results) Duration of Step 2 (Injection Phase): From End of Step 1 to Week 153 Duration of Step 3 (Follow-up Phase): Offered at Week 153 and continued for 48 weeks
Hypothesis	In this non-inferiority trial, the null hypothesis was HR=1.23 and the design alternative was HR=0.75. Once non-inferiority was established, a superiority test was performed.

Treatments groups	Arm A (CAB):	In Step 1 (Oral Lead-in Phase), participants received daily oral active CAB (30 mg tablets) and oral placebo TDF/FTC for 4 weeks (up to 5 weeks allowed for any delays in testing results); then In Step 2 (Injection Phase), participants received active CAB LA (600 mg as a single IM injection at 2 timepoints 4 weeks apart and every 8 weeks thereafter) and daily oral placebo TDF/FTC to Week 153 Step 3 (Follow-up Phase Both arms): Open-label daily oral TDF/FTC no later than 8 weeks after the last injection (in order to cover the PK tail for Arm A participants), for up to 48 weeks. Arm A (CAB group): - 2283 (randomized) - 2282 (treated)	
	Arm B (TDF/FTC):	In Step 1 (Oral Lead-in Phase), participants received daily oral active TDF/FTC (300 mg/ 200 mg FDC tablets) and oral placebo CAB for 4 weeks (up to 5 weeks allowed for any delays in testing results); then in Step 2 (Injection Phase), participants received daily oral active TDF/FTC (300 mg/ 200 mg FDC tablets) and IM placebo (at 2 timepoints 4 weeks apart and every 8 weeks thereafter) to Week 153. Step 3 (Follow-up Phase Both arms): Open-label daily oral TDF/FTC no later than 8 weeks after the last injection (in order to cover the PK tail for Arm A participants), for up to 48 weeks. Arm B (TDF/FTC group): - 2287 (randomized) - 2284 (treated)	
Endpoints and definitions	Primary endpoint	Number of participants infected (Steps 1 and 2)	Number of documented incident HIV infections in Steps 1 and 2
	Secondary endpoint - Primary Supportive Analysis	Number of participants infected in Step 2 (OBSP Censored)	Number of documented incident HIV infections that occurred in Step 2 while participants were on blinded study product (OBSP)

	Secondary endpoint	Number of participants infected (Step 2)	Number of documented incident HIV infections in Step 2
	Secondary endpoint	Number of participants infected in subgroups	Number of documented incident HIV infections in participants in subgroups broken down by region, age, race, ethnicity, baseline risk, and gender identity.
Database lock	16-December-2020		
Results and Analysis			
Analysis description	Primary Endpoint: Number of documented incident HIV infections in Steps 1 and 2		
Analysis population and time point description	Modified Intent-to-Treat (mITT) Population: The Intent-to-Treat (ITT) population (All participants who were randomized, excluding those who were inappropriately enrolled), and excluding those who were found to be HIV infected at randomization. Analysis period: Primary analysis follow-up data included study time through the completion of the blinded injection phase of study follow-up (i.e. Week 153 or the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurred first). Per the ITT principle, person time and endpoint events were included in the primary analysis regardless of whether participants remained on their blinded study product, including when participants moved to open-label TDF/FTC (Step 3) early.		

<table>
<tr><td rowspan="11">Descriptive statistics and estimate variability</td><td colspan="3">Descriptive Statistics and Estimate Variability</td><td colspan="3">Effect Estimate per Comparison</td></tr>
<tr><td></td><td colspan="2">Treatment group</td><td colspan="3"></td></tr>
<tr><td></td><td>CAB</td><td>TDF/ FTC</td><td>Hazard Ratio (95% CI)</td><td>Superiority p-value</td><td>Non-inferiority p-value</td></tr>
<tr><td colspan="6">mITT Population (Steps 1 and 2)</td></tr>
<tr><td>n</td><td>2278</td><td>2281</td><td></td><td></td><td></td></tr>
<tr><td rowspan="4">Number of participants infected</td><td rowspan="4">12[b]</td><td rowspan="4">39</td><td colspan="3">Cox regression</td></tr>
<tr><td>0.30[a,b] (0.16, 0.58)</td><td>0.0003</td><td><0.0001</td></tr>
<tr><td colspan="3">Bias-adjusted, corrected for early stopping[b,c]:</td></tr>
<tr><td>0.31 (0.16, 0.58)</td><td>0.0003</td><td><0.0001</td></tr>
<tr><td>Person-years</td><td>3211</td><td>3193</td><td></td><td></td><td></td></tr>
<tr><td>Incidence rate (per 100 PY)</td><td>0.37</td><td>1.22</td><td></td><td></td><td></td></tr>
<tr><td>95% CI for incidence rate (per 100 PY)[d]</td><td>0.19, 0.65</td><td>0.87, 1.67</td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Notes:
HR <1.0 indicates a lower risk on CAB as compared to TDF/FTC.
The p-values are two-sided.
The trial was stopped based on a breach of the first interim stopping bound (z = -4.00, p-value= 0.000063), which was derived from an O'Brien-Fleming design with three planned interim analysis plus one final analysis.
a. The unadjusted hazard ratio is based on a Cox proportional hazards model stratified by region.
b. Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV infections. As a result, one of the 13 incident infections on CAB was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.34 (0.18, 0.62).
c. The bias-adjusted hazard ratio, CI, and p-value account for the group-sequential trial design and the early stopping time. The adjusted point estimate is the Median Unbiased Estimate (MUE), and the confidence interval and p-value are based on the Maximum Likelihood Estimate (MLE) ordering of the sample space.
d. The 95% CI for incidence rate is calculated using the exact Poisson method.</td></tr>
<tr><td>Analysis description</td><td colspan="5">Secondary endpoint - Primary Supportive Analysis: Number of documented incident HIV infections that occurred in Step 2 while participants were on blinded study product (OBSP)</td></tr>
</table>

<table>
<tr><td>Analysis population and time point description</td><td>Injection (Step 2) Efficacy Population: The mITT population who received at least one injection and were uninfected at the time of the first injection.

Analysis period: Follow-up time included primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up.

On Blinded Study Product (OBSP) Efficacy Analysis: To support the non-inferiority hypothesis, a supportive analysis was presented using the OBSP censoring in the Injection (Step 2) Efficacy population, where study follow-up was censored when a participant did not receive blinded injection study product on time.

Censoring:
Censoring for the OBSP efficacy analysis excluded any time affected by delayed injections. Participants were censored the first time an injection was delayed, which was defined as follows:

For STEP 2:
1. Last non-delayed injection: The earliest of an injection whose subsequent injection was delayed for the first time (i.e. given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation.

2. For participants with a delayed injection, follow-up time was censored at the last visit with HIV status determined up through 6 weeks after the Week 5 injection, if that was the last non-delayed injection, or 10 weeks after the last non-delayed injection for subsequent injections.

3. For participants with no delayed injections, analysis time was defined as for primary efficacy analysis.</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td>
<table>
<tr><td colspan="3">Descriptive Statistics and Estimate Variability</td><td colspan="2">Effect Estimate per Comparison</td></tr>
<tr><td></td><td colspan="2">Treatment group</td><td colspan="2"></td></tr>
<tr><td></td><td>CAB</td><td>TDF/FTC</td><td>Hazard Ratio (95% CI)[a]</td><td>Superiority p-value</td></tr>
<tr><td colspan="5">Injection Step 2 Efficacy Population with OBSP Censoring</td></tr>
<tr><td>n</td><td>2109</td><td>2069</td><td></td><td></td></tr>
<tr><td>Number of participants infected</td><td>4</td><td>24</td><td>0.164 (0.06, 0.47)</td><td>0.0008</td></tr>
<tr><td>Person-years</td><td>2459</td><td>2445</td><td></td><td></td></tr>
<tr><td>Incidence rate (per 100 PY)</td><td>0.16</td><td>0.98</td><td></td><td></td></tr>
<tr><td>95% CI for incidence rate[b] (per 100 PY)</td><td>0.04, 0.42</td><td>0.63, 1.46</td><td></td><td></td></tr>
<tr><td colspan="5">Note: The P-Values are two-sided.
a. HR <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by region.
b. The 95% CI for incidence rate is calculated using the exact Poisson method.</td></tr>
</table>
</td></tr>
<tr><td>Analysis description</td><td>Secondary Endpoint: Number of documented incident HIV infections in Step 2</td></tr>
</table>

<table>
<tr><td>Analysis population and time point description</td><td colspan="5">Injection (Step 2) Efficacy Population: The mITT population who received at least one injection and were uninfected at the time of the first injection.

Analysis period: Follow-up time included primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up.</td></tr>
<tr><td rowspan="9">Descriptive statistics and estimate variability</td><td colspan="3">Descriptive Statistics and Estimate Variability</td><td colspan="2">Effect Estimate per Comparison</td></tr>
<tr><td></td><td colspan="2">Treatment group</td><td colspan="2"></td></tr>
<tr><td></td><td>CAB</td><td>TDF/FTC</td><td>Hazard Ratio (95% CI)[a]</td><td>Superiority p-value</td></tr>
<tr><td colspan="5">Injection Step 2 Efficacy Population</td></tr>
<tr><td>n</td><td>2114</td><td>2079</td><td></td><td></td></tr>
<tr><td>Number of participants infected</td><td>8</td><td>37</td><td>0.210 (0.10, 0.45)</td><td><0.0001</td></tr>
<tr><td>Person-years</td><td>2923</td><td>2877</td><td></td><td></td></tr>
<tr><td>Incidence rate (per 100 PY)</td><td>0.27</td><td>1.29</td><td></td><td></td></tr>
<tr><td>95% CI for incidence rate[b] (per 100 PY)</td><td>0.12, 0.54</td><td>0.91, 1.77</td><td></td><td></td></tr>
<tr><td colspan="5">Note: The P-Values are two-sided.
HR <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by region.
The 95% CI for incidence rate is calculated using the exact Poisson method.</td></tr>
<tr><td>Analysis description</td><td colspan="5">Secondary endpoint: Number of documented incident HIV infections in participants in subgroups broken down by region, age, race, ethnicity, baseline risk, and gender identity.</td></tr>
</table>

Analysis population and time point description	Modified Intent-to-Treat (mITT) Population: The Intent-to-Treat (ITT) population (All participants who were randomized, excluding those who were inappropriately enrolled), and excluding those who were found to be HIV infected at randomization. Analysis period: Primary analysis follow-up data included study time through the completion of the blinded injection phase of study follow-up (i.e. Week 153 or the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurred first). Per the ITT principle, person time and endpoint events were included in the primary analysis regardless of whether participants remained on their blinded study product, including when participants moved to open-label TDF/FTC (Step 3) early.

Descriptive statistics and estimate variability

Descriptive Statistics and Estimate Variability					Effect Estimate per Compari-son
Sub-group	CAB incidence per 100 person years	CAB person years	TDF/FTC incidence per 100 person years	TDF/FTC person years	HR (95% CI)
Age					
<30 years	0.47	2110	1.66	1987	0.29 (0.15, 0.59)
≥30 years	0.18	1101	0.50	1206	0.39 (0.08, 1.84)
Gender					
MSM	0.35	2836	1.14	2803	0.32 (0.16, 0.64)
TGW	0.54	371	1.80	389	0.34 (0.08, 1.56)
Race (US)					
Black	0.58	691	2.28	703	0.26 (0.09, 0.76)
Non-Black	0.00	836	0.50	801	0.11 (0.00, 2.80)

	Region					
	US	0.26	1528	1.33	1504	0.21 (0.07, 0.60)
	Latin America	0.49	1020	1.09	1011	0.47 (0.17, 1.35)
	Asia	0.35	570	1.03	581	0.39 (0.08, 1.82)
	Africa	1.08	93	2.07	97	0.63 (0.06, 6.50)
	Note: The hazard ratios are generated from separate Cox proportional hazards models for each subgroup, with treatment arm as the main effect and stratified by region (except in the case of region subgroups and U.S. race subgroups). The P-values for each subgroup are from a type III test of the interaction term in a Cox proportional hazards model on the entire population with treatment arm and subgroup as main effects and a treatment arm by subgroup interaction.					

Table 14: Summary of efficacy for trial 201739 (HPTN 084)

Title: A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women (HPTN 084)	
Study identifier	201739 (HPTN 084), NCT03164564

<table>
<tr><td>Design</td><td colspan="2">This study is an ongoing Phase III, multi-center, double-blind, two-arm, randomized (1:1), controlled superiority study of the safety and efficacy of CAB LA compared to daily oral TDF/FTC for HIV prevention in a population of sexually-active HIV-uninfected women at risk for HIV.
Participants were randomized to the CAB or TDF/FTC group on Day 1. Participants in the CAB group received daily oral active CAB (30 mg tablets) and oral placebo TDF/FTC for 4 weeks (up to 5 weeks allowed for any delays in testing results) during Step 1 (OLI Phase), followed by active CAB LA injections (600 mg IM injection at 2 timepoints 4 weeks apart and then Q8W thereafter) and oral placebo TDF/FTC until the required number of incident HIV endpoints (114) was accrued during Step 2 (Injection Phase). Participants in the TDF/FTC group received daily oral active TDF/FTC (300 mg/200 mg FDC tablets) and oral placebo CAB for 4 weeks (up to 5 weeks allowed for any delays in testing results) during Step 1 (OLI Phase), followed by daily oral active TDF/FTC (300 mg/200 mg FDC tablets) and IM placebo injections until the required number of incident HIV endpoints (114) was accrued during Step 2 (Injection Phase). Participants in each group received placebo on the same dosing schedule and with matching vehicle as the drug in the other group. The study was originally designed to include a Step 3 (in which participants were to receive open-label daily oral TDF/FTC for up to 48 weeks; this step was to start no later than 8 weeks after the last injection), and after completion of Step 3, all participants were to be transitioned to local HIV prevention services. However, due to meeting pre-specified stopping criteria for superiority of CAB LA to TDF/FTC, the blinded, randomized portion of HTPN 084 was stopped early, at which time, no participants had been transitioned to protocol-planned Step 3.
For any participants with a positive pregnancy test during the study, confirmation of pregnancy at a subsequent visit at least 4 weeks later was required. All pregnant participants with a confirmed positive pregnancy test (at least 4 weeks after the initial pregnancy test) were unblinded and followed on study every 12 weeks. Regardless of the randomization assignment or point in the study, all pregnant participants were to be placed on open-label TDF/FTC for the duration of the pregnancy. No participant with a positive pregnancy test was to be administered CAB, CAB LA, or CAB LA placebo.
Once a pregnancy outcome was reached, if the participant was not breastfeeding, she was allowed to resume taking study product and continue study visits/assessments according to the protocol's schedule of events. For any participant who delivered a child during the study and then elected to breastfeed, she was to stay on open-label TDF/FTC and was followed per the schedule of events. Once the participant finished breastfeeding, she was allowed to resume study product and continue study visits/assessments according to the schedule of events. Unblinded participants had the option to return to open-label study product in their original randomization arm (either CAB LA or oral TDF/FTC).
The population included adult (age 18 to 45 years) cisgender women who were HIV-negative and at risk for acquiring HIV infection.</td></tr>
<tr><td></td><td>Duration of Step 1 (OLI Phase):

Duration of Step 2 (Injection Phase):

Duration of Step 3 (Follow-up Phase):</td><td>-For 4 weeks (up to 5 weeks allowed for any delays in testing results)

-From End of Step 1 until the required number of endpoints (114) was reached, estimated to be 81 weeks after enrolling the last participant, or until a stopping boundary was crossed.

-8 weeks after the last injection, for up to 48 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority: This study was designed to evaluate the safety and efficacy of CAB LA for PrEP in HIV-uninfected women. The hypothesis Ho: HR = 1.0 versus Ha: HR ≠ 1.0 using α = 0.05 was tested.</td></tr>
</table>

Treatments groups	Arm A (CAB):		In Step 1 (Oral Lead-in Phase), participants received daily oral active CAB (30 mg tablets) and oral placebo TDF/FTC for 4 weeks (up to 5 weeks allowed for any delays in testing results); then In Step 2 (Injection Phase), participants received active CAB LA (600 mg as a single IM injection at 2 timepoints 4 weeks apart and every 8 weeks thereafter) and daily oral placebo TDF/FTC until the required number of endpoints (114) was reached, estimated to be 81 weeks after enrolling the last participant, or until a stopping boundary was crossed. In Step 3 (Follow-up Phase), participants will be provided Open-label daily TDF/FTC no later than 8 weeks after the last injection, for up to 48 weeks plus an HIV prevention package. Arm A (CAB group): - 2283 (randomized) - 2282 (treated)
	Arm B (TDF/FTC):		In Step 1 (Oral Lead-in Phase), participants received daily oral active TDF/FTC (300 mg/ 200 mg FDC tablets) and oral placebo CAB for 4 weeks (up to 5 weeks allowed for any delays in testing results); then In Step 2 (Injection Phase), participants received daily oral active TDF/FTC (300 mg/ 200 mg FDC tablets) and IM placebo (at 2 timepoints 4 weeks apart and every 8 weeks thereafter) until the required number of endpoints (114) was reached, estimated to be 81 weeks after enrolling the last participant, or until a stopping boundary was crossed. In Step 3 (Follow-up Phase), participants will be provided Open-label daily TDF/FTC no later than 8 weeks after the last injection, for up to 48 weeks plus an HIV prevention package. Arm B (TDF/FTC group): - 2287 (randomized) - 2284 (treated)
Endpoints and definitions	Primary endpoint	Number of participants infected	Number of documented incident HIV infections in Steps 1 and 2
	Secondary endpoint Supportive analysis	Number of participants infected	Number of incident HIV infections in Steps 1 and 2 for the Per-Protocol Population
	Secondary endpoint Primary Supportive analysis	Number of participants infected	Number of documented incident HIV infections that occurred in Step 2 while participants were on blinded study product (OBSP)
	Secondary endpoint	Number of participants infected	Number of documented incident HIV infections in Step 2

	Secondary endpoint	Number of participants infected	Number of documented incident HIV infections in participants in subgroups broken down by Baseline age and BMI </≥25 kg/m^2
Database lock	16-April-2021		
Results and Analysis			
Analysis description	Primary Endpoint: Number of documented incident HIV infections in Steps 1 and 2		
Analysis population and time point description	Analysis Population: Modified Intent-to-treat (mITT): All participants who were randomized, excluding those who were inappropriately enrolled (ITT), and excluding those who were found to be HIV infected at randomization Analysis Period: Primary analysis follow-up data included study time through the completion of the blinded injection phase of study follow-up (i.e. the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurred first). Per the ITT principle, person time and endpoint events were included in the primary analysis regardless of whether participants remained on their blinded study product, including when participants moved to open-label TDF/FTC (Step 3) early.		

<table>
<tr><td>Descriptive statistics and estimate variability</td><td colspan="4">
<table>
<tr><td colspan="2">Descriptive Statistics and Estimate Variability</td><td colspan="2">Effect Estimate per Comparison</td></tr>
<tr><td></td><td>CAB</td><td>TDF/FTC</td><td>Hazard Ratio (95% CI)[a]</td><td>Superiority p-value</td></tr>
<tr><td colspan="5">mITT Population[b]</td></tr>
<tr><td>n</td><td>1613</td><td>1610</td><td></td><td></td></tr>
<tr><td rowspan="4">Number of participants infected</td><td rowspan="4">3[c]</td><td rowspan="4">36</td><td colspan="2">Cox regression</td></tr>
<tr><td>0.08[c] (0.03, 0.27)</td><td><0.0001</td></tr>
<tr><td colspan="2">Bias-adjusted, corrected for early stopping[c,d]:</td></tr>
<tr><td>0.10 (0.04, 0.27)</td><td><0.0001</td></tr>
<tr><td>Person-years</td><td>1960</td><td>1946</td><td></td><td></td></tr>
<tr><td>Incidence rate (per 100 PY)</td><td>0.15</td><td>1.85</td><td></td><td></td></tr>
<tr><td>95% CI for incidence rate[e] (per 100 PY)</td><td>0.03, 0.45</td><td>1.30, 2.56</td><td></td><td></td></tr>
</table>
Note: The p-values are two-sided.
Hazard ratio <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by site.
Efficacy analyses using the mITT Population include data from Steps 1 and 2 as well as from participants who discontinued study product altogether and moved to annual follow-up in Step 1 or 2
Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 4 HIV-1 incident infections in participants receiving cabotegravir was determined to be a prevalent infection. The original hazard ratio corrected for early stopping (95% CI) from the primary analysis is 0.12 (0.05, 0.31).
The bias-adjusted hazard ratio, CI, and p-value account for the group sequential trial design and the decision to stop the trial at the second interim analysis. This was calculated outside of this report using additional data from the first interim analysis that is not part of the submission data package used for this report.
The 95% CI for incidence rate was calculated using the exact Poisson method.</td></tr>
<tr><td>Analysis description</td><td colspan="4">Supportive Analysis: Incident HIV-1 Infections in Steps 1 and 2 for the Per-Protocol Population</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Analysis Population: Per-Protocol Population: The mITT population excluding all participants with protocol violations that were judged to be exclusionary from the per-protocol population.

Analysis period: Analysis Period: Primary analysis follow-up data included study time through the completion of the blinded injection phase of study follow-up (i.e. the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurred first).

Per the ITT principle, person time and endpoint events were included in the primary analysis regardless of whether participants remained on their blinded study product, including when participants moved to open-label TDF/FTC (Step 3) early. However, for the per-protocol analysis, person time and endpoint events after a protocol violation were excluded.</td></tr>
</table>

	Descriptive Statistics and Estimate Variability			Effect Estimate per Comparison	
		CAB	TDF/FTC	Hazard Ratio (95% CI)	Superiority p-value
	Per-Protocol Population[a]				
	n	1598	1600		
	Number of participants infected	4	36	Cox regression	
				0.11 (0.04, 0.31)	<0.0001
	Person-years	1884	1883		
	Incidence rate (per 100 PY)	0.21	1.91		
	95% CI for incidence rate (per 100 PY)	0.06, 0.54	1.34, 2.65		
	Note: Hazard ratio <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by site. Note: The 95% CI for incidence rate was calculated using the exact Poisson method. Note: The p-values are two-sided. 26 subjects were excluded from the Per-Protocol population. An additional 65 subjects were partially excluded, by censoring on the date of the deviation that resulted in partial exclusion.				
Analysis description	Secondary endpoint - Primary Supportive Analysis: Number of documented incident HIV infections that occurred in Step 2 while participants were on blinded study product (OBSP)				

Analysis population and time point description	Injection Step 2 Efficacy Population with OBSP Censoring Analysis Population: Injection (Step 2) Efficacy Population: The mITT Population who received at least 1 injection and were uninfected at the time of the first injection (excluding those who were inappropriately enrolled). Analysis period: Follow-up time included primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up. <u>OBSP Efficacy Analysis Censoring:</u> Censoring for the OBSP efficacy analysis excluded any time affected by delayed injections. Participants were censored the first time an injection was delayed, which was defined as follows: For STEP 2: 1. Last non-delayed injection: The earliest of an injection whose subsequent injection was delayed for the first time (i.e. given >6 weeks after the Week 5 injection or >10 weeks after any other injection) or the last injection before a termination or a permanent product discontinuation. 2. For participants with a delayed injection, follow-up time was censored at the last visit with HIV status determined up through 6 weeks after the Week 5 injection, if that was the last non-delayed injection, or 10 weeks after the last non-delayed injection for subsequent injections. 3. For participants with no delayed injections, analysis time was defined as for primary efficacy analysis.

Descriptive statistics and estimate variability

Descriptive Statistics and Estimate Variability			Effect Estimate per Comparison	
	CAB	TDF/FTC	Hazard Ratio (95% CI)[a]	Superiority p-value
Injection Step 2 Efficacy Population with OBSP Censoring				
n	1495	1494		
Number of participants infected	1[b]	20	0.05 (0.01, 0.37)	0.0034
Person-years	1413	1431		
Incidence rate (per 100 PY)	0.07	1.40		
95% CI for incidence rate[c] (per 100 PY)	0.00, 0.39	0.85, 2.16		

Note: The p-values are two-sided.
Hazard ratio <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by site.
The analysis with OBSP censoring did not count 1 of the 2 total participants who seroconverted during Step 2; the participant had several delayed injections outside of the protocol allowance windows, and the OBSP analysis follow-up time was censored at the last non-delayed injection, resulting in the seroconversion event for this participant not being counted in the OBSP analysis.
The 95% CI for incidence rate was calculated using the exact Poisson method.

Analysis description	Secondary Endpoint: Number of documented incident HIV infections in Step 2
Analysis population and time point description	Injection Step 2 Efficacy Population: Analysis Population: The mITT population who received at least 1 injection and were uninfected at the time of the first injection. Analysis period: Follow-up time will include primary analysis study time from the time of the first injection through the completion of the blinded injection phase of study follow-up.

Descriptive statistics and estimate variability	Descriptive Statistics and Estimate Variability			Effect Estimate per Comparison	
		CAB	TDF/FTC	Hazard Ratio (95% CI)[a]	Superiority p-value
	Injection Step 2 Efficacy Population				
	n	1495	1494		
	Number of participants infected	2	34	0.06 (0.01, 0.24)	<0.0001
	Person-years	1766	1750		
	Incidence rate (per 100 PY)	0.11	1.94		
	95% CI for incidence rate[b] (per 100 PY)	0.01, 0.41	1.35, 2.72		
	Note: The p-values are two-sided. HR <1.0 indicates a lower risk on CAB as compared to TDF/FTC. The hazard ratio is based on a Cox proportional hazards model stratified by site. The 95% CI for incidence rate is calculated using the exact Poisson method.				
Analysis description	Secondary Endpoint: Number of documented incident HIV infections in participants in subgroups broken down by Baseline age and BMI </≥25 kg/m^2				
Analysis population and time point description	Analysis Population: The mITT population who received at least 1 injection and were uninfected at the time of the first injection Analysis Period: Primary analysis follow-up data included study time through the completion of the blinded injection phase of study follow-up (i.e. the study-wide transition to Step 3, or end of the blinded phase of the study, whichever occurred first). Per the ITT principle, person time and endpoint events were included in the primary analysis regardless of whether participants remained on their blinded study product, including when participants moved to open-label TDF/FTC (Step 3) early.				

Descriptive statistics and estimate variability	Descriptive Statistics and Estimate Variability					Effect Estimate per Comparison
	Sub-group	CAB incidence per 100 person years	CAB person years	TDF/FTC incidence per 100 person years	TDF/FTC person years)	HR (95% CI)
	Age					
	<25 years	0.23	868	2.34	853	0.12 (0.03, 0.46)
	≥25 years	0.09	1093	1.46	1093	0.09 (0.02, 0.49)
	BMI					
	<30	0.22	1385	1.88	1435	0.12 (0.04, 0.38)
	≥30	0.00	575	1.76	511	0.04 (0.00, 0.93)
	Note: The hazard ratios are generated from separate Cox proportional hazards models for each subgroup, with treatment arm as the main effect and stratified by site. The P-values for each subgroup are from a type III test of the interaction term in a Cox proportional hazards model on the entire population with treatment arm and subgroup as main effects and a treatment arm by subgroup interaction.					

2.5.5.3. Clinical studies in special populations

According with a positive opinion (PIP nr P/0102/2022) the analysis of the combined PopPK model with the inclusion of both adolescent and adult PK data confirmed no impact of age on CAB PK parameters indicating a good precision of the final model (final111) PopPK model built without the adolescent data.

Successful external validations confirmed a good precision of the model to predict the exposures in adolescents after different dosing regimen (Q8W) without requiring PK data in adolescents at this regimen. Data from 8 adolescents were included in the model and these were found to be sufficient. This Key Element appears to be compliant.

Analysis of the combined PopPK model with the inclusion of both adolescent and adult PK data has been conducted and confirmed no impact of age on CAB PK parameters or exposure.

Successful external validations confirmed a good precision of the model to predict the exposures in adolescents after different dosing regimen (Q8W) without requiring PK data in adolescents at this regimen.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.5.5.6. Supportive studies

Not applicable. No data concerning efficacy could be retrieved from the supportive studies presented.

2.5.6. Discussion on clinical efficacy

The sought indication is:

Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

Two pivotal and supportive studies are included in this application. No pooled data could be obtained due to the different population included, namely different “HIV risk” and geographic regions involved. No efficacy data could be obtained from the supportive studies due to their design.

The Cabotegravir dose rationale was based on maintaining Cabotegravir dose concentrations 4 times greater that the in vitro protein-adjusted 90% inhibitory concentration (PA-IC90) value of 0.166 µg/mL (i.e., 0.664 µg/mL), a concentration range shown to have significant antiviral activity in vitro and in Phase IIa monotherapy studies used for the approval of the use of Cabotegravir in HIV-1 infected participants (in combination with rilpivirine).

From the data presented the timing to achieve 4x PA-IC90 of 0.664 µg/mL was similar in population on CAB submitted to OLI and the ones in the DTI group.

The Injection Phase of the dosing regimen used in the pivotal studies HPTN 083 and HPTN 084 is initiated by 2 injections (single 600 mg, 3 mL IM) administered 4 weeks apart, with subsequent

injections administered Q8W. This is the same dose used for HIV1 treatment in combination with rilpivirine.

Study 208580 evaluated the use of the adult Q4W CAB regimen in HIV-infected adolescents (age 12 years to <18 years and >=35 kg) and provided PK and safety data that were considered supportive of the proposed indication for the use of the adult CAB PrEP regimen in individuals weighing at least 35 kg. The same dosing used for HIV1 treatment in adolescents.

The clinical studies design was adequate with both pivotal studies being robust, both randomized 2 arm double blinded;

-HTPN083 was a non-inferiority study including cisgender MSM and TGW in 43 centers (none in Europe); this multicentre Double Blind controlled study design allows a comparison of the study drug with the only alternative medicinal product (TDF/FTC) available in the claimed indication. The Applicant justifies the choice of a non-inferiority design by the fact that TDF/FTC has been shown to be highly effective in high-risk MSM populations so that it is sufficient to establish that CAB LA has similar effectiveness to TDF/FTC.

-HPTN084 was a superiority study that included cisgender women, all from SSA. This is a multicenter, double blind controlled study with a similar study design to that of HPTN 083. However, the study was designed as a superiority trial instead of a non-inferiority as expected for a drug compared to an active comparator with a proven efficacy. The Applicant justified this choice by the fact that trials of TDF/FTC in women in SSA have yielded mixed results, probably due to non-adherence, with some showing no efficacy and therefore a non-inferiority design was not advisable, and this is considered acceptable. According to the study protocols, participants who became pregnant were to be placed on open-label TDF/FTC and could resume unblinded study product only once pregnancy outcome was reached if not breastfeeding. This approach is in principle acceptable. However, due to the long-lasting effect of CAB, some women could have been exposed to the study drug at the initiation of pregnancy, therefore having all available information on pregnancies occurred during the study is of importance (see pharmacology and safety section).

For both pivotal trials CAB PrEP dosage regimen was daily oral CAB (30 mg tablets) for up to 5 weeks followed by single 3 mL injection of 600 mg CAB LA 4 weeks apart for the first 2 doses followed by Q8W thereafter.

The Applicant provided justifications on generalizability of the study results to the EU population by firstly highlighting the need for new interventions given the incidence rate of new HIV diagnoses in the European Region, which have not decreased sufficiently, despite the availability of effective HIV prevention tools (daily, oral TDF/FTC since 2016) and due in particular to adherence that wanes over time. This can partially be supported. Indeed, while over the last decade new HIV diagnoses in the EU population declined, incidence rates among some subpopulations (adolescents, adults >50 yoa) or specific geographical areas (Central and Eastern Europe) remained unchanged despite TasP and PrEP of HIV/AIDS. In addition, the Applicant argues that considerable data used for popPK model design and validation were obtained from participants in the ATLAS and FLAIR studies that were enrolled in the EU, and that popPK model has not shown an effect of race on CAB PK, thus supporting the conclusion that race is not a factor that influences safety outcomes.

In both studies the main inclusion criteria was to have an HIV negative test. The in- and exclusion criteria reflect a population above 18 years old, sexually active, that should benefit from PrEP, MSM and TGW (HTPN083) or born female (HTPN084) with an exclusion in both studies of AgHBs positive patients, which is acceptable taking into account the comparator used.

Overall, inclusion and exclusion criteria are considered appropriate reflecting a MSM and TGW HIV high-risk population and are in line with those used in iPrEx study supporting Truvada authorisation for

PrEP. Key criterion for eligibility in pivotal studies were to be at substantial risk of HIV infection based on self-reported sexual activity and/or self-assessed risk scores; this is recognized.

According to ECDC operational guidance (HIV Pre-exposure prophylaxis in the EU/EEA and the UK: implementation, standards and monitoring), populations in greatest need of effective PrEP may include people who inject drugs and physicians could consider off-label prescription of PrEP for these at-risk individuals. However, as for EMA reflection paper (EMA/171264/2012), the efficacy that is achieved by an oral PrEP against HIV acquisition during sexual encounters cannot predict efficacy transmission via contaminated needles and this could be probably applied also to parenteral administration (IM) PrEP. Moreover, apparently, none of the submitted studies included people who inject drugs (exclusion criteria in HPTN 083), making difficult to draw any conclusion on CAB LA PrEP B/R in this population.

In both studies the Primary efficacy endpoint was the number of documented HIV infections in Step 1 and 2 of the trials. They match the objectives of the studies and are acceptable.

The Study Medication Satisfaction Questionnaire (SMSQ) was used in HPTN 083 to evaluate participant-reported tolerability of and satisfaction with the study drugs. In HPTN 084 overall treatment satisfaction was assessed by asking participants about inconvenience and pain or discomfort experienced with receiving the oral and injectable study medication.

Study HPTN 083: The rate of participants who discontinued from randomized treatment or terminated from the study was similar between the two treatment groups, with the primary reason of discontinuation being participant unwilling or unable to comply with required study procedures (168 [7%] and (178 [8%]) in CAB and TDF/FTC groups, respectively).

The majority of participants in both treatment groups completed Step 1 and entered Step 2 (CAB: 2117 participants [93%]; TDF/FTC: 2081 participants [91%]). At the time of the data cut of interim analysis (14-May-2020), the number of ongoing participants in Step 2 was similar in both groups (CAB: 1803 participants [79%]; TDF/FTC: 1786 participants [78%]).

Study HPTN 084: Among 3224 participants randomized, all entered in Step 1 of which 94% per arm entered in Step 2. At the time of the data cut at interim analysis (05 November 2020), a similar number of participants (91% in CAB and 89% in TDF/FTC arm) were ongoing in Step 2. Approximately 5% in each arm discontinued from randomized treatment and the most frequent reason in CAB group was Participant request – unwilling or unable to comply with required study procedures.

Similar proportions of participants in both groups terminated from the study during the randomized treatment phase without prior study product discontinuation in both studies.

Baseline characteristics were well balanced between the two arms of the studies. HTPN 083 only including MSM and TGW and HTPN084 only including cis women from SSA origin.

In both clinical studies none of the subjects included was below 18 years of age.

Demographic characteristics are well balanced between groups in both studies, with the majority of subjects in HPTN 083 being <30 years old (with a median age of 26 years), MSM and with a SexPro Score ≤16 among US/South American participants. In HPTN 084 the majority of women were black, aged <35 years (with a median age of 25 years), with a BMI <30 kg/m^2, and a screening modified VOICE risk score of ≥5. Just over half of participants had a main or primary partner.

As reported in literature SexPro scores ≤16 and VOICE risk score ≥5 both predict incident HIV infections with good sensitivity and specificity and are associated with high HIV incidence rates. This approach is generally used to improve self-assessment of HIV risk, to support linkage and uptake of HIV prevention strategies such as PrEP, as well as more for participant recruitment in HIV prevention studies.

Notably, individuals aged >55 years are under-represented in HPTN 083 and no subjects >45 years old were enrolled in HPTN 084, limiting strength of evidence of CAB effect in PrEP in older population groups.

STI

In both studies a similar number of participants had STIs in the two treatment groups at baseline. In HPTN 083 almost half of participants were HbsAb+ compatible with HBV vaccination. A low percentage of subjects were also HBcAb+ suggesting previous HBV infection. HBV vaccination was provided to most participants in HPTN 084 at screening (78%).

Concomitant medications

In Study HPTN 083 a major use of antipyretic and anti-inflammatory drugs has been reported by participants randomized to the CAB group when compared to that receiving TDF/FTC. The greater use of antipyretic and anti-inflammatory drugs observed in CAB group from HPTN 083 study was due to the occurrence of AEs, in particular injection site reactions (ISRs), reported more frequently in CAB than in TDF/FTC group with injection site pain being the most common. Injection site reactions, including pain, are already reported in the table in 4.8 section of the SmPC and described under the paragraph “Description of selected adverse reactions”.

In HPTN 084 concomitant medications were similar between the two study groups with a prevalence of medroxyprogesterone acetate (CAB 59% vs. TDF/FTC 58%) and paracetamol (CAB 47% vs. TDF/FTC 44%).

Adherence

Adherence to oral pill count and injection visits was similar between the two groups, with 67% and 66% of participants in the CAB and TDF/FTC groups, respectively, with pill counts corresponding to 90 to 100% adherence in HPTN 083 and only <1% injection missed visits. Compared to HPTN 083, in HPTN 084 a slightly higher non-adherence to study treatments was observed (injection missed visits: CAB 8% and TDF/FTC 7%).

According to EMA reflection paper (EMA/171264/2012), the duration of the study should be minimum two years to provide at least preliminary data on longer-term adherence and detection of usage fatigue. However, the blinded portion of the CAB pivotal trials was stopped at interim analysis based on DSMB review. Participants could remain on study in an open label extension. No new data on safety or efficacy is available.

The primary efficacy endpoint in pivotal studies HPTN 083 and HPTN 084 is the rate of incident HIV infections in Steps 1 and 2. The rate of incident HIV infections in Step 2 was evaluated as a secondary endpoint.

HTPN083

Primary efficacy endpoint

A total of 13 incident infections were identified in the CAB group, for an incidence of 0.40/100 PY, and 39 in the TDF/FTC group, for an incidence of 1.22/100 PY. Comparing the incidence across the groups yields of bias adjusted HR of 0.340 (adjusted 95% CI: 0.18 to 0.62), demonstrating a 66.0% reduction in incident HIV infections for participants randomized to receive CAB, relative to participants randomized to receive TDF/FTC, in this population of MSM and TGW.

Of the 13 incident HIV-1 infections reported for the CAB group, 3 occurred while the participant was receiving oral lead-in CAB, 5 occurred while the participant was receiving active CAB LA injections, and

5 occurred following prolonged periods when the participant was off CAB (oral CAB or CAB LA) due to product non-adherence or a study-related discontinuation. The Applicant specified that from a retrospective virologic testing, one participant in the CAB group, originally categorized as becoming positive while receiving active CAB LA injections, had been HIV-positive at Baseline, prior to receiving any study drug. Thus, overall, there were 12 (rather than 13) of those occurring in the CAB group, 4 (rather than 5) incident infections that occurred while the participant was receiving active CAB LA injections.

37 of 39 incident cases of seroconversion in the TDF/FTC group have been explained by low adherence based on plasma TFV and intraerythrocytic TFV-DP concentrations.

Upper bound of the CI was much lower than the NIM (1.23) in addition, as 1 (equal effect of both treatments) was not included in the CI there is evidence of superiority in terms of statistical significance (EMA guideline points-consider-switching-between-superiority-non-inferiority). The power to detect superiority is 47%.

Secondary efficacy analyses

Incident HIV-1 infections in Step 2 Only

The overall rate of HIV-1 acquisition in Step 2 of HPTN 083 was consistent with the overall observed treatment effect in Steps 1 and 2 of this study. In this analysis, the HR of 0.210 (95% CI: 0.10 to 0.45) indicates a 79.0% reduction in the incidence of HIV-1 infections for the CAB group compared with the TDF/FTC group during Step 2 of the study, when the active drug received by participants was either IM injections of CAB LA every 2 months or oral TDF/FTC once daily. Thus, non-inferiority was shown.

Resistance mutations to study products (including but not limited to K65R, M184V/L, Q148R) among seroconverters

HIV genotyping results were obtained for 12 of the 15 CAB cases (1 failed analysis and 2 had no viremic visits). Three participants in the CAB group had integrase resistance mutations. 3 of the infected patients had a major INSTI mutation Q148R (2 subtype B and while on oral CAB, 1 subtype C while on LA CAB with no record of non-adherence).

None of the 3 participants with Baseline infections had resistance. Twelve participants with incident infection had resistance at the first viremic visit; 7 had NNRTI resistance only, 1 had NRTI resistance only, 1 had a single PI resistance mutation only, and 3 had NNRTI and NRTI resistance.

The 4 participants with NRTI resistance (including 3 who had multi-class resistance) included 3 with M184V/I and 1 with K65R. These mutations could have been selected by TDF/FTC.

<u>HTPN084</u>

Primary efficacy endpoint

In HPTN 084 at unblinding, 40 HIV incident infections were identified, 4 in the CAB group, for an incidence of 0.20 per 100 PY, and 36 in the TDF/FTC group, for an incidence of 1.85 per 100 PY.

Comparing the incidence between the groups yields an HR of 0.11 (95% CI 0.04 to 0.31, p-value <0.0001) (HR of 0.12 when bias-adjusted for early stopping at second interim analysis) demonstrating an 89% reduction in incident HIV-1 infections for participants randomized to receive CAB, relative to participants randomized to receive TDF/FTC, in this population of cisgender women.

Of the 4 incident HIV-1 infections reported for the CAB group in the primary analysis, 1 seroconversion was due to non-adherence; 1 seroconversion was detected when the participant was off CAB due to a

temporary study-related discontinuation (i.e., due to pregnancy); 2 seroconversions were detected during Step 2 while the participants were receiving CAB injections.

One of these 4 incident infections was determined to be a prevalent infection following the primary analysis. Therefore, in the CAB group, the incident rate was 0.15/100 PY and the TDF/FTC group was 1.85/100 PY. Based on this, the bias adjusted HR (95% CI) is 0.10 (0.04, 0.27).

For the TDF/FTC group, seroconversion events were largely due to low adherence to the daily PrEP regimen based on PK findings.

Secondary efficacy analyses

Incident HIV-1 infections in Step 2 Only

This secondary analysis, demonstrated that treatment with the CAB regimen was superior ($p<0.0001$) to treatment with the TDF/FTC regimen for the prevention of HIV-1 acquisition in Step 2 of the clinical study. In this analysis, the HR of 0.06 (95% CI: 0.01, 0.24) indicates a 94% reduction in the incidence of HIV-1 infections for the CAB group compared with the TDF/FTC group during Step 2 of the study (i.e., during the Blinded Injection Phase, when the active drug was either IM injections of CAB LA every 2 months or oral TDF/FTC once daily).

Overall, the primary efficacy analyses from the two pivotal studies show consistent results. However, risk reduction resulted higher in HPTN 084 than in HPTN 083 (88% vs 66%, respectively). The evaluation of results along follow up show that, while incident infections in the TDF/FTC control arm increase comparably, CAB seems to protect to a lesser extent MSM/TGW than cisgender women. The Applicant provided the following possible explanations as reasons underlying lower efficacy in MSM/TGW from study HPTN 083 when compared to cisgender women from HPTN 084: a) HIV transmission is less effective through the vaginal mucosa in respect to anal sex (risk of HIV transmission estimated through unprotective receptive vaginal sex, insertive anal sex and receptive anal sex was estimated to be 0.08%, 0.62% and 1.4%, respectively); b) in HPTN 084, geometric mean CAB trough concentrations following CAB LA injections increased upon repeat administration from 1.48 µg/mL at Week 9 to 2.68 µg/mL at Week 57, before the 8th injection, conversely to what observed in HPTN 083 study (ranging from 1.63 to 1.91 µg/mL); c) a Phase 1 study of healthy adults showed a median CAB tissue to plasma ratios of 0.14 (cervical tissue/plasma), 0.09 (rectal tissue/plasma), and 0.16 (vaginal tissue/plasma) following single CAB LA 600 mg IM gluteal injections, suggesting CAB concentrations in cervicovaginal tissue likely to be higher than in rectal tissue. No new PK data were submitted regarding CAB concentrations in peripheral tissues and fluids. The potential justification provided by the Applicant is based on results of study 201767, a Phase 1, Multicompartmental Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers aimed to describe the PK profile of CAB LA in blood plasma, vaginal tissue (VT), cervical tissue (CT), cervicovaginal fluid (CVF), rectal tissue (RT), and rectal mucosal fluid (RF) following a single 600 mg intramuscular dose. As per table below, CAB was detected in different proportions in peripheral tissues and fluids: tissue concentrations were 1/6th (CT, VT) to 1/10th (RT) of plasma concentrations.

Table 15: Summary of CAB Tissue to plasma concentration ratios by visit and across all visits

Regimen	Period	Visit	Median (Min, Max)				
			CVF/BP (N=7)	CT/BP (N=7)	RF/BP (N=12)	RT/BP (N=13)	VT/BP (N=7)
CAB 30 mg QD	Oral Lead-in	Day 28	0.133 (0.023, 0.357)	0.175 (0.105, 0.246)	0.447 (0.151, 10.4)	0.100 (0.073, 0.166)	0.143 (0.026, 0.178)
CAB LA 600 mg IM Single Injection	Injection Phase	Day 3	0.208 (0.018, 0.403)	0.255 (0.113, 0.270)	0.289 (0.00, 1.956)	0.090 (0.022, 0.106)	0.138 (0.064, 0.212)
		Day 8	0.142 (0.046, 0.291)	0.192 (0.096, 0.297)	0.546 (0.153, 4.871)	0.103 (0.082, 0.161)	-
		Week 4	0.047 (0.007, 0.436)	0.213 (0.034, 0.309)	0.298 (0.021, 11.38)	0.109 (0.072, 0.136)	-
		Week 8	0.035 (0.028, 0.231)	0.104 (0.00, 0.304)	0.230 (0.055, 1.855)	0.091 (0.00, 0.143)	0.180 (0.00, 0.340)
		Week 12	0.08 (0.022, 0.385)	0.055 (0.00, 0.138)	0.520 (0.079, 6.232)	0.00 (0.00, 0.158)	-
		All Visits	0.08 (0.007, 0.436)	0.139 (0.00, 0.309)	0.324 (0.00, 11.380)	0.091 (0.00, 0.161)	0.158 (0.00, 0.340)

Data Source: Table 3.9
BP=Blood plasma

A PK/efficacy relationship based on the CAB concentrations in peripheral tissues and fluids cannot be established, since the study was not powered to detect efficacy of CAB. In conclusion, all the explanations provided could be in principle considered reasonable. However, the clinical relevance of tissue or fluid concentrations with respect to the clinical targets is uncertain in the setting of HIV prevention and the number of infections in both studies is low not allowing for a clear conclusion on this issue.

Resistance mutations to study products (including but not limited to K65R, M184V/L, Q148R) among seroconverters

HIV genotyping results were available for 3 of the 4 CAB participants. One of the 3 participants had an integrase mutation at the first viremic visit (L74I). None had a major INSTI mutation.

Although resistance was present in both studies in the CAB arm, the resistance in the TDF/FTC arm was higher and in probable related to poor adherence. Noteworthy is the presence of a subject (HTPN 083) that had HIV infection that was only confirmed afterwards (had HIV infection at screening), and the inability to, in some patients, have a resistance test due to low viremia.

In Study HTPN 083, 18 new HIV incident infections in the CAB arm were identified:

- in 2 of these cases the patients where adherent to CAB;

.in one case, an infection seemed to occur possibly due to increased clearance of CAB with levels of CAB below 4-fold adjusted IC90, even with timely administrations, as already stated. The applicant could not find an explanation.

.in one case, the infection occurred despite adequate levels of CAB (>4x PA-IC90)

-in 3 cases a delay between the 8 week scheduled injections and 10 or more weeks was found with inadequate levels of CAB (<4x PA-IC90)

- in 2 cases infection occurred more than 6 months from the last CAB injection but were re-exposed to CAB in the setting of undetected HIV infection at the clinical site, to be found that the HIV-RNA test was positive

-11 cases occurred at least 6 months after the last administration

In study HTPN 084 no-on injections cases where identified.

Clearly of concern are the 2 cases of infection while on-time injections. The data suggest that an HIV RNA based test should be performed prior to the administration of Cabotegravir at the initial administration and following injections complementing the Ag/Ab test (if negative). Of note, in the blinded phase of the HPTN 083 and HPTN 084 studies, HIV RNA testing was conducted at the Screening visit, and subsequently, only when acute HIV infection was suspected. In the open label extension, the testing algorithm was modified to include RNA testing for all participants at all visits in conjunction with an FDA-cleared HIV Rapid test and an HIV Immunoassay (Antigen/antibody test).

The type of test used for HIV detection should be clearly mentioned in the SmPC (see Section 4.2.) and the diagnostic algorithm used for establishing HIV diagnosis was clarified by the Applicant.

The proposed dose schedule for evaluation in humans is based on maintaining CAB plasma concentrations well above the protein-adjusted 90% inhibitory concentration (PA-IC90) value of 0.166 µg/mL, a concentration shown to have significant antiviral activity. In HPTN 083 full concentration-time profiles of the 4 participants who acquired HIV infection during the active Injection Phase of the study (Step 2) showed that CAB concentrations were >8 x PA-IC90 at first HIV positive visit in all participants. Even though the Applicant states that lower CAB concentrations were observed at preceding visits possibly reflecting an increased vulnerability to viral acquisition, this statement is not completely agreed with since CAB concentrations were always higher than the PA-IC90 value of 0.166 µg/mL. The same applies to one of the two participants in HPTN 084. Plasma CAB concentrations were >8x PA-IC90 at all visits during the Injection Phase prior to the first HIV positive visit, which occurred at Week 73. The plasma CAB concentration at the first HIV positive visit was 0.416 µg/mL (1-4x PA-IC90).

Given the high injection adherence and adequate CAB plasma concentrations, reasons for incident HIV infections and PrEP-associated drug resistance mutations remain largely unclear. The Applicant specified that in study HPTN 084 there were no on-injection breakthrough infections in any of the participants randomized to CAB LA during the blinded phase of the study, and that in study HPTN 083, 4 incident HIV infections occurred during on-time CAB LA injections. Regarding CAB concentrations, they were >8x PA-IC90 at all 4 HIV-positive visits, however lower CAB concentrations at preceding visits may reflect increased vulnerability to viral acquisition. Only 1 participant is known to have plasma concentrations <0.65 µg/mL (<4x PA-IC90), which occurred 8 weeks prior to the HIV+ visit. It is argued that a clear exposure-response relationship for CAB in Study HPTN 083 participants cannot be found. Further the Applicant states that the potential role of other factors, such as viral burden, viral phenotype, and integrity of rectal mucosa, as well as risk behaviors that may have contributed to the development of incident HIV infections in HPTN 083 remains undefined. In the Applicant's view no clear exposure-response relationship for CAB can be found and multifactorial aspects cannot be uncovered.

Based on extended half-life of CAB LA, individuals discontinuing the drug experience prolonged plasma cabotegravir exposure (approximately 12 months as reported in the SmPC). Thus, in case of HIV infection following CAB LA discontinuation INSTI-resistance mutation occurrence needs to be considered. To this regard it is noted that HPTN 083 and HPTN 084 studies both included open-label TDF/FTC in STEP 3 for 48 weeks after stopping study drug, and that in the SmPC Section 4.4 an alternative form of PrEP following discontinuation of cabotegravir injection for those individuals at continuing risk of HIV acquisition and initiated within 2 months of the final cabotegravir injection, is suggested.

The Applicant considers that the duration of an alternative PrEP after CAB LA discontinuation depends on the individual risk of HIV acquisition, and this is reasonable as PrEP should be maintained as long as

risk behaviours are in place. Further, the Applicant argues that due to possible availability in the future of alternative long-acting forms of PrEP, the original test “alternative forms of PrEP” should be maintained. However, as the question posed focused on the minimum time that an at-risk subjects discontinuing CAB LA should be prescribed with an alternative form of PrEP, the Applicant’s response was not considered acceptable. Subsequently, the Applicant agreed to modify the original text to include “alternative not long-acting forms of PrEP”. In both HPTH 083 and 084 participants received post-CAB LA prophylaxis with an alternative PrEP and this information should be specified in Apretude’s SmPC. To protect subject from acquiring HIV while having waning CAB plasma levels, an alternative form of PrEP is to be used after stopping CAB LA injections and should in any case be based on medicinal products with non-LA characteristics. This is considered relevant to the prescriber, and even more in the next future in case other options with LA PK will be available.

With regards to resistance at diagnosis almost all subjects in study HPTN 083 who had infection during oral lead-in phase showed INSTI resistance. Moreover, INSTI resistance was reported also in subjects with infection despite on-time CAB injections (3 out 6 subjects of which two had no viremic visit).

ARV follow-up treatments for seroconversions are also included. Only two patients in each study received follow-up cART based on integrase inhibitors (bictegravir in study HPTN 083 and dolutegravir in study HPTN 084). The Applicant states that no further information is available regarding time to virological suppression. Unfortunately, this missing piece of information inevitably limits evaluation of future treatment success in subjects infected during CAB LA administration.

Subgroups analyses

In Study HPTN 083, the overall incidence rate of 0.94 incident infections per 100 person years in participants <50 kg is similar to the overall incidence rate of 0.8 incident infections per 100 person years in participants >= 50 kg, and that in HPTN 084 the overall incidence rate of 1.31 incident infections per 100 person-years in participants <50 kg is similar to the overall incidence rate of 1.0 incident infections per 100 person-years in participants >= 50 kg.

Findings for all subgroups, including region, were consistent with the overall treatment effect with a lower rate of incident HIV-1 infections observed for participants randomized to CAB group compared with participants randomized to TDF/FTC group. The US region, representing the most person years in a stratum, shows this effect more than the other three regions. This could possibly be due to adherence to TDF/FTC being less in the US than in other regions. The larger confidence interval around the outcome estimates is driven mainly by the smaller person-years in each of the subgroup categories; all point estimates for the hazard ratio favor CAB. NB that there was only one site from the African region in HPTN 083 that enrolled 65 participants.

Assessment of paediatric data on clinical efficacy

The European Medicines Agency has deferred the obligation to submit the results of studies with Apretude injection in the paediatric population weighing at least 35 Kg and aged >12 to 18 years old in the prevention of HIV-1 infection.

The Applicant is compliant with PIP approved final opinion.

Efficacy extrapolation from adult source population to the adolescent target population is agreed and is in line with guideline “Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018)”. As no age-dependent PK variability is observed, in case of an

appropriate adherence, LA CAB PrEP is expected to provide similar protection rates in subjects aged between 12 and 17, as in adults.

No efficacy outcomes are foreseen for the adolescent sub-studies of Study HPTN 084-01 and HPTN 083-01. Nonetheless, data on seroconversions are available and none of the participants developed HIV infection.

Sub-study HPTN 083-01

Sub-study HPTN 083-01 enrolled only 9 adolescents with age below 18 years (range 15-17 years) out of the 35 originally planned. All participants' weight was >35 kg at Enrolment (range 63 – 167 kg) as per inclusion criteria and all were male at birth (6 MSM, 2 TGW, 1 'other'). No adolescents under 50 kg of weight were included. It is acknowledged that, due to the small sample size, no substantial conclusions can be made in terms of PK exposure in adolescents within sub-study HPTN 083-01. Such small number of participants, likely together with a lack of adherence to the treatment, led to a very high variability in the oral lead-in phase (CVb about 400%). However, the variability became moderate in the injection phase (CVb about 40%). Taking into account the above limitations, HPTN 083-01 data show that CAB mean concentration in the injection phase (week 33) for adolescents was about 2.0 µg/mL, thus quite in line with the one registered in adults (1.78 µg/mL) for main study HPTN 083. The same is for the oral lead-in phase, where CAB mean concentration is 4.7 µg/mL in adolescents and 4.29 µg/mL in adults. Mean Ctau from the second injection (week 9) onwards was confirmed to be above 8xPA-IC90 (preclinical benchmark suggesting efficacy for maintenance of HIV suppression in HIV infected subjects).

Sub-study HPTN 084-01

PK results of sub-study HPTN 084-01 confirm that age does not influence CAB PK, but some issues remain regarding the impact of lower weight on CAB exposure.

2.5.7. Conclusions on the clinical efficacy

Overall, it can be concluded that the efficacy of cabotegravir, in prevention of acquisition of HIV-1 infection has been established. Both pivotal studies had a significative number of subjects, one including MSM and TGW and the other cis women and the comparator used was TDF/FTC the actual mainstay of HIV PrEP approved in the EU.

A similar efficacy outcome is expected in adolescents based on a PK extrapolation.

All concerns and issues raised along the procedure have been addressed by the applicant as explained in the discussion section and reflected in the SmPC.

2.5.8. Clinical safety

Table 16: Patient exposure

	Pivotal		Supportive	
Study Conclusion Record	Study 201738 / HPTN 083 CAB (N=2283) n (%) cut-off date: 14 May 2020	Study 201739 / HPTN 084 CAB (N=1614) n (%) cut-off date: 5 November 2020	Study 201120 / ÉCLAIR CAB (N=106) n (%) cut-off date: completed	Study 201103 / HPTN 077 CAB (N=151) n (%) cut-off date: completed
Study Completion Status				
Ongoing [a]	2210 (97)	1586 (98)	NA	NA
Completed	6 (<1) [b]	3 (<1) [c]	84 (79)	123 (81.5)
Terminated from the Study [d]	67 (3)	25 (2)	22 (21) [e]	28 (18.5)
Safety Population	2281 (99.9)	1614 (100)	105 (99.1)	151 (100)
Injection Safety Population	2117 (92.7)	1519 (94.1)	94 (88.7)	134 (88.7)

Data Source: 201738 CSR Table 1.001 and Table 1.003; 201739 CSR Table 1.001 and Table 1.003; 201120 Week 41 CSR Table 6.2, 201120 W81 CSR Table 6.2; 201103 CSR Table 1.102

a. Ongoing in the study indicates the participant has not terminated or completed the study.
b. Completed the study indicates a participant has seroconverted or has entered Step 3 after reaching Week 145 visit and was subsequently followed for 48 weeks in Step 3 without prior IP discontinuation or study termination or has entered Step 3 after discontinuation of IP and was subsequently followed for 48 weeks and was followed for a total of 3 years from Enrolment.
c. Any seroconverters (per site results or EAC) in Step 1 and seroconverters in Step 2 who have completed 48 weeks of follow-up. No participant reached the Week 185 visit and entered Step 3 in Study 201739.
d. Excludes participants who completed the study or who are still ongoing.
e. A total of 13 participants (12%) terminated from study 201120 at Week 41 analysis.

In pivotal study HPTN 083 the median (range) exposure was 457 (1 to 1093) days for the CAB group and 471 (1 to 1131) days for the TDF/FTC group. The median time of exposure of the Oral Lead-In was similar in both treatment groups (CAB group: 29 [1 to 115] days and TDF/FDC group: 29 [1 to 485] days). In pivotal study HPTN 084 the median (range) exposure was 452.5 (CAB, 1 to 1072 days; TDF/FTC, 1 to 1018 days) days for both groups. Among participants with a confirmed pregnancy during the study, the median (range) exposure was 210 (1 to 703) days for the CAB group and 241 (30 to 732) days for the TDF/FTC group. The median time of exposure of the Oral Lead-In was similar in both treatment groups (CAB group: 29 (1 to 334) days and TDF/FDC group: 29 (1 to 224) days).

For supportive study ÉCLAIR, a total of 105 participants received at least one dose of CAB including a total of 272 injections of CAB LA in 94 of these participants (median exposure of 287 days). In supportive study HPTN 077, a total of 151 participants received at least one dose of CAB including a total of 682 injections in 134 participants.

The overall exposure can be considered sufficient to establish a safety profile for the CAB PrEP for the proposed population and indication.

2.5.8.1. Adverse events

Table 17: Overall summary of Adverse Events of pivotal HPTN 083 and HPTN 084 studies OBSP (on blinded study product) AEs in Steps 1 and 2 - Safety Population; OBSP ISRs in Step 2 - Injection Safety Population)

	Study 201738 / HPTN 083		Study 201739 / HPTN 084	
	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Any AE	2174 (95)	2157 (94)	1556 (96)	1540 (96)
Drug-related AEs	1874 (82)	1355 (59)	1098 (68)	1014 (63)

Any AE, excluding ISRs	2143 (94)	2151 (94)	1554 (96)	1540 (96)
Drug-related AEs, excluding ISRs	1075 (47)	1134 (50)	980 (61)	998 (62)
ISR AE	1740 (76) [a]	726 (32) [a]	578 (38) [b]	166 (11) [b]
Drug-related ISR AE	1724 (81) [c]	652 (31) [c]	575 (38) [b]	163 (11) [b]
Any Grade 2 to 5 AEs	2115 (93)	2107 (92)	1489 (92)	1480 (92)
Drug-related Grade 2 to 5 AEs	1391 (61)	951 (42)	903 (56)	848 (53)
Grade 2 to 5 AEs, excluding ISRs	2092 (92)	2103 (92)	1482 (92)	1478 (92)
Drug-related Grade 2 to 5 AEs, excluding ISRs	871 (38)	900 (39)	833 (52)	841 (52)
Grade 2 to 5 ISR AEs	1022 (48) [c]	139 (7) [c]	196 (13) [b]	27 (2) [b]
Drug-related ISR Grade 2 to 5 AEs	1009 (48) [c]	121 (6) [c]	192 (13) [b]	25 (2) [b]
Any Grade 3 to 5 AEs	745 (33)	754 (33)	265(16)	274 (17)
Drug-related Grade 3 to 5 AEs	131 (6)	93 (4)	86 (5)	99 (6)
Grade 3 to 5 AEs, excluding ISRs	716 (31)	754 (33)	264 (16)	274 (17)
Drug-related Grade 3 to 5 AEs, excluding ISR	84 (4)	93 (4)	85 (5)	98 (6)
Grade 3 to 5 ISR AEs	54 (3) [c, d]	0	1 (<1) [b, e]	1 (<1)[b, e]
Drug-related ISR Grade 3 to 5 AEs	54 (3) [c]	0	1 (<1) [b]	1 (<1) [b]
AEs leading to discontinuation of study drug	135 (6)	91 (4)	17 (1)	22 (1)
Drug-related AEs leading to discontinuation of study drug	67 (3)	24 (1)	0	0
ISRs leading to discontinuation of study drug	47 (2)	0	0	0
Any SAE	109 (5)	104 (5)	25 (2)	33 (2)
Drug-related SAEs	4 (<1)	3 (<1)	1 (<1)	3 (<1)
Fatal SAEs	4 (<1)	6 (<1)	2 [f]	0
Drug-related fatal SAEs	0	1 (<1) [g]	0	0

Data Source:
Study 201738: Table 3.004, Table 3.005, Table 3.008, Table 3.009, Table 3.015 (Injection Step 2 Safety Population); Table 3.016, Table 3.017, Table 3.019 (Injection Step 2 Safety Population); Table 3.021, Table 3.024 (Injection Step 2 Safety Population); Table 3.025, Table 3.026, Table 3.030 (Injection Step 2 Safety Population), Table 3.031, Table 3.032, Table 3.034, Table 3.035, Table 3.041, Table 3.044, Table 3.047, Table 3.170; Listing 16.150; CAB PrEP ISS 201738 Table 3.266
Study 201739: Table 3.004, Table 3.008, Table 3.009, Table 3.011 (Injection Step 2 Safety Population), Table 3.013, Table 3.015 (Injection Step 2 Safety Population), Table 3.016, Table 3.017, Table 3.021, Table 3.025, Table 3.026, Table 3.031, Table 3.034, Listing 16.150, Table 3.035, Table 3.041, Table 3.044, Table 3.047, Listing 16.130; Table 3.866
Note: Drug-related is based on investigator assessment.

a. 201738 CSR Table 3.170 (CAB: N=2281, TDF/FTC: N=2285)
b. N for this category is the number of participants in HPTN 084 who received at least one injection of study drug (Injection Step 2 Safety Population) in Step 2 only (CAB: N=1519, TDF/FTC: N=1516).
c. N for this category is the number of participants in HPTN 083 who received at least one injection of study drug (Injection Safety Population) in Step 2 only (CAB: N=2117, TDF/FTC: N=2081).
d. In HPTN 083, no participant in either group experienced a Grade 4 or 5 ISR.
e. In HPTN 084, no participant experienced a Grade 4 or 5 ISR and 1 participant in each group experienced 1 or more Grade 3 ISRs
f. An additional AE (PT: hypertensive heart disease) was reported during Step 2 Non-OBSP.
g. PT: cardiac disorder

Common Adverse Events

Table 18: Most common adverse events (reported in ≥5% of participants in any treatment group) by PT of study HPTN 083 – Steps 1 and 2 (Safety Population)

Preferred Term	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Any Adverse Event	2174 (95)	2157 (94)
Injection site pain	1713 (75)	688 (30)
Creatinine renal clearance decreased	1576 (69)	1661 (73)
Blood creatine phosphokinase increased	506 (22)	497 (22)
Blood creatinine increased	379 (17)	426 (19)
Nasopharyngitis	383 (17)	379 (17)
Headache	377 (17)	356 (16)
Diarrhoea	328 (14)	336 (15)
Anal chlamydia infection	264 (12)	297 (13)
Upper respiratory tract infection	264 (12)	271 (12)
Injection site nodule	263 (12)	13 (<1)
Lipase increased	255 (11)	272 (12)
Injection site induration	255 (11)	8 (<1)
Blood glucose increased	247 (11)	166 (7)
Pyrexia	232 (10)	112 (5)
Proctitis gonococcal	220 (10)	236 (10)

Preferred Term	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Aspartate aminotransferase increased	213 (9)	220 (10)
Injection site swelling	206 (9)	9 (<1)
Syphilis	201 (9)	217 (9)
Alanine aminotransferase increased	186 (8)	220 (10)
Amylase increased	158 (7)	183 (8)
Oropharyngeal pain	151 (7)	164 (7)
Nausea	144 (6)	201 (9)
Insomnia	137 (6)	127 (6)
Cough	130 (6)	135 (6)
Fatigue	128 (6)	117 (5)
Pharyngitis	128 (6)	101 (4)
Back pain	123 (5)	141 (6)
Gastroenteritis	110 (5)	120 (5)
Blood pressure increased	109 (5)	120 (5)
Blood glucose decreased	109 (5)	118 (5)
Myalgia	109 (5)	97 (4)
Blood phosphorus decreased	107 (5)	126 (6)
Hypertension	107 (5)	74 (3)
Blood bilirubin increased	99 (4)	117 (5)
Dizziness	95 (4)	123 (5)
Procedural pain	91 (4)	111 (5)

Data Source: 201738 CSR Table 3.007
Note: Deceasing frequency from the CAB group

Table 19: Most common adverse events (reported in ≥5% of participants in any group) by PT of study HPTN 084 (Safety Population)

Preferred Term	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Number of participants with any AE	1556 (96)	1540 (96)
Creatinine renal clearance decreased	1160 (72)	1192 (74)
Blood glucose increased	584 (36)	451 (28)
Amylase increased	558 (35)	573 (36)
Injection site pain	522 (32)	147 (9)
Blood glucose decreased	425 (26)	439 (27)
Headache	377 (23)	373 (23)
Blood creatinine increased	363 (22)	347 (22)
Blood phosphorus decreased	278 (17)	322 (20)
Upper respiratory tract infection	268 (17)	293 (18)
Blood creatine phosphokinase increased	237 (15)	263 (16)
Alanine aminotransferase increased	232 (14)	228 (14)
Urinary tract infection	225 (14)	210 (13)
Aspartate aminotransferase increased	212 (13)	181 (11)
Lipase increased	198 (12)	171 (11)
Dysfunctional uterine bleeding	161 (10)	161 (10)
Genitourinary chlamydia infection	147 (9)	148 (9)
Vulvovaginal candidiasis	139 (9)	162 (10)
Back pain	137 (8)	130 (8)
Hyperglycaemia	132 (8)	105 (7)
Vulvovaginitis trichomonal	127 (8)	109 (7)
Metrorrhagia	118 (7)	101 (6)
Chlamydial infection	110 (7)	141 (9)
Blood calcium increased	107 (7)	78 (5)
Injection site swelling	105 (7)	5 (<1)
Diarrhoea	101 (6)	119 (7)
Menorrhagia	99 (6)	98 (6)
Gastroenteritis	95 (6)	100 (6)
Dizziness	95 (6)	114 (7)

Preferred Term	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Vaginal discharge	93 (6)	71 (4)
Nasopharyngitis	82 (5)	96 (6)
Gastritis	82 (5)	85 (5)
Blood calcium decreased	82 (5)	97 (6)
Abdominal pain	80 (5)	83 (5)
Injection site nodule	80 (5)	5 (<1)
Nausea	79 (5)	157 (10)
Abnormal loss of weight	79 (5)	104 (6)
Haemoglobin decreased	77 (5)	80 (5)
Tension headache	75 (5)	84 (5)
Blood pressure increased	74 (5)	64 (4)
Dyspepsia	70 (4)	81 (5)
Blood bilirubin increased	70 (4)	78 (5)
Decreased appetite	58 (4)	94 (6)
Dysmenorrhoea	55 (3)	74 (5)
Vomiting	49 (3)	91 (6)

Data Source: 201739 CSR Table 3.007
Note: PTs are listed in the order of decreasing frequency in the CAB group.
Note: AEs were coded to Preferred Term using MedDRA Coding Dictionary Version 23.1.

The most frequently reported AEs in the Phase II supportive studies ÉCLAIR and HPTN 077 were generally consistent with the results of pivotal studies. Results from the supportive Phase II studies demonstrated that CAB was generally well-tolerated.

Adverse Events by maximum intensity

- HPTN 083

Table 20: Summary of OBSP Adverse Events by maximum intensity in Steps 1 and 2 of study HPTN 083 (Safety Population)

	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Any Adverse Event	2174 (95)	2157 (94)
Grade 1	59 (3)	50 (2)
Grade 2	1370 (60)	1353 (59)
Grade 3	500 (22)	487 (21)
Grade 4	241 (11)	261 (11)
Grade 5	4 (<1)	6 (<1)

Data Source: 201738 CSR Table 3.012

Table 21: Grade 3 or higher Adverse Events that occurred in at least 1% participants in either treatment group - Steps 1 and 2 of study HPTN 083 (Safety Population)

Preferred Term	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Number of participants with any event Grade 3 or higher	745 (33)	754 (33)
Blood creatine phosphokinase increased	323 (14)	308 (13)
Creatinine renal clearance decreased	155 (7)	188 (8)
Blood creatinine increased	79 (3)	76 (3)
Lipase increased	76 (3)	76 (3)
Aspartate aminotransferase increased	51 (2)	69 (3)
Injection site pain	50 (2)	0 (0)
Alanine aminotransferase increased	22 (<1)	31 (1)

Data Source: 201738 CSR Table 3.031

- HPTN O84

Table 22: Summary of OBSP Adverse Events by maximum intensity in Steps 1 and 2 of study HPTN 084 (Safety Population)

	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Any Adverse Event	1556 (96)	1540 (96)
Grade 1	67 (4)	60 (4)
Grade 2	1224 (76)	1206 (75)
Grade 3	228 (14)	238 (15)
Grade 4	35 (2)	36 (2)
Grade 5	2 (<1)	0

Data Source: 201739 CSR Table 3.012
Note: The number of participants was considered only once for the highest toxicity grade.

Table 23: Grade 3 or higher OBSP AEs that occurred in ≥10 participants in either group – Steps 1 and 2 of study HPTN 084 (Safety Population)

Preferred Term	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Participants with any event Grade 3 or higher	265 (16)	274 (17)
Creatinine renal clearance decreased	110 (7)	123 (8)
Blood creatinine increased	72 (4)	66 (4)
Blood creatine phosphokinase increased	41 (3)	32 (2)
Abnormal loss of weight	19 (1)	34 (2)
Blood glucose decreased	15 (<1)	13 (<1)
Aspartate aminotransferase increased	14 (<1)	13 (<1)
Alanine aminotransferase increased	11 (<1)	15 (<1)

Data Source: 201739 CSR Table 3.031
Note: PTs are listed in the order of decreasing frequency in the CAB group.
Note: AEs were coded to preferred term using MedDRA Coding Dictionary Version 23.1.

Drug related Adverse Events

In HPTN 083, the proportion of participants who experienced 1 or more drug-related AEs was greater in the CAB group (1874 [82%] participants) compared with the TDF/FTC group (1355 [59%] participants) primarily due to the difference in the proportion of participants who experienced 1 or more drug-related ISR AEs between the 2 groups. The drug-related AE PTs reported in ≥5% participants were injection site pain (1697 [74%] participants), creatinine renal clearance decreased (671 [29%]), injection site nodule (263 [12%]), injection site induration (255 [11%]), injection site swelling (204 [9%]), and blood creatinine increased (166 [7%]) in the CAB group. In HPTN 084, the proportion of participants who experienced 1 or more drug-related AEs was greater in the CAB group (1098 [68%] participants) compared with the TDF/FTC group (1014 [63%] participants) primarily due to the difference in the proportion of participants who experienced 1 or more drug-related ISR AEs between the 2 groups. The drug-related AE PTs reported in ≥10% participants were creatinine renal clearance decreased (692 [43%] participants), injection site pain (519 [32%]), amylase increased (252 [16%]), blood creatinine increased (213 [13%]), headache (190 [12%]), and blood phosphorous decreased (169 [10%]) in the CAB group.

2.5.8.2. Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 24: Summary of on blinded study product SAEs by Preferred Term reported in more than one participant – Steps 1 and 2 of study HPTN 083 (Safety Population)

Preferred Term	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Total Number of SAEs	116	128
Number of participants with at least one SAE	109 (5)	104 (5)
Suicide attempt	7 (<1)	9 (<1)
Suicidal ideation	6 (<1)	6 (<1)
Dengue fever	5 (<1)	3 (<1)
Influenza	4 (<1)	2 (<1)
Appendicitis	3 (<1)	8 (<1)
Pneumonia	3 (<1)	3 (<1)
Concussion	3 (<1)	2 (<1)
Cellulitis	3 (<1)	1 (<1)
Depression	2 (<1)	6 (<1)
Gastroenteritis	2 (<1)	5 (<1)
Hepatitis A	2 (<1)	2 (<1)
Dengue haemorrhagic fever	2 (<1)	1 (<1)
Pyrexia	2 (<1)	1 (<1)
Seizure	2 (<1)	1 (<1)
Abscess limb	2 (<1)	0
Acute hepatitis B	2 (<1)	0
Affective disorder	2 (<1)	0
Pharyngitis	2 (<1)	0
Acute hepatitis C	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	1 (<1)
Multiple injuries	1 (<1)	1 (<1)
Ankle fracture	1 (<1)	1 (<1)
Atrial fibrillation	1 (<1)	1 (<1)
Bronchitis	1 (<1)	1 (<1)
Foreign body in gastrointestinal tract	1 (<1)	1 (<1)
Haemorrhoids	1 (<1)	1 (<1)
Pulmonary tuberculosis	1 (<1)	1 (<1)
Tonsillitis	1 (<1)	1 (<1)
Upper respiratory tract infection	1 (<1)	1 (<1)
Meniscus injury	0	2 (<1)
Deep vein thrombosis	0	2 (<1)
Pancreatitis	0	2 (<1)
Stab wound	0	2 (<1)

Data source: 201738 CSR Table 3.035
Note: Deceasing frequency from the CAB group

Table 25: Summary of on blinded study product SAEs by Preferred Term Reported in more than one participant – Steps 1 and 2 of study HPTN 084 (Safety Population)

Preferred Term	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Total Number of SAEs	29	39
Number of participants with at least one SAE	25 (2)	33 (2)
Malaria	5 (<1)	3 (<1)
Pelvic inflammatory disease	1 (<1)	2 (<1)
Blood creatine phosphokinase increased	1 (<1)	2 (<1)
Depression	1 (<1)	1 (<1)

Preferred Term	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Intentional self-injury	1 (<1)	1 (<1)
Hepatitis acute	1 (<1)	0
Bartholin's abscess	1 (<1)	0
COVID-19	1 (<1)	0
Endometritis	1 (<1)	0
Gastritis bacterial	1 (<1)	0
Hepatitis A	1 (<1)	0
Peritonsillar abscess	1 (<1)	0
Respiratory tract infection	1 (<1)	0
Arthropod sting	1 (<1)	0
Post-concussion syndrome	1 (<1)	0
Soft tissue injury	1 (<1)	0
Diabetic ketoacidosis	1 (<1)	0
Lumbar spinal stenosis	1 (<1)	0
Uterine leiomyoma	1 (<1)	0
Cerebrovascular accident	1 (<1)	0
Headache	1 (<1)	0
Ectopic pregnancy	1 (<1)	0
Anxiety	1 (<1)	0
Panic disorder	1 (<1)	0
Peptic ulcer	0	2 (<1)
Tonsillitis bacterial	0	2 (<1)
Suicide attempt	0	2 (<1)
Hypersplenism	0	1 (<1)
Hepatitis alcoholic	0	1 (<1)
Hepatotoxicity	0	1 (<1)
Appendiceal abscess	0	1 (<1)
Escherichia pyelonephritis	0	1 (<1)
Pneumonia bacterial	0	1 (<1)
Pulmonary tuberculosis	0	1 (<1)
Urinary tract infection	0	1 (<1)
Head injury	0	1 (<1)
Humerus fracture	0	1 (<1)
Intentional overdose	0	1 (<1)
Skin laceration	0	1 (<1)
Stab wound	0	1 (<1)
Alanine aminotransferase increased	0	1 (<1)
Aspartate aminotransferase increased	0	1 (<1)
Diabetes mellitus	0	1 (<1)
Hypoglycaemia	0	1 (<1)
Seizure	0	1 (<1)
Ruptured ectopic pregnancy	0	1 (<1)
Major depression	0	1 (<1)
Psychotic disorder	0	1 (<1)
Dysfunctional uterine bleeding	0	1 (<1)

Data Source: 201739 CSR Table 3.035
Note: AEs were coded to SOC and Preferred Term using MedDRA Coding Dictionary Version 23.1.
Note: PTs are listed in the order of decreasing frequency in the CAB group.

Drug-related serious Adverse Events

In pivotal study HPTN 083, the proportion of participants with 1 or more study drug-related SAEs was comparable between the 2 groups. In the CAB group, 5 drug-related SAEs occurred in 4 (<1%) participants (PTs: 2 suicide attempts, 1 affective disorder, 1 seizure, and 1 immune thrombocytopenia). In the TDF/FTC group, 4 drug-related SAEs occurred in 3 (<1%) participants (PTs: 1 suicide attempt, 1 ALT increased, 2 cardiac disorder). In study HPTN 084, a total of 5 OBSP drug-related SAEs occurred in 1 (<1%) CAB participant (1 PT: respiratory tract infection) and 3 (<1%) TDF/FTC participants (4 PTs: AST increased, ALT increased, hepatotoxicity, and seizure).

Deaths

In study HPTN 083 ten deaths were reported during Steps 1 and 2 (4 in the CAB group; 6 in the TDF/FTC group). Of the 10 deaths, 1 participant in either treatment group experienced a fatal SAE with cardiovascular event; of which 1 (PT: cardiac disorder in the TDF/FTC group) was deemed drug related as assessed by the investigator. Regarding the CAB group, gunshot wound, cardiopulmonary failure possible methamphetamine overdose and homicide due to secondary traumatic bleeding are not related to CAB. Regarding asphyxia, the time-to-onset and the verbatim provided in the narrative, i.e., 'mechanical asphyxia' is unlikely to be attributed to CAB. In study HPTN 084 three participants in the CAB group experienced AEs that resulted in a fatal outcome (two during Step 2 OBSP [PTs hypertensive heart disease and headache] and one during Step 2 Non-OBSP [PT cerebrovascular accident]). None were considered by the investigator to be related to study drug, but the fatal SAEs hypertensive heart disease and cerebrovascular event are poorly documented. No deaths were reported during the supportive studies.

Adverse Events of special interest

- *Injection site reactions:* in HPTN 083, a higher proportion of participants experienced ISRs in the CAB group (82%) compared to the TDF/FTC group (35%). The ISRs reported in ≥10% participants in the CAB group, by PT, were injection site pain (81%), injection site nodule (12%), injection site induration (12%), and injection site swelling (10%). A total of 81% participants in the CAB group and 31% participants in the TDF/FTC group experienced a drug-related ISR. No participants in the TDF/FTC group experienced an ISR leading to study drug discontinuation whereas in the CAB group, a total of 2.5% (53/2117) discontinued drug due to ISR. In HPTN 084, a higher proportion of participants experienced ISRs in the CAB group (38%) compared to the TDF/FTC group (11%). Injection site pain was the only ISR reported in ≥10% participants in either group (34% CAB group vs 10% TDF/FTC group). A total of 38% participants in the CAB group and 11% participants in the TDF/FTC group experienced a drug-related ISR. Injection site pain was the most frequently reported drug-related ISR in the CAB group (34%). Noteworthy, the proportion of participants with at least one drug-related ISR AE reported in HPTN 083 (81% in CAB group) more than double the proportion reported in HPTN 084 (38% in CAB group). In general, the incidence and intensity of ISRs decreased over the course of both pivotal studies. The Applicant provided a multifactorial reasoning to explain the difference of reported ISRs by gender at birth focusing on the following aspects: a) number of safety visits in the Step 2 injection phase (which included active capture of solicited ISR events) for HPTN083 (19 visits through week 147) and HPTN084 (4 visits through week 145); b) prevalence exposure of IM or SC contraceptives in HPTN084 (93.4% participants concomitant or prior use); c) ISR frequency by gender for the phase 3 CAB treatment studies [In ATLAS-2M, 87 females (65%) on Q8W dosing and 95 females (69%) on Q4W dosing reported ISRs compared to 305 males (80%) on Q8W dosing and 295 males (78%) on Q4W dosing. From the week 48 pooled ATLAS and FLAIR data, 126 females (81%) and 361 males (86%) reported ISRs. For the week 96 pooled ATLAS and ATLAS-2M, 201 female (95%) and 719 male (>99%) participants reported ISRs] and; d) data post-marketing experience studies with CAB PrEP (CAB LA PrEP Cohort: Prospective post-marketing Cohort Study to Assess Effectiveness and Safety of, and Adherence and Resistance to Cabotegravir for Pre-Exposure Prophylaxis in the United States; out of 52 participants in the study with documented injections of CAB LA for PrEP as of 28 February 2023, 2 ISRs were documented through ICD-10 codes; one ISR was in a male individual and the other had unspecified gender).
- *Hepatoxicity*: the frequency of Hepatotoxicity AESIs was similar across the CAB and TDF/FTC groups in both pivotal studies for both pivotal trials. Overall, the frequency of Hepatotoxicity AESI (<1%) in the CAB group was similar compared with the CAB+RPV group in the CAB treatment pooled pivotal studies (<1%) (CAB Treatment pooled ATLAS/FLAIR safety analysis). When liver

related study product discontinuations were assessed by the HHAC, similar numbers of these events were assessed as probable or possible DILI in both groups. In HPTN 083, 14 cases in the CAB group were considered as probable (n=5) or possible DILI (n=9). These events are uncommon occurrences, mild in severity and generally reversible. For Hepatotoxicity AESIs, no SAEs of DILI were reported on either group. In HPTN 084, 8 cases in the CAB group were considered as probable (n=1) or possible DILI (n=7).

- *Hypersensitivity:* in HPTN 083, the proportion of participants who experienced 1 or more potential hypersensitivity AEs and other potentially associated AEs (Hypersensitivity AESI) during Steps 1 and 2 OBSP was similar between groups (2%); but slightly higher when compared with the CAB+RPV group in the CAB treatment pooled pivotal studies (<1%) (CAB treatment pooled ATLAS/FLAIR safety analysis). 4 participants in the CAB group experienced potential hypersensitivity AESIs ≥Grade 3. The PT of hypersensitivity was the most common potential Hypersensitivity AESI in both groups (CAB:1%; TDF/FTC:<1%). In HPTN 084, the frequency of Hypersensitivity AESIs was low and similar between groups during Step 1 OBSP and Step 2 OBSP (<1%). The PT of hypersensitivity was the most frequently reported Hypersensitivity AESI in both groups.
- *Hyperglycemia and Diabetes:* In both pivotal studies, there was no suggestion of worsening of glycaemic profile of participants receiving CAB in CAB PrEP studies. Although there was increase in the proportion of participants reporting AEs of blood glucose increased for participants in the CAB group in both pivotal studies, other AEs associated with Hyperglycaemia AESI were reported with a similar frequency across both groups. The frequency of AEs of blood glucose increased in the CAB group was higher in study HPTN 084 (43%) compared to HPTN 083 (12%), but is should be acknowledged differences between study protocols. When the totality of laboratory abnormalities are also taken into consideration, there is no apparent trend of increased blood glucose levels with treatment with CAB.
- *Rash*: in both pivotal studies, the proportion of participants with 1 or more rash and other potentially associated AEs (Rash AESI) was similar between groups (4%). Of the Rash AESI PTs, PT rash was reported in the greatest proportion of participants in both groups (3% in HPTN 083 and 2% in HPTN 084). For both pivotal studies, all other reported Rash AESI PTs occurred in <1% of participants in either group. In HPTN 083, drug-related (n=8), ≥Grade 3 in intensity (n=2) Rash AESIs, study drug discontinuations (4 participants) and study drug interruptions (3 participants) were infrequent. In HPTN 084, no participants experienced Rash AESIs that were serious or that led to study drug discontinuation.
- *Neuropsychiatric Adverse Events:* in both pivotal studies, the proportion of participants with Neuropsychiatric AESIs was similar across both groups.

Table 26: Summary of Neuropsychiatric AESIs During Steps 1 and 2 from study HPTN 083 (Safety Population)

Neuropsychiatric AESI	CAB (N=2281)		TDF/FTC (N=2285)	
	Number (%) Participants	Number of Events	Number (%) Participants	Number of Events
Sleep Disorders	217 (10%)	282	248 (11%)	298
Depression	115 (5%)	124	108 (5%)	122
Anxiety	99 (4%)	118	97 (4%)	104
Mood Disorders	30 (1%)	34	19 (<1%)	23
Suicidal Ideation and Behavior	25 (1%)	28	23 (1%)	30
Bipolar Disorder	5 (<1%)	5	6 (<1%)	6
Psychosis	3 (<1%)	3	4 (<1%)	4

Data Source: 201738 CSR Table 3.170
Note: Number Events - total number of AEs during Steps 1 and 2.
Note: Number (%) Participants - total (%) number of unique participants.
Note: AEs were coded to SOC and PT using MedDRA coding dictionary version 23.1.

Note: Sites were instructed to only enter Grade 2 or higher laboratory abnormalities AEs, however all laboratory abnormalities AEs that were entered into the case report form are included in this table even if they are Grade 1.
Note: Decreasing frequency from the CAB group.

Table 27: Summary of Neuropsychiatric AESIs During Steps 1 and 2 from study HPTN 084 (Safety Population)

	CAB (N=1614)		TDF/FTC (N=1610)	
Neuropsychiatric AESI	Number (%) Participants	Number of Events	Number (%) Participants	Number of Events
Sleep Disorders	81 (5)	94	76 (5)	88
Anxiety	16 (<1)	18	11 (<1)	11
Mood Disorders	9 (<1)	10	6 (<1)	7
Depression	7 (<1)	8	12 (<1)	13
Suicidal Ideation and Behavior	3 (<1)	3	6 (<1)	7
Psychosis	1 (<1)	1	2 (<1)	3
Bipolar Disorder	0	0	0	0

Data Source: 201739 CSR Table 3.768, Table 3.771, Table 3.774, Table 3.777, Table 3.780, Table 3.783, Table 3.786
Note: Number of Events – total number of AEs during Step 1 and 2.
Note: Number (%) Participants – total (%) number of unique participants.
Note: If a participant had more than 1 AE for a specific term, they are only counted once in the Number of Participants with AEs for that SOC and term.
Note: PTs are listed in the order of decreasing frequency in the CAB group.

- *Seizures and Seizure-like events:* events of seizure and related terms were reported at a low and similar frequency (<1%) in both groups during both HPTN 083 and HPTN 084 studies. In CAB group of HPTN 083, 5 participants experienced AESIs ≥Grade 3 and 4 participants had SAEs. There were 2 participants who experienced study drug-related AESIs and 3 participants who had AESIs leading to study drug discontinuation. Narratives were reviewed and most of the cases of seizures occurred in participants with concurrent or pre-existing risk factors, or alternative aetiologies for the events; there were no cases reported in association with CAB that provided convincing evidence to support a causal association. In HPTN 084, reports of Seizure AESIs were infrequent, with the same number of participants reporting any Seizure AESI in both groups (2 [<1%] participants) in each group. Of the 2 participants in the CAB group with a Seizure AESI, both experienced a Grade 1 or 2 event, and no participants had a Grade 3 or higher Seizure AESI. Neither participant experienced an event that was serious, related to study drug, or led to study drug discontinuation.

- *Weight gain:* in both pivotal studies, the proportion of participants who experienced 1 or more AEs of weight gain and other potentially associated AEs (Weight Gain AESI) was low and comparable between groups (<1% participants in each group). In HPTN 083, there was a numerically higher number of AEs reported for the PT obesity in the CAB group (CAB: 13 participants; TDF/FTC: 8), although there were no ≥Grade 3 Weight Gain AESIs, Weight Gain SAEs, Weight Gain AESIs related to study drug, or Weight Gain AESIs leading to study drug discontinuation. In HPTN 084, neither participant experienced an event that was serious, related to study drug, or led to withdrawal.

- *Rhabdomyolysis | Myalgia:* In HPTN 083, rhabdomyolysis was reported infrequently throughout the CAB PrEP program. None of the cases were considered by the investigator to be related to study drug. In HPTN 084, there were no reported events of rhabdomyolysis in either the CAB or TDF/FTC group. In HPTN 083, the proportion of participants who experienced 1 or more Rhabdomyolysis AESI PTs was comparable between groups. The most common Rhabdomyolysis AESI PT was myalgia (CAB: 5% participants; TDF/FTC: 4%). The overall frequency of myalgia was similar between the CAB and TDF/FTC groups, however the number of participants with drug-related AEs, as determined by the investigator, was higher in the CAB group. In HPTN 084, myalgia was the only Rhabdomyolysis AESI PT that was reported (CAB: 3% participants; 2% TDF/FTC).

- *Pancreatitis:* SAEs of pancreatitis were reported during the CAB Treatment program. Based on a review of the medical history/risk factors and/or investigators' opinion, the Applicant considers that there were compelling etiologies (*e.g.,* gallstones) for most of these cases. In the CAB PrEP program, one participant experienced an AE of pancreatitis (in study HPTN 083). An expanded analysis to look at additional AEs potentially suggestive of pancreatitis ('Pancreatitis Plus') has been conducted by the Applicant in both of the pivotal CAB PrEP studies. The available data from the CAB PrEP program, including data from the expanded analysis, does not provide evidence of a causal association with CAB.
- *Impact on creatinine:* There were no reported pre-specified AESIs for the Impact on Creatinine AESI for CAB in both pivotal studies. However, there were reports of AE PTs (blood creatinine increased and creatinine renal clearance decreased) reported frequently in similar proportions in both groups in pivotal trials and supportive study HPTN 077. These observations were reviewed by the Applicant as part of a comprehensive expanded analysis. Taken together these results with the objective laboratory values for creatinine clearance and creatinine reported during CAB PrEP it is agreed that these findings do not suggest clinical relevant trends and a significant impact of CAB PrEP on renal function. This is supported by the findings from the CAB Treatment program that there is no clinically relevant effect of CAB on creatinine or creatinine clearance of HIV-infected participants.
- *Pyrexia*: in HPTN 083, a higher proportion of participants experienced pyrexia events and events associated with pyrexia defined as Pyrexia Plus has been shown to occur more frequently in the CAB group compared to the TDF/FTC group whereas in HPTN 084 no differences were found among groups. Overall, pyrexia events occurred following IM injections and are known to occur following CAB injections in the Treatment (up to 8%) (CAB Treatment pooled ATLAS/FLAIR safety analysis).

Laboratory findings

Clinical Chemistry

Table 28: Post Baseline for Step 1 and 2 of study HPTN 083 and study HPTN 084 (Safety Population)

		Study 201738 / HPTN 083		Study 201739 / HPTN 084	
Clinical chemistry parameter groups	Max post-Baseline Grade	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Renal function test (creatinine [μmol/L] and creatinine clearance [mL/min])					
	Grade 1	57 (2)	48 (2)	13 (<1)	18 (1)
	Grade 2	1547 (68)	1635 (72)	1104 (68)	1137 (71)
	Grade 3	164 (7)	196 (9)	120 (7)	125 (8)
	Grade 4	2 (<1)	1 (<1)	1 (<1)	1 (<1)
Liver function test (alanine aminotransferase [IU/L], alkaline phosphatase [IU/L], aspartate aminotransferase [IU/L], and bilirubin [μmol/L])					
	Grade 1	906 (40)	963 (42)	355 (22)	358 (22)
	Grade 2	319 (14)	358 (16)	69 (4)	67 (4)
	Grade 3	72 (3)	95 (4)	17 (1)	18 (1)
	Grade 4	29 (1)	31 (1)	6 (<1)	8 (<1)
Other clinical chemistry parameters (amylase [IU/L], creatine kinase [IU/L], lipase [IU/L], and phosphate [mmol/L])					
	Grade 1	722 (32)	746 (33)	761 (47)	790 (49)
	Grade 2	430 (19)	459 (20)	290 (18)	287 (18)
	Grade 3	206 (9)	181 (8)	32 (2)	31 (2)
	Grade 4	210 (9)	231 (10)	21 (1)	17 (1)

Data Source: 201738 CSR Table 4.021, Table 4.022, Table 4.023 & 201739 CSR Table 4.021, Table 4.022, Table 4.023
Note: Grades are based on the DAIDS grading scale.
Note: Data after seroconversion per site, or while on open-label TDF/FTC, or after treatment discontinuation or emergency unblinding are excluded from the table.

The incidence and severity of clinical chemistry abnormalities is comparable between treatment groups. However, differences of Grade 1-2 liver function test abnormalities between HPTN 083 and HPTN 084 (more than twice the proportion among MSM and transgender women as compared to cisgender women) were found.

Liver Chemistry

In HPTN 083, a total of 78 participants (CAB: 40 [1.8%]; TDF/FTC: 38 [1.7%]) were reviewed by the HHAC and discontinued from study drug due to liver-related reasons. A total of 14 participants in the CAB group were assigned to the DILI likelihood category of "probable" (n=5) or "possible" (n=9). 15 participants receiving TDF/FTC were assessed by the HHAC as 'probable' DILI (n=2) or 'possible' DILI (n=13). In HPTN 084, a total of 33 participants (CAB: 15; TDF/FTC: 18) were reviewed by the HHAC and discontinued from study drug due to liver-related reasons. A total of 8 participants in the CAB group were assigned to the DILI likelihood category of "probable" (n=1) or "possible" (n=7). 7 participants receiving TDF/FTC were assessed by the HHAC as "probable" DILI (n=2) or "possible" DILI (n=5).

Table 29: Likelihood of Drug-induced Liver Injury by Study Group in Study HPTN 083 and Study HPTN 084

	Study 201738 / HPTN 083			Study 201739 / HPTN 084		
	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)	Overall	CAB (N=1614) n	TDF/FTC (N=1610) n	Overall
Total Participants enrolled	2822	2284	4566	1614	1610	3224
Liver-related study product discontinuations	40 (1.8)	38 (1.7)	78 (1.7)	15	18	33 (1%)
Likelihood of drug liver-induced injury						
Probable (≥50%)	5 (0.2)	2 (0.1)	7 (0.2)	1	2	3 (9%)
Possible (25% - 49%)	9 (0.4)	13 (0.6)	22 (0.5)	7	5	12 (37%)
Unlikely (0% - 24%)	23 (1)	18 (0.8)	41 (0.9)	6	9	15 (46%)
Unassessable	3 (0.1)	5 (0.2)	8 (0.2)	1	2	3 (9%)

Data Source: Table 1 in HPTN 083 Hepatic Adjudication Committee Report #1, Version 1.0
Data Source: Table 1 in HPTN 084 Hepatic Adjudication Committee Report #1, Version 2.0

Table 30: Summary of Participants with ALT Greater Than or Equal to 3XULN During Steps 1 and 2 of Study HPTN 083 and HPTN 084 (Safety Population)

	Study 201738 / HPTN 083		Study 201739 / HPTN 084	
Laboratory Parameter Grade	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Alanine Aminotransferase				
Grade 1	478 (21)	532 (23)	183 (11)	181 (11)
Grade 2	138 (6)	167 (7)	39 (2)	34 (2)
Grade 3	24 (1)	34 (1)	6 (<1)	12 (<1)
Grade 4	16 (<1)	10 (<1)	6 (<1)	6 (<1)
Aspartate Aminotransferase				
Grade 1	400 (18)	439 (19)	171 (11)	144 (9)
Grade 2	136 (6)	136 (6)	25 (2)	24 (1)
Grade 3	42 (2)	53 (2)	10 (<1)	8 (<1)
Grade 4	26 (1)	26 (1)	5 (<1)	6 (<1)
Bilirubin				
Grade 1	225 (10)	267 (12)	55 (3)	60 (4)
Grade 2	93 (4)	108 (5)	14 (<1)	19 (1)
Grade 3	10 (<1)	16 (<1)	2 (<1)	2 (<1)
Grade 4	3 (<1)	1 (<1)	0	0
Alkaline Phosphatase				
Grade 1	56 (2)	84 (4)	51 (3)	72 (4)
Grade 2	3 (<1)	6 (<1)	1 (<1)	0
Grade 3	0	2 (<1)	0	0
Grade 4	0	0	0	0

HTPN03 - Data Source: 201738 CSR Table 4.022 | Note: Includes events Grade 1 or higher at Baseline
HTPN04 - Data Source: 201739 CSR Table 4.022 | Note: Includes events Grade 1 or higher at Baseline;
Data after seroconversion per site, or while on open-label TDF/FTC, or after treatment discontinuation or emergency unblinding are excluded from the table.

Table 31: Liver Laboratory Parameters by Intensity Grade 2 or Higher from Baseline to Maximum Post Baseline of studies HPTN 083 and HPTN 084 (Safety Population)

	Study 201738 / HPTN 083		Study 201739 / HPTN 084	
Hepatobiliary Criteria	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
n	2237	2244	1566	1561
ALT ≥3 x ULN to <5 x ULN	100 (4)	119 (5)	31 (2)	21 (1)
ALT ≥5 x ULN to <10 x ULN	31 (1)	40 (2)	7 (<1)	12 (<1)
ALT ≥10 x ULN to <20 x ULN	10 (<1)	9 (<1)	4 (<1)	5 (<1)
ALT ≥20 x ULN	9 (<1)	4 (<1)	2 (<1)	2 (<1)

Data Source: 201738 CSR Table 4.026
Data Source: 201739 CSR Table 4.026

Creatinine and Creatine Clearance

Table 32: Renal function laboratory parameters by intensity grade from baseline to maximum post baseline for Step 1 and 2 in study HPTN 083 and study HPTN 084 (Safety population)

	Study 201738 / HPTN 083		Study 201739 / HPTN 084	
Laboratory Parameter Grade	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Creatinine				
Grade 1	57 (2)	48 (2)	13 (<1)	18 (1)
Grade 2	303 (13)	352 (15)	269 (17)	263 (16)

Grade 3	76 (3)	78 (3)	72 (4)	65 (4)
Grade 4	2 (<1)	1 (<1)	1 (<1)	0 (0)
Creatinine Clearance				
Grade 1	0	0	0 (0)	0 (0)
Grade 2	1475 (65)	1534 (67)	1061 (66)	1082 (67)
Grade 3	155 (7)	190 (8)	111 (7)	121 (8)
Grade 4	2 (<1)	1 (<1)	1 (<1)	1 (<1)

Data Source: 201738 CSR Table 4.021
Note: Includes events Grade 1 or higher at Baseline

Overall, no notable trends in creatinine abnormalities were identified with CAB PrEP and new safety concerns were raised regarding potential impact on renal function. Similar findings were found across arms from different pivotal studies.

Lipid Parameters and Fasting Glucose: shifts in lipid parameters and fasting glucose in both pivotal studies were similar between treatment groups and did not raise additional concerns.

Clinical Hematology: No clinically relevant patterns nor differences were observed in clinical laboratory abnormalities, for hematology parameters between the CAB and TDF/FTC groups in both pivotal trials.

2.5.8.3. Safety in special populations

No prespecified safety analyses were done based on sex (at birth) in HPTN 083; for HPTN 084, prespecified safety analyses based on age (but not sex [at birth] or race) were performed. Of note, no Caucasians participated in HPTN 084 (cisgender women).

For both pivotal trials, there was no difference in the trend of most common AEs when CAB PrEP was administered in a subgroup of participants <25 years of age when compared with the full study population. Moreover, the requested detailed analysis of the safety data (any event, SOC/PT, AE grade) per age subgroup (18-19 years, 20-21 years and 22 to <25 years of age), showed no overall discernible difference in the trend of most common AEs and ADRs reported with CAB PrEP compared with the total study population across both pivotal studies.

Table 33: Most Common Adverse Events in a Subgroup of Participants <25 years of Age from Study 201738/ HTPN083 (Reported in ³5% in Any Treatment Group) by Preferred Term – Steps 1 and 2 (Safety Population)

Preferred Term	CAB (N=930) n (%)	TDF/FTC (N=915) n (%)
Any Adverse Event	877 (94)	842 (92)
Injection site pain	704 (76)	258 (28)
Creatinine renal clearance decreased	614 (66)	638 (70)
Blood creatinine phosphokinase increased	191 (21)	196 (21)
Nasopharyngitis	179 (19)	158 (17)
Headache	169 (18)	157 (17)
Blood creatinine increased	144 (15)	152 (17)
Anal chlamydia infection	126 (14)	152 (17)
Diarrhoea	120 (13)	121 (13)
Injection site induration	106 (11)	2 (<1)
Upper respiratory tract infection	106 (11)	113 (12)
Proctitis gonococcal	104 (11)	111 (12)
Pyrexia	104 (11)	57 (6)
Oropharyngeal pain	84 (9)	77 (8)
Injection site swelling	83 (9)	2 (<1)
Aspartate aminotransferase increased	78 (8)	86 (9)
Injection site nodule	75 (8)	7 (<1)

Preferred Term	CAB (N=930) n (%)	TDF/FTC (N=915) n (%)
Syphilis	74 (8)	80 (9)
Blood glucose increased	72 (8)	52 (6)
Alanine aminotransferase increased	68 (7)	71 (8)
Lipase increased	66 (7)	65 (7)
Amylase increased	64 (7)	62 (7)
Cough	60 (6)	63 (7)
Pharyngitis	56 (6)	41 (4)
Nausea	53 (6)	96 (10)
Insomnia	50 (5)	43 (5)
Fatigue	47 (5)	35 (4)
Dizziness	44 (5)	56 (6)
Procedural pain	38 (4)	48 (5)
Blood glucose decreased	37 (4)	45 (5)
Blood bilirubin increased	36 (4)	55 (6)
Gastroenteritis	40 (4)	47 (5)

Data Source: <25 Yrs Subgroup 201738 Table 3.512

Note: Deceasing frequency from the CAB group

Note: Sites were instructed to only enter Grade 2 or higher laboratory abnormalities AEs, however all laboratory abnormalities AEs that were entered into the CRF are included in this table even if they are Grade 1.

Note: The Number of Participants is considered only once for the highest toxicity grade.

Table 34: Most Common Adverse Events in a Subgroup of Participants <25 years of Age from Study 201739 / HTPN 084 (Reported in ³5% in Any Group) by Preferred Term – Steps 1 and 2 (Safety Population)

Preferred Term	CAB (N=800) n (%)	TDF/FTC (N=794) n (%)
Number of participants with any adverse event	769 (96)	755 (95)
Creatinine renal clearance decreased	557 (70)	555 (70)
Amylase increased	285 (36)	289 (36)
Injection site pain	269 (34)	66 (8)
Blood glucose increased	241 (30)	175 (22)
Blood glucose decreased	243 (30)	241 (30)
Blood creatinine increased	181 (23)	167 (21)
Headache	171 (21)	164 (21)
Blood phosphorus decreased	111 (14)	101 (13)
Blood creatine phosphokinase increased	108 (14)	127 (16)
Alanine aminotransferase increased	105 (13)	108 (14)
Genitourinary chlamydia infection	100 (13)	85 (11)
Upper respiratory tract infection	95 (12)	112 (14)
Urinary tract infection	97 (12)	93 (12)
Aspartate aminotransferase increased	92 (12)	75 (9)
Lipase increased	84 (11)	78 (10)
Dysfunctional uterine bleeding	89 (11)	76 (10)
Hyperglycaemia	66 (8)	60 (8)
Chlamydial infection	60 (8)	80 (10)
Vulvovaginal candidiasis	58 (7)	74 (9)
Vulvovaginitis trichomonal	55 (7)	49 (6)
Blood calcium increased	54 (7)	37 (5)
Injection site swelling	44 (6)	3 (<1)
Back pain	46 (6)	33 (4)
Diarrhoea	46 (6)	52 (7)
Dizziness	45 (6)	50 (6)
Injection site nodule	46 (6)	4 (<1)
Menorrhagia	44 (6)	39 (5)
Metrorrhagia	43 (5)	46 (6)
Nasopharyngitis	36 (5)	47 (6)
Abnormal loss of weight	36 (5)	36 (5)

Preferred Term	CAB (N=800) n (%)	TDF/FTC (N=794) n (%)
Blood bilirubin increased	36 (5)	34 (4)
Injection site induration	40 (5)	4 (<1)
Genitourinary tract gonococcal infection	39 (5)	33 (4)
Gastroenteritis	33 (4)	42 (5)
Vomiting	28 (4)	53 (7)
Nausea	35 (4)	83 (10)
Haemoglobin decreased	33 (4)	39 (5)
Amenorrhoea	32 (4)	39 (5)
Blood alkaline phosphatase increased	29 (4)	42 (5)
Decreased appetite	27 (3)	46 (6)

Data Source: 201739 CSR Table 3.112
Note: PTs are listed in the order of decreasing frequency in the CAB group.

To support the CAB PrEP use in adolescents the Applicant conducted the study MOCHA/208580 that evaluated the use of CAB in HIV-infected adolescents (n=8) in addition to cART (Cohort 1C). Data from submission package revealed that at week 16, the most common AEs (occurring in ≥3 participants) were injection site pain, cough, and nasal congestion. All reported ISRs (62.5%) were Grade 1 or 2, predominantly comprising injection site pain. There were no SAEs or AEs leading to premature permanent discontinuation. Three participants had Grade 3 AEs (neutropenia and insomnia; n=1 each) or Grade 4 (n=1; blood creatine phosphokinase increased). There were no deaths or pregnancies, and no clinically important findings were noted with respect to laboratory assessments, ECGs, or vital signs.

The Applicant provided an update safety report of Mocha study, though the Applicant recognized the limitations of the data given – *i.e.* data were produced for internal review purposes and were not in a submission-ready format. Following the completion of the first interim analysis of Cohort 1, an additional 22 participants were enrolled in Cohort 1C with a total of 29/30 completing Week 16. No participants discontinued due to AEs. There were no SAEs considered related to CAB and no other SAEs or deaths among the CAB exposed participants in Cohort 1. No pregnancies have been reported to the Applicant for Cohort 1 participants. 43.3% of participants reported AEs in the oral phase, of note, there were no events with a severity above Grade 2. Moreover, as noted previously, the MOCHA study is ongoing, Cohort 2 is fully enrolled and has reached its primary end point. The only in-stream data to which the Applicant has current direct access were SAEs and pregnancies reported to DAIDS in an expedited manner. To date the Applicant was aware of 4 SAE reports (one of which was received during the reporting period of the interim CSR and involved a participant in Cohort 1R during Long-term safety and washout pharmacokinetic follow-up. There is also one report of pregnancy (non-serious, outcome unknown) for a Cohort 2 participant. Overall, new data provided do not raise any new safety concerns, or change the conclusions presented in the interim CSR.

No firm conclusions regarding the safety of CAB PrEP in patients co-infected with HBV and/or HCV can be drawn. No safety data are available in subjects with renal or hepatic impairment.

The safety of CAB PrEP during human pregnancy and breastfeeding has not been established.

2.5.8.4. Safety related to drug-drug interactions and other interactions

CAB drug interactions have been evaluated in Phase I studies and clinically relevant data for the CAB PrEP program. Overall, CAB has a favourable drug interaction profile with few clinically relevant interactions that require dose modifications or contraindication. Therefore, it is not expected to experience clinically meaningful drug interactions, except for strong inducers of UGT1A1 (*e.g.* rifampin)

and chelation with antacids containing polyvalent cations (applicable to oral CAB only). Of note, no CAB dose adjustment is necessary when co-administered with hormonal contraceptives or gender-affirming hormone therapy, proton pump inhibitors, histamine-2 receptor antagonists, statins, HBV medications, HCV medications, and opioid dependence treatments.

2.5.8.5. Discontinuation due to adverse events

In pivotal study HPTN 083, 135 (6%) participants in the CAB group and 91 (4%) participants in the TDF/FTC group experienced AEs leading to discontinuation of study drug. The higher proportion of participants in the CAB group was driven by ISRs. Of note, 24 participants (1%) discontinued study drug during the Step 1 period and never received IM CAB injections.

Table 35: Summary of AEs leading to discontinuation of study drug in more than 1 participant across treatment groups – Steps 1 and 2 of study HPTN 083 (Safety Population)

System Organ Class Preferred Term	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Total Number of AEs Leading to Discontinuation of Study Drug	182	104
Number of participants with at least one AE leading to Discontinuation of Study Drug	135 (6)	91 (4)
Investigations	45 (2)	50 (2)
Alanine aminotransferase increased	29 (1)	31 (1)
Aspartate aminotransferase increased	7 (<1)	8 (<1)
Creatinine renal clearance decreased	3 (<1)	9 (<1)
Lipase increased	5 (<1)	4 (<1)
Blood creatine phosphokinase increased	2 (<1)	2 (<1)
Amylase increased	1 (<1)	2 (<1)
Blood creatinine increased	1 (<1)	1 (<1)
Blood glucose increased	1 (<1)	1 (<1)
General disorders and administration site conditions	48 (2)	0 (0)
Injection site pain	43 (2)	0 (0)
Injection site nodule	4 (<1)	0 (0)
Fatigue	3 (<1)	0 (0)
Injection site induration	3 (<1)	0 (0)
Injection site warmth	2 (<1)	0 (0)
Malaise	2 (<1)	0 (0)
Infections and infestations	18 (<1)	12 (<1)
Acute hepatitis C	6 (<1)	3 (<1)
Acute hepatitis B	4 (<1)	3 (<1)
Hepatitis A	4 (<1)	2 (<1)
Hepatitis E	1 (<1)	1 (<1)
Latent tuberculosis	1 (<1)	1 (<1)
Psychiatric disorders	10 (<1)	4 (<1)
Suicide attempt	3 (<1)	1 (<1)
Depression	2 (<1)	0 (0)
Suicidal ideation	2 (<1)	0 (0)
Nervous system disorders	6 (<1)	7 (<1)
Seizure	2 (<1)	5 (<1)
Dizziness	2 (<1)	0 (0)
Skin and subcutaneous tissue disorders	6 (<1)	5 (<1)
Pruritus	1 (<1)	1 (<1)
Rash	1 (<1)	1 (<1)
Rash pruritic	1 (<1)	1 (<1)
Urticaria	0	2 (<1)
Gastrointestinal disorders	4 (<1)	3 (<1)
Gastritis	0	2 (<1)
Nausea	1 (<1)	1 (<1)
Hepatobiliary disorders	1 (<1)	3 (<1)

System Organ Class Preferred Term	CAB (N=2281) n (%)	TDF/FTC (N=2285) n (%)
Hepatic steatosis	0	2 (<1)

Data Source: 201738 CSR Table 3.047

In the CAB group of HPTN 083, 9 (<1%) participants had drug-related Grade 3 and higher AEs leading to discontinuation of study drug. In the TDF/FTC group, 17 (4%) participants had drug related Grade 3 or higher AEs leading to <1 discontinuation of study drug.

In pivotal study HPTN 084, 17 (1%) participants in the CAB group and 22 (1%) participants in the TDF/FTC group had AEs leading to discontinuation of study drug. 4 (<1%) participants in the CAB group and 6 (<1%) participants in the TDF/FTC group discontinued study drug during Step 1.

Table 36: Summary of AEs leading to discontinuation of study drug in more than 1 participant across treatment groups – Steps 1 and 2 of study HPTN 084 (Safety Population)

System Organ Class Preferred Term	CAB (N=1614) n (%)	TDF/FTC (N=1610) n (%)
Total Number of AEs Leading to Discontinuation of Study Drugs	17	22
Number of participants with at least one AE leading to discontinuation of study drugs	17 (1)	22 (1)
Investigations	12 (<1)	16 (<1)
Alanine aminotransferase increased	12 (<1)	15 (<1)
Lipase increased	0	1 (<1)
Infections and infestations	1 (<1)	2 (<1)
Hepatitis A	1 (<1)	2 (<1)
Hepatobiliary disorders	1 (<1)	1 (<1)
Hepatitis acute	1 (<1)	0
Hepatitis alcoholic	0	1 (<1)
Immune system disorders	0	2 (<1)
Drug hypersensitivity	0	1 (<1)
Hypersensitivity	0	1 (<1)
Psychiatric disorders	2 (<1)	0
Sleep disorder	1 (<1)	0
Suicidal ideation	1 (<1)	0
Blood and lymphatic system disorders	0	1 (<1)
Hypersplenism	0	1 (<1)
Nervous system disorders	1 (<1)	0
Cerebrovascular accident	1 (<1)	0

Data Source: 201739 CSR Table 3.047

Note: AEs were coded to SOC and PT using MedDRA coding dictionary Version 23.1.

In the CAB group of HPTN 084, 5 (<1%) participants had drug-related Grade 3 or higher non-ISR AEs leading to discontinuation of study drug. None of these AEs reported for participants in the CAB group were SAEs. In the TDF/FTC group, 8 (<1%) participants had drug-related Grade 3 or higher non-ISR AEs leading to discontinuation of study drug.

2.5.8.6. Post marketing experience

The applicant stated that CAB PrEP received its first marketing approval in the US in December 2021. CAB Treatment has received marketing approval in several countries/regions (including US, EU, Canada and Australia).

Cumulative post-marketing exposure to CAB PrEP available up to 30 June 2022 on the basis of the absolute number of vials of cabotegravir 200 mg/mL sold as CAB for PrEP, was 3362, equivalent to 280 patient years of exposure. The Applicant has provided an update of all post-marketing data related to CAB PrEP/Apretude since the initial approval (20 December 2021) up to 6 March 2023. A total of 216 cases were retrieved from the GSK safety database, of those 21 (10%) met the criteria for a SAE report. The safety profile reported is consistent with the established profile that has been seen in the clinical studies for both CAB PrEP and CAB+RPV for HIV Treatment and post-marketing experience with CAB+RPV.

Based on post-marketing experience with CAB+RPV for HIV treatment, since the launch of CAB PrEP, validated signals have been assessed for hypersensitivity and suicide and self-injurious behaviour. As a result of these reviews, the Global Datasheets for CAB for HIV treatment and CAB for PrEP have been updated to reflect the new identified risks of hypersensitivity, including angioedema and urticaria, and suicide attempt and suicidal ideation. Hence and as requested, identified risks of hypersensitivity, including angioedema and urticaria, and suicide attempt and suicidal ideation were reflected in the 4.8 section of the CAB PrEP SmPC.

Update clinical safety data from the on-going HPTN083 and HPTN084

The Applicant presented updated clinical safety data from the ongoing HPTN 083 and 084 studies, where the main findings are summarized and listed below. Of note, as the Applicant is not the Sponsor of the HPTN studies, and since the data cut-off of the CSRs, which were submitted as part of the MAA, only SAEs have been provided by the Sponsor. Unless otherwise specified, all initial SAEs hereby described were received in the GSK Global Safety Database from the respective CSR data cut-off dates of 14 May 2020 for HPTN 083, and 05 November 2020 for HPTN 084, up to 31 January 2023. Clinically relevant follow-up information for SAEs presented in the CSRs, and received up to 31 January 2023, were also presented where appropriate. The Sponsor has provided additional outputs from the open label extension (OLE) of the studies: cumulative pregnancies and pregnancy outcomes occurring in HPTN 084 and the HPTN 084 OLE (up to 21 February 2023), and adverse events leading to withdrawal for the HPTN 083 study only (from 14 May 2020 up to 22 November 2021). A similar listing has not been provided by the Sponsor for HPTN 084.

Overall, no new significant safety concerns were identified from the CAB PrEP updated safety data.

- Analysis of all new SAE

  During the reporting period of this Safety Update report, there were 409 new SAEs from both studies (259 in participants taking CAB and 150 in participants taking TDF/FTC) in 363 participants. This includes new SAEs, new serious AESI and those serious cases with a fatal outcome. SAEs were most frequently reported from the Infections and infestations SOC (36%), Psychiatric disorders SOC (12%) and Injury, poisoning and procedural complications SOC (12%). The frequency of SAEs mapping to other SOCs, not specified above, were <10% for either treatment. Individual SAEs across both treatments were mostly assessed as unrelated to study drug by the investigator.

- Deaths

  Since the respective data cut off dates for the CSRs for HPTN 083 and HPTN 084, 15 deaths have been reported (9 participants taking CAB and 6 taking TDF/FTC). None of the deaths were drug related by the investigator.

- New AEs leading to study discontinuation (only HPTN 083)

  There were no AEs of ISRs leading to study drug discontinuation. There were 56 AEs leading to study drug discontinuation (30 in the CAB group, 26 in the TDF/FTC group). These occurred in 49 participants (27 in the CAB group and 22 in the TDF/FTC group) with some participants experiencing more than one AE that led to study drug discontinuation. The most frequently reported AE was the PT ALT increased. During Step 2, the number of Grade 3 or 4 ALTs increased were 12 in the CAB group and 11 in the TDF/FTC group. All reports of ALT increased leading to discontinuation were assessed as unrelated to study drug by the investigators. Participants who experienced AEs related to study drug (*per* investigator assessment) which led to discontinuation of study drug were: 1) electrocardiogram QT prolonged (grade 3; onset date: 735 days); nausea (Grade 2; onset 712 days); hypersensitivity (grade 2; onset: 932 days)

2.5.9. Discussion on clinical safety

The safety profile of CAB PrEP is based on on-going Phase IIb/III CAB PrEP pivotal studies in cisgender men and transgender women ≥18 years who have sex with men (HTPN 083) and cisgender women aged 18-45 years (HTPN 084), who were HIV-negative and at high risk of acquiring HIV infection. When relevant, safety analysis also comprised data from supportive completed phase II studies (ÉCLAIR and HPTN 077) in men aged 18 to 65 years who were HIV-negative but were at low risk of acquiring HIV infection as well as data from the on-going MOCHA HIV treatment study in adolescents at least 12 years of age and weighing at least 35 kg, receiving CAB and in addition to cART (cohort 1C).

For pivotal HPTN 083 and HPTN 084 studies, the safety population consisted of 4570 and 3224 subjects, respectively, that were randomized to receive CAB and TDF/FTC placebo and TDF/FTC and CAB placebo. For both pivotal trials CAB PrEP dosage regimen was daily oral CAB (30 mg tablets) for up to 5 weeks followed by single 3 mL injection of 600 mg CAB LA 4 weeks apart for the first 2 doses followed by Q8W thereafter. The median duration of exposure was similar in both pivotal trials: 457 days for the CAB group and 471 days for the TDF/FTC group in HPTN 083 and of 452.5 days for both groups in HPTN 084. The overall exposure can be considered acceptable to establish a safety profile for CAB PrEP. Of note, however, <1% of participants have completed Step 2 due to the early termination of the blinded phase of both trials. In HPTN 083, few participants had reached Week 105 by the time of the data cut off. Similarly, in HPTN 084, the number of participants reaching the later weeks of each pivotal study were limited and only few participants had available data at the Week 153 visit. The Applicant clarified that at the time of data analysis, there were 475 participants exposed to CAB for at least 2 years in the HPTN 083 study, and 126 participants in the HPTN 084 study. The Applicant updated the clinical safety data from the on-going HPTN 083 and 084 pivotal studies (non-blinded phase). Overall results did not lead to any changes to the important identified and potential risks for CAB PrEP.

Updated data from the on-going MOCHA supportive study in HIV infected adolescents (an additional 22 participants were enrolled in Cohort 1C with a total of 29/30 completing Week 16), revealed no new safety concerns, or changed the conclusions previously presented in the interim CSR. Nevertheless, neuropsychiatric events among adolescent population deserve further discussion as mentioned below.

In respect of the adolescent target population for this indication and from a PK/PD perspective, it is acknowledged that the applicant followed an extrapolation approach that was agreed within a recent PIP procedure for both efficacy and safety that is based on the outcomes of a modelling and simulation study. The PopPK model was already considered as validated and demonstrating no effect of age on PK. Also, it concluded that the same Q8W dosing regimen, shown to be efficacious in adults, leads to comparable exposures in adolescents and adults. Although, adolescents with weights <50kg would result in higher exposures, this was similarly observed in adults in the same weight band. Moreover, although exposures were higher in the <50 kg group, the Cmax and Ctau values were inside the limits observed in all clinical studies as consider as safe and efficacious. As such, from the PK perspective, the two populations behave in a similar way. The Applicant proposes to further characterise safety in adolescents through routine pharmacovigilance in the post-authorisation environment setting and through longer term safety data derived from ongoing studies in HIV treatment (e.g., MOCHA) and in PrEP (HPTN 084-01 OLE). Moreover, the Applicant proposes a PASS category 3 (*CAB LA PrEP EU Cohort Study, to Assess Adherence and Effectiveness, and Monitor for Hepatotoxicity and Resistance*) in the RMP – which is a 5-year long prospective EU cohort study of individuals weighing ≥35 kgs, initiating CAB LA PrEP, in real world clinical setting.

Although no PK/PD relationship was defined for CAB, the fact that the therapeutic regime is resulting in concentrations within the same margins as observed previously, gives added reassurance in the extrapolation process. As mentioned, new data from adolescent subjects were presented for MOCHA and HPTN 084-01 (that are still ongoing) and for HPTN 083-01 (considered completed, 9 adolescents).

Based on data from two open-label multicenter clinical trials in 64 HIV-uninfected at-risk adolescents (below age 18 years of age and body weight ≥35 kg at enrolment) receiving CAB PrEP, no new safety issues were identified in adolescents compared with the safety profile established in adults receiving Apretude for HIV-1 PrEP in HPTN 083 and HPTN 084. Nevertheless, special attention should be provided to INSTI class effect of neuropsychiatric AEs, especially suicidal ideation/attempt which may be of concern in this more vulnerable population.

Adverse Events

The overall frequency and intensity of participants who reported at least 1 AE were similar in the CAB and TDF/FTC groups in Steps 1 and 2 OBSP for both pivotal studies. In HPTN 083, in the CAB group 95% participants reported at least 1 AE and the maximum intensity was Grade 2 and Grade 3 in most participants (60% and 22%, respectively), whereas in the TDF/FTC, 94% participants had at least 1 AE and the maximum intensity was Grade 2 in 59% and Grade 3 in 21% of participants. In HPTN 084, 96% participants reported at least 1 AE in the CAB group and the maximum intensity was Grade 2 and 3 in most participants (76% and 14%, respectively) whereas in TDF/FTC group, 96% participants had at least 1 AE and the maximum intensity was Grade 2 in 75% and Grade 3 in 15% of participants.

Common Adverse Events

In HPTN 083, the most frequently reported individual AE (PTs) in participants in both groups were creatinine renal clearance decreased (CAB group: 69%; TDF/FTC group: 73%) and injection site pain (CAB group: 75%; TDF/FTC group: 30%), whereas in HPTN 084, was creatinine renal clearance decreased (CAB group: 72%; TDF/FTC group: 74%).

Overall, the proportion of participants who reported events considered drug-related by the investigator was higher in the CAB group compared with the TDF/FTC group due to ISRs. The difference in drug-related AEs between the groups was lower in HPTN 084 compared to HPTN 083 (5% vs. 23%, respectively) because ISRs were reported less frequently in HPTN 084 compared to HPTN 083.

In HPTN 083, the drug-related AE PTs reported in ≥5% participants were injection site pain (1697 [74%] participants), creatinine renal clearance decreased (671 [29%]), injection site nodule (263 [12%]), injection site induration (255 [11%]), injection site swelling (204 [9%]), and blood creatinine increased (166 [7%]) in the CAB group and creatinine renal clearance decreased (723 [32%]), injection site pain (612 [27%]), blood creatinine increased (169 [7%]), nausea (125 [5%]), and diarrhoea (115 [5%]) in the TDF/FTC group. In HPTN 083, Grade 3 or higher drug-related AEs occurred in 6% (131) CAB participants and 4% (93) of TDF/FTC participants. The higher frequency of Grade 3 or higher drug-related AEs in the CAB group can mainly be attributed to ISRs. In HPTN 084, the drug-related AE PTs reported in ≥10% participants were creatinine renal clearance decreased (692 [43%] participants), injection site pain (519 [32%]), amylase increased (252 [16%]), blood creatinine increased (213 [13%]), headache (190 [12%]), and blood phosphorous decreased (169 [10%]) in the CAB group and creatinine renal clearance decreased (699 [43%]), amylase increased (264 [16%]), blood creatinine increased (202 [13%]), headache (213 [13%]), and blood phosphorous decreased (190 [12%]) in the TDF/FTC group. In HPTN 084, Grade 3 or higher drug-related AEs occurred 5% (86) CAB participants and 6% (99) of TDF/FTC participants.

Serious Adverse Events and Deaths

In HPTN 083, a total of 10 participants died (4 in the CAB group: gunshot wound, mechanical asphyxia, cardiopulmonary failure with possible methamphetamine as a possible risk factor and traumatic bleeding due to homicide). An additional death (stab wound in the TDF/FTC group) occurred in Step 3. In HPTN 084, there were 3 SAEs with fatal outcome reported (all in the CAB group; hypertensive heart disease, cerebrovascular accident, headache). An update safety report data revealed that since the respective data cut off dates for the CSRs for HPTN 083 and HPTN 084, 15 deaths have been reported (9 participants taking CAB and 6 taking TDF/FTC). None of the deaths were drug related by the investigator. In the study HPTN 084, the additional headache fatal case, was discussed by the Applicant regarding the plausibility of relatedness for this AE. Based on the limited information provided it is agreed that a possible causal association with CAB exposure cannot be firmed.

SAEs reported as drug-related occurred with a frequency of <1% in both groups in both pivotal studies. In study HPTN 083, the proportion of participants with 1 or more study drug-related SAEs was comparable between the 2 groups. In the CAB group, 5 drug-related SAEs occurred in 4 (<1%) participants (PTs: 2 suicide attempts, 1 affective disorder, 1 seizure, and 1 immune thrombocytopenia). In the TDF/FTC group, 4 drug-related SAEs occurred in 3 (<1%) participants (PTs: 1 suicide attempt, 1 ALT increased, 2 cardiac disorder). Regarding the SAE of immune thrombocytopenia in the HPTN 083 study, the Applicant was requested to describe clear timeline regarding platelet count (until final recovery), CAB administration and treatment with steroids, but also regarding the presence of CAB during PK tail and relative platelet count after CAB discontinuation. The narrative of subject developing immune thrombocytopenia reports low platelet count at baseline, persistence of the event even after stopping CAB and concomitant medication (ketorolac). Thus, it is agreed that relatedness with CAB cannot be established. However, attention should be paid for any possible future case of thrombocytopenia with CAB exposure, considering also that thrombocytopenia was observed post-marketing with some other INSTI.

In HPTN 084, two events (PTs) of suicide attempts and 1 SAE of PT affective disorder occurred in the CAB group. One suicide attempt occurred in the TDF/FTC group. One PT of seizure, considered serious and related occurred during the study in the CAB group and none in the TDF/FTC group. One event (PT) of immune thrombocytopenia considered drug-related occurred in the CAB group and 1 event (PT) of alanine aminotransferase increased considered drug related occurred in the TDF/FTC group.

In study HPTN 084, a total of 5 OBSP drug-related SAEs occurred in 1 (<1%) CAB participant (1 PT: respiratory tract infection) and 3 (<1%) TDF/FTC participants (4 PTs: AST increased, ALT increased, hepatotoxicity, and seizure).

In the study HPTN 077, the case of impaired sensation in left upper limb, considered related to CAB by the investigator but not by the Applicant, was discussed regarding the plausibility of relatedness for this AE. Based on provided narrative showing sensory disturbances in a subject between 20 and 30 years of age during CAB exposure and with no definitive diagnosis, there are not enough elements to establish AE causality with CAB.

Adverse Events Leading to Discontinuation

In HPTN 083, AEs leading to study drug discontinuation were low and higher in the CAB group (6%) compared to the TDF/FTC group (4%), which was mainly due to ISRs. In HPTN 084, AEs leading to discontinuation of study drug were low and similar in both groups (reported in 1% participants in each group). In HPTN 083, it is noteworthy that out of 135 participants in CAB group with at least one AE leading to discontinuation of study drug, 45 and 29 were due to ALT increased and to AST increased, respectively. These were the most frequent reported AE leading to discontinuation in HPTN 083. In HPTN 084, ALT was the most reported AE leading to discontinuation in CAB group (12 out 17 participants that discontinued CAB). Moreover, in both pivotal trials ALT increased were seen as drug-related Grade 3-4 events that led to discontinuation and therefore are clinically relevant. Transaminase increased are included in the SmPC (frequency common).

Adverse Events of Special Interest

- ISRs – As expected ISRs are considered an AE of special interest to CAB PrEP. Overall, CAB injections were generally well tolerated and the overall trend of ISR incidence and intensity decreased over time. ISRs were generally mild (Grade 1 to Grade 2), of short duration, and resulted in few study drug discontinuations. However, the difference of ISRs drug-related between pivotal studies (81% in CAB group of HPTN 083 *vs* 38% in CAB group of HPTN 084) was observed. The Applicant provided a multifactorial reasoning (e.g. number of safety visits in the Step 2 injection phase, prevalence exposure of IM or SC contraceptives in HPTN084) to explain the difference of reported ISRs by gender at birth which is acceptable. The Applicant also provided description of ISR event not resolved or resolved with sequelae for both HPTN 083 and HPTN 084 studies that accounted for <0.2% in each study. Most cases were injection pain or injection swelling of Grade 1 and 2 in severity; in most of the cases cabotegravir injections were not discontinued. CAB injections must be administered to the ventrogluteal (the recommended) or dorsogluteal sites. The Applicant was asked to specify, if available, relative frequencies of administration modes and to describe ISR incidence by site. This issue is not further pursued given no data on frequencies or ISR rate by administration site (ventrogluteal *vs* dorsogluteal) are available as this variable was not foreseen by the protocol.
- Pyrexia - In HPTN 083, there was a higher frequency of pyrexia with CAB compared to those in the TDF/FTC group. Pyrexia has been shown to occur more frequently following IM injections with the majority of events occurring within 7 days of injection. In HPTN 084, the frequency of pyrexia was low and similar in both the CAB and TDF/FTC group in this study. In HPTN 084, a temporal association has not been established between Pyrexia Plus events with ISRs or Pyrexia Plus events (influenza like illness, chills, feeling hot, body temperature increased and feeling of body temperature change) with injection visits. Pyrexia is known to occur following CAB injections in the Treatment program in HIV-infected participants.

- Myalgia - The frequency of myalgia in the CAB PrEP pivotal studies was similar to the observed frequency in the CAB Treatment. Overall, less than 2% participants across the groups of both pivotal studies experienced drug-related AE of myalgia. In HPTN 083, the majority of the drug-related events in the CAB group occurred on the same day or shortly after AEs of injection site pain.
- Hepatoxicity: The frequency of Hepatotoxicity AESIs in HPTN 083 and HPTN 084 was similar to what was observed in the CAB HIV Treatment studies (CAB Treatment pooled ATLAS/FLAIR safety analysis). When liver related study product discontinuations were assessed by the HHAC, similar numbers of these events were assessed as probable or possible DILI in both groups.
- Hypersensitivity reactions: No cases of delayed or immediate type hypersensitivity causally associated with CAB were identified in the CAB PrEP program. The frequency of Hypersensitivity AESI was similar across the CAB and TDF/FTC groups in both pivotal studies. For Hypersensitivity AESI, no SAEs no AE led to discontinuation were reported. As requested, the Applicant has proposed to add a warning in 4.4. of CAB PrEP SmPC considering that HSR is a class-adverse reaction, which is endorsed. Hypersensitivity, urticaria and angioedema were tabled as an ADR in 4.8 section of the SmPC of CAB PrEP. In addition, the Applicant clarified that from the data available, the use of the oral lead in was not a predictor of the occurrence of HSR events occurring in Step 2 in either of the pivotal studies. Conversely, HSR AESI events occurring while on CAB LA in Step 2 were not contingent on the occurrence of an HSR event occurring in Step 1 OBSP.
- Rash: Rash AESIs, typically of Grade 1 and Grade 2 intensity were observed. Overall, of the reported AEs analyzed as Rash AESIs in CAB PrEP were consistent with those considered as ADRs for CAB Treatment. Overall, the proportion of participants with 1 or more rash and other potentially associated AEs (Rash AESI) was similar between groups and pivotal studies (4%). Unlike HPTN 084, study drug discontinuations due to Rash and drug interruptions occurred in HPTN 083, but these were infrequent cases.
- Hyperglycemia and Diabetes: In both pivotal CAB PrEP studies, the AE of blood glucose increased was reported in a higher proportion of participants in the CAB group than in the TDF/FTC group; however, corresponding lab values do not suggest a trend for hyperglycemia. Furthermore, AE reporting of other relevant terms do not suggest a trend for hyperglycaemia or diabetes.
- Weight gain: In both pivotal trials the proportion of participants who experienced 1 or more AEs of weight gain and other potentially associated AEs (Weight Gain AESI) was low and comparable between groups (<1% participants in each group). Weight gain is tabled in 4.8 of CAB PrEP SmPC with an ADR frequency of uncommon.
- Neuropsychiatric events: The Applicant presented a comprehensive review of neuropsychiatric AESI. It is agreed that based on the overall similarity of frequency of SAEs, study drug discontinuations and study drug-related cases between the CAB and TDF/FTC groups in both pivotal studies, CAB is considered to have in general a tolerable neuropsychiatric safety profile when used in these study populations for PrEP. The Applicant acknowledged the request regarding the inclusion of 'suicide attempt' and 'suicidal ideation', to the proposed CAB PrEP SmPC.

  The Applicant also agreed that the reason to exclude 'Anxiety AESI' for the CAB PrEP program based on the fact that '*the time to onset for Anxiety AESI did not suggest a compelling temporal relationship with CAB administration'* was disputable. Therefore, the Applicant included 'Anxiety' in 4.8 of the SmPC as it is tabled for CAB treatment. Moreover, the Applicant

acknowledged the rationale for requesting the inclusion of somnolence in the section 4.8 of the SmPC. Consequently, corresponding updates have been made to Section 4.7 'Effects on ability to drive and use machines' of the SmPC, with inclusion of somnolence, dizziness and fatigue as ADRs observed with CAB PrEP to this section.

From the pivotal studies HPTN 083 and 084 and the supportive studies for participants who developed neuropsychiatric AEs, the Applicant reviewed the time to onset of these AEs and the time to onset since the last CAB LA injection. CAB LA reaches T-max at 7 days. The time to onset since the start of CAB and since CAB LA is variable, and a temporal relationship was not observed at the time of peak plasma CAB concentrations and the occurrence of the Neuropsychiatric AEs observed.

The applicant has provided a Table of all psychiatric disorder SOCs stratified by age groups (< and ≥ 25 years of age). Overall, in HPTN 083, in those <25 years of age, the majority of AEs from the psychiatric disorders SOC were Grade 1-2, and a higher proportion occurred in age group 22-24 years of age (which was also observed in the TDF/FTC arm). In HPTN 084, there were considerably less participants reporting AEs from the psychiatric disorders SOC. Even though, in those <25 years of age the majority of AEs from the psychiatric disorders SOC were Grade 1-2 and a higher proportion of these occurred in age group 22-24 years of age. This was also observed in the TDF/FTC arm. Nevertheless, with new data on adolescents exposed to CAB [MOCHA and HPTN 084-01 (that are still ongoing) and for HPTN 083-01 (considered completed, 9 adolescents)], the Applicant was requested to discuss the rate of some psychiatric AEs (in particular, suicidal ideation/attempt) with respect to adult subjects. Overall, no new safety issues were identified in adolescents compared with the safety profile established in adults receiving Apretude for HIV-1 PrEP in HPTN 083 and HPTN 084.

For neuropsychiatric events of special interest, the Applicant provided an additional analysis concerning participants' body weight classes: <50 kg and ≥ 50 Kg. In HPTN 083-01, none out of the 9 participants that experienced neuropsychiatric AESIs had a body weight <50 kg whereas in HPTN 084-01, none of the 15 participants with body weight <50 kg experienced any of these events. The Applicant presented the narratives describing SAEs of suicidal ideation and suicide attempt in the adolescent sub-studies. The causal assessment performed by the Applicant is agreed. Although it is acknowledged that a potential contribution of CAB cannot be completely excluded in the narratives of the cases provided, the events were reported as resolved, and CAB was not discontinued in all these cases. Based on the limited sample size as well as other limitations, the existent frequency proposed in the section of 4.8 of the SmPC should be maintained and no differences at this stage should be defined for adolescents. However, the adolescent population at-risk for HIV infection is a particular vulnerable sub-set with elevated background rate of neuropsychiatric events (and in particular, young LGBT are at particular risk for suicidal ideation and suicide attempt) (Pettifor et al, 2018; Shanaube K et al, 2022; D'Augelli AR et al, 2001; Donenberg GR et al, 2001; Marshal MP et al , 2011). Therefore, although clinical studies did not show an increased incidence of psychiatric illness in adolescents in respect to adult subjects, particularly in case of pre-existing of psychiatric illness, a warning in section 4.4 of the SmPC was included to invite the prescribing physician to accurately counsel the adolescents before the prescription and during the treatment.

Creatinine renal clearance decreased PT and blood creatinine increased PT were reported frequently in similar proportions in both groups in HPTN 083 and HPTN 084. However, the objective laboratory values for creatinine clearance and creatinine reported during these studies do not reveal clinically relevant trends. This conclusion is supported by the findings from the CAB Treatment program that there is no clinically relevant effect of CAB on creatinine or creatinine clearance of HIV-infected participants.

Laboratory Assessments

The incidence and severity of clinical chemistry abnormalities is comparable between treatment groups. However, differences of Grade 1-2 liver function test abnormalities between HPTN 083 and HPTN 084 (more than twice the proportion among MSM and transgender women as compared to cisgender women) were found. The applicant presented a possible justification to explain the differences concerning the Grade 1-2 maximum post-baseline LFT abnormalities which might be related to the differences in the respective study populations at baseline, rather than any differential response to CAB during the studies. The Applicant reviewed the participants' medical histories in pivotal studies at baseline which showed that 303 participants in HPTN 083 versus 86 participants in HPTN 084 had a known medical history of elevated liver chemistries (ALT, AST, ALP or bilirubin) prior to starting CAB. Once on study, there were no clinically significant differences between the studies in the median change from baseline for any LFT parameters in the CAB groups at approximately 1 year.

The Applicant acknowledged that bilirubin is considered an ADR in the SmPC for CAB PrEP and section 4.8 of the SmPC was changed accordingly. In what concerns to lipase elevations, the analysis provided by the Applicant is endorsed. The frequencies of the reported events of increased lipase across both study arms and between trials in the CAB PrEP pivotal studies were similar. All events were non-serious, the majority were Grade 1 to 3 in severity, and resolved without interruption or discontinuation of study drug. Moreover, it is acknowledged that lipase elevations are common in people living with HIV and that increased lipase is a recognized ADR with rilpivirine.

Regarding 'Transaminase increased' it was proposed as an ADR for inclusion in Section 4.8 of the CAB PrEP SmPC under the Hepatobiliary Disorders SOC at the time of submission of the MAA, this was amended for inclusion under the Investigations SOC. This ADR has been proposed at a frequency of 'very common' based on reporting rates in the CAB PrEP clinical trial programme from the pivotal trials HPTN 083 and HPTN 084 and supportive studies ÉCLAIR and HPTN 077.

In general, it is envisaged that the Applicant would like to compare CAB PrEP to TDF/FTC for PrEP label, including for hepatic monitoring. However, currently, there is a major difference that needs to be considered. Unlike TDF/FTC, hepatoxicity is considered an important identified risk (safety concerns) for both CAB treatment and CAB PrEP. Given the data available, the Applicant changed the wording in section 4.4 of the SmPC to recommend clinical and laboratory monitoring and to discontinue Apretude in case of confirmed hepatoxicity. This will better inform prescribers about hepatic monitoring in subjects taking PrEP which is of relevance, since the applicability of hepatic monitoring might differ between people living with HIV and in subjects taking PrEP.

Special Populations

No specific analysis of CAB PrEP tolerability in participants with hepatic or renal impairment was performed given the enrolment criteria of the HPTN 083 and HPTN 084 trials. Dose adjustments were based in Phase I data and are reflected in the SmPC. Moreover, no firm conclusions regarding the safety of CAB PrEP in patients co-infected with HBV and/or HCV can be drawn. This has also been adequately reflected in the proposed SmPC.

The observed safety data reported for adolescent participants within MOCHA did not identify any new safety concerns relative to adult data and no new safety signals were identified based on the data provided. The data from the popPK model and the data retrieved MOCHA do not suggest a different overall safety profile for CAB in adolescents (>=35 kg) relative to adults with HIV infection. In alignment and in addition to MOCHA safety results presented in the SmPC, the Applicant proposed to add information concerning HPTN 083-01 and HPTN 084-01 study results in the section 4.8 of the

SmPC, which is agreed. Overall, no new safety issues were identified in adolescents compared with the safety profile established in adults receiving Apretude for HIV-1 PrEP in HPTN 083 and HPTN 084.

The safety of CAB PrEP during human pregnancy and breastfeeding has not been established. Use in pregnancy is stated as missing information. Following the same rationale, the Applicant added 'use in breastfeeding' as missing information in the safety concerns.

Considering pregnancy, the Applicant provided a single table with overall 358 confirmed CAB-exposed pregnancies and their outcomes (if available) from the study HPTN 084 (i) and its open-label extension phase (ii) that after amendments permitted CAB administration during pregnancy. Moreover, the data from Antiviral Pregnancy registry (iii) on 10 CAB exposure pregnancies in HIV-infected women were provided, with additional two pregnancies reported to EPPICC database, iv) the cumulative pregnancy data from the CAB+RPV Phase 2/3/3b trials for HIV-1 treatment were presented: 43 confirmed pregnancies have been reported with no reports of congenital anomalies or adverse outcomes reported from those pregnancies that have reached full term.

From the presented HPTN 084 + OLE data, observed rates of Stillbirth/Intrauterine Foetal Demise (>= 20 weeks) and of Spontaneous Abortion (<20 weeks) were respectively 1.6-4.3% and 12.9-15.2% in CAB-exposed pregnancies. Although rates may reflect the trial setting, a difference is noted in respect to TDF/FTC only Arm (0.0% and 2.4%, respectively). Further, 3 cases of congenital anomalies in the women exposed to CAB PrEP were reported (1 CAB blinded Arm and 2 OLE). While the narratives for 2 of them were initially provided (one with multiple congenital anomalies and omphalocele and other SGA with hypospadias), the Applicant was requested to provide as well data on missing case and to discuss on the uncertainties of INSTI exposure on foetal outcomes. The Applicant stated that 3 cases of congenital abnormalities were reported from participants exposed to CAB on the HPTN 084/OLE study – two cases were previously presented and a recent case of polydactyly which was later described. Regarding the missing congenital anomaly case previously identified, the Applicant was informed by the HPTN 084 Sponsor, that a duplicate report was included in the number of congenital anomalies presented. While 3 cases of congenital anomalies occurring in participants receiving CAB were presented in the tabulations, there were only 2 congenital anomalies (one congenital anomaly was reported twice in error, once for the mother and once for the neonate). Regarding uncertainties of INSTI exposure on foetal outcomes, the Applicant summarized cumulative data from the following studies a) Antiretroviral Pregnancy Registry (DTG) (Data through January 2023), b) Eswatini Surveillance Study (Sept 2021-Sept 2022 update) and c) Tsepamo study. None of these databases confirmed or refuted the neural tube development (NTD) signal. Additionally, the Applicant stated that reviewed the available data from the APR, GSK's Safety database, and the literature during the period, and has not identified other concerns relating to the use of DTG at conception or during pregnancy.

The Applicant stated that no safety findings have been identified from the limited pregnancy outcomes data in humans and from pre-clinical reproductive toxicity studies at therapeutic doses. According to Applicant, there are currently no safety findings or efficacy concerns which justify making contraception a condition of use in the real-world PrEP population. It is anticipated that participants will be effectively counselled on the use of contraception as part of the benefit/risk discussions between HCP/prescriber and CAB PrEP user. Currently CAB PrEP is not recommended during pregnancy unless the expected benefit justifies the potential risk for the foetus, as stated in the SmPC.

Considering the new data on a relevant number of CAB-exposed pregnancies provided with the responses, the Applicant was requested to clarify how many of these have actually received CAB injections during pregnancy, duration of exposure and maternal and foetal outcomes. The Applicant presented a summary of CAB-exposed pregnancies from HPTN 084 and OLE. In total (data lock point 23rd May 2023), there were 314 confirmed pregnancies on CAB, 218 where the participant received

CAB LA during their pregnancy and 96 where the participant had received CAB LA within a year of the estimated pregnancy start date but not during their pregnancy.

In light of the prolonged release characteristics of CAB PrEP, HCP should discuss the benefit/risk of CAB PrEP with women of childbearing potential. As requested, the Applicant added the following statements to the SmPC/package leaflet: a) to Section 4.4. Long-acting properties of Apretude injections: “Healthcare providers should discuss the benefit-risk of using Apretude with individuals of childbearing potential or during pregnancy (see section 4.6).”; b) to section 4.6: Women of childbearing potential: Women of childbearing potential should be counselled about prolonged release characteristics of Apretude injection. If a woman plans a pregnancy, the benefits and the risks of starting/continuing pre-exposure prophylaxis with cabotegravir should be discussed (see section 4.4).” The package leaflet (PL) is amended accordingly.

Medication Errors

Medication errors occurred in both pivotal trials, being more pronounced in HPTN 084. The Applicant was requested to characterize medication errors in both trials. In HPTN 084, medication errors occurred in 73 participants. Of these, 56 participants were traced to a single site due to a systematic error in the volume of CAB LA/placebo dispensed (these participants received 80% of the protocol-prescribed dose). For these 56 participants, the occurrences of underdosing ranged from a single episode up to 4 episodes per participant. There were no events of HIV-seroconversion or lack of efficacy reported at the time of the HPTN 084 submission for those participants who experienced underdosing at this site. Of the 17 remaining participants who experienced medication errors in HPTN 084, 5 participants were on CAB LA and 12 participants were on the TDF/FTC arm. No AEs indicative of HIV seroconversions and or lack of efficacy were reported by any participant who experienced these medication errors. The Applicant agreed to review medication errors as part of ongoing routine pharmacovigilance and will present interval updates in future PSUR/PBRERs. Nevertheless, even though CAB PrEP exposure in real-world setting is low, there were medication errors reported to spontaneous reporting system, albeit no cases of seroconversion or resistance were reported as a consequence of these reported medication errors. Additionally, from the existent PrEP post-marketing data other situations/cases classified as ‘off-label use’ by the Applicant were reported, *e.g.* HCP intentionally injecting the individual at another injection site, individuals were self-injecting CAB PrEP into their arm, CAB PrEP dosing at unapproved intervals or outside of the target window, etc. Also, in what concerns to adherence, cases were reported where individuals missed their injection appointment in routine clinical practice. All in all, - “Medication errors, including treatment non-compliance” were considered as an important potential risk in the safety concerns of RMP for CAB PrEP.

Post-marketing experience

The Applicant has provided an update of all post-marketing data related to CAB PrEP/Apretude since the initial approval (20 December 2021) up to 6 March 2023. A total of 216 cases were retrieved from the GSK safety database, of those 21 (10%) met the criteria for a SAE report. The safety profile reported is consistent with the established profile that has been seen in the clinical studies for both CAB PrEP. Identified risks of hypersensitivity, including angioedema and urticaria, and suicide attempt and suicidal ideation were reflected in the 4.8 section of the SmPC.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

The available data from Phase II and Phase IIb/III CAB PrEP, as well as supportive data from the Study MOCHA HIV treatment study in adolescents at least 12 years of age and weighing at least 35 kg, suggest that CAB PrEP is generally well tolerated in both adults and adolescents. This was overall reassured by the updated clinical safety data from the on-going HPTN083 and HPTN084 (non-blinded phase), updated MOCHA safety database as well as available post-marketing experience.

CAB PrEP was well-tolerated with a safety profile comparable to the active comparator daily oral TDF/FTC in the pivotal studies, excluding the incidence of ISRs, which occurred more frequently in CAB participants. Overall, no clinically significant new safety issues have been identified in participants for CAB PrEP from the pivotal studies HPTN 083 and HPTN 084 relative to the findings from approved CAB treatment.

2.6. Risk Management Plan

2.6.1. 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

2.6.2. Pharmacovigilance plan

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				

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
None				
Category 3- Required additional pharmacovigilance activities				
CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance Planned	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	Draft protocol submission	3 months after marketing authorisation.
			Estimated Study start	EMA/PRAC approval of protocol and CAB LA being commercially available
			Final report	To be defined after EMA/PRAC approval of protocol
The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy Planned	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	Use in pregnancy	Draft protocol Submission	3 months after marketing authorisation
			Estimated Study start	EMA/PRAC approval of protocol and CAB LA being commercially available
			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
			Regular updates	A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	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.			presented in the CAB PrEP PSUR/PBRER

2.6.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation 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

Safety concern	Risk minimization measures	Pharmacovigilance activities
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 Additional risk minimization measures CAB PrEP Educational materials (including prescribers 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
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. 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 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 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)

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the new indication of pre-exposure prophylaxis, the PRAC is of the opinion that a separate entry in the EURD list for Apretude is needed, as it cannot follow the already existing entry for cabotegravir. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 18.03.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vocabria. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

- On the basis of article 63.3 of Dir 2001/83 (use by a HCP only) the applicant claimed that the very limited space of the vial label does not allow the printing of the long pharmaceutical form in a legible way.

After thorough assessment the QRD group granted an exemption to omit the pharmaceutical form from the vial label, provided that it appears on the outer package and that it will be used by HCPs only.

Moreover, the applicant's request to omit the statement on lactose from the bottle label of the film-coated tablets was not accepted. The QRD group considered that there is enough space to add "contains lactose" on the EN label, and even more on the trilingual version submitted. The particulars to be omitted as per the QRD Group decision described above will, however, be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Apretude (cabotegravir) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The therapeutic indication for this application after CHMP discussion and applicant's agreement is:

Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

The HIV pandemic remains a public health emergency with an estimated annual 1.5 million incident infections worldwide in 2020 [UNAIDS, 2021a]. Although the annual number of infections has been decreasing on a global scale with a 30% decline since 2010, new infections continue to occur despite advances in the development of ART for HIV treatment and data demonstrating that individuals on stable ART with undetectable HIV-1 viral load do not transmit virus to uninfected partners [Cohen, 2016; UNAIDS, 2021b]. Of the 37 377 new HIV diagnoses in US made in 2018, 7734 diagnoses (21%) occurred in adolescents and young adults aged 12 to 24 years; of these, 1707 diagnoses (22%) occurred in adolescents aged 13 to 19 years *(JAMA Pediatrics May 11, 2020).*

HIV can be transmitted via the exchange of a variety of body fluids from infected people, such as blood, breast milk, semen and vaginal secretions. HIV can also be transmitted from a mother to her child during pregnancy, delivery and breastfeeding.

The intended benefit of PrEP is the prevention of HIV infection.

3.1.2. Available therapies and unmet medical need

PrEP is a key component of the overall strategy to reduce the number of new HIV infections worldwide, not being available in all countries.

The current standard of care for HIV PrEP in the EU includes the tenofovir-based, fixed dose antiretroviral combination regimen, TDF/FTC, to be orally administered daily.

However, the use of daily oral tenofovir-based PrEP regimens for PrEP has limitations. Oral PrEP efficacy requires adherence to daily dosing regimen.

Clinical trials have demonstrated that oral PrEP efficacy is strongly correlated with adherence in key population groups including:

- MSM and TGW: Of the 22 HIV infections in the DISCOVER study, 5 were likely infected at study entry; excluding these 5 participants, 15 out of 17 (88%) had low (i.e., taking <2 doses/week) or undetectable tenofovir diphosphate concentrations in dried blood spots on the day of HIV diagnosis [Mayer, 2020]. In the iPrEX study, low drug exposure was associated with the majority of incident HIV infections; of the 34 participants with incident HIV infection in the TDF/FTC group, at least 1 study drug component was detected in any plasma or cell specimen from 3 participants [Grant, 2010].
- Cisgender women: The FEM-PrEP study was stopped early due to lack of efficacy attributable to low drug adherence; less than 40% of the HIV-uninfected women in the TDF/FTC group had evidence of recent pill use at visits that were matched to the HIV-infection window for women with seroconversion [Van Damme, 2012]. Similarly, all tenofovir-based regimens assessed in the VOICE trial failed to significantly reduce the risk of HIV acquisition, and the lack of efficacy was associated with low adherence as assessed by measurement of tenofovir levels in plasma [Marrazzo, 2015].

Alternatives to daily oral PrEP

Apart from daily oral TDF/FTC the following PrEP regimens have been studied or approved:

- Individuals who are not at ongoing risk for HIV infection can consider using “on demand” (also known as “intermittent,” “non-daily,” or “event-driven”) PrEP, not approved in the EU.

The dapivirine vaginal ring may provide a long-acting option for HIV-uninfected women for PrEP to reduce the risk of HIV-1 infection via vaginal intercourse in combination with safer sex practices when oral PrEP is not used, cannot be used, or is not available. The dapivirine vaginal ring 25 mg was assessed by the EMA as part of its coordinated efforts with the WHO to evaluate medicines not intended for use in the EU and was provided with a positive opinion on 23 July 2020. Two clinical studies, The Ring Study and ASPIRE, demonstrated a 27-31% risk reduction of HIV acquisition among women who used the dapivirine ring [Nel, 2016; Baeten, 2016]. Both clinical studies were followed by open-label extension studies, DREAM and HOPE, which illustrated an increase in use of the vaginal ring and a slightly higher risk reduction of approximately 50% (39% - 62%) [Nel, 2021; Baeten, 2021]. As a result, the WHO updated its clinical guidelines to include a conditional recommendation that the dapivirine vaginal ring can be offered as an additional prevention choice for women as a part of combination prevention strategy [WHO, 2021]. Although the prolonged drug exposure associated with

an every month dosing regimen may improve adherence, some of the associated risks of the inserted vaginal ring – including urinary tract infection, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain – may impose some limitations on acceptability. In addition, this PrEP regimen is only an option for women.

3.1.3. Main clinical studies

Study 201738/HTPN 083

Title: A Phase IIb/III Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who have Sex with Men

Study 201739 / HPTN 084

Title: A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV Uninfected Women

The main difference between two pivotal studies above is the population included MSM and TGW in HTPN 083 and women in HTPN 084. HTPN083 is a non-inferiority study and HTPN 084 is a superiority study. Both use as comparator TDF/FTC.

Both studies include the main population that could benefit from this therapy directly compared with the actual approved therapy for PrEP in the EU.

3.2. Favourable effects

For HPTN 083, results of the primary efficacy endpoint analyses demonstrated that in the PrEP regimen containing every 2 months injections of CAB LA a total of 13 incident infections were identified, for an incidence of 0.40/100 PY, and 39 in the TDF/FTC group, for an incidence of 1.22/100 PY. Comparing the incidence across the groups yields of bias adjusted HR of 0.340 (adjusted 95% CI: 0.18 to 0.62), demonstrating a 66.0% reduction in incident HIV infections for participants randomized to receive CAB, relative to participants randomized to receive TDF/FTC, in this population of MSM and TGW.

If only non-inferiority but not superiority had been concluded, the efficacy demonstration of cabotegravir could have been challenged due to the difficulties to determine an appropriate non-inferiority margin (variable outcome in the previous TDF/FTC studies). In these studies, the absolute efficacy of PrEP has been a function of the level of risk in the treated population and of the adherence to prophylaxis. Thus, assay sensitivity could not have been ascertained. Of note, defining an appropriate NI-margin was raised as a major concern by the SAWP/CHMP in Scientific advice (EMEA/H/SA/2517/2/FU/1/2015/III).

For HPTN 084, results of the primary efficacy endpoint analyses demonstrated that the PrEP regimen of every 2 months injections of CAB LA was superior ($p<0.0001$) to the daily oral regimen of TDF/FTC in preventing acquisition of HIV-1 infection based on the rate of incident HIV-1 infections in Steps 1 and 2. Comparing the incidence between the groups yields an HR of 0.11 (95% CI 0.04 to 0.31, p-value <0.0001) (HR of 0.12 when bias-adjusted for early stopping at second interim analysis) demonstrating an 88% reduction in incident HIV-1 infections for participants randomized to receive CAB, relative to participants randomized to receive TDF/FTC, in this population of cisgender women.

3.3. Uncertainties and limitations about favourable effects

Regarding the adolescent population, the extrapolation exercise for efficacy may be considered adequate based on PK modelling even if further efficacy data would be of value. The Applicant specified that no efficacy outcomes are foreseen for the adolescent sub-studies of Study HPTN 084-1 and HPTN 083-1. Nonetheless, data on seroconversions are available and none of the participants developed HIV infection.

Of note no data is available on subjects above 75 years old; less than 1% of subjects in HTPN 083 study where between 65 and 74 years old. No subjects above 35 years were included in HTPN 084.

3.4. Unfavourable effects

Injection Site Reactions are higher on the CAB arm of both pivotal studies, as expected, and in some cases led to product discontinuation (injection site pain, swelling, induration). As expected ISRs are considered an AE of special interest to CAB PrEP. Overall, CAB injections were generally well tolerated and the overall trend of ISR incidence and intensity decreased over time. ISRs were generally mild (Grade 1 to Grade 2), of short duration, and resulted in few study drug discontinuations. However, the difference of ISRs drug-related between pivotal studies (81% in CAB group of HPTN 083 *vs* 38% in CAB group of HPTN 084) was observed. The Applicant provided a multifactorial reasoning (e.g. number of safety visits in the Step 2 injection phase, prevalence exposure of IM or SC contraceptives in HPTN084) to explain the difference of reported ISRs by gender at birth which is acceptable. The Applicant also provided description of ISR event not resolved or resolved with sequelae for both HPTN 083 and HPTN 084 studies that accounted for <0.2% in each study. Most cases were injection pain or injection swelling of Grade 1 and 2 in severity; in most of the cases cabotegravir injections were not discontinued. CAB injections must be administered to the ventrogluteal (the recommended) or dorsogluteal sites. The Applicant was asked to specify, if available, relative frequencies of administration modes and to describe ISR incidence by site. This issue is not further pursued given no data on frequencies or ISR rate by administration site (ventrogluteal *vs* dorsogluteal) are available as this variable was not foreseen by the protocol.

Neuropsychiatric events, namely suicide attempts, suicidal ideation, anxiety, somnolence, were more frequent in both studies in the CAB arm; although there were confounding factors as stated by the applicant, these events are already present in the SmPC of cabotegravir treatment and need to be more detailed, mainly because the subjects intended to benefit from this intervention could have sometimes underlying baseline risk factors. Moreover, given the neuropsychological functioning in adolescents, the relevance of known neuropsychiatric AEs in the context of prophylactic use of CAB for adolescent population is unknown.

The Applicant presented a comprehensive review of neuropsychiatric AESI. It is agreed that based on the overall similarity of frequency of SAEs, study drug discontinuations and study drug-related cases between the CAB and TDF/FTC groups in both pivotal studies, CAB is considered to have in general a tolerable neuropsychiatric safety profile when used in these study populations for PrEP. From the pivotal studies HPTN 083 and 084 and the supportive studies for participants who developed neuropsychiatric AEs, the Applicant reviewed the time to onset of these AEs and the time to onset since the last CAB LA injection. CAB LA reaches T-max at 7 days. The time to onset since the start of CAB and since CAB LA is variable, and a temporal relationship was not observed at the time of peak plasma CAB concentrations and the occurrence of the Neuropsychiatric AEs observed. Overall, in HPTN 083, in those <25 years of age, the majority of AEs from the psychiatric disorders SOC were Grade 1-2, and a higher proportion occurred in age group 22-24 years of age (which was also observed in the TDF/FTC arm). In HPTN 084, there were considerably less participants reporting AEs from the

psychiatric disorders SOC. Even though, in those <25 years of age the majority of AEs from the psychiatric disorders SOC were Grade 1-2 and a higher proportion of these occurred in age group 22-24 years of age. This was also observed in the TDF/FTC arm. Nevertheless, with new data on adolescents exposed to CAB [MOCHA and HPTN 084-01 (that are still ongoing) and for HPTN 083-01 (considered completed, 9 adolescents)], there is a concern of potentially higher rate of some psychiatric AEs (in particular, suicidal ideation/attempt) with respect to adult subjects; hence discussion with additional analysis was requested and provided. Although clinical studies did not show an increased incidence of psychiatric illness in adolescents in respect to adult subjects, a warning in section 4.4 of the SmPC was included to invite the prescribing physician to accurately counsel the adolescents before the prescription and during the treatment.

In regard to hepatotoxicity, the incidence and severity of clinical chemistry abnormalities is comparable between treatment groups. However, differences of Grade 1-2 liver function test abnormalities between HPTN 083 and HPTN 084 (more than twice the proportion among MSM and transgender women as compared to cisgender women) were found. Hence, the applicant was requested to explain this difference but failed to provide an adequate response. Although the Applicant states that across the groups, no clinically significant differences were observed for graded abnormalities for any of the following parameters: ALT, AST, bilirubin, or lipase, those parameters are albeit with frequency uncommon already in the SmPC of CAB treatment. The Applicant acknowledged that bilirubin is considered an ADR in the SmPC for CAB PrEP and the 4.8 section of the SmPC was changed accordingly. In what concerns to lipase elevations, the analysis provided by the Applicant is endorsed. The frequencies of the reported events of increased lipase across both study arms and between trials in the CAB PrEP pivotal studies were similar. All events were non-serious, the majority were Grade 1 to 3 in severity, and resolved without interruption or discontinuation of study drug. Moreover, it is acknowledged that lipase elevations are common in people living with HIV and that increased lipase is a recognized ADR with rilpivirine.

Regarding ‘Transaminase increase’ it was proposed as an ADR for inclusion in Section 4.8 of the CAB PrEP SmPC under the Hepatobiliary Disorders SOC at the time of submission of the MAA, this was amended for inclusion under the Investigations SOC. In contrast to CAB treatment, this ADR has been proposed at a frequency of ‘very common’ based on reporting rates in the CAB PrEP clinical trial programme from the pivotal trials HPTN 083 and HPTN 084 and supportive studies ÉCLAIR and HPTN 077.

Considering the new data on a relevant number of CAB-exposed pregnancies provided with the responses, the Applicant clarified how many of these have received CAB injections during pregnancy, duration of exposure and maternal and foetal outcomes. In total (data lock point 23rd May 2023), there were 314 confirmed pregnancies on CAB, 218 where the participant received CAB LA during their pregnancy and 96 where the participant had received CAB LA within a year of the estimated pregnancy start date but not during their pregnancy. There were only 2 congenital anomalies. Regarding uncertainties of INSTI exposure on foetal outcomes, the Applicant summarized cumulative data from different databases/registries and none confirmed or refuted the NTD signal.

3.5. Uncertainties and limitations about unfavourable effects

There are no major uncertainties based on the observed clinical safety profile. The Applicant has provided an update of all post-marketing data related to CAB PrEP/Apretude since the initial approval (20 December 2021) up to 6 March 2023. A total of 216 cases were retrieved from the GSK safety database, of those 21 (10%) met the criteria for a SAE report. The safety profile reported is consistent with the established profile that has been seen in the clinical studies for both CAB PrEP and CAB treatment and post-marketing experience with CAB treatment.

Identified risks of hypersensitivity, including angioedema and urticaria, and suicide attempt and suicidal ideation were reflected in the 4.8 section of the SmPC. The neuropsychiatric events seem more frequent in the cabotegravir arm of both studies. Although clinical studies did not show an increased incidence of psychiatric illness in adolescents in respect to adult subjects, caution is need when prescribing cabotegravir in this vulnerable population, particularly for pre-existing psychiatric illness, which is reflected in section 4.4 of the SmPC. At present, safety data for adolescent population as well as pregnant and breastfeeding women is limited.

3.6. Effects Table

Effects Table for Apretude indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
HIV infection	Number of documented incident HIV infections in Steps 1 and 2		Cabotegravir	TDF/FTC	A total of 13 incident infections were identified, for an incidence of 0.40/100 PY, and 39 in the TDF/FTC group, for an incidence of 1.22/100 PY. Comparing the incidence across the groups yields of bias adjusted HR of 0.340 (adjusted 95% CI: 0.18 to 0.62), demonstrating a 66.0% reduction in incident HIV infections for participants randomized to receive CAB, relative to participants randomized to receive TDF/FTC, in this population of MSM and TGW	1
HIV infection	Number of documented incident HIV infections in Steps 1 and 2		Cabotegravir	TDF/FTC	Comparing the incidence between the groups yields an HR of 0.11 (95% CI 0.04 to 0.31, p-value <0.0001) (HR of 0.12 when bias-adjusted for early stopping at second interim analysis) demonstrating an 88% reduction in incident HIV-1 infections for participants randomized to receive CAB, relative to participants randomized to receive TDF/FTC, in this population of cisgender women	2
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref
ISR	Injection Site reactions		Cabotegravir	TDF/FTC	81% patients in HTPN083 19% patients in HTPN084	1,2
Neuropsychiatric events	Suicide attempt Suicidal ideation Anxiety Somnolence		Cabotegravir	TDF/FTC	>10% HTPN 083 5% HTPN084	1,2
Hepatotoxicity	DILI		Cabotegravir	TDF/FTC	More detailed description needed	

Abbreviations:
ISR_Injection Site Reactions
TDF/FTC Emtricitabine/Tenofovir disoproxil
Notes:
1-Study 201738/HTPN083
2-Study 201739/HTPN084

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Studies HTPN083 and HTPN 084 were robust, double blind, using as comparator TDF/FTC (the actual approved therapy for PrEP in the EU) and included MSM and TGW (HTPN083) and cisgender women (HTPN084). In HTPN083 the non-inferiority and HTPN 084 the superiority against TDF/FTC was proven.

The safety of cabotegravir is overall favourable and consistent with the established profile that has been seen in the clinical studies for both CAB PrEP and CAB treatment and post-marketing experience with CAB treatment.

The ISR were more common, as expected, in the Cabotegravir arm of both studies and sometimes lead to product discontinuation. The unfavourable effects known to date namely neuropsychiatric events, seem more frequent in the cabotegravir arm of both studies. Although clinical studies did not show an increased incidence of psychiatric illness in adolescents in respect to adult subjects, caution is need when prescribing cabotegravir in this vulnerable population, particularly for pre-existing psychiatric illness.

According to the PDCO (EMEA-C-001418-PIP02-15-M03), the submitted PIP is in full compliance check with the measures included in the PIP in the view of the MAA for the prevention of HIV-1 indication in adults and adolescents 12 to <18 years of age and weighing >=35kg.

The SmPC and the PL have been revised to address these issues. In addition, post authorization measures have been proposed and added as part of the RMP (please see section 2.6)

3.7.2. Balance of benefits and risks

The benefit/risk balance of Apretude in the claimed indication is positive.

3.8. Conclusions

The overall benefit/risk balance of Apretude is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Apretude is favourable in the following indication(s):

Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

Prior to the launch of Apretude in a Member State, the 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 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 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 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).