15 October 2020
EMA/586324/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vocabria

International non-proprietary name: cabotegravir

Procedure No. EMEA/H/C/004976/0000

Note

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

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List of abbreviations

3TC lamivudine
AAG α1-acid glycoprotein
ABC abacavir sulfate
ADME Absorption, Distribution, Metabolism, Excretion
ADR adverse drug reaction
AE adverse event
ALAG1 Lag time (time between administration and measurable concentrations)
ALT Alanine aminotransferase
ANCOVA Analysis of covariance
ANOVA Analysis of variance
ART antiretroviral treatment
ARV antiretroviral
AS active substance
ATV atazanavir
AUC Area under concentration-time curve
AUC(0-24h) Area under the concentration-time curve from zero (pre-dose) to 24 h
AUC(0-28d) Area under the concentration-time curve from zero (pre-dose) to 28 days (4 weeks)
AUC(0-inf) or AUCinf Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex Percentage of AUC(0-inf) obtained by extrapolation
AUC(0-t) Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-tau) Area under the concentration-time curve over the dosing interval
AUClast Area under the concentration-time curve from time zero (pre-dose) until last measured time point
AUCtd Area under the plasma concentration-time curve from time of administration to t days after dosing
BCRP Breast cancer resistance protein
BID Twice daily
BMI body mass index
BSEP Bile salt export pump
BWT Baseline body weight
C0, C0h, or Cpre-dose Pre-dose concentration
C2h_unb Change in the unbound concentration at 2 hours
C24 Plasma concentration 24 hours after dosing
C28d Plasma concentration 28 days (4 weeks) after dosing
CAB Cabotegravir (GSK1265744)
CAR Current antiretroviral regimen
Cavgi Average concentration
CC50 Cell cytotoxicity 50%
CCR5 Chemokine receptor 5
CBZ Carbamazepine
CD4+ cluster of differentiation antigen 4
CD8+ cluster of differentiation antigen 8
CDC Centers for Disease Control (US)
CFB Change from Baseline
CI confidence interval
CK Creatine Kinase
Clast Last measurable plasma concentration
CLcr Creatinine clearance
CLr Renal clearance
CL Systemic clearance of parent drug
CL/F Apparent clearance following oral and LA dosing
Cmax Maximum observed plasma concentration

Cmax,ss Maximum observed plasma concentration at steady state
Cmin Minimum observed plasma concentration
CMH Cochran-Mantel Haenszel
COBI cobicistat
CPPs Critical Process Parameters
CQAs Critical Quality Attributes
CRF Case Report Form
CSR clinical study report
Css,av Average steady state plasma concentration
Ctau Trough concentration at the end of the dosing interval
CV Coefficient of variance
CVb% Between-subject coefficient of variance
CVF Confirmed virologic failure
CYP Cytochrome P450
CVT Cervicovaginal tissue
CVw% Within-subject coefficient of variance
CVF Confirmed Virologic Failure
DILI Drug-induced Liver Injury
DNA deoxyribonucleic acid
DoE Design of experiments
DRESS Drug Reaction with Eosinophilia and Systemic Symptoms
DRV darunavir
DS design space
DTG dolutegravir
DVT Deep vein thrombosis
ECG echocardiogram
eCRF electronic Case Report Form
Ethinyl estradiol
EFV efavirenz
ENF enfuvirtide
EVG elvitegravir
Emax maximum effect
EPK50 PK parameter value associated with 50% of maximum effect (Emax) eq Equivalents
ERCP Endoscopic retrograde cholangiopancreatography
ESRD End-stage renal disease
ETV Etravirine
F Bioavailability
FC fold change
FCBP Females of childbearing potential
FDC fixed-dose combination
F1 Bioavailability of oral CAB relative to CAB LA
F4 Relative bioavailability after oral administration
Fe Fraction excreted
Fm Fraction metabolised
Frac Fraction of the IM dose absorbed via a fast absorption pathway
FSFV First Subject First Visit
FSH Follicle-stimulating hormone
FTC emtricitabine
Fu Unbound fraction
Fu2h Unbound fraction at 2 hours post-dose
Fu24h Unbound fraction at 24 hours post-dose
GC gas chromatography
GCP Good Clinical Practice
GFR Glomerular filtration rate
GHO Global Health Outcomes
GI Gastrointestinal
GLS Geometric Least-Squares

HAART Highly Active Antiretroviral Therapy
HAV Hepatitis A Virus
HAT-QoL HIV/AIDS-Targeted Quality of Life Instrument
HBV Hepatitis B virus
HCV Hepatitis C virus
HDPE high density polyethylene
HEV Hepatitis E Virus
HIV-1 Human Immunodeficiency Virus Type 1
HIVTSQc HIV Treatment Satisfaction Questionnaire (change)
HIVTSQs HIV Treatment Satisfaction Questionnaire (status)
HPLC high pressure liquid chromatography
HSR Hypersensitivity Reaction
ICH International Council for Harminisation
IC50 50% inhibitory concentration
IC90 90% inhibitory concentration
IDMC Independent Data Monitoring Committee
IIV Inter-individual variability
IM Intramuscular
INI integrase inhibitor
IPC in-process control
IPRED Individual predicted value
IQR interquartile range
IRIS Immune reconstitution syndrome
ISE integrated summary of efficacy
ISR Injection Site Reaction
ISS integrated summary of safety
ITT-E Intent-to-treat Exposed
ITT-ME Intent-to-treat-exposed-Maintenance Exposed
IM intramuscular
KA1, KA2 First-order absorption rate constant (CAB KA1=oral and KA2=IM)
Kel First order elimination constant
Ki Inhibitory constant
KTZ Ketoconazole
LA Long-acting Injectable
LH Luteinizing hormone
LLDPE linear low-density polyethylene
LLOD Lower limit of detection
LLQ Lower limit of quantification
LNG Levonorgesterol
LOCF last observation carried forward
LPV lopinavir
LSC Liver Stopping Criteria
MATE Multidrug and toxin extrusion transporter
MDZ Midazolam
MCID Minimal Clinical Important Difference
MOI Multiplicity of infection
Molt-4 Human T cell lymphocytic leukemia cell line
MRP Multidrug resistance protein
MS mass spectrometry
MSDF Missing, Switch or Discontinuation = Failure
MT-2 Human T cell lymphocytic leukemia cell line
MT4 Human T cell lymphocytic leukemia cell line
MVC Maraviroc
M8166 Human T cell
NIH National Institutes of Health
NNRTI non-nucleoside reverse transcriptase inhibitor
NOAEL No observed adverse effect level

NRTI nucleoside reverse transcriptase inhibitor
NSAID Nonsteroidal Anti-inflammatory Drugs
NVP nevirapine
OAT Organic anion transporter
OATP Organic anion transporter polypeptide
OCT Organic cation transporter
OLI Oral lead-in
OMP Omeprazole
PA-IC90 Protein binding adjusted IC90
PAR proven acceptable range
PBMC peripheral blood mononuclear cell
PBPK Physiologically-based PK
pcVPC Prediction corrected visual predictive check
PD Pharmacodynamic
PDE permitted daily exposure
PDVF Protocol-defined virological failure
pg Picogram
P-gp P-glycoprotein
PGx Pharmacogenetics
Ph. Eur. European Pharmacopoeia
PK pharmacokinetic
PI protease inhibitor
PIN Perception of Injection
PP Per-protocol
PPs process parameters
PRO Patient Reported Outcomes
PSD particle size distribution
QbD Quality by Design
Q Inter-compartment clearance
Q/F Apparent inter-compartmental clearance
Q4W dosing every 4 weeks
Q8W dosing every 8 weeks
QTc Corrected QT Interval
QTcB Heart Rate-corrected QT Interval
QTcF QT Interval Corrected using Fridericia's Formula
QTPP Quality Target Product Profile
r ritonavir
R2 Coefficient of determination
RAL raltegravir
RAM resistance-associated mutations
RAP Reporting and Analysis Plan
RH relative humidity
RNA ribonucleic acid
RPV rilpivirine
RT Reverse Transcriptase
SCSR synoptic clinical study report
SD standard deviation
SDAP Summary Document Analysis Plan
SDM Site Directed Mutant
SE Single Entity
SJS Stevens Johnson Syndrome
SOC Standard of Care
SRDP Study Results Dissemination Plan
SVF suspected virologic failure
t Time of last observed quantifiable concentration
t1/2 Terminal phase elimination half-life
tau Dosing interval
TAF tenofovir alafenamide

TDF tenofovir disoproxil fumarate
TdP Torsades de pointes
TENS Toxic Epidermal Necrolysis
TFV Tenofovir
tlag Lag time before observation of drug concentrations in sampled matrix
tlast Time of last quantifiable concentration
tmax Time of occurrence of Cmax
TQT Thorough QT
TQTc Thorough Corrected QT Interval
UDP Uridine diphosphate
UGT1A1 UDP-glucuronosyltransferase 1A1
UGT1A9 UDP-glucuronosyltransferase 1A9
UK United Kingdom
ULN Upper limit of normal
US United States
UV ultra violet spectrometry
V2 Central compartment volume of distribution
V2/F apparent central volume of distribution
V3 Peripheral compartment volume of distribution
V3/F Apparent peripheral compartment volume of distribution
Vc Volume of distribution of the central compartment
Vc/F, V2/F Apparent volume of the central compartment
V/F or Vz/F Apparent volume of distribution after extravascular (e.g., oral) administration
VF Virologic failure
VL Viral Load
VPC Visual predictive check
XRPD X-ray powder diffreaction
ZDV zidovudine

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ViiV Healthcare B.V. submitted on 26 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Vocabria, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2018.

The applicant applied for the following indication:

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine (see section 5.1).

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.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision *P/0312/2017* on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

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 because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance cabotegravir contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

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 April 2013	EMEA/H/SA/2517/1/2013/III	*Dr Kerstin Wickström, Dr Hans Ovelgönne*
28 April 2016	EMEA/H/SA/2517/1/FU/1/2016/II	*Dr Hans Ovelgönne, Dr Filip Josephson*
26 January 2017	EMEA/H/SA/2517/3/2016/I	*Dr Mair Powell, Dr Peter Mol*

The clinical development programme is based on the assessment of PK/PD properties of CAB, the selection of the oral and injectable dose of CAB in combination with RPV, and the assessment of efficacy and safety of CAB + RPV in Phase 3 switch studies in virologically-suppressed subjects treated with usual tritherapy.

There were scientific advices from EMA and US FDA for the development of CAB and the combination CAB + RPV. Overall, the development plan was approved, and the clinical Phase 3 studies were performed as recommended through these scientific advices.

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

- *Manufacturing, substance and product specification and acceptance criteria*
- *Dissolution methods*
- *In vitro in vivo correlation model*
- *Adequacy of the Preclinical toxicology package and Carcinogenicity studies*
- *Clinical pharmacology package*
- *Dose and dose regimen*
- *Concurrence that the Ph2b oral CAB dose ranging study in combination with RPV 25mg oral tablet will inform dose selection for the long acting injection of both agents for Phase 2b*
- *Design of the Ph2b utilising the long acting injectable formulations of CAB LAP and RPV LA for maintenance therapy. Adequacy of the Ph2b programme to proceed to Ph3*
- *Design of the 2 planned phase 3 switch studies (i.e. primary endpoint, studies will be conducted open label)*
- *Statistical strategy for pooling data from the 2 switch studies and NI margins for the pooled and individual studies*
- *Indication statements*
- *Data requirement to remove the oral lead in dosing for both CAB and RPV at the time of MAA*

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: Johann Lodewijk Hillege

During the assessment of this application, a revised timetable had been adopted by the CHMP accounting for a delay from the initially planned timetable due to unforeseeable reasons related to the COVID-19 pandemic. This was done in line with the European Medicines Regulatory Network COVID-19 Business Continuity Plan (EMRN COVID-19 BCP) which describes mitigation measures in case of

COVID-19 related delays.

The application was received by the EMA on	26 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	6 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	12 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	30 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 July 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 July 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	03 September 2020
SAG HIV/Viral diseases meeting was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	08 September 2020
The CHMP agreed on a second list of outstanding issues in writing to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 October 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive pinion for granting a marketing authorisation to Vocabria on	15 October 2020

2. Scientific discussion

2.1. Problem statement

There are more than 35 million people worldwide living with HIV. While advances in the development of new antiretroviral therapies (ART) provide extensive insights into the management of Human immunodeficiency (HIV)-infected individuals, chronic HIV infection continues to be characterised by increased development of resistant virus, increasing transmission of resistant virus, and issues associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires that we continue to improve on the durability, safety and tolerability, and convenience of all antiretroviral classes.

Standard of care for the treatment of HIV-1 infection uses combination of antiretrovirals (ARV) to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consists of 2 NRTIs and either 1 PI, 1 NNRTI or 1 INI.

Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification in order to improve compliance and quality of life. Thereupon, total pill burden, dosing frequency, and safety concerns are the greatest obstacles to achieving adherence, which is essential to maintain viral suppression and prevent emergence of resistance mutations.

Various approaches to simplify a patient's antiretroviral therapy regimen, after achieving virologic suppression, have been studied, notably by reducing the number of ARVs. Several bitherapies had demonstrated their non-inferiority to maintain virologic suppression in comparison to usual tritherapies, and some of them have even been marketed (RPV/DTG – Juluca; DTG/3TC – Dovato). New formulations reducing pill burden and improving compliance are welcome.

2.1.1. Disease or condition

The applicant seeks the following therapeutic indication for Vocabria (cabotegravir):

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine.

2.1.2. Biologic features, clinical presentation and diagnosis.

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (i.e. viral load). The aim of treatment of HIV-1 infection is therefore to suppress, and subsequently maintain, the HIV-1 viral load to levels that are at least below the limit of detection of most commonly used assays (50 copies/ml of blood) and therefore the preservation of the immune system.

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms (including fever, rash, or diarrhoea), or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Among those presenting with symptoms, the number of symptoms correlates with higher pre-seroconversion peak plasma viral load.

Diagnosis, therefore, most often occurs during chronic infection. In some settings, up to half of the people present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 disease. Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia.

Following HIV diagnosis, the initial laboratory workup includes assessment of HIV staging parameters (CD4 cell count, HIV RNA) as well as an HIV genotype test for detection of drug resistance. The spectrum of drug resistance in an individual patient can range from minimal resistance that affects the activity of one or two drugs, to multidrug resistance that includes resistance to several drug classes. However, the risk of developing multidrug-resistant virus is much lower than in the past due to simpler regimens that better tolerated.

2.1.3. Management

According to EU HIV treatment guidelines, antiretroviral therapy (ART) is recommended in all patients with HIV infection, irrespective of CD4 cell counts. The main goal of ART is to suppress viral replication to below detectable limits (<50 c/ml), increase CD4+ cell counts, and prevent transmission. It is a life-long treatment, as the viral load will rebound as soon as an individual stop taking effective antiretroviral therapy.

Current treatment options are generally considered to be potent, with an overall acceptable toxicity profile. Mutations in the viral genome can, however, occur when the virus replicates, which can make the virus resistant to antiretroviral drugs or classes of drugs. Therefore, there is a continued need for development of new antiretroviral treatment options.

About the product

Cabotegravir (CAB) is a new active substance; an integrase strand transfer inhibitor (INI) that has been developed by ViiV Healthcare. CAB possesses attributes that allow formulation and delivery as a long-acting (LA) parenteral product (prolonged-release suspension for injection).

ViiV Healthcare, in partnership with Janssen Sciences Ireland UC (Janssen), are developing a two-drug regimen for the treatment of HIV-1, consisting of concomitant but separate administration of CAB prolonged-release suspension for injection and rilpivirine (RPV) prolonged-release suspension for injection.

CAB + RPV is intended for use as a 2-drug long acting (LA) regimen for the treatment of HIV-1 infection. According to the applicant, such a regimen offers reduced dosing frequency (monthly) compared with daily oral ARVs. With less frequent dosing, the daily reminder of their HIV status may be avoided, and associated stigma related to taking oral treatment regimens may be lessened. A reduced dosing schedule holds promise for increased patient compliance with dosing requirements. This novel treatment option may result in improved overall satisfaction with treatment and longer retention in care for individuals with HIV infection. This NRTI-sparing regimen avoids exposure to this class of ART thereby avoiding possible NRTI-class-related resistance, and longer term NRTI-related toxicities. Given the parenteral route of administration, a 2-drug LA injectable regimen may result in fewer gastrointestinal adverse events, eliminate dosing restrictions with regard to food, and will have fewer drug-drug interactions at the level of the gastrointestinal tract.

This application focuses on the CAB component of this 2-drug regimen. RPV is owned by Janssen and will be the subject of a separate marketing application.

CAB is a novel INI that possesses attributes that allow formulation and delivery as an LA parenteral product for IM administration. An oral tablet formulation of CAB has also been developed and will be used in combination with oral RPV as part of a 1-month oral lead-in (OLI) before LA therapy is initiated, in order to assess the tolerability and safety of this bitherapy before starting the LA injections.

Type of Application and aspects on development

The legal basis for this application refers to Article 8(3) of Directive 2001/83/EEC, as amended, i.e. a complete and independent application. The eligibility to the Centralised Procedure (CP) has been granted by the CHMP on January 2018 under Article 3(1) Indent 3 of Regulation (EC) No 726/2004.

ViiV Healthcare, in partnership with Janssen Sciences Ireland UC (Janssen), are developing a two-drug regimen for the treatment of HIV-1, consisting of concomitant but separate administration of CAB prolonged-release suspension for injection and rilpivirine (RPV) prolonged-release suspension for injection. ViiV Healthcare is the Sponsor of the CAB + RPV clinical programme.

Of note, the application for RPV prolonged-release suspension for injection (Rekambys) is assessed in parallel of Vocabria.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a prolonged-release suspension for injection containing 400 mg (2 ml) or 600 mg (3 ml) of cabotegravir (as free acid) as active substance; and film-coated tablets containing 30 mg of cabotegravir (as sodium salt) as the active substance.

Other ingredients, in the prolonged-release suspension for injection are: mannitol (E421), polysorbate 20 (E432), macrogol 3350 (E1521) and water for injections.

Other ingredients, in the film-coated tablets, are: lactose monohydrate, microcrystalline cellulose (E460), hypromellose (E464), sodium starch glycolate (Type A), magnesium stearate, and a film-coating consisting of hypromellose (E464), titanium dioxide (E171), and macrogol (E1521).The prolonged-release suspension is available in clear brown Type I glass vials with bromobutyl rubber stoppers; the glass vials are packaged together with1 syringe, 1 vial adaptor and 1 injection needle.

The film-coated tablets are available in 30 count white HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures, with a polyethylene faced induction heat seal liner.

2.2.2. Active Substance

Cabotegravir

General information

The chemical name of cabotegravir is (3S,11aR)-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.

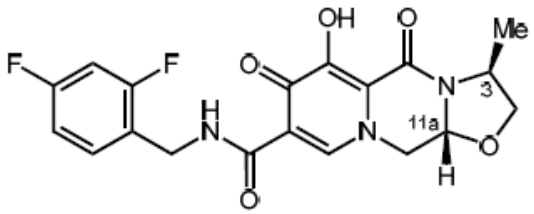


Figure 1. Structure of cabotegravir

Cabotegravir 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. It has two pKa, pKa1 = 7.7 (measured), OH group and pKa2 =11.1 (calculated), NH group.

The structure of the active substance (AS) 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 centres and is the isomer with the 3S, 11aR configuration. The 3S and the 11aR configuration are derived are determined either by starting materials or by the synthetic process. The absolute stereochemistry of the active substance is 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 under process relevant conditions.

Manufacture, characterisation and process controls

The active substance manufacturer has been stated. Cabotegravir manufacturing process consists of 6 steps including a purification step from well-defined starting materials (SMs). These SMs have been sufficiently justified in line with ICH Q11 and are controlled by suitable specifications. There are three isolated intermediates controlled by acceptable specifications. The stereochemistry of cabotegravir is determined either by the starting materials or by the process conditions of the synthetic process.

A systematic, science and risk-based approach has been applied in evaluating, understanding and improving the manufacturing process for cabotegravir consistent with ICH Q11 for the development and manufacture of active substance. The Quality Target Product Profile (QTPP) was clearly presented. Based on the QTPP, the Critical Quality Attributes (CQAs) of the active substance have been identified and presented. Based on the CQAs for the active substance, every stage of the manufacturing process has been evaluated and optimised 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. Design spaces, supported by multivariate experimentation, have been defined and clearly presented for certain steps of the process. The CPP ranges are within the ranges studied in the DoEs.

Sufficient information was presented for the verification of the proposed DSs to the commercial scale. The history of manufacturing process development was presented, and the impact of the final AS quality was adequately discussed and shown comparable.

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 materials has been described. The materials comply with EU Commission Regulation No 10/2011 for food contact use and 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.

Specification

Cabotegravir active substance specification, includes appropriate tests and limits 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 (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.).

The proposed specification is acceptable; the proposed limits are in line with the relevant European guidelines and the provided batch analyses. The limits for specified and unspecified impurities comply to ICH Q3B 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 control strategy for the residual solvents is satisfactory. 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 require ICH M7 Option 1 control and therefore they are not included on the active substance specification. A risk assessment according to ICH Q3D has been conducted and the proposed controls for elemental impurities is 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, data from an additional 17 batches of cabotegravir, manufactured using a process representative of that intended for commercial manufacture and produced 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 and include primary stability batches. Batches were tested by the proposed commercial methods or validated clinical release methods. All batches complied with the proposed specification.

Stability

Stability data have been provided for four pilot scale batches stored at long term conditions 30°/75% RH for up to 24 months and at accelerated conditions 40°C/75% RH for 6 months. Although a higher humidity was used for the long-term stability studies at 30 °C, than required according to ICH Q1A(R2), no objection is made as the higher humidity is seen as more stressful (worst case). The batches were stored in the commercial packaging. Samples from one batch were also stored at 5 ± 3°C and 50°C, both without humidity control.

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, as the proposed storage condition "Store up to 30°C" is acceptable since, in general, it will not require any special measures for storage.

In addition to ICH stability studies, stress studies (50°C, 40°C/75%RH exposed, photostability, and freeze-thaw cycles) were performed for one pilot batch over one months. Photostability was conducted on a pilot batch, according to ICH Q1B. No significant changes were observed and the he 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 are stability indicating.

Based on the available stability data the proposed retest period of 36 months with storage condition "Store up to 30°C" is acceptable.

Cabotegravir sodium

General information

The chemical name of cabotegravir sodium is sodium (*3S,11aR*)-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.

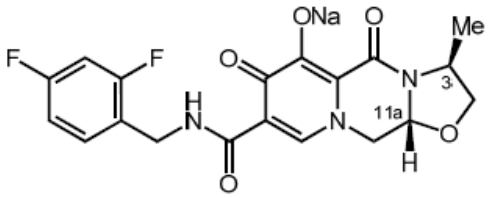


Figure 2. Structure of cabotegravir sodium

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. It has two pKa, pKa1 = 7.8 (measured), OH group and pKa2 =11.1 (calculated), NH group. Its partition coefficient is 1.1.

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

Cabotegravir sodium possesses two stereogenic centres and is the isomer with the 3S, 11aR configuration. The 3S and the 11aR configuration are derived are determined either by starting materials or by the synthetic process. The absolute stereochemistry of the active substance is confirmed by single crystal X-ray crystallography.

It 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 at ambient conditions and under process relevant conditions. Solid state form is not impacted by micronisation.

Manufacture, characterisation and process controls

The active substance manufacturer has been stated. Cabotegravir sodium is produced from cabotegravir free acid as described above with an additional 5th stage to transform the 'free acid' to the sodium salt, the same starting materials are used. Non-micronised cabotegravir sodium and the final active substance, cabotegravir sodium (micronised), packaging material has been described. These are the same packaging materials as used for cabotegravir (see above).

Specification

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

The proposed specification is acceptable; the proposed limits are in line with the relevant European guidelines and the provided batch analyses. The limits for specified and unspecified impurities comply to ICH Q3B and for residual solvents to Q3C and are justified through fate and purge studies. The control strategy for the residual solvents and microbiological quality is satisfactory.

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 cabotegravir sodium micronised, which were manufactured according to the proposed commercial method by the proposed manufacturer and micronised at each of the three commercial micronisation sites. In addition, data from another 4 batches of cabotegravir sodium (micronised), manufactured using a process representative of that intended for commercial manufacture and synthesised 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 and includes batches used to manufacture Cabotegravir Tablets used in Phase 3 clinical and primary stability studies. Batches were tested by the proposed commercial methods or validated clinical release methods. All batches complied with the proposed specification

Stability

Stability data for cabotegravir sodium micronised have been provided for five pilot scale batches stored at long term conditions 30 °C / 75% RH for up to 24 months and 40 °C / 75% RH for 6 months. The batches were stored in the intended commercial packaging. One batch of micronised material was also stored at 5 ± 3 °C and 50 °C, both without humidity control. In addition, one pilot batch of non-micronised material was also stored at 30 °C / 75% RH (24 months), 40°C/75% RH (6 months), 5 ± 3°C and 50°C, in the latter two without humidity control. Although a higher humidity was used for the long-term stability studies at 30°C, than required according to ICH Q1A, no objection is made as the higher humidity is seen as more stringent condition.

Stability batches were tested for description, assay, impurities, enantiomer and diastereomer content, water content (non-micronised cabotegravir sodium only), particle size (tested for information only for non-micronised 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 change neither any 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 micronised and one non-micronised). Based on the provided results from photostability studies, according to ICH Q1B, cabotegravir sodium requires protection from light, therefore, for cabotegravir sodium the storage condition "protect from light" has been set.

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, for a total of 1-month exposure. No significant changes were observed and the he results demonstrate chemical and physical stability of cabotegravir under these storage conditions.

Forced degradation studies have been performed on cabotegravir and cabotegravir sodium to identify potential degradation products that might be formed in active substance. 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 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 combination of HPLC methods are stability indicating, for both active substances. The results from the forced degradation studies demonstrate that the HPLC methods are stability indicating.

Based on the available stability data the proposed retest period of 36 months with storage conditions "Store up to 30°C" and "protect from light" is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Prolonged-release suspension for injection

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 vial of cabotegravir injectable suspension is intended to provide a dose of 400 mg or 600 mg. No dilution is required prior to IM administration. The two strengths are differentiated by labelling and plastic cap colors; the 2 ml fill presentation has a dark gray cap and the 3 ml fill presentation has an orange cap.

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

The quality target product profile (QTPP) and CQA of the finished product have been established and discussed. Cabotegravir free acid was chosen due to its low aqueous solubility in order to achieve 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 minimises injection volume required to achieve desired dose.

The formulation development studies to ensure the desired finished product attributes were described. The same formulation (formulation A), has been used for phase 2 and 3 studies and represents the commercial formulation. The in-process specifications for PSD are in-line with bioavailability study and clinical batches. The presence of small orange-coloured regions was observed in a small number of vials. The cause of these orange-coloured regions has been identified as a transient solution species and therefore will be present across a product batch. The clinical batches (using the same formulation) did not have any efficacy or safety issue linked to this and thus it is accepted that it does not pose a safety or efficacy concern.

All chosen excipients are widely used in parenteral products and the levels chosen for this product are within typical ranges used for suspensions. The function of the chosen excipients has been adequately discussed. There are no novel excipients. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The development of dissolution method has been elaborated and justified. The development of the manufacturing process is discussed in detail for each process stage, the resulting manufacturing process parameters and control strategy are adequately discussed and justified. The manufacturing process applied for clinical batches has also been discussed; some slight differences with the proposed commercial manufacturing process are not expected to result in critical quality differences between batches of finished product. Supplies for the last clinical studies were produced at the same site as proposed for commercial production, but with a different gamma irradiation site.

The control strategy has been developed based on risk assessment and process knowledge and the CQA of finished product are ensured through attributes of the input materials, parameters of the manufacturing process, in-process controls, and finished product specification.

The manufacturing process consists of gamma irradiation of the active substance, compounding of formulation vehicle, compounding of bulk suspension by milling, filling into vials, and terminal sterilisation. Microbial control of the finished product occurs at various stages of the process. The manufacturing process development is described in relation to the impact of process parameters and in-process controls to the finished product CQAs.

Studies to define and confirm the ranges of PPs, CPPs and IPCs were conducted for the different steps of the process i.e. compounding of bulk suspension for milling, milling, and transfer to filling tank. It has been demonstrated that the process has no impact on the solid-state polymorph (Form 1). The proposed in-process particle size specification is based on the data for clinical and stability batches at the production scale batch size. The fill weight has been determined so that the target extractable volume and pH of the solution are achieved. The gamma irradiation dose applied for the terminal sterilisation is justified. The selection of terminal sterilisation by irradiation versus steam sterilisation has been justified.

For both strengths, one single-use vial of Cabotegravir prolonged-release suspension for injection is packaged with the following aspiration and dosing devices: one sterile, single-use vial adaptor, one 5-mL sterile, single-use syringe and one sterile, single-use 23 gauge, 1.5-inch safety needle.

Compatibility with the primary packaging components with the finished product and the manufacturing process (gamma irradiation) and closure integrity have been demonstrated. CE-certificates issued by notified bodies are submitted for all medical devices delivered with the finished product. Compatibility of the medical devices with Finished product during the proposed in-use stability of two hours at room temperature has been demonstrated. The product is into Type I clear glass vials and sealed with bromobutyl rubber stoppers in two nominal fill presentations, 2ml and 3 ml for the 400 and 600 mg strength respectively. The stopper is secured with an aluminium overseal with a removable plastic cap. The specifications for vial and stopper are presented. The supplier has confirmed that the rubber stopper is not made with natural rubber latex and that they comply with the requirements of Ph. Eur. 3.2.9. The vials comply with Ph. Eur. 3.2.1. Extractables and leachables studies have been conducted and demonstrated that the leachables potentially present in the cabotegravir suspension, after long-term storage (up to 12 months) do not pose a risk to the patient.

Manufacture of the product and process controls

The manufacturer of finished product has been stated.

The manufacturing process is described with process parameters and IPCs and consists of: sterilisation of cabotegravir active substance by gamma irradiation, compounding of formulation vehicle, compounding of cabotegravir bulk suspension, milling of the suspension with 3mm milling beads, filling into vials, stoppering and over-sealing, terminal sterilisation by gamma irradiation, and vials inspection. The manufacturing process is a non-standard one. The critical in process controls were identified and justified.

Product sterility and bacterial endotoxins of the finished product are assured by controls on the excipients, active substance, primary packaging components, the manufacturing process (including gamma irradiation of active substance prior to compounding, use of suitable manufacturing equipment and manufacturing processing environment), terminal sterilisation, and in-process and finished product testing. The claim for parametric release for sterility has been sufficiently supported and is accepted.

Process validation has been adequately performed in line with the relevant guideline on three full scale batches of each strength. The report of the validation of the terminal sterilisation process, including dose mapping studies, was also provided. Sterility assurance is achieved by means of validation of different steps of the process. The sterilisation and depyrogenation processes applied for stoppers, vials and beads are fully validated. The process is considered successfully validated and that it is adequately under control in order to consistently obtain a product that complies with the specifications.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (HPLC, UV), uniformity of dosage units (Ph. Eur.), cabotegravir content (HPLC), 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 proposed specifications are set based on the requirements of Guideline ICH Q6A. The limits for impurities are set in line with ICH Q3B and testing frequency is justified. Certain parameters were not included in the specifications and this has been justified. The dissolution limit is based on the clinical and primary stability batches and is compliant with general compendial requirements.

A risk assessment on elemental impurities was provided, which substantiates that no control for elemental impurities is needed at release of finished product. No elemental impurities were identified as having the potential to be present at a level of greater than 30% of the PDE limit for parenteral administration, using Option 2b defined in ICH Q3D.

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 and no risk for cross-contamination with other products.

For sterility, parametric release is proposed. The justification for parametric release is in accordance to the 'guideline on real time release testing'.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis results were presented for 10 commercial size batches of the finished product, manufactured by the same process proposed for commercial use and at the same site. All results are in line with the proposed specifications, confirming robustness of the process. In addition, sufficient information about the finished product batches used in clinical studies was provided, for each of the 26 batches.

Stability of the product

Stability data from 4 commercial scale batches of finished product manufactured at the proposed site and stored for up to 12 months under long term conditions at 5 ± 3ºC and at 30 ± 2 °C/ 75 ± 5 % RH and under accelerated conditions (40 ± 2ºC / 75 ± 5 % RH) for up to 6 months according to the ICH guidelines were provided. Vials were stored in inverted position. As the 2 ml filled vials (400 mg strength) have a relative larger head space volume, they are considered at greater stability challenge, therefore

testing was performed on three batches of 400 mg strength and one of 600 mg strength (3 ml filled vials).

Samples were tested for description, assay, impurities, particle size, pH, dissolution and sterility (yearly). The analytical methods used in the stability studies are the same as for release. In addition, testing also included some additional methods (resuspendability and syringeability, evaluation of glass vials, elemental impurities) used in freeze-thaw and in-use stability studies. The description of these methods and their validation was presented.

No significant changes were observed in description, cabotegravir content, drug-related impurities, pH, and sterility when stored for up to 12 months at 5°C and 30 °C/ 75 % RH. Particle size and dissolution also remained unchanged when stored for up to 12 months at 5 °C. An increase in particle size and a corresponding decrease in dissolution were observed following storage at 30 °C/ 75 % RH, however the results still complied with the specification.

Under accelerated conditions no significant changes were observed in description, cabotegravir content, drug-related impurities, and pH when stored for up to 6 months at 40 °C/ 75 % RH, except for one batch, where the assay decreased after 6 months but was still within the specification. Based on a statistical analysis of the available results of assay at 30 °C/ 75 % RH (up to 12 months), the applicant states that a 24 months shelf life is supported. Similar to long term results, an increase in particle size and the expected decrease in dissolution were also observed under accelerated conditions, however the results still complied with the specification.

Stress tests on a full-scale batch of each strength included freeze/thaw cycles and exposure to 50 °C. On these batches, in addition to the test mentioned above, glass elements by ICP and microscopic evaluation of glass is performed. No significant changes were observed in description, cabotegravir content, drug-related impurities or pH when stored for up to 3 months at 50°C. In line with the results observed in long term and accelerated condition studies, particle size increase and dissolution decrease have been observed after 3 months at 50°C, however the results were still within the specification. The freeze-thaw study (-20 °C/ 30 °C) showed that freezing impacts irreversibly the particle size and therefore the redispersibility of the suspension, therefore SmPC 6.4 recommends "Do not freeze".

A photostability study according to ICH Q1B Option 1 was performed on a full-scale batch of each strength; no significant change was observed, confirming that the finished product is photostable.

In-use stability studies have been performed on samples from two batches of the 400 mg strength and one batch from the 600 mg strength. The samples were tested for description, assay, impurities, pH, extractable volume, particle size and elemental impurities. No significant change was observed in all tested parameters.
Results of an in-use stability study substantiate the proposed in-use stability of 2 hours for the finished product when withdrawn in the provided plastic syringe (SmPC 6.3).

Based on the overall stability data the proposed shelf-life of 2 years and storage conditions as described in SmPC sections 6.3 and 6.4 can be accepted. The shelf life and storage conditions of suspension in syringe as stated in SmPC sections 6.3 and 6.4 are also accepted.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of the finished product. The excipient Polysorbate 20 is of vegetable origin.

Film coated tablets

Description of the product and pharmaceutical development

The finished product is an immediate release film coated tablet for oral administration, containing 31.62 mg of cabotegravir sodium (micronised), equivalent to 30 mg of cabotegravir free acid.

Vocabria tablets are white film-coated, oval-shaped tablets, (approximately 8.0 mm by 14.3 mm), debossed with "SV CTV" on one side.

The finished product (FP) is packaged into opaque, white high-density polyethylene (HDPE) bottles with a polypropylene child-resistant closure that include a polyethylene faced induction heat seal liner.

A science and risk-based approach, applying Quality by Design (QbD) and quality risk management (QRM) in accordance with ICH Q8, Q9, Q10, has been used to develop Vocabria film-coated tablets.

The Quality Target Product Profile (QTPP) has established the desired quality characteristics of the finished product. The finished product Critical Quality Attributes (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 has been established.

The knowledge gained from the pharmaceutical development and manufacturing experience have provided the scientific understanding to support the control strategy to assure product quality, which incorporates target values/set points, PARs, and a design space for the granulation unit operation.

The active substance for the cabotegravir tablets is the sodium salt of cabotegravir, solid state Form 4, and is micronised to meet the QTPP of finished product. Cabotegravir sodium is classified a BCS class 2 compound (see pK report). The sodium salt has higher solubility than the free acid form ensuring oral bioavailability and appropriate pharmacokinetics. The solid-state form 4 is the most thermodynamically stable. Particle size distribution (PSD) was studied in a human pharmacokinetics study that showed that micronised cabotegravir sodium gave an increased AUC and Cmax when compared to non-micronised substance. The PSD of cabotegravir sodium has been confirmed as an active substance CQA and ensures that dissolution profile is met. It is well controlled by the micronisation process for the active substance and is tested in the AS specification. Comparative dissolution profiles are obtained regardless of micronisation site.

All chosen excipients are widely used in solid oral products and the levels chosen for this product are within typical ranges used for tablets in view of the functions stated in the composition table. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The choice of AS crystal form, particle size limits, the excipients, their functions and quantity were sufficiently justified and explained.

The development of the formulae used for clinical studies was described. Design of experiments (DoE) studies were performed in order to select the formulation responding to the QTPP profile. The DoE outcome determined the levels of the binder, disintegrant and drug load. The formula used in phase 2b studies had low solubility; a bio-equivalent formula has been developed for phase 3 studies and was used in all phase 3 studies, including pivotal studies, in stability studies and is the commercial formula.

The development of the dissolution method has been well described. A DoE study was performed for the selection of surfactant concentration and rotation speed. The discriminatory power of the method has been sufficiently demonstrated.

The manufacturing process used for Vocabria film coated tablets consists of dry mixing of intragranular excipients with the active substance, high shear wet granulation, wet screening, and fluid bed drying

followed by dry milling. The film-coated tablets are packaged in HDPE bottles. The selected process ensured that the finished product CQAs are met consistently.

The finished product CQAs and the input materials attributes or process parameters that determine the CQA are identified. A risk assessment has been conducted and the relationship between process parameters and intermediate CQA and the finished product CQA 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 classification of process parameters as critical and non-critical has been supported and the proposed post authorisation management is acceptable.

Vocabria film coated tablets are packed into opaque, white HDPE bottles with polypropylene child resistant closures, with a polyethylene faced induction heat seal liner. Stability studies confirmed that a desiccant in the packaging is not necessary. The HDPE is pigmented white with titanium dioxide. The plastic packaging materials components comply with the EU Commission Regulation No. 10/2011 on plastic materials and articles intended to come into contact with food. The HDPE bottles comply with Ph. Eur. 3.1.3 Polyolefines. Acceptable specifications are provided for the bottles and closures as well as Certificates of analysis from the suppliers.

Manufacture of the product and process controls

The manufacturer of Vocabria film coated tablets has been stated. The manufacturing process consists of pre-mix of intra-granular components, wet granulation, screening and drying of granulate, milling, blending with extra-granular excipients, lubrication, compression, film-coating, and packaging. The manufacturing processes is a standard process. A DS is applied to the wet granulation unit operation which has been adequately discussed during pharmaceutical development studies. The critical process parameters have been identified and justified during development have been identified and justified during development.

Process validation scheme is presented. Process validation of cabotegravir tablets is being performed via a lifecycle approach, based on a systematic and structured risk management approach, which demonstrates and documents evidence that the process, together with the defined control strategy, is capable of reproducibly manufacturing product which meets all of the finished product CQAs.

The bulk tablets (intermediate) packaging material was described. The packaging material comply with the requirements of Commission Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food and with Ph. Eur. 3.1.3 on Polyolefins. Holding time and conditions, and transport are supported by stability data.

A process validation scheme in line with the Guideline on process validation was presented. According to this scheme validation will be performed on three commercial size batches before commercial launch. Process validation results from at least one production scale batch have been submitted to confirm the robustness of the process. Based on the extensive pharmaceutical development data provided and on the nature of the manufacturing process, it is expected that the process will be robust within the established parameters.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (HPLC, UV), uniformity of dosage units (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. Testing frequency has been sufficiently justified. The specifications are sufficiently justified and together with the manufacturing process control ensure the finished product quality attributes will be consistently met. The control strategy for cabotegravir 30 mg tablets is acceptable. Certain parameters were not included in the specifications and this has been justified.

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, elemental impurities are not 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 and no risk for cross-contamination with other products.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data were presented for 7 production scale batches manufactured according to the commercial process and at the commercial site. Results results comply with the specifications confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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 12 months under long term conditions (5ºC, 25ºC / 60% RH and 30ºC / 75% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. These batches were packed in the primary packaging proposed for marketing.

Stability samples were tested as per the release specifications and test methods. Slight method optimisations applied to the method for dissolution and impurities after start of the stability studies. These changes were discussed and are not expected to impact the results. Water content is tested in the stability studies but not included in the release specifications. Water content is performed 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 at accelerated conditions only.

In addition, stress condition studies have been performed on one full-scale batch at 50ºC/ ambient humidity, a freeze/thaw cycle (-20ºC / 30ºC) and exposed photostability testing in accordance with ICH Q1B (Option 1). No significant changes in description, content, drug related impurities and dissolution were observed. The results demonstrate the chemical and physical stability of the finished product at all storage conditions and confirms that the finished product is photostable.

Forced degradation studies have been performed on one full-scale batch in three conditions: 80°C for 14 days, 80 °C/ 75% RH for 14 days and after UV-Vis light exposure (ICH Q1B conditions). The

samples have been tested by the HPLC method for impurities. No increase in degradation products above the ICH Q3B limit has been measured and mass balance was always achieved. No significant changes in description, assay, impurities, dissolution and water content were observed and all results comply with specification.

In-use stability studies were presented at the initial timepoint and after storage at the long-term storage condition for 12 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. Based on the EMA Q&A on quality and on the results of the main stability study, performance of an in-use stability study was not necessary and therefore the study protocol has not been assessed. No indication on in-use stability needs to be included in the SmPC.

The applicant states that the presented data support the proposed shelf-life and storage conditions for Cabotegravir Tablets: a shelf-life of 24 months will be applied to the product. No storage condition statement is required on the label.

Based on available stability data, the proposed shelf-life of 2 years without any special storage conditions as stated in the SmPC (section 6.3 and 6.4), is acceptable.

Adventitious agents

No materials of human or animal origin are used in the manufacture of Vocabria film coated tablets except for lactose monohydrate. The magnesium stearate is of vegetable origin.

Lactose monohydrate is derived from bovine milk. The suppliers of the lactose confirm that the milk used in the manufacture of the lactose is sourced from healthy animals in the same conditions as for human consumption. 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.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. Cabotegravir free acid was chosen for the prolonged release suspension for injection due to its low aqueous solubility in order to achieve desired pharmacokinetic performance. Cabotegravir sodium micronised is used in the film coated tablets, in order to enhance solubility and therefore ensuring oral bioavailability and appropriate pharmacokinetics. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance and finished product. The design spaces have been adequately verified and are accepted. The proposed RTRT approach (parametric release for the sterility test) for the suspension for injection is accepted.

The manufacturing process for the prolonged release suspension for injection is non-standard and the required validation data has been provided. The manufacturing process for the film coated tablets is a standard process.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Cabotegravir (CAB, GSK1265744) is a novel, potent and selective HIV Integrase Strand Transfer Inhibitor (INSTI) developed for the treatment of HIV-1 infection. CAB is being developed as the sodium salt for oral (tablet) administration and as the free acid for a long acting (LA) injectable formulation, to be co-administered with rilpivirine.

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. Rilpivirine (RPV) is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment for HIV-1 infection in antiretroviral treatment naïve adult patients and is already approved in multiple markets including the United States of America, Europe, Canada and Japan as EDURANT®.

Integration of viral DNA into the host chromosome is a necessary process in the HIV replication cycle. The key steps of DNA integration are carried out by the viral integrase, which, along with protease and reverse transcriptase (RT), is 1 of 3 enzymes encoded by HIV. Integrase is an attractive target for HIV therapy because it is essential for HIV replication. The primary role of integrase is to catalyse the insertion of the viral cDNA into the chromosome of infected cells. Integration, catalysed via integrase, requires 2 metal-dependent consecutive steps in the viral replication cycle: 3'-processing and strand transfer. Viral cDNA is primed for integration in the cytoplasm by integrase-mediated trimming of the 3'-ends of the viral DNA. Integrase remains bound to the viral cDNA ends in the pre-integration complexes (PICs). Following nuclear translocation of the PICs, integrase catalyses the insertion of the viral cDNA ends into the host chromosomes. Following integration of viral cDNA into a chromosome, viral genome is transcribed, and viral proteins are produced. HIV integrase strand transfer inhibitors (INSTI), such as CAB, preferentially block the strand transfer step.

Non-clinical studies conducted to support the development of CAB include primary pharmacology (virology) studies, which demonstrated the inhibition of integrase activity and HIV-1 replication *in vitro* as well as studies to determine the potential for HIV resistance to develop via mutations. *In vitro* secondary pharmacologic activity was assessed, and safety pharmacology studies were conducted to investigate any untoward pharmacologic actions of CAB on the respiratory, cardiovascular, central and peripheral nervous systems.

2.3.2. Pharmacology

Primary pharmacodynamics

The primary pharmacodynamics of CAB regarding antiviral activity, selectivity and studies on resistance are presented and discussed in detail in the clinical part of the report.

Secondary pharmacology

The applicant has *in vitro* evaluated the binding properties of CAB to a panel of 16 enzymes, 64 receptors/ion channels and 12 isolated tissues. No considerable changes in assay responses were found as a result of CAB administration. The only exception was significant inhibition (53%) of the MC4 receptor at 10 µM CAB, which is >100-fold above the unbound clinical Cmax. The applicant did not test for inhibition of other MC receptors. These receptors are involved in e.g. pigmentation, feeding behaviour and regulation of metabolism. However, in agreement with the applicant, absence of *in vivo* effects (in toxicity studies) that could be related to MC(4) receptor inhibition by CAB indicate that no off-target biological effects are to be expected with the use of CAB.

The secondary pharmacology of CAB has been sufficiently investigated.

Safety pharmacology

CAB was tested in a battery of safety pharmacology assays including assessing effects on central nervous system (CNS)/neurobehavior, cardiovascular, and respiratory function.

In vitro pharmacology studies showed that CAB did no inhibit of the hERG channel up to the highest concentration tested due to solubility propriety (7.14 µg/mL, ~ 1x / ~ 2x the clinical CAB concentration following 30 mg/d PO 1 month / 400 mg IM once monthly following initial administrations respectively).

CAB had no effects in respiratory assay whereas a slight effect on arterial pressure (mild transient increase 3.7 to 8.6%) and transient increase in heart rate (16 to 23%) during the first 2h after dosing was observed in monkeys at the highest oral dose of 1000 mg/kg (C_{max} ~ 67 µg/mL) without ECG change associated following single dose or in the 14-day toxicity study. According the applicant, since the increase in heart rate was evident during the time of elevated arterial pressures, this suggests that the increase in heart rate was not baroreflex mediated; but rather, due to a positive chronotropic effect of CAB on the heart. The exposure margin of CAB in the safety pharmacology assays was at least 4-fold compared to the clinical Cmax (8.1 µg/mL / 4.2 µg/mL at the clinical CAB concentration following 30 mg/d PO 1 month / 400 mg IM once monthly following initial administrations respectively in POPPK).

Taken together, CAB does not appear to have a potential for adverse cardiovascular (CV) effects.

Effects on neurobehavioral function have been assessed in a rat 14-day oral toxicity study. The applicant stated that no effects occurred throughout the assessment interval of up to 25 hours following dosing on Day 5.

In general, the exposure margins of CAB in the safety pharmacology assays were in the range 1-8-fold compared to the clinical C_{max} in subjects.

In conclusion, no major safety issues were identified in the non-clinical safety pharmacology studies performed. Moreover, no adverse safety concerns related to CNS, CV or respiratory function were observed in the assessment of the clinical studies for CAB. Generally, sufficient exposure margins were observed in rats and monkeys as compared to the exposures seen with the proposed human doses.

Pharmacodynamic drug interactions

No specific non-clinical pharmacodynamic drug interaction studies have been conducted for CAB. Based on the pharmacodynamics data, CAB is a highly specific and selective HIV-1 integrase inhibitor and the potential for pharmacodynamic drug interactions is unlikely.

The concomitant administration of CAB with RPV is intended to provide two different mechanisms of inhibition of viral growth and so ensure that viral breakthrough does not occur in HIV-infected patients with undetectable viral load. Thus, pharmacodynamic interaction is an intended component of the therapeutic activity of this combination, and no adverse interaction is anticipated.

Primary pharmacology data showed that anti-viral activity of CAB was compatible with rilpivirine, lamivudine, tenofovir disoproxil fumarate and emtricitabine. Because CAB will only be used in combination with RPV, this will be sufficient. In addition, other -primarily PK- drug interactions have been evaluated clinically (see clinical section). Therefore, the absence of specific non-clinical PD drug interaction studies for CAB can be endorsed. There is no need to mention any PD drug interaction with CAB in the SmPC.

2.3.3. Pharmacokinetics

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

CAB was rapidly absorbed after repeat oral dose in rat, dog and monkey, with mean Tmax in plasma ranging from <4h in rats and monkeys, which is similar to Tmax in humans (3h). Moderate to high oral bioavailability is observed from a solution formulation and low when administered as a suspension or capsule formulation. The oral absorption of CAB seems to be limited by its solubility and/or dissolution rate.

No apparent gender differences were observed in mouse, rat and monkey after oral or IM administration.

Increases in plasma exposure (AUC) was less than dose proportional to oral dose in mouse, rat, monkey. No apparent major accumulation after multiple daily dosing was noted for mouse, rat or monkey.

Concerning IM administration, CAB was slowly released with Tmax up to 7d in rats, and Tmax 5d and mean half-life (up to 21 days) in monkey which is similar to PK in humans (Tmax 7d / t1/2: 5.6 to 11.5 weeks). Increases in plasma exposure (AUC) was less than dose proportional to IM dose in rat and monkey. No accumulation has been observed.

No PK interaction between CAB and rilpivirine has been observed in rat or monkeys.

The plasma clearance (<2% of hepatic plasma flow) and steady-state volume of distribution (<0.35 L/kg) were low after IV administration of CAB, with half-life values of 4 to 6 hours in dogs and monkeys (the sampling regimen in the rat was insufficient to characterise the pharmacokinetic parameters by IV).

Distribution

The percentage of CAB bound to plasma proteins was >99.9% in rats, 99.3% in dogs, 99.7% in monkeys and 99.6% in humans.

Concerning distribution following oral administration, concentrations of radioactivity reached maximal levels for the majority of tissues at D1, and was slowly absorbed (most tissues containing low but quantifiable radioactivity at 28 days). Excluding the GI tract, highest levels were associated with blood (23.0 µg equivalents of CAB/g of tissue), lung (19.0 µg equivalents of CAB/g of tissue), bulbourethral gland (14.6 µg equivalents of CAB/g of tissue), renal medulla (12.5 µg equivalents of CAB/g of tissue), adrenal medulla (12.0 µg equivalents of CAB/g of tissue) and pigmented skin (10.7 µg equivalents of CAB/g of tissue). At the final sampling time of 28 days, radioactivity was still present at low but quantifiable levels (0.546 – 0.095 µg equivalents of CAB/g of tissue) in over 50% of the tissues. Levels of radioactivity in the brain were low but quantifiable up to 28 days post-dose (in meninges and pineal body). It could be noted that radioactivity is higher in pigmented skin than non-pigmented skin at 1h and 28 days post-dose. However, no selective association of radioactivity with melanin has been observed with similar radioactivity observed between pigmented and non-pigmented skin over the remaining time, and the radioactivity remains low.

Metabolism

The *in vitro* metabolism of CAB was evaluated in liver microsomes and hepatocytes of rat, dog, monkey and human and *in vivo* in mouse, rat, monkey and human.

In vivo

Following a single oral dose in mice, rat, monkey, human unchanged compound was the only radiochemical component of drug-related material in plasma, representing 92-99% of radioactivity, without any metabolite present in the plasma at concentrations above the quantifiable limit (i.e. 5% of parent or drug related material).

The predominant biotransformation product in mice, rats, monkey and humans was CAB glucuronide (M1) eliminated by renal and biliary routes (1-20%), and a glucose conjugate (M2; 1-2%) was also observed only in rats and monkeys. These conjugated metabolites (M1 and M2) are not pharmacologically active because according the applicant they disrupt the two-metal binding capability of the carbamoyl pyridine motif of CAB thereby completely abrogating any antiviral activity resulting from the active site binding to the integrase enzyme. CAB conjugates were not present in faeces in all species but were present only in urine/bile and therefore according the applicant were likely deconjugated in the intestine by host or bacterial enzymes after secretion in the bile to reform CAB. The only metabolite identified in human *in vivo (M1)* was present in other species following oral administration of CAB. Other metabolites observed in animal (M2, M3, M5, M6) were present at low or trace levels. M2, M3 and M4 were minor metabolites in human, indicating that there were no metabolites in humans that were not identified in the nonclinical species.

CAB has two chiral centres, and the potential for metabolism of CAB to its respective enantiomer (GSK1245960) and one of the two diastereomers (GSK1417963) was investigated. The other diastereomer of CAB was not available as a synthetic standard at the time of this study and its formation could not be monitored. *In vitro* studies showed no significant metabolic conversion of CAB to its enantiomer or one of two possible diastereomers occurs in rat, dog, monkey or human hepatocytes.

A glutathione adduct of CAB was detected in rat, monkey and human (but not in dog) liver microsomes. Covalent binding of CAB-associated radioactivity to liver microsomes was moderate in human (180 pmol-eq/mg of protein/h) and high in rat and monkey (984 and 794 pmol-eq/mg of protein/h). The applicant estimates that the risk of hepatotoxicity in humans is low at clinically relevant doses of CAB. The argument was that metabolic products produced via this pathway represented only a very small fraction of CAB metabolic clearance and the fact that no liver toxicity was observed in the nonclinical species. However, since patients may individually slightly differ in the metabolism of CAB or CAB/rilpivirine combination, a risk of idiosyncratic liver toxicity in patients cannot be excluded on theoretical grounds. In human, elevated ALT values have been observed with exposure to CAB + rilpivirine during the Phase III development programme during the phase III studies, there were no cases of drug-induced liver injury (DILI) in subjects receiving CAB LA + rilpivirine LA. However, DILI was identified during Phase II and a clinical pharmacology study, in 5 subjects receiving oral CAB (incidence was <1%) and during the Phase IIIb study, in one subject receiving oral CAB + oral rilpivirine (see also in clinical safety).

Elimination

The parent compound, CAB, was excreted via the faeces, accounting for ~95% in mice and rats, ~80% in monkeys and ~60% in humans, relative to the administered CAB dose. The urinary excretion of CAB-related material was greater in humans (approximately 27%) than in the nonclinical species (≤11.1%).

The metabolite M1 (CAB glucuronide) was not observed in faeces of the nonclinical species and human. Metabolites were excreted in the bile and urine. In rodents, most of the CAB-related material was secreted into the bile and renal excretion was minimal. In mice and rats, the absorbed radioactivity was

eliminated via both the biliary and renal routes. Biliary excretion accounted for 1.60 to 1.79% of the CAB dose in mice (M1, M5) and rats (M1), for 14.5% in monkeys (M1, M2, M3). Since no CAB glucuronide is found in faeces, it is assumed that M1 is deconjugated in the intestine, after secretion in the bile to reform CAB. It is unlikely that enterohepatic circulation plays a relevant role in human. The urinary excretion of CAB-related material was 0.81% in mice (M1, M6) 0.31% in rats (CAB, M1, M2, M6), 11.1% in monkeys (M1, M2, M3) and 26.8% in humans (M1).

2.3.4. Toxicology

The toxicological profile of CAB has been evaluated in a comprehensive set of non-clinical studies. The performed studies include repeat-dose toxicity studies up to 6 months in rats and 9 months in monkey, *in vitro* and *in vivo* genotoxicity, male and female fertility and early embryonic development in rodents, embryo-foetal development toxicity in rodents and rabbits, peri- and post-natal development studies in rodents, carcinogenicity studies and impurity qualifying studies. In general, the non-clinical toxicology programme has been performed according to relevant guidelines and in agreement with CHMP advices.

The main species for toxicological evaluation was rat and monkey. 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.

Single dose toxicity

Single dose oral acute toxicity studies have not been conducted in rats or monkeys with CAB; however, the potential for acute toxicity was assessed in repeat dose studies at the highest possible systemic exposure based on saturation of absorption (rat) or highest tolerable dose (monkey). No adverse clinical observations were noted following administration of CAB to rats at ≤1000 mg/kg/day in the 4-week toxicity study. CAB was not tolerated at a dose of 1000 mg/kg/day in the 14-day monkey toxicity study and resulted in morbidity associated with clinical signs suggestive of GI effects including body weight loss, emesis, loose/watery faeces, inappetence and moderate to severe dehydration.

A series of single dose toxicity studies were performed to assess the effects of administration of oral, subcutaneous and intramuscular doses of CAB, and to compare the toxicokinetics for the different routes of administration; results were consistent with findings from repeat dose toxicity studies.

Repeat-dose toxicity

The toxicological profile of CAB has been evaluated in general oral toxicity studies up to 26-week duration in the rat, 13-week duration in mouse and 39-week duration in the monkey in addition to the 3 months duration in rat treated by IM. CAB was well tolerated without major adverse effects in repeat-dose toxicity studies in mice, rats and monkey. In the 14-day toxicity study in monkey, a high mortality was observed in males given 1000 mg/kg/day, and were 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 and have not been consistently observed in clinical trials to date. It could be noted that ocular effect has been observed in two monkeys in the 39-weeks study. Slight vascular inflammation was noted unilaterally near the optic nerve of a single monkey (Animal No. 402) 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 (302) dosed with 50 mg/kg/day. The applicant considers this ocular event as incidental. Maximum achieved CAB plasma exposures in the longest duration studies were 3203 and 542 µg·hr/mL for the rat and monkey respectively. These AUC exposures correspond to 22-fold and 4-fold the clinical AUC exposure in patients, respectively.

After monthly SC and IM administration of the CAB injectable solution in rats, sufficient exposure levels were reached (3 months, 100 mg/kg monthly SC, MOE: 26.64-47.38; 75 mg/kg monthly IM, MOE: 31.72-43.51). Four high dose animals were euthanised 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 unlikely treatment related. Besides dose-proportional signs of redness, swelling and inflammation following SC and IM injections at all dose levels, no additional adverse effects were noted. Injections site reactions are also observed in clinical trials.

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 at doses corresponding 7 and 19-fold the clinical AUC exposure in patients.

Reproductive and developmental toxicity

In male and female rats, no cabotegravir-related effect on fertility was observed at oral doses up to 1000 mg/kg/day inducing exposure levels (AUC) at least 20-fold higher than those reached in patients treated at the oral recommended dose of 30 mg/day.

Embryo-fetal toxicity studies were conducted in rats and rabbits at oral doses up to 1000 and 2000 mg/kg/day, respectively. In rats, there was no evidence of a treatment-related increase incidence of fetal anomalies at any dose level. Based on a decrease in fetal weights at the high dose level, the developmental NOAEL was determined at 5 mg/kg/day. At this dose, maternal exposure levels were approximately 4-fold those reached in patients treated orally at 30 mg/day. In rabbits, the absence of treatment-related effect on embryo-fetal development is claimed at all dose levels. The applicant provided the relevant historical control data and discussed adequately on the findings reported at ovarian examination and fetal morphological examination. It can be concluded that that there was neither treatment-related increase in postimplantation loss nor treatment-related increase in fetal malformations at oral doses up to 2000 mg/kg/day (0.7-fold exposure at MHRD) under the experimental conditions used in this study.

In the initial PPND study, rats were treated from GD6 to LD20 at oral doses ranging from 0.5 to 1000 mg/kg/day. At the high dose level, treatment-related decreases in F_1 pup survival and viability at the 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. A follow-up study confirmed these adverse findings and cross-fostering experiments showed that perinatal mortality was attributable to gestational, but not to lactational, exposure to CAB. 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 stillbirth 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 stillbirth was not reported on GD22 in the control group (0/305 pups) whereas it affected 2/99 pups (2%) 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.

The applicant provided the relevant historical control data and discussed adequately on the findings reported at ovarian examination and foetal morphological examination. It can be concluded that there was neither treatment-related increase in post-implantation loss nor treatment-related increase in

foetal malformations at oral doses up to 2000 mg/kg/day (0.7-fold exposure at MHRD) under the experimental conditions used in this study.

SmPC is amended to report that the 2000 mg/kg/day dose level actually induced maternotoxicity in rabbits: *In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits up to a maternal toxic dose of 2000 mg/kg/day (0.66 times the exposure in humans at the MRHD) or to pregnant rats at doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD (see section 5.3)*

Investigations conducted showed that perinatal mortality was not related to decreased maternal care, or treatment-related malformations. An additional investigative TK study indicates that exposure levels of both maternal animals and pups were similar at GD20 when dams were treated from GD6. Therefore, although the NOAEL for perinatal mortality is set at 5 mg/kg/day, determining a safety margin based on systemic exposure levels measured at this dose could be misleading. Postnatal development of pups surviving on PND4 was not shown to be affected by treatment.

No study was conducted with the CAB-RPV combination which is acceptable. RPV is already marketed in Europe, and studies conducted in animals have shown no effect on reproductive function. Studies in rats and rabbits reported also no evidence of embryo-foetal toxicity or teratogenicity.

Phototoxicity

CAB did not absorb light within the range of natural sunlight and is not considered to pose a risk for phototoxicity in humans.

Other studies

CAB could be considered to be non-irritant and non-sensitiser, non-immunosuppressive. No antigenicity, dependence or metabolite studies were performed with CAB. This is agreed.

Concerning the association CAB/RPV, it should be acknowledged the lack of combination toxicity studies due to the clinical experience with CAB and RPV, the lack of similar target organ indicating a potential additive/synergic interaction. Concerning the association CAB/RPV, it should be acknowledged the lack of combination toxicity studies due to the clinical experience with CAB and RPV, the lack of similar target organ indicating a potential additive/synergic interaction. The scientific advice adopted by the CHMP (EMEA/H/SA/2517/1/2013/III) was agreed for this point.

Impurities

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.

Local Tolerance

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

2.3.5. Ecotoxicity/environmental risk assessment

Cabotegravir is considered not to be PBT, nor vPvB. The PBT assessment can be finalised.

A risk to the STP, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of Cabotegravir. It can be concluded that there is no potential risk to the surface water compartment, the ground water compartment, the sediment compartment and the sewage treatment plant.

2.3.6. Discussion on non-clinical aspects

Pharmacology

In general, the pharmacology of CAB is well established and described. See also discussion in clinical section.

Pharmacokinetics

The analytical methods developed for the analysis of CAB-glucuronide in the in-vitro and in-vivo metabolism studies and the *in vitro* drug transporter assays have been described in the individual studies.

The metabolite M1 (CAB glucuronide) was not observed in faeces of the nonclinical species and human. Since no CAB glucuronide is found in faeces, it is assumed that M1 is deconjugated in the intestine, after secretion in the bile to reform CAB. It is unlikely that enterohepatic circulation plays a relevant role in human.

Toxicology

It could be noted that ocular effect has been observed in two monkeys in the 39-weeks study. Slight vascular inflammation was noted unilaterally near the optic nerve of a single monkey (Animal No. 402) 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 (Animal No. 302) dosed with 50 mg/kg/day. The applicant considers that these ocular effects as incidental.

Besides the combined female fertility and early embryonic developmental toxicity study in rats, the effects of CAB on embryofoetal development were also examined in Dutch belted rabbits. No findings were observed; however exposure was very low (high dose 2000 mg/kg/day, MOE: 0.66).

The applicant states that all 6 specified impurities (GSK3117145A, GSK3117146A, GSK3036873A, GSK1265748A, GSK1245960A and GSK1417963A) were considered not genotoxic based on in silico assessments.

ERA

It can be concluded that there is no potential risk to the surface water compartment, the ground water compartment, the sediment compartment and the sewage treatment plant.

2.3.7. Conclusion on the non-clinical aspects

The overall programme including the data from CAB studies is considered adequate to support the efficacy and safety CAB in combination with RPV.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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.

In Phase 2 studies LATTE and LATTE-2, significant GCP concerns associated with an investigator were observed. This site was closed and the ongoing participants were transferred to another site and investigator. Actions were taken to ensure the safety of subjects and the integrity of study data. A sensitivity analysis was performed for both studies, concluding that the exclusion of the data is not expected to have an impact on the overall study interpretations.

In Phase 3 studies FLAIR and ATLAS, significant GCP concerns associated with an investigator were observed. This site was closed and the ongoing participants were transferred to another site and investigator. Data from these subjects was not compromised, and therefore not excluded from analyses.

The applicant was requested to provide more information regarding the deficiencies at these sites. This information was provided and was considered that they did not have an impact on the overall conclusions of the studies.

Table 1 Tabular overview of clinical studies

Study	Study Design	Population	Treatment details	Key conclusions
201584 (FLAIR) GSK Document Number: 2017N345267_00 Status: Ongoing; Week 48 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC	HIV-1 infected ARV treatment-naïve adult subjects	**Induction Phase (20 weeks):** Oral ABC/DTG/3TC FDC (NRTI substitution allowed) **Maintenance Phase (100 weeks):** CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs) **Extension Phase and beyond:** Details are provided in the CSR.	The primary analysis demonstrated that CAB + RPV is non-inferior to CAR (ABC/DTG/3TC FDC), with 2.1% of subjects in the CAB + RPV group and 2.5% of subjects in the CAR group with plasma HIV-1 RNA ≥50 c/mL based on the Snapshot algorithm at Week 48 (ITT-E population). The adjusted treatment difference between CAB + RPV and CAR was -0.4% (95% CI, -2.8%, 2.1%), which met the non-inferiority criterion, set below 6%.
201585 (ATLAS) GSK Document Number: 2018N370336_00 Status: Ongoing; Week 48 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen	HIV-1-infected ARV-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (52 Weeks):** CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: 2 NRTIs + INI or 2 NRTIs + PI or 2 NRTIs + NNRTI. **Extension Phase and beyond:** details are provided in the CSR.	The primary analysis demonstrated that CAB + RPV is non-inferior to CAR, with 1.6% of subjects in the CAB + RPV group and 1% of subjects in the CAR group with plasma HIV-1 RNA ≥50 c/mL based on the Snapshot algorithm at Week 48 (ITT-E population). The adjusted treatment difference between CAB + RPV and CAR was 0.6% (95% CI, -1.2%, 2.5%), which met the non-inferiority criterion, set below 6%.
207966 (ATLAS-2M) GSK Document Number: 2019N397739_00 Status: Ongoing; Week 24 Data Summary completed	Open-label, randomized, Phase IIIb trial to demonstrate non-inferiority of LA CAB + LA RPV Q8W compared with LA CAB + LA RPV Q4W	HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (52 Weeks):** CAB + RPV Q4W group: CAB LA 600 mg + RPV LA 900 mg loading dose*, CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) CAB + RPV Q8W group: CAB LA 600 mg + RPV LA 900 mg loading dose*, CAB LA 600 mg + RPV LA 900 mg second loading dose* administered 4 weeks after the initial loading dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks (±7 days) *Note: Subjects were either transitioned from Study 201585 (CAB + RPV Q4W or SOC) or from their current SOC. Those transitioning from SOC received oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks followed by appropriate loading doses. Those transitioning from CAB + RPV Q4W received OLI and loading doses during their participation in Study 201585 and started maintenance doses on Day 1 of Study 207966 according to their randomization assignment. **Extension Phase and beyond**: Details are provided in the 24 Week Data Summary.	Based on the Week 24 Snapshot analysis, similar rates of plasma HIV-1 RNA ≥50 c/mL and HIV-1 RNA <50 c/mL were observed in Study 207966 for the ITT-E population across the Q8W and Q4W groups.

Study	Study Design	Population	Treatment details	Key conclusions
200056 (LATTE-2) GSK Document Number: 2018N380094_00 Status: Ongoing; Week 96 CSR completed, Week 160 CSR completed	Open-label, randomized, dose ranging, Phase IIb trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression	HIV-1 infected ARV treatment-naïve adult subjects	**Induction Phase (20 weeks):** Oral CAB 30 mg + ABC/3TC once daily. With oral RPV 25 mg once daily for last 4 weeks **Maintenance Phase (96 weeks):** CAB + RPV Q4W group: CAB LA 800 mg + RPV LA 600 mg loading dose, CAB LA 400 mg + RPV LA 600 mg every 4 weeks CAB + RPV Q8W group: CAB LA 800 mg + RPV LA 900 mg loading dose, CAB LA 600 mg second loading dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks Control group: Oral CAB 30 mg + ABC/3TC once daily **Extension Phase and beyond**: details are provided in the CSR.	The proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 32 was similar between Q4W (94%) and Q8W (95%). The proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 was 7% (n=8) for the Q8W group and <1% (n=1) for the Q4W group. These results, in combination with the observed safety profile evident at Week 32 and 48, contributed to the selection of Q4W dosing for further investigation in Studies 201584 and 201585. Data up to Week 160 is available in this submission.
LAI116482 (LATTE) GSK Document Number: 2016N280049_00 and 2014N216014_00 Status: Completed; Week 96 CSR completed; Week 144 SCSR completed	Randomized, dose ranging, Phase IIb trial evaluating oral CAB in combination with oral RPV	HIV-1 infected ARV treatment-naïve adult subjects	**Induction Phase (24 weeks):** CAB group: Oral CAB 10, 30, or 60 mg + ABC/3TC or TDF/FTC once daily Control group: EFV + ABC/3TC or TDF/FTC **Maintenance Phase (72 weeks):** CAB + RPV group: Oral CAB 10, 30, or 60 mg + oral RPV 25 mg once daily Control group: EFV + ABC/3TC or TDF/FTC **Open-Label Phase (post 96 weeks)**: CAB 30 mg + RPV 25 mg	The combination of oral CAB and oral RPV effectively maintained plasma HIV-1 RNA <50 c/mL. Results of this study supported the selection of CAB 30 mg in combination with RPV 25 mg for future use to support LA therapy as an oral lead in and/or bridging supply.
LAI115428 GSK Document Number: 2013N159813_00 Status: Completed; CSR completed	Open-label, randomized, repeat dose escalation, Phase I trial to determine the safety, tolerability, and PK profile of IM and SC injections of CAB LA alone and in combination with RPV LA	Healthy adult subjects	**Cohort 2 (4 months):** Loading dose of CAB LA 800 mg IM at month 1, followed by CAB LA 200 mg IM at months 2-4 + RPV LA 1200 mg IM at month 3 and RPV LA 900 mg IM at month 4 **Cohort 3 (4 months):** Loading dose of CAB LA 800 mg IM at month 1 followed by CAB LA 400 mg IM at months 2-4 + RPV LA 1200 mg IM at month 3 and RPV LA 600 mg IM at month 4 Details of the run-in period, and Cohorts 1, 4 are described in the CSR.	RPV LA did not alter the PK of CAB LA and vice versa when the two drugs were co-administered.
LAI116181 GSK Document Number: 2011N130484_00 Status: Completed; CSR completed	Open-label, repeat dose, three-period, single-sequence, Phase I drug-drug interaction trial: Cohort 2 evaluated coadministration of oral RPV with oral CAB	Healthy adult subjects	CAB 30 mg once daily for 12 days alone followed by a 14-day washout, and then RPV 25 mg once daily for 12 days alone, immediately followed by CAB 30 mg + RPV 25 mg once daily for 12 days	Oral RPV did not alter the PK of oral CAB and vice versa when the two drugs were co-administered.

2.4.2. Pharmacokinetics

Thirteen Pharmacokinetic studies were provided, as well as five studies with punctual PK data, a population PK modelling report, and a meta-analysis report on relationships between UGT1A1 and 1A9 genotypes and Cabotegravir PK.

Absorption

After IM injection of the LA form, cabotegravir exhibits absorption rate-limited (flip-flop) PK because CAB is slowly absorbed into the systemic circulation following IM injection into the gluteus medius muscle. CAB LA absorption rate-limited PK is reflected in a long apparent t1/2.

CAB is rapidly absorbed following oral administration, with an absorption rate of 1.41 h-1 and a median tmax of 3 hours.

Bioavailability

Mass-balance study LAI117008 showed that 26.8% of the radioactivity was eliminated in urine after a single oral dose of marked Cabotegravir, therefore it can be inferred that absolute bioavailability is at least 26.8%. Along with information on solubility (see introduction here and see Quality report), the suggested BCS classification for Cabotegravir in BCS class II is acceptable from a PK standpoint.

Bio-equivalence

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 formulations provided relative bioavailability of at least 50% to that of the current sodium salt. The AUC of the nanomilled and micronised formulations were approximately 12% and 48% lower than those of the sodium salt tablet formulation, respectively. These data suggest 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 micronised drug substance met the preestablished acceptance criteria. Neither of the test formulations made with unmicronised 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 micronised GSK1265744B drug substance was selected for progression into phase 3 studies.

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

Influence of food

Food effect data came from studies 205696, LA1I17020 and ITZ111682.

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

Overall, the food effect can be considered consistent enough through oral formulations and small enough (15%) that cabotegravir can be administered with or without food.

Distribution

Distribution volumes are in the smaller range but suggest some distribution of cabotegravir to extracellular space. Population PK estimates were for Vc/F 5.27 L and Vp/F 2.43 L, slightly lower than the estimates from the studies.

The *in vitro* protein binding of cabotegravir in serum or plasma was high (>99%) across species, the association of cabotegravir related material with blood cellular components was minimal in both nonclinical species and human ranging from 0.44 to 0.57.

Elimination

Average CL/F ranged between 0.25 L/h (CV 20%) and 0.37 L/h (CV 32%). Average T1/2 after oral dosing ranged from 36.3 h (CV 20%) and 42.83h (CV 23%). For IM doses, the terminal elimination half-life was

representative of the release rate from injection site (in Study LAI116815: T1/2 geometric mean CV% were between 337.43 h (40%) and 615.08 h (29%)). This very long release made estimating this parameter complicated, hence the uncertainty.

Excretion

Following single dose administration of [14C]-CAB 30 mg oral solution in humans, 85.3% of the administered dose was recovered in the excreta; 58.5% of the dose was recovered in faeces and 26.8% was recovered in urine. CAB accounted for 46.8% of the administered dose in faeces and was not detected in urine. The glucuronide metabolite GSK3388352 (M1) represented the majority of the radioactivity recovered in urine.

Both CAB and GSK3388352 were detected in bile.

Metabolism

In the human mass balance study, CAB was the predominant circulating metabolite in plasma, representing 80.5 to 100% of plasma total radiocarbon in pooled plasma samples collected 2 to 24 hours post-dose and the majority of the plasma radiocarbon AUC(0-inf); no metabolites were quantified in pooled plasma samples.

Based on metabolic profiling in urine, faeces, and bile, glucuronidation leading to formation of GSK3388352 (M1) is the primary metabolic pathway, accounting for 20% of the administered dose. Glucose conjugation leading to formation of M2 is a minor pathway for CAB metabolism; M2 was detected, but not quantified, in urine. Unchanged CAB and GSK3388352 (M1) were detected in duodenal bile samples. CAB is the major component in plasma and the glucuronic acid metabolite is the predominant component in urine, regardless of route of administration

In human studies LAI115428 and LAI114433, mass spectrometric analyses determined that M3 (a metabolite formed by oxidation, fluorine loss and cysteine conjugation) represented <1% of the drug-related material present in the urine following oral, IM, and SC administration.

These conjugated metabolites, CAB glucuronide and M2, are not pharmacologically active.

Only unchanged CAB was observed in the faeces of all species.

The only quantifiable metabolite observed in human urine was CAB glucuronide and this was also the predominant metabolite observed in the urine of the nonclinical species.

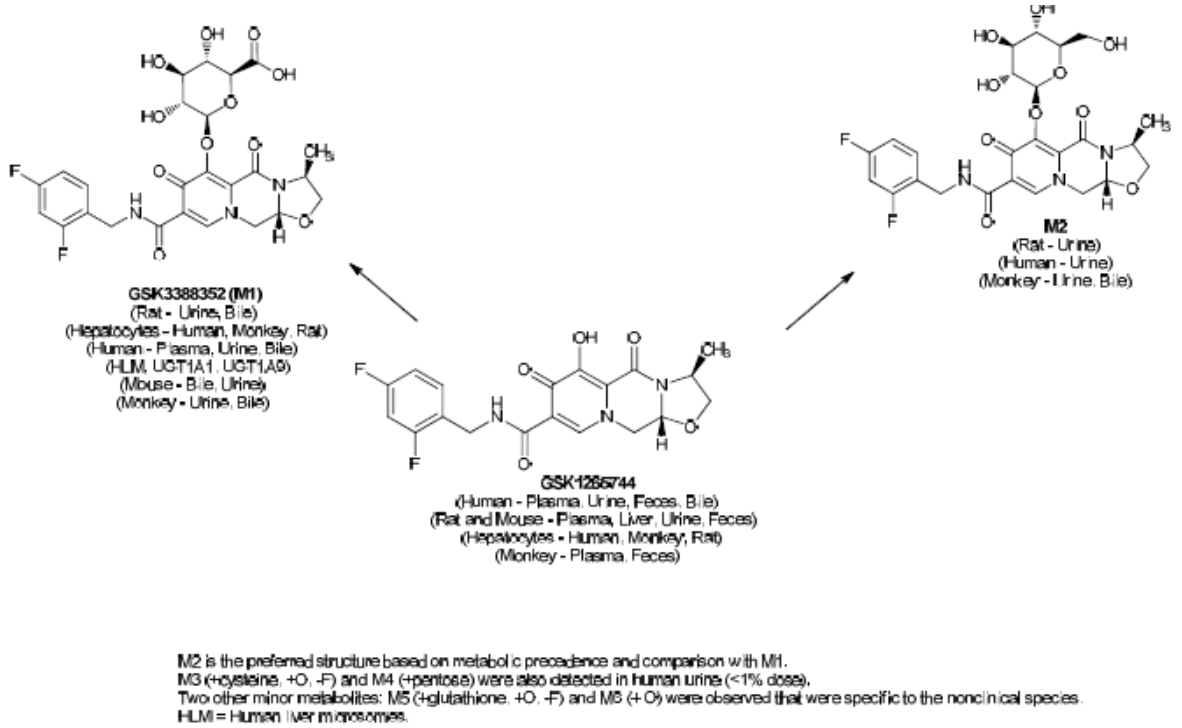


Figure 3 Metabolic profiling of Cabotegravir

Inter-conversion

CAB has 2 chiral centres. Following repeat oral administration of CAB for 14 days to healthy human volunteers, no evidence for the *in vivo* epimerisation of CAB to any of its stereoisomers was observed.

Pharmacokinetics of metabolites

As none of the metabolites are pharmacologically active and no metabolites were quantified in pooled plasma samples, PK of metabolites was not further studied.

Consequences of possible genetic polymorphism

Meta-analysis 2051612 shows that 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

In Study ITZ111451, PK exposure increased less than proportionally between 5 and 50 mg oral SD and proportionally between 5 and 25 mg oral MD.

In study LAI114433, Plasma GSK1265744 PK parameters increased less than proportionally to dose following single unsplit injections from 100-400mg IM; plasma PK parameters appeared to increase proportionally to dose following split injections from 400mg (2x 200mg) IM to 800mg (2x 400mg) IM and following 100mg to 400mg SC.

In study LAI115428, PK parameters after IM dosing between 200 mg and 400 mg show under proportionality.

Overall, plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat dose administration of CAB LA 100 to 800 mg IM and oral CAB 5 to 60 mg.

Following single dose administration of a higher dose of oral CAB 150 mg, geometric mean plasma CAB Cmax (10.4 microg/mL) and AUC(0-inf) (418 microg.h/mL) were markedly lower than expected compared with oral CAB 30 mg (geometric mean Cmax of 3.61 microg/mL and AUC(0-inf) of 146 microg.h/mL).

In ITZ111451, steady state was reached at Day 12 after oral MD, and accumulation ratio was consistent with a terminal elimination half-life of 40 hours (2.5 observed with truncated data, 2.9 expected). Overall, PK of cabotegravir appears to be time-independent.

Inter and intra-variability

Moderate between-subject variability (%CVb) in plasma CAB PK was observed following repeat-dose administration of CAB. Following administration of CAB LA 400 mg Q4W in healthy or HIV-1 infected subjects, between subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 26 to 39% across studies. Following administration of oral CAB 30 mg once daily, between-subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 26 to 34% across healthy subject studies and 28 to 56% across HIV-1 infected subject studies. Higher between-subject variability (41 to 89%) in plasma CAB PK was observed with single dose administration of CAB LA.

Within-subject variability (%CVw) in plasma CAB PK was low following administration of oral CAB. Within-subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 7 to 11% following repeat dose administration of oral CAB 30 mg once daily. Plasma CAB AUC(0-inf), Cmax, and C24 ranged from 13 to 32% following single-dose administration of oral CAB 30 mg. Within-subject variability data are not available for CAB LA because CAB LA studies were parallel design.

Pharmacokinetics in target population

Study LAI116181 showed the absence of PK interaction between Cabotegravir and co-prescribed drug Rilpivirine are acceptable. Population PK modelling and comparison of data between studies show that there is no major difference in PK between target population (HIV1-infected patients) and healthy volunteers.

Regarding population PK modelling, gender, weight and BMI effects are shown, but should not have clinical impact, refer to Special Populations section for discussion. Oral treatment for up to 2 months is an appropriate replacement in case of missed LA injections.

Special populations

The clinical study and the population PK analysis lead 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.

In pop PK modelling, categorisation of Cmin-LD by gender showed that the median was lower in females than males by 31%. For Cmin-SS, the impact of all covariates was predicted to be relatively small (≤15%). The impact of gender on Cmax-SS were all predicted to be relatively small (≤21%).

At steady-state, median predicted Cmax-SS was lower and median predicted Cmin-SS was higher in females than males, consistent with slower absorption in females than males. The effect of gender did not justify any dose modification.

Race was not a covariate with clinically relevant impact on the PK of CAB after IM dosing.

In pop PK modelling, a categorisation of Cmin-LD by BMI showed that subjects with BMI ≥30 kg/m2 had 31% lower median Cmin-LD than those with BMI <30 kg/m2. For Cmin-SS, the impact of all covariates was predicted to be relatively small (≤15%). The impact of WT and BMI on Cmax-SS were all predicted to be relatively small (≤21%). There was an effect of weight and BMI, but small enough to no justify any dose modification.

Age was not a covariate with clinically relevant impact on the PK of CAB after IM dosing.

There are no PK data for Cabotegravir in children, it is not intended for paediatric use.

There were only very few elderly subjects enrolled in the clinical studies. Patients are recorded in the table below.

Table 2 Number of subjects according to age group.

	Group	**Age 18-64 (Older subjects number /total number)**	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Pooled Clin Pharm Studies	CAB Overall	534 (99%)	8 (1%)	0	0
	CAB+RPV	19 (100%)	0	0	0
	RPV only	188 (100%)	0	0	0
LATTE	Overall	241 (>99%)	2 (<1%)	0	0
	CAB+RPV (all)	181 (100%)	0	0	0
	Control	60 (97%)	2 (3%)	0	0
LATTE-2	Overall				
	CAB+RPV (all)	230 (100%)	0	0	0
	Control	56 (100%)	0	0	0
ATLAS	Overall	601 (98%)	14 (2%)	1 (<1%)	0
	Q4W	303 (98%)	5 (2%)	0	0
	control	298 (97%)	9 (3%)	1 (<1%)	0
FLAIR	Overall	563 (>99%)	3 (<1%)	0	0
	Q4W	281 (>99%)	2 (<1%)	0	0
	control	282 (>99%)	1 (<1%)	0	0

ATLAS-2M	Overall	1017 (97%)	26 (2%)	2 (<1%)	0
	Q8W	502 (96%)	19 (4%)	1 (<1%)	0
	Q4W	515 (98%)	7 (1%)	1 (<1%)	0

Exposure relevant for safety evaluation

Examples of exposures obtained after oral and LA dosings are presented below.

Table 3 Oral Cabotegravir exposures observed at steady state of oral dose in LAI116482

Virologic Response or PK Parameter	Study LAI116482			
	Oral CAB + Oral RPV 25 mg Once Daily [a]			Comparator [b]
	10 mg Once Daily (n=52)	30 mg Once Daily (n=53)	60 mg Once Daily (n=55)	EFV + 2 NRTIs (n=47)
Primary Endpoint Week 48 (Maintenance Week 24) Plasma HIV-1 RNA <50 c/mL n (%) [c]	48 (92)	48 (91)	53 (96)	44 (94)
Plasma CAB Ctau (µg/mL) geometric mean (min-max) [d]	1.34 (0.2-5.2) [n=50]	3.93 (1.3-9.6) [n=51]	8.22 (3.5-21.7) [n=49]	-
Plasma CAB Ctau/PA-IC90 geometric mean (min-max) [d,e]	8.07 (1.20-31.3)	23.7 (7.83-57.8)	49.5 (21.1-131)	-

Data Source: Study LAI116482 Week 96 CSR Table 7.5, Table 9.4

a. The combinations of oral CAB (10 mg, 30 mg, and 60 mg once daily) + oral RPV 25 mg once daily were evaluated as maintenance regimens in HIV-1-infected subjects with virologic suppression following 24 weeks induction with oral CAB + 2 NRTIs.
b. Subjects in the comparator arm received EFV 600 mg once daily + 2 NRTIs for induction therapy; subjects with virologic suppression continued this regimen for the maintenance phase of the study.
c. The proportion of subjects achieving plasma HIV-1 RNA <50 c/mL is per the Snapshot (MSDF) Analysis (ITT-ME Population)
d. Plasma CAB Ctau = individual average of Week 26 and Week 36 values
e. CAB PA-IC90 = 0.166 µg/mL

Table 4 Oral Cabotegravir exposures observed at steady state after IM LA form in two other studies

Virologic Response or PK Parameter (Maintenance Phase Week 48)	CAB + RPV [a]		Comparator Regimens	
	201584 [b] (n=283)	201585 [c] (n=308)	201584 [b] CAR (n=283)	201585 [c] CAR (n=308)
Primary Endpoint Plasma HIV-1 RNA >50 c/mL[d] n (%)	6 (2.1)	5 (1.6)	7 (2.5)	3 (1.0)
Secondary Endpoint Plasma HIV-1 RNA <50 c/mL[d] n (%)	265 (94)	285 (93)	264 (93)	294 (95)
Plasma CAB Ctau (µg/mL) geometric mean (min-max)	3.13 (0.910-74.2)	2.84 (0.406-8.53)	-	-
Plasma CAB Ctau/PA-IC90 [e] geometric mean (min-max)	18.9 (5.48-447)	17.1 (2.45-51.4)	-	-
Plasma RPV Ctau (ng/mL) geometric mean (min-max)	82.4 (22.3-214)	90.3 (8.1-256)	-	-
Plasma RPV Ctau/PA-IC90 [e] geometric mean (min-max)	6.87 (1.86-17.8)	7.53 (0.675-21.3)	-	-

Data Source: Study 201584 CSR Table 2.1, Table 2.15, Table 4.3, Table 4.4; Study 201585 CSR Table 2.1, Table 2.47, Table 4.3, Table 4.4

a. CAB + RPV Regimen: CAB 30 mg once daily + RPV 25 mg once daily for 4 weeks followed by an initial dose of CAB LA 600 mg IM + RPV 900 mg IM and Q4W doses of CAB LA 400 mg IM + RPV 600 mg IM
b. Study 201584: ART-naïve subjects received ABC/DTG/3TC FDC (or DTG + 2 other NRTIs) for 20 weeks as induction therapy and then were randomized to remain on this regimen or switch to the CAB LA + RPV LA Q4W regimen.
c. Study 201585: ART-experienced subjects who were virologically suppressed on their current ART were randomized to continue this regimen or switch to the CAB LA + RPV LA Q4W regimen.
d. The proportion of subjects achieving plasma HIV-1 RNA >50 c/mL and <50 c/mL is per the Snapshot Analysis (ITT-E Population)
e. CAB PA-IC90 = 0.166 µg/mL; RPV PA-IC90 = 12 ng/mL

Pharmacokinetic interaction studies

The applicant conducted a large programme of *in vitro* and *in vivo* studies to establish the DDI profile of cabotegravir. Hence, around twenty *in vitro* studies, one PBPK modelling and simulation, one mechanistic analysis and 5 clinical DDI studies.

- ***In vitro***
  - *CAB and CYP*

CAB does not undergo metabolism through CYP enzymes: oxidation of CAB accounts for <1% dose in humans. Consequently, any drug-drug interactions with CAB, as a victim, driven by CYPs inhibition or induction are not expected to be clinically relevant. Of note, CAB is mainly glucuronidated and some CYP inducers (e.g. rifampin, phenobarbital) or inhibitors (e.g. imatinib, ketoconazole) also induce or inhibit UGTs.

The ability of CAB to be a competitive and mechanism-based inhibitor (MBI) of the main CYP450 enzymes, CYP1A2, CYP2C8, 2B6 CYP2C9, 2C19, 2D6, 3A4/5, 2A6, was investigated (study 2012N151766) and with a range of CAB concentrations from 0.1 to 100 µM. Results show that, at the highest tested concentration (which is more than 3-fold CAB worst expected concentrations at the intestinal level, i.e. 29.6 µM), no direct or time-dependant inhibition was observed by CAB on CYP1A2, 2A6, CYP2C9, 2C19, 2D6 and CYP2C8. As regards CYP2B6, no TDI or metabolism inhibition by CAB up

to 100µM appeared but a direct inhibition, about 20% of the enzyme, at 100 µM. Nonetheless this is not expected to have any clinical consequence considering the worst concentration of CAB expected at the systemic level, i.e. 19 µM. Conversely, on CYP3A4 different results were observed according to the control substrate used: a direct inhibition with atorvastatin and nifedipine whereas no direct inhibition with midazolam. After 30 minutes preincubation with pooled human liver microsome (PHLM) with NADPH, CYP3A4 metabolism-dependant inhibition by CAB is observed. 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 (see *In vivo* part). No study was performed with testosterone as substrate, but this may well be because the *in vitro* interaction studies were performed before the outcome of the current Guideline on the Investigation of Drug Interactions (i.e. in 2007 and 2012). It is agreed that there is likely low risk of CYP3A inhibition by CAB because no relevant inhibition potential was found *in vitro* using 3 different substrates and CAB had no clinically relevant effect on the exposure to midazolam in the clinic. Also, CAB had no significant effect on the exposure to ethinyl estradiol and rilpivirine, which are also CYP3A substrates. The effect of CAB on the exposure to rilpivirine is shown in the table below. Overall, the risk of CYP3A inhibition by CAB is likely to be low.

The CYP inducing potential of CAB on CYP1A2, 2B6 and 3A4 was investigated in study 2013N166279. The applicant concluded that CAB does not induce any tested CYPs. However, this conclusion is not supported based on the data provided. Results that arise from this study remain inconclusive. Indeed, the main issue is the inconsistency of mRNA level responses according to each donor and according to CAB concentrations. As the EU Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1) highlights the appraisal of any inducing potential should be made at the mRNA donor level (*"the donor cells with the most pronounced induction effect on the specific enzyme should then be used as a "worst case" in the subsequent calculations")* and not based on the mean mRNA level, as done by the applicant. Then, for at least one donor, at CAB 0,03 µM the lower tested concentration, CAB increased more than 2-fold mRNA level of CYP1A2 or CYP2B6.

There is an unsolved experimental reason that perhaps could explain such irregular responses to induction through the range of CAB concentrations. Therefore, the applicant agreed to perform another *in vitro* study assessing the CAB inducing potential on CYP1A2 and 2B6 to be included in a future type II variation. CAB will be incubated with cryopreserved human hepatocytes for 48 hrs and mRNA levels for CYP1A2 and CYP2B6 will be determined. Positive control inducers will be included, and cell viability checks will be performed.

Table 5 mRNA level responses according to each donor and to CAB concentrations

Donor ID	24h Incubation Treatment \ Donor	mRNA level (ratio of treated over control) Donor 1	Donor 2	Donor 3	Mean ± st. Dev.	Percent Induction
CYP1A2[1]	DMSO Control	1.0	1.0	1.0	1.0 ± 0.0	0.0%
	0.03 µM GSK1265744	1.2	1.8	2.3	1.8 ± 0.55	1.0%
	0.1 µM GSK1265744	1.0	0.85	0.87	0.92 ± 0.10	<1.0%
	0.3 µM GSK1265744	1.0	0.80	1.2	1.0 ± 0.19	<1.0%
	1.0 µM GSK1265744	1.1	1.6	1.5	1.4 ± 0.24	<1.0%
	3 µM GSK1265744	1.0	1.1	0.99	1.0 ± 0.036	<1.0%
	10 µM GSK1265744	1.3	0.74	1.4	1.2 ± 0.36	<1.0%
	30 µM GSK1265744	0.93	1.8	1.9	1.5 ± 0.53	<1.0%
	Prototypical inducer[3]	31	170	60	88 ± 75	100%
CYP2B6[2]	DMSO Control	1.0	1.0	1.0	1.0 ± 0.0	0.0%
	0.03 µM GSK1265744	1.1	3.2*	2.0	2.1* ± 1.1	9.4%
	0.1 µM GSK1265744	0.84	0.85	0.94	0.88 ± 0.053	<1.0%
	0.3 µM GSK1265744	0.91	0.99	1.1	1.0 ± 0.10	<1.0%
	1.0 µM GSK1265744	0.97	2.0	1.5	1.5 ± 0.50	4.2%
	3 µM GSK1265744	0.88	1.6	1.3	1.3 ± 0.35	2.5%
	10 µM GSK1265744	0.89	1.4	1.3	1.2 ± 0.27	1.9%
	30 µM GSK1265744	1.0	2.6*	0.82	1.5 ± 0.97	5.5%
	Prototypical inducer[3]	12	11	22	15 ± 6.3	100%
CYP3A4[1]	DMSO Control	1.0	1.0	1.0	1.0 ± 0.0	0.0%
	0.03 µM GSK1265744	1.1	2.4	2.2	1.9 ± 0.75	8.2%
	0.1 µM GSK1265744	1.0	0.98	1.2	1.1 ± 0.10	<1.0
	0.3 µM GSK1265744	1.1	1.1	1.4	1.2 ± 0.17	1.7%
	1.0 µM GSK1265744	1.2	2.5	1.1	1.6 ± 0.80	5.8%
	3 µM GSK1265744	0.71	2.2	1.3	1.4 ± 0.73	4.3%
	10 µM GSK1265744	1.0	1.4	0.92	1.1 ± 0.22	1.2
	30 µM GSK1265744	0.86	2.6	1.1	1.5 ± 0.95	5.3%
	Prototypical inducer[3]	9.1	12	12	11 ± 1.8	100%

Controls are defined as 0.5% (v/v) DMSO. Data presented to 2 significant figures.

1. Increase in mRNA level of ≥ 5 mean ratio of treated over control is considered as a notable induction response for both omeprazole and GSK test compound.
2. Increase in mRNA level of ≥ 3 mean ratio of treated over control is considered as a notable induction response for phenytoin and rifampicin. Increase in mRNA level of ≥ 2 mean ratio of treated over control is considered as a notable induction response for GSK test compound.
3. Prototypical CYP Inducers: 50 µM Omeprazole (CYP1A2), 50 µM Phenytoin (CYP2B6), 10 µM Rifampicin

CAB and UGTs

CAB is predominantly metabolised by UGT1A1 and, in a lesser extent, UGT1A9. Therefore, clinically relevant drug-drug interactions related to inhibition or induction UGT1A1 are expected (see *In vivo* part).

The applicant concludes that it is not necessary to perform DDI studies with UGT inhibitors based on the pharmacogenetics analysis, in which the exposure to orally administered CAB was shown to increase by approximately 1.5-fold in subjects with low UGT1A1 activity. This result can however not be generalised to UGT inhibitors, because individuals with low UGT1A1 activity still have some activity, while some strong UGT1A1 inhibitors can completely eliminate UGT1A1 activity. Hence based on this estimation, the following statement has been added to the SmPC: *The impact of an UGT1A1 inhibitor may be slightly more pronounced, however, considering the safety margins of cabotegravir, this increase is not expected to be clinically relevant. No dosing adjustments for Vocabria are, therefore, recommended in the presence of UGT1A1 inhibitors (e.g. atazanavir, erlotinib, sorafenib).* Of note, PBPK modelling and simulations (see *In silico* part) predicted no clinically significant increase in CAB exposure if combined with atazanavir, an UGT1A1 inhibitor. However, since major issues have been raised on the model building results observed cannot be validated and then no conclusion drawn **(see *in silico* part)**

CAB is an inhibitor of 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.

In this experiment investigating UGT inhibition, it was indicated that no positive controls were qualified for UGT2B4, UGT2B15 and UGT2B17 but the metabolic activity of these UGTs was confirmed by the rates of substrate metabolism. The results of the positive controls of the other enzymes show that the system was functioning adequately. It can also be reasonably assumed that the Supersomes used in the study were adequately characterised by Corning® Gentest.

- *CAB and efflux transporters*

CAB is both a P-gp and BCRP substrate. The applicant claims that clinically relevant interactions related to CAB combination with a P-gp or BCRP inhibitor is expected to be unlikely due to its high apparent passive permeability. If this assumption could be supported for a combination with either a P-gp or a BCRP inhibitor, the clinical consequence of co-administration with a compound that is both a P-gp and a BCRP inhibitor (e.g. cyclosporin) is unclear. The applicant attempted to clarify this issue by using rilpivirine as an example of both a P-gp and BCRP inhibitor. The limit of this assertion is the lack of data demonstrating rilpivirine is both P-gp and BCRP inhibitor. *In vitro* rilpivirine has the potential to inhibit P-gp, with an IC50 value of 9.2 µM in Caco-2 cells but the clinical relevance of this feature has not been explored yet. As regards its effect on BCRP, the applicant justification remains unclear since no *in vitro* and in vivo data have been found out. The applicant additional explanation to ensure safe use of CAB with a P-gp and BCRP inhibitor was the high permeability of CAB which varies in a range of 44–83%. The lowest bioavailability value reported for CAB is 44% (data from a pharmacokinetic study in dog); therefore, the maximum possible increase in systemic exposure of orally administered CAB is 2.3-fold assuming complete inhibition of Pgp and BCRP (1/1- fraction excreted ie 1/1-0.56, Zamek-Gliszczynski et al, 2009). The bioavailability of CAB in human is estimated to be >85% based on the PBPK model (Report 2018N389974); therefore, the clinical drug interaction potential with a dual Pgp and BCRP inhibitor will be at most <1.2-fold (ie 1/1-0.15). Long-term administration of CAB 60 mg once daily to HIV infected subjects in the LAI116482 (LATTE) study and short-term administration of oral CAB 150 mg q12h x 3 doses in the LAI117009 (TQT) study provides safety margins of 2-fold to 5.6-fold for the unlikely increase due to co-administration of CAB 30 mg with P-gp and BCRP inhibitors. Due to the clinical safety cover for the worst-case increases in CAB exposure due to P-gp and BCRP inhibition, the applicant proposes that a clinical study with CAB and cyclosporine is not required. This is considered acceptable.

At therapeutic concentrations, clinically relevant drug-drug interactions related to P-gp and BCRP inhibition by CAB are not expected.

CAB is neither a BSEP nor a MRP2 and MRP4 inhibitor. However, it is unknown whether CAB inhibits or not MRP3. The applicant used methotrexate as an example to demonstrate any lack of interaction related to MRP3 inhibition with CAB but since other efflux transporters may overcome to a potential MRP3 inhibition of MTX by CAB, MTX appears to not be an adequate probe substrate of MRP3. However, MRP3 functions as a bile acid basolateral overflow pump in conjunction with MRP4, when canalicular excretion of bile acids via BSEP and MRP2 is impaired (Kenna et al, 2018). Unlike Mrp4-knockout mice, bile duct ligation in Mrp3-knockout mice did not elicit increases in liver bile acids and liver toxicity. Therefore, in the absence of BSEP, MRP2, and MRP4 inhibition, physiological relevance of MRP3 inhibition alone to bile acid disposition is unclear (Zamek-Gliszczynski et al, 2018; Kenna et al, 2018). CAB does not inhibit

BSEP, MRP2 or MRP4. Hence determination of MRP3 inhibition potential in isolation is not of biological or clinical significance making an *in vitro* MRP3 inhibition assay with CAB unnecessary.

Considering the available data on MRP3 inhibition and its clinical relevance in the absence of BSEP, MRP2, and MRP4 inhibition, no further investigations are needed as regards the ability of CAB to inhibit this transporter.

CAB inhibits both MATE1 and MATE2-K with IC50= 18.2µM and 14.2 µM, respectively, covering the worst expected at the systemic level, i.e., 19µM. Therefore, clinically relevant interaction with a probe substrate as metformin, cannot be ruled out. In order to predict the clinical impact of this effect, the applicant developed a mechanistic static model to evaluate CAB as a perpetrator of DDI driven, notably by MATE1 and MATE2-K inhibition. AUC ratio appeared to be < 1.25. Therefore, no clinically relevant DDI expected between CAB and MATE1 and MATE2-K substrates.

- *CAB and uptake transporters*

CAB does not seem to be an OATP1B1, 1B3 or OCT1 uptake transporters substrate. Nonetheless, in the experiment, uptake of CAB into human hepatocytes was investigated using a mixture of OATP1B1, OATP1B3, OATP2B1 and OCT1 inhibitors. This study is considered less reliable than studies with cells transfected with human transporters, which are more sensitive. Result of the hepatic uptake assay and the high permeability of CAB indicate that hepatic uptake is not the rate-determining step in its clearance. It is therefore agreed that further studies for investigating the effect on transporters relevant for hepatic uptake are not expected to provide additional relevant information.

CAB does not inhibit both OATP1B1 and OATP1B3 up to 30 µM. Therefore, clinically relevant DDI with substrates of these uptake transporters (e.g. statins) are unlikely.

CAB inhibits both OCT1 and OCT2 but with an IC50>30 µM. Therefore, clinically relevant interactions with substrates of these uptake transporters are not expected to be meaningful.

CAB inhibits both OAT1 and OAT3 with IC50= 0.8 µM and 0.4 µM, respectively, covering the worst expected at the systemic level, i.e., 19 µM. Therefore, clinically relevant interactions related to their inhibition by CAB cannot be ruled out. To clarify this, feature a mechanistic static model and a PBPK modelling and simulation were conducted. However, since major issues have been raised on the PBPK model building, results observed cannot be validated and then no conclusion drawn. A warning has been then added in the proposed SmPC as regards this risk.

- *CAB glucuronide as a victim and a perpetrator*

CAB glucuronide is a substrate of OATP1B1, OATP1B3, OAT3, MRP2, MRP3, MRP4, but was not transported by OAT1 and OAT4.

Considering the high proportion of CAB glucuronide in urine (CAB glucuronide was the major component, representing >75% of drug related material in urine) and the low proportion of CAB glucuronide in bile in non-clinical species, and the fact that there is only limited indication for hepatic recirculation (see also question 125), it is agreed that most likely, CAB glucuronide is primarily excreted via the urine via rapid active elimination. Hence, BSEP is not expected to be relevant in the transport of CAB glucuronide.as well as the transporters MATE1 and MATE2-K.

CAB glucuronide is unlikely to be an inhibitor of MATE1, MATE2-K, OAT1 and OAT3.

- **Mechanistic static approach and *in silico***

In vitro studies demonstrate the ability of CAB to inhibit UGT1A3, UGT1A9, OAT1, OAT3, MATE1 or MATE2-K. For tested UGT1A3, UGT1A9, MATE1 or MATE2-K substrates, the predicted AUC are < 1.25. Therefore, it can be concluded that no clinically DDI are expected when CAB is combined with drugs metabolised by these UGTs or transporters. Regarding OAT1 and OAT3, it cannot be excluded that their inhibition by CAB leads to clinically relevant DDI (AUC ratio>1.25). To clarify such results a PBPK modelling and simulations were carried out.

The applicant performed PBPK modelling to investigate drug interactions with CAB as an inhibitor of OAT1 and OAT3 substrates, the impact of UGTs inhibitors and inducers on CAB pharmacokinetics and some issues remains as regards the qualification and validity of this approach:

i/ PBPK model for OAT1/3 inhibition

According to the applicant's explanation, the PBPK sensitivity investigation predicted a maximum increase in exposure of up to 1.8-fold with OAT1/3 substrates. The applicant considered these data not clinically relevant. Such a conclusion is not acceptable knowing the narrow safety margin of the OAT substrate Methotrexate and its toxicity notably on the bone marrow. These results are considered as positive and cannot rule out CAB to be a clinically relevant OAT1 and OAT3 inhibitor. Hence according to the EU Guideline on DDI studies, when positive results are identified from PBPK modelling, an in vivo dedicated DDI study should be performed to assess the real magnitude of the interaction.

Of note as regards the examples from the clinical data by the applicant using safety data, the low number of subjects analysed cannot allow a relevant and reliable appreciation of the impact of CAB on the patient safety to be made. Furthermore, safety data are not a very accurate method to establish whether there are DDI interactions.

Considering the limits and deficiency from the PBPK modelling and simulation, the applicant proposed SmPC amendment by adding this risk in the SmPC. Additionally, the combination of CAB with OAT1/3 substrates having a narrow therapeutic index (e.g. methotrexate) should be added in the RMP as an" important potential risk" and this combination should be monitored as part of PSUR.

ii/ Impact of strong UGT inhibitors on CAB PK

Considering the limits and deficiency from the PBPK modelling and simulation, the applicant proposed SmPC amendment by adding this risk in the SmPC.

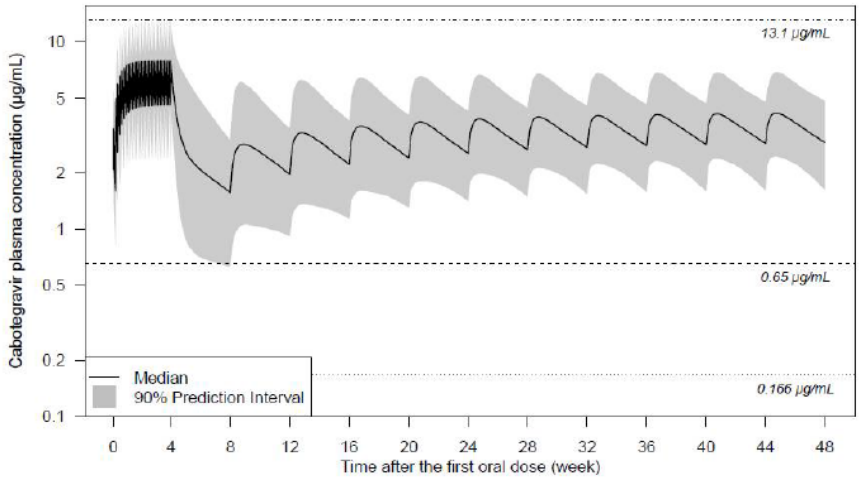
- ***In vivo***

The provided clinical DDI studies were performed with CAB oral route. Results can be extrapolated to CAB LA because data observed with the oral route constitute the worst-case scenario.

- RIF significantly decreases CAB AUC ratio about 59% with 95%IC [0.36-0.46]. Therefore, the combination of CAB with rifampicin and then with other strong UGT inducers (e.g carbamazepine, phenytoin, phenobarbital) is contra-indicated.

- Rifabutin significantly decreases CAB AUC and Cmax about 21% and 17%, respectively, with 95%IC outside the bioequivalence bound of [0.8-1.25], the applicant proposes no dose adjustment of CAB when combined with rifabutin. To justify that these exposures are still sufficiently high to maintain viral suppression, the normal concentration-time profiles are shown for CAB, including the oral lead-in period (see Figure 1, for the monthly regimen, also included below). In these figures it can be seen that during the oral lead-in period, estimated exposure to CAB is clearly higher than the 0.65 µg/mL benchmark (the 5th percentile of individual predicted trough concentrations following the CAB 600mg IM initiation

injection). Reduction of the concentrations of CAB following oral ingestion during the lead-in period by 17-26% is not expected to lead to exposures below the 0.65 µg/mL benchmark. The combination of CAB with rifabutin during the oral lead-in period is therefore not expected to reduce exposures below the benchmark concentration for clinical efficacy.



Reference lines: 0.166 µg/mL=PA-IC90; 0.65µg/mL=5th percentile predicted W8 trough following initiation injections in FLAIR and ATLAS; 13.1µg/mL= median Cmax following CAB 60 mg PO QD observed in LATTE

Figure 4

Simulated Median (90% PI) Cabotegravir Concentration-Time Profile for the Monthly Regimen Evaluated in P3 Studies 201585 (ATLAS) and 201584 (FLAIR)

In section 4.5 of the SmPC for the oral product, ~~t~~there is a difference between the effect of rifabutin on CAB exposure during the oral lead-in period and afterwards during the monthly regimen with CAB LA. It is agreed that the reduction in CAB exposure following co-administration of oral CAB with rifabutin is considered not clinically relevant. From the simulation of the proposed monthly regimen of CAB LA with rifabutin, it appears that only during the first month, the 5th percentile is expected to fall below the 0.65 µg/mL benchmark. Instead of advising completely against co-medication of CAB LA with rifabutin, it could be considered to advise against this co-medication during the first month only.

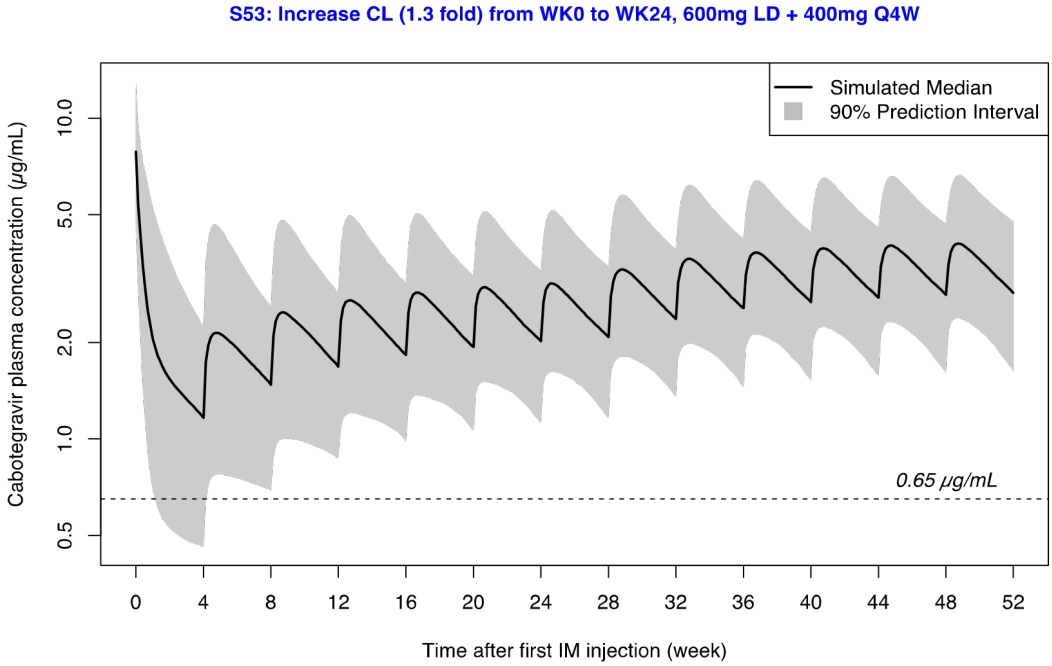


Figure 5 Simulated CAB Plasma Concentration-versus-Time Profile for Scenarios of Increased Metabolism with the UGT Inducer RBT

Furthermore, Rifabutin reduced CAB $AUC_{(0\text{-}tau)}$, C_{max}, and C_{tau} by 21%, 17%, and 26%, respectively. - No DDI observed when CAB is co-administrated with etravirine. The ratio of CAB AUC and Cmax fell within the 95%CI of [0.8-1.25].

Midazolam pharmacokinetics is not significantly altered after repeated doses of oral CAB 30 mg. If *in vitro* data suggest the ability for CAB to be a CYP3A4 inducer and a time-dependant inhibitor (by MBI), the clinical relevance of these features is then not expected to be meaningful.

The conclusion of the applicant that moderate and weak UGT inducers do not reduce plasma CAB to a clinically relevant extent is based on the clinical studies with etravirine and rifabutin. Induction of UGT1A1 expression by rifabutin was shown, at lower fold change than rifampin (up to 2.9-fold versus up to 5.1-fold). Exposure to raltegravir in combination with rifabutin was decreased by 19-39%. Exposure to raltegravir in combination with rifampin was reported to be reduced by 40%, which could however not be found in the referred publication by Brainard et al (2011). However, according to the CDC (Centers for Disease Control and Prevention), rifampin decreased the trough concentrations of raltegravir 400 mg twice daily by ~ 60% (https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations02.htm).

Compared to rifampin, which is a known potent inducer of UGT1A1, rifabutin can be considered a moderate inducer. Etravirine reduced raltegravir exposure by 10-34%, which can be considered comparable to the reduction caused by rifabutin. Overall, it is plausible that etravirine and rifabutin can be considered representative for the moderate UGT1A1 inducers.

- Oral contraceptives undergo metabolism through UGT and CYP pathways the inhibition or induction of which may alter their efficacy or their safety. In the study LAI117011, EE AUC ratio as well as LVG exposure fell within the 95%CI of [0.8-1.25]. It can be concluded that no significant DDI are expected between CAB and oral contraceptives. No dose adjustment is then recommended in the SmPC of CAB when combined with midazolam or EE/LVG. Nonetheless, knowing the hepatotoxicity of ethinylestradiol, an issue is raised as regards the increase risk of hepatotoxicity in case of co-administration with CAB. This will be monitored in the post-marketing and as part of the next PSUR.

- Other Drug-drug interactions

The combinations of CAB with antacids and other mineral supplements has been discussed by extrapolation of results observed from other integrase inhibitors.

Based on table 12, administration of antacids and mineral supplements 4 hours after oral Vocabria, as is recommended in the SmPC, is not expected to be a problem, considering that bictegravir and dolutegravir were at 70-100% of their normal exposure in case of administration of antacids/supplements at 2 h after the bictegravir or dolutegravir.

The advice of using antacids at least 2 hours before oral Vocabria has been clarified. The combination of bictegravir with antacids is the only example given for this situation and it resulted in a decrease in the exposure to bictegravir by 52-58%. The examples under "Simultaneous administration" indicate that there is considerable variation in the effect of antacids or supplements on the exposure to bictegravir and dolutegravir. Also, the applicant states that polyvalent cation antacid products are not recommended for chronic use. However, since these products are available over the counter, it cannot be known whether they are used chronically or not.

Table 6 Summary of Impact of Polyvalent Cation-containing Products on Plasma INI PK (Table 97 MAA m2.7.2)

Co-administered Drug	**INI Dose**	**Geometric Mean Ratio (90% CI) of INI PK parameters with/without co-administered drug No Effect = 1.00**		
		Cmax	**AUC**	**Cmin**
Simultaneous Administration				
Maximum strength antacid 20 mL	Bictegravir 50 mg single dose, fasted	0.20 (0.16, 0.24)	0.21 (0.18, 0.26)	-
Maximum strength antacid 20 mL	Dolutegravir 50 mg single dose, fasted	0.28 (0.23, 0.33)	0.26 (0.22, 0.32)	0.26 (0.21, 0.31)
Calcium carbonate 1200 mg	Bictegravir 50 mg single dose, fasted	0.58 (0.51, 0.67)	0.67 (0.57, 0.78)	-
Calcium carbonate 1200 mg	Dolutegravir 50 mg single dose, fasted	0.63 (0.50, 0.81)	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)
Ferrous fumarate 324 mg	Bictegravir 50 mg single dose, fasted	0.29 (0.26, 0.33)	0.37 (0.33, 0.42)	-
Ferrous fumarate 324 mg	Dolutegravir 50 mg single dose, fasted	0.43 (0.35, 0.52)	0.46 (0.38, 0.56)	0.44 (0.36, 0.54)
Administration 2 hours After INI				
Maximum strength antacid 20 mL	Bictegravir 50 mg single dose, fasted	0.93 (0.88, 1.00)	0.87 (0.81, 0.93)	-
Maximum strength antacid 20 mL	Dolutegravir 50 mg single dose, fasted	0.82 (0.69, 0.98)	0.74 (0.62, 0.90)	0.70 (0.58, 0.85)

Calcium carbonate 1200 mg	Dolutegravir 50 mg single dose, fasted	1.00 (0.78, 1.29)	0.94 (0.72, 1.23)	0.90 (0.68, 1.19)
Ferrous fumarate 324 mg	Dolutegravir 50 mg single dose, fasted	0.99 (0.81, 1.21)	0.95 (0.77, 1.15)	0.92 (0.74, 1.13)
Administration 2 hours Before INI				
Maximum strength antacid 20 mL (2 h before BIKTARVY, fasted)	Bictegravir 50 mg single dose, fasted	0.42 (0.33, 0.52)	0.48 (0.38, 0.59)	-

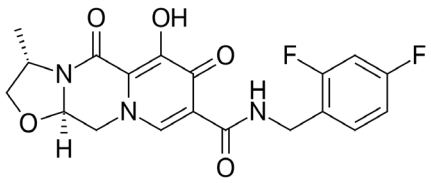
Data Source: BIKTARVY US PI, 2018; TIVICAY US PI, 2018.
Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.

As regards combination with HCV protease inhibitors, the clinical consequence of CAB combination with HCV inhibitors ledipasvir, pibrentasvir, velpatasvir, voxilaprevir, glecaprevir, sofosbuvir, daclatasvir, elbasvir is expected to be limited considering the permeability of CAB and its safety margin (see above impact of P-gp and BCRP inhibitors on CAB PK).

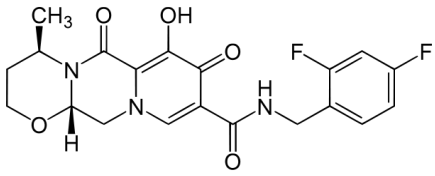
2.4.3. Pharmacodynamics

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 (1 additional carbon):

Cabotegravir:



Dolutegravir:



Similarly to DTG, CAB was highly active with broad activity against all HIV-1 and HIV-2, with comparable EC50. Furthermore, virologic resistance properties of CAB and DTG are close:

- *In vitro*, a significant decrease of the CAB susceptibility was observed with the emergence of mutations Q148K + E138K, and the mutations Q148H + at least 2 INI mutations. The presence of mutation Q148K/R/H at baseline seems associated to a higher risk of decreased susceptibility to CAB and potentially virological failure. The INI mutations N155H and E92Q seems to not significantly impact CAB activity. However, considering the fold-change values in INI-resistant mutant HIV, DTG seems to have a somewhat better susceptibility to the main INI RAM (notably the Q148-mutations):

Table 7 Fold Change (FC) of CAB, DTG and RAL against INI-Resistance Multiple Mutant Viruses by HeLa-CD4 Assay

virus	CAB FC (SD)	DTG FC (SD)	RAL FC (SD)
Wild type (NL432)	1.0 (IC_{50}=1.6 nM, SD=0.27)	1.0 (IC_{50}=2.1 nM, SD=0.36)	1.0 (IC_{50}=6.1 nM, SD=0.89)
T66I, I74M	0.38 (0.11)	0.35 (0.08)	2.0 (0.81)
T66I, E92Q	1.0 (0.38)	1.2 (0.19)	18 (3.6)
T66K, L74M	6.3 (1.8)	3.5 (0.94)	40 (13)
L74M, N155H	2.5 (0.04)	0.91 (0.17)	28 (12)
E92Q, N155H	5.3 (2.8)	2.5 (1.2)	>130
T97A, N155H	2.9 (0.27)	1.1 (0.46)	26 (7.9)
V72I, F121Y, T125K	2.0 (0.61)	1.3 (0.54)	13 (7.1)
V72I, F121Y, T125K, I151V	1.6 (0.66)	1.2 (0.32)	7.0 (2.8)
F121Y, T125K	1.4 (0.55)	0.98 (0.35)	11 (0.49)
E138K, Q148H	0.92 (0.08	0.89 (0.24)	17 (5.9)
E138K, Q148K	81 (24)	19 (8.0)	330 (75)
E138K, Q148R	12 (3.4)	4.0 (1.1)	110 (37)
G140C, Q148R	22 (4.9)	4.9 (1.8)	200 (42)
G140S, Q148K	5.6 (2.5)	1.5 (0.10)	3.7 (1.3)
G140S, Q148R	12 (3.5)	8.4 (4.0)	200 (5.3)
G140S, Q148H	6.1 (0.75)	2.6 (1.4)	>130
Q148R, N155H	61 (28)	10 (1.4)	>140

- In the clinical studies, the number of subjects experiencing virologic failure with CAB treatment is low, which makes it delicate to fully assess the resistance profile of CAB:

Table 8 Number of subjects experiencing virologic failure.

	FLAIR		**ATLAS**		**LATTE-2**			**ATLAS-2M**	
SVF Time Point	CAB+RPV **Q4W**	CAR	CAB+RPV **Q4W**	CAR	CAB+RPV **Q8W**	CAB+RPV **Q4W**	CAB oral	CAB+RPV **Q8W**	CAB+RPV **Q4W**
Week 4	0	0	0	0	1	0	0	0	0
Week 8	1	1	1	0	0	0	1	1	0
Week 12	0	1	1	0	0	0	0	0	0
Week 16	0	1	0	0	0	0	0	3	1
Week 20	1	0	0	2	0	0	0	0	0
Week 24	0	0	1	0	0	0	0	3	0
Week 28	1	0	0	0	0	0	0		

Week 32	0	0	0	1	0	0	0	0	1
Week 40	0	0	0	1	0	0	0		
Week 48	1	0	0	0	1	0	0	1	0
Week 96	0	1	0	0	0	0			
Any time point	**4/283** (1.41%)	**4/283** (1.4%)	**3/308** (0.97%)	**4/308** (1.30%)	**2/115** (1.74%)	**0/115** (0%)	**1/56** (1.79%)	**8/522** (1.5%)	**2/523** (0.4%)

Among the 591 subjects treated by CAB + RPV in the Phase 3 studies ATLAS and FLAIR, 7 subjects experienced virologic failure. The resistance emergence of these 7 subjects is as follows:

Table 9 Patients who experienced virologic failure

FLAIR study:

Study Group	SVF Timepoint	NNRTI RAMs		INI RAMs		HIV Subtype at Baseline
		BASELINE (FC)	SVF (FC)	BASELINE (FC)	SVF (FC)	
CAB + RPV	Week 28	V90I RPV (1.0)	V90I, K101E RPV (2.63) Week 24	L74I CAB (0.95)	L74I, G140R CAB (6.72) DTG (2.23) Week 24	A1
CAB + RPV	Week 20	V179V/ RPV (1.06)	E138E/A/K/T RPV (7.09)	L74I CAB (0.67)	L74I, Q148R CAB (5.22) DTG (0.95)	A1
CAB + RPV	Week 48	V179V/I RPV (0.43)	E138K RPV (0.97)	L74I CAB (0.69)	L74I, Q148R CAB (9.36) DTG (1.11)	A1
CAB + RPV	Week 8	ND[a]	ND	ND	ND	AG

aBaseline genotype was confirmed only for CVF. Genotype/phenotype assays were not done for this subject since no CAB + RPV injections were administered and subject was off-treatment for 18 days at time of suspected failure.

ATLAS study:

Study ARM (Study ART)	On-Treatment, RAMs (HIV-1 RNA) SVF Timepoint				Drugs with reduced sensitivity (FC) SVF Timepoint[a]	Baseline RAMs[b] (PBMC/HIV-1 DNA) (Day 1)		Virus Subtype	
	RT		PR	IN		RT	IN	Day 1 (PBMC/HIV-1 DNA	SVF
	NRTI	NNRTI							
LA-CAB/LA-RPV	none	E138A	none	L74I	RPV(2.4)	E138E/A	L74I	A1	A
LA-CAB/LA-RPV	none	E138E/K	none	N155H L74I	EFV(3.3) ETR(5.2) RPV(6.5) EVG(33) RAL(16) CAB(2.7)	none	L74I	A	A1
LA-CAB/LA-RPV	none	V108I E138K	N88N/S	none	EFV(4.2) ETR(5.8) RPV(3.7)	V108V/I E138K	none	AG	AG

[a]Reduced sensitivity was determined from the Clinical cutoffs or biological cutoffs used in PhenoSense GT assay by Monogram Biosciences
b No PI RAM s were observed in Baseline PBMC vDNA

In addition, the applicant has performed an efficacy analysis according to the presence or absence of the INI RAM L74I. This mutation, present in several subjects at baseline, seems not impact the virologic response.

In study ATLAS-2M, 10 subjects had confirmed virologic failure at Week 48.

Overall, a higher emergence of CAB RAM (E138E/K, Q148Q/R, N155H) and RPV RAM (K101E, E138A, Y188L) is observed with the Q8W regimen.

The most common HIV-1 subtype for all subjects was subtype B (174 subjects in each arm, 61%). Among the 4 CVF subjects in the FLAIR CAB + RPV group, 3 subjects were from Russia and had Subtype A1 virus. In ATLAS, all three subjects with PDVF in the CAB + RPV arm were infected with HIV-1 subtype A, A1 or AG. The two subjects with PDVF in LATTE-2 were infected with virus of Subtype B (no phenotypic or genotypic resistance to RPV or CAB) and Subtype AG. In ATLAS-2M, HIV-1 subtypes were more diverse.

Table 10 Proportion with CVF by Subtype up to week 48 in Phase 2/3b CAB+RPV LA Treatment Groups.

	FLAIR	ATLAS	LATTE-2		ATLAS-2M	
HIV-1 Subtype	CAB+RPV Q4W	CAB+RPV Q4W	Q8W	Q4W	Q8W	Q4W
A	0/46	1/10 (10%)	0/1	0/2	1/14 (7%)	0/9
A1	3/8 (38%)	1/17 (6%)	0/0	0/0	2/30 (7%)	0/30
AE	0/1	0/7	0/0	0/1	0/7	0/6
AG	1/10 (10%)	1/10 (10%)	1/1 (100%)	0/1	0/14	0/8
B	0*/174	0/162	1/95** (1%)	0/89***	2/309**** (0.6%)	2/302***** (0.7%)
C	0/18	0/24	0/0	0/3	2/33 (6%)	0/37
Other	0/19	0/27	0/14	0/17	1/37 (3%)	0/46
Missing	0/7	0/51	0/4	0/2	0/78	0/85
Non-B	4/102 (4%)	3/95 (3%)	1/16 (6%)	0/24	6/135 (4%)	0/136

* two subjects with subtype B had Snapshot HIV-1 RNA ≥50 copies/mL at Week 48 in the CAB + RPV group that did not qualify as CVF
** 6 subjects with subtype B had Snapshot HIV-1 RNA ≥50 copies/mL at Week 48 in the Q8W group that did not qualify as CVF
*** 1 subjects with subtype B had Snapshot HIV-1 RNA ≥50 copies/mL at Week 48 in the Q4W group that did not qualify as CVF
**** 2 subjects with subtype B had Snapshot HIV-1 RNA ≥50 copies/mL at Week 48 in the Q8W group that did not qualify as CVF
***** 3 subjects with subtype B had Snapshot HIV-1 RNA ≥50 copies/mL at Week 48 in the Q4W group that did not qualify as CVF

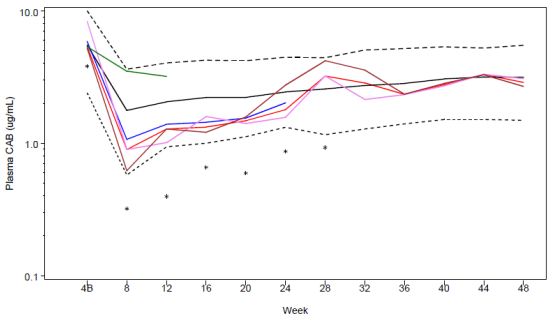
Source: 201584 (FLAIR) W48 CSR 2017N345267_00; 201585 (ATLAS) W48 CSR 2018N370336_00; 200056 (LATTE-2) W48 CSR 2016N273084_00; 207966 (ATLAS-2M) W48 CSR 2019N406358_00.

As regards the PD properties of CAB on cardiac conduction, the study LAI117009 did not show any effect of supratherapeutic doses of CAB (3 doses of CAB 150 mg BID) on QTcF, QTcB and QTci, PR and QRS intervals, T wave and U wave, and heart rate.

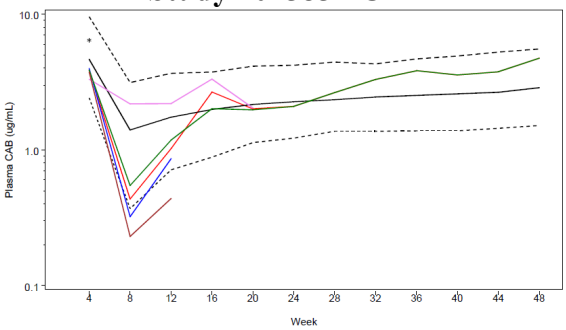
Similarly to DTG, there was no relationship between plasma CAB PK parameters and efficacy parameters (reduction in plasma HIV-1 RNA concentrations in the Phase II studies, emergence of virologic failure in the Phase III studies). The occurrence of virologic failure should rather due to genotypic characteristics of the virus. In both FLAIR and ATLAS studies, no clinically significant relationships between CAB concentrations and QTc changes, ALT changes, bilirubin changes and toxicity grades of the most frequently reported non-ISR AEs (e.g., diarrhea, headache, nasopharyngitis, pyrexia, upper respiratory tract infection).

In both Studies 201584 and 201585, CAB and RPV plasma concentration-time profiles for subjects in the LA arm with snapshot HIV-1 RNA ≥50 c/mL at Week 48 (n=11 across both studies) were generally below the median but within the 5th and 95th percentile of observed data for the remainder of the population (n=580 across both studies)

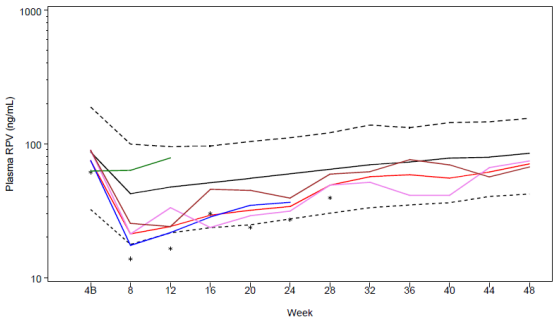
Study 201584 – CAB



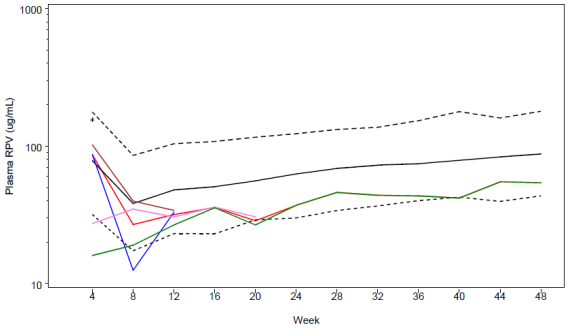
Study 201585 - CAB



Study 201584 – RPV



Study 201585 - RPV



Snapshot HIV-1 ≥50 c/mL (Virologic Failure) at Week 48 (Study 201584 n=6; Study 201585 n=5)	All Other Subjects (Study 201584 n=277; Study 201585 n=303)
— Median Failure —, —, —, —, * * * Individual Subject Data Note: 1 subject in Study 201584 did not have PK samples and is not included in figure Subjects identified in blue (both studies), pink (both studies), asterisks (Study 201584), and brown (Study 201585) were confirmed virologic failures.	— Median Success - - - P5 and P95 Success Note: Success is comprised of subjects with HIV<50 c/mL or 'No virologic Data' per the Snapshot algorithm at Week 48

Figure 6 Individual Plasma CAB and RPV Ctau vs. Time for Subjects with Snapshot HIV-1 ⩾50 c/mL (Virologic Failure) at Week 48 vs. Median (5th & 95th percentile) of CAB and RPV Ctau for All Other Subjects

Data Source: Mod5.3.5.1/Study 201584 CSR/Figure 5.7, Figure 5.8; Mod5.3.5.1/Study 201585 CSR/Figure 5.7, Figure 5.8

The applicant was requested to discuss the observation that for certain subjects, exposure of both RPV as well as CAB is low (suggesting there may be a potential subject–related cause), whereas for other subjects this is applicable to only one of the two components (pointing more towards an accidental administration error). Additionally, an in-depth analysis of potential factors that these subjects may have in common that may have predisposed them to experience virologic failure was requested.

A post-hoc multivariable logistic regression analysis of the pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M) was performed to examine the influence of baseline viral, participant characteristics, dosing regimen, and post-baseline plasma drug concentrations on confirmed virologic failure (CVF). This analysis included data from 1039 HIV-infected adults with no prior exposure to CAB+RPV, including 13 subjects 1.25%) with CVF at Week 48.

Four covariates were significantly associated ($P<0.05$ for each adjusted odds ratio) with increased risk of CVF: RPV-RAM at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), C_t RPV at 4 weeks following initial injection dose, BMI≥30 kg/m2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF.

No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI≥30 kg/m2.

2.4.4. Discussion on clinical pharmacology

Overall, CAB is a structural analogue to DTG, as evidenced by their similar chemical structures.

Average T1/2 after oral dosing is around 40 hours and up to around 5.6 to 11.5 weeks for IM doses.

Following single dose administration of [14C]-CAB 30 mg oral solution in humans, 85.3% of the administered dose was recovered in the excreta; 58.5% of the dose was recovered in faeces and 26.8% was recovered in urine. CAB accounted for 46.8% of the administered dose in faeces and was not detected in urine. The glucuronide metabolite GSK3388352 (M1) represented the majority of the radioactivity recovered in urine.

The conjugated metabolites, CAB glucuronide and M2, are not pharmacologically active.

The clinical study and the population PK analysis lead 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) and that CAB may be taken without dose adjustment in subjects with mild to moderate hepatic impairment.

Individually, gender (31% lower PK exposure in females) and BMI (31% lower exposure in BMI>30) effects are unlikely to be of clinical relevance.

Cabotegravir exhibits a drug-drug interaction profile that seems similar to other integrase inhibitors notably as DTG and BIC. No clinically relevant interaction is expected with CYPs as well as OATPs, OCT2 uptake and efflux transporters (P-gp/BCRP/BSEP/MATE1/MATE2K) substrates. Likewise, CAB does not inhibit OCT2 at therapeutic concentrations, as BIC, whereas DTG is contra-indicated with dofetilide, a probe OCT2 substrate.

Several aspects needed to be clarified to further substantiate the interaction profile of the drug. During the review process it was acknowledged that considering the relatively small increase in CAB exposure expected with OAT1/3 substrate, this issue could be monitored as part of routine pharmacovigilance only.

Similarly to DTG, CAB is effective on all HIV-1 subtypes and HIV-2, with comparable EC50 on these clinical isolates. According to their very close chemical structures, the resistance profile of CAB is quite similar to DTG, with nonetheless a lower resistance barrier. This is supported in the literature[1] and the comparative genetic barrier to resistance of the current INI may be rated RAL < EVG < CAB < DTG and BIC. The CAB RAM isolated throughout *in vitro* and clinical studies were E138K and Q148R/K/H. The INI mutations L74I, N155H and E92Q, associated to resistance to EVG and/or RAL, seems not significantly impact CAB activity. However, the development of Q148R/K with CAB can result in high-level cross-resistance to all INI. CAB was not intended to be administered in subjects with INI RAM, but physicians should be aware that emergence of the high-level INI cross-resistance Q148-mutations may be more frequent with CAB than DTG and BIC.

Similarly to the other INIs, no relationship between exposure and efficacy was observed. A minimal CAB concentration level (0.65 µg/ml) was defined by the applicant, but the few cases of virologic failures reported in the clinical studies seem rather due to genotypic resistance than lower exposure to CAB. Likewise, there was no statistically significant correlation between exposure and occurrence of AEs, notably increase of transaminases and total bilirubin. Supratherapeutic doses of CAB has no impact on the cardiac conduction.

The relatively high frequency of virologic failure in subjects infected with HIV-1 subtype A1/AG in FLAIR is of interest (4/18 (22%) in the CAB + RPV arm vs. 1/20 (5%) in the CAR arm). Additional information that may inform on the relative risk of virologic failure for different HIV subtypes, from ATLAS(-2M) or from earlier studies (including studies with the oral tablets), as well as any relevant information from *in vitro studies*, was requested, as was an analysis of virologic response rates based on the plasma HIV-1 RNA <2 c/mL cut-off (ultrasensitive viral load measurements) by HIV-1 subtype. The low overall number of events and the relative proportion of participants with similar factors and durable efficacy responses, however, it limits the conclusions that can be drawn.

A post-hoc multivariable logistic regression analysis of the pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M) was performed to examine the influence of baseline viral, participant characteristics, dosing regimen, and post-baseline plasma drug concentrations on CVF. Four covariates were significantly associated (P<0.05 for each adjusted odds ratio) with increased risk of CVF: RPV-RAM at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), C_t RPV at 4 weeks following initial injection dose, BMI≥30 kg/m2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in

[1] Oliveira M et al. Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir. Retrovirology, 2018.

isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI≥30 kg/m2

Two different regimens have been tested during clinical development, the currently recommended Q4W regimen or a Q8W regimen. There is a notable difference between the proportion of subjects with CVF in the Q8W (1.74% and 1.34%, respectively) and Q4W arms (0% and 0.19%, respectively), in the two studies that investigated both regimens simultaneously (LATTE-2 and ATLAS-2M). Based upon the post-hoc multivariable analysis presented, an increased risk of CVF is associated with the presence of two or more baseline factors of rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI≥30 kg/m2, rather than the Q4 vs Q8 Week dosing regimen in itself. The additional information on the risk factors for CVF has been incorporated in section 5.1 of the SmPC, which can be endorsed.

It is uncertain whether patients will be sufficiently adherent to the visits schedule in real life, and what fraction will at some point be lost to follow-up (either for a short period of time or longer). If not adequately treated with an appropriate oral ARV regimen, these patients will be at great risk of virologic failure, due to prolonged exposure to subtherapeutic levels of RPV and CAB, and subsequent resistance development. This should be clearly communicated to patients before they start treatment with these long-acting ARVs and reiterated at subsequent visits. The SAG experts considered adherence is a key element and should be reinforced, however, there is not a unique tool to ensure good adherence to treatment. Hence, measures should be adapted to the centres, resources, patients' characteristics etc.

The main issue in clinical practice will be the management of missed visits and discontinuation. Both CAB and RPV exposures slowly decrease after discontinuation, and the long period during which subtherapeutic levels of CAB and RPV are present poses a substantial risk of resistance development when patients are not adequately treated with an appropriate oral ARV regimen.

A warning box in section 4.4 of the SmPC will state that to minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of Vocabria when dosed monthly and no later than two months after the final injection of Vocabria when dosed every 2 months.

2.4.5. Conclusions on clinical pharmacology

The overall programme including the data from CAB studies is considered adequate to support the efficacy and safety CAB in combination with RPV.

2.5. Clinical efficacy

Dose-response studies

Four Phase I/II studies were performed in HIV-1 infected subjects:

- ITZ111451 and ITZ112929, assessing oral CAB in a 10 days monotherapy in ART-naïve and experienced (INI naïve) HIV-1 infected subjects who were not currently receiving ART.

- LAI116482 (LATTE study), assessing 3 doses of oral CAB in combination with oral RPV in ART-naïve adults.

- 200056 (LATTE-2 study), assessing 2 doses of CAB IM in combination with RPV IM in ART-naïve adults, after an oral induction phase.

The dose-response studies ITZ112929 and ITZ111451 have assessed 10 days of monotherapy of CAB 5 mg/day and CAB 30 mg/day in HIV-1 infected subjects. Overall, the antiviral activity of CAB vs placebo

was demonstrated, with mean change values from Baseline to Day 11 within the range of those observed with the other INI DTG and BIC:

Table 11 Dose-response studies

Study	Dose regimen	Mean change from Baseline to Day 11 (SD) (log_{10} c/ml)
ITZ112929	CAB 5 mg QD during 10 days	-2.17 (0.24)
ITZ111451	CAB 30 mg QD during 10 days	-2.34 (0.65)
ING111521	DTG 2 mg QD during 10 days	-1.51 (0.58)
	DTG 10 mg QD during 10 days	-2.03 (0.49)
	DTG 50 mg QD during 10 days	-2.46 (0.35)
GS-US-141-1219	BIC 5 mg QD during 10 days	-1.45 (0.10)
	BIC 25 mg QD during 10 days	-2.08 (0.21)
	BIC 50 mg QD during 10 days	-2.06 (0.35)
	BIC 100 mg QD during 10 days	-2.43 (0.39)

Although the population of these both studies was not strictly comparable, there is a higher decrease of viral load from baseline with CAB 30 mg (difference treatment vs placebo: -2.865 log_{10} c/ml) than CAB 5 mg (-2.090 log_{10} c/ml).

Study LAI116482 (LATTE) was a Phase IIb, randomised, multicentre, parallel group, partially-blinded, two part study assessing in HIV-1 ART-naïve subjects 3 doses of oral CAB (10, 30 and 60 mg QD) in combination with 2 NRTIs during a 24 weeks induction phase, followed by a maintenance phase of CAB (10, 30 and 60 mg QD) + RPV 25 mg. The comparator was EFV + 2 NRTIs. A rapid virologic response (HIV-1 RNA <50 c/mL) was observed across all CAB plus NRTI treatment groups by the end of the 24 week induction (CAB subtotal: 87% vs EFV: 74%) with a shorter time to virologic suppression for the CAB arms compared to EFV (each $p<0.001$).

Table 12 **Summary of Study Outcomes (HIV-1 RNA <50 c/mL) at Week 48 and Week 96- Snapshot (MSDF) Analysis (ITT-E Population)**

Outcome	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Week 48					
Virologic Success	**48 (80)**	**48 (80)**	**53 (87)**	**149 (82)**	**44 (71)**
Virologic Non-response[a]	**5 (8)**	**7 (12)**	**2 (3)**	**14 (8)**	**9 (15)**
Data in window not below threshold (<50 c/mL)	3 (5)	3 (5)	1 (2)	7 (4)	1 (2)
Discontinued for lack of efficacy	1 (2)	1 (2)	1 (2)	3 (2)	3 (5)
Discontinued for other reason while not below threshold	1 (2)	0	0	1 (<1)	4 (6)
Prior change in ART	0	3 (5)	0	3 (2)	1 (2)
No Virologic Data	**7 (12)**	**5 (8)**	**6 (10)**	**18 (10)**	**9 (15)**
Discontinued due to AE[b]	1 (2)	1 (2)	4 (7)	6 (3)	7 (11)
Discontinued for Other Reasons	6 (10)	4 (7)	2 (3)	12 (7)	2 (3)
Week 96					
Virologic Success	**41 (68)**	**45 (75)**	**51 (84)**	**137 (76)**	**39 (63)**
Virologic Non-response[a]	**9 (15)**	**6 (10)**	**3 (5)**	**18 (10)**	**10 (16)**
Data in window not below threshold (<50 c/mL)	4 (7)	1 (2)	1 (2)	6 (3)	1 (2)
Discontinued for lack of efficacy	2 (3)	1 (2)	1 (2)	4 (2)	3 (5)
Discontinued for other reason while not below threshold	3 (5)	1 (2)	1 (2)	5 (3)	5 (8)
Prior change in ART	0	3 (5)	0	3 (2)	1 (2)
No Virologic Data	**10 (17)**	**9 (15)**	**7 (11)**	**26 (14)**	**13 (21)**
Discontinued due to AE[b]	1 (2)	1 (2)	4 (7)	6 (3)	8 (13)
Discontinued for Other Reasons	8 (13)	8 (13)	3 (5)	19 (10)	4 (6)
Missing data during window but on study	1 (2)	0	0	1 (<1)	1 (2)

Data Source: Table 7.3; Table 7.31 (Week 48)

a. Virologic failure

b. No deaths occurred during this study.

These results suggest that a bitherapy CAB + RPV seems effective to obtain and maintain a satisfying virologic suppression. Based on the Week 96 data, better results may be expected with CAB 30 mg or 60 mg than with CAB 10 mg, although no statistically significant difference was raised between these 3 CAB groups. However, a numerically higher rate of discontinuation due to AE is observed in the CAB 60 mg arm vs the other CAB arms. PK data show that CAB exposure (AUC, Cmax and C0) is relatively dose-proportional between 10 mg and 60 mg, although a slight less-than-proportional increase was highlighted between 30 mg and 60 mg with the intensive PK data. Considering these data, an oral CAB dose at 30 mg was selected.

Study 200056 (LATTE-2) was a Phase IIb, randomised, multicentre, parallel group, open-label, three-part study in HIV-1 infected ART-naive adults. In the Induction Period, subjects began an oral regimen of CAB 30 mg once daily plus ABC/3TC 600/300 mg once daily during 20 weeks (from Week -20 to Day 1). Four weeks before the end of the Induction Period (i.e. from Week -4 to Day 1), their regimen was modified with the addition of RPV 25 mg once daily. All subjects with an undetectable HIV-1 RNA (<50

c/mL) at the Week (-4) visit were eligible to enter the Maintenance Period. In the Maintenance Period, eligible subjects were randomised 2:2:1 to receive for 96 weeks (from Day 1 to Week 96) an IM Q4W regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks (after a loading dose of CAB LA 800 mg + RPV LA 600 mg at Day 1), an IM Q8W regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks (after loading doses of CAB LA 800 mg + RPV LA 900 mg at Day 1 and CAB LA 600 mg at Week 4), or to continue on the oral Induction Period regimen of CAB 30 mg + ABC/3TC once daily. These doses were selected by the applicant using POPPK simulations and considering notably a mean Ct above that obtained with oral CAB 10 mg once daily during treatment (CAB trough concentrations ≥1.35 µg/mL). The applicant considers that maintaining a target at approximately the level of the 30 mg oral dose is not needed in Maintenance, as viral suppression and short-term tolerability have been established during Induction.

At Week 96, 94% (Q8W IM arm) and 87% (Q4W IM) of subjects receiving injectable dosing maintained virologic suppression (HIV-1 RNA <50 c/mL) compared to 84% of subjects continuing oral CAB + 2 NRTIs.

Table 13 Summary of Study Outcomes (<50 c/mL) at Week 96 – Snapshot (MSDF) Analysis (ITT-ME Population)

Outcome	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	Oral CAB[c] N=56 n (%)	Subtotal IM N=230 n (%)
Virologic Success, n (%)	**108 (94)**	**100 (87)**	**47 (84)**	**208 (90)**
Virologic Failure, n (%)	**5 (4)**	**0**	**1 (2)**	**5 (2)**
Data in window not below threshold	2 (2)	0	0	2 (<1)
Discontinued for lack of efficacy	1 (<1)	0	1 (2)	1 (<1)
Discontinued for other reason while not below threshold	2 (2)	0	0	2 (<1)
No Virologic Data	**2 (2)**	**15 (13)**	**8 (14)**	**17 (7)**
Discontinued due to AE or Death	1 (<1)	9 (8)	2 (4)	10 (4)
Discontinued for Other Reasons	1 (<1)	5 (4)	6 (11)	6 (3)
Missing data during window but on study	0	1 (<1)	0	1 (<1)

Data Source: Table 7.1002

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks
c. Oral CAB: GSK744 30 mg + ABC/3TC once daily

As regards the efficacy results of this Phase II study, both IM regimen provided high antiviral efficacy with few virologic failure. However, some differences between these two regimens may be highlighted:

- Some cases of virologic failures were observed with the Q8W regimen vs no case of virologic failure in the Q4W regimen, suggesting that the Q8W regimen, with larger interval between each injection, may be suboptimal. This will be further explored in Phase III studies.

- At Week 96, the Snapshot outcome of rate of discontinuations due to AEs was higher with the Q4W regimen (n=9, 8%) than the Q8W (n=1, <1%) or oral regimen (n=2, 4%). Moreover, these rates in each group did not strictly match with the proportions of AEs leading to withdrawal described in the safety section (7.4) of the study report, which makes it difficult to assess these differences. In addition, this trend is maintained in the Week 160 analysis, where the Snapshot outcome of rate of discontinuation due to AEs is considerably higher in the Q4W regimen (n=12, 10%) than in the Q8W regimen (n=1, <1%). The applicant argues that the difference in rate of AEs that have led to withdrawal between the Q8W and the Q4W arm may be partially attributable to the additional visits experienced by subjects on

the Q4W arm. While it is acknowledged that subjects in the Q4W arm have more injections and visits, it is not expected that this would be fully accountable for the observed different discontinuation rates.

The list of these AEs at D160 did not highlight particular safety concern which could occur more frequently with the monthly injections. Overall, phase III studies did not point towards an unacceptably high discontinuation rate for the LA treatment.

Overall, based on the results of the Phase II studies LATTE and LATTE-2, the applicant's decision to continue the development of these two LA IM regimen in Phase III studies is acknowledged.

Main studies

The clinical efficacy of the dual maintenance regimen with cabotegravir LA in combination with rilpivirine LA both administered every 4 weeks is based on the 48 weeks data from two large open label randomised controlled pivotal Phase III switch studies in HIV-1 infected subjects (201584 [FLAIR study, N=566] and 201585 [ATLAS study, N=616]). In addition, Weeks 48 data from an additional Phase III study (207966 [ATLAS-2M study]), comparing the 4W regimen versus an alternative 8W dose regimen, have been made available during the procedure in support of the additionally claimed Q8W regimen.

Since the D120 AR, Week 96 results of ATLAS and FLAIR studies became available.

Study 201584 (FLAIR study)

Methods

This is a Phase III, multi-phase, randomised, open label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1, ART-naïve adult subjects.

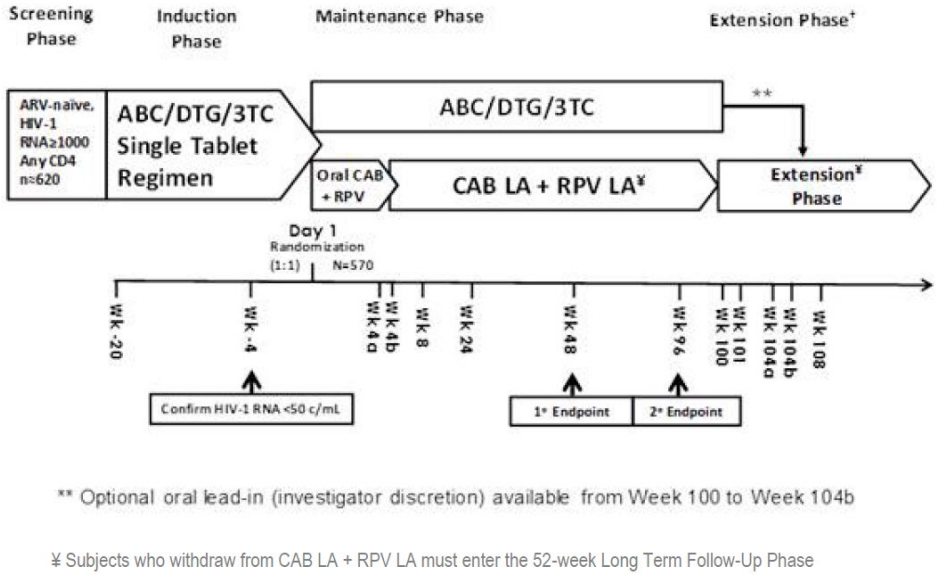


Figure 7 FLAIR study

Study Participants

Included subjects were HIV-1 infected, ART-naive men or women aged 18 years or greater, with HIV-1 RNA ≥1000 c/ml.

Exclusion criteria included notably resistance to NNRTIs (except for K103N) or INI, pregnancy, active CDC stage 3 disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy or CD4+ cell count <200 cells/mm^3), moderate to severe hepatic impairment, HBV infection (asymptomatic chronic HCV infection is allowed), creatinine clearance <50 ml/min, high risk of seizures, significant suicide risk and need for chronic anti-coagulation.

Treatments

Induction Phase:

All subjects initiated a treatment with ABC/DTG/3TC (or DTG + the alternative non-abacavir backbone for subjects HLA-b5701 positive) for 20 weeks.

Maintenance Phase:

Subjects were randomised to receive either:

- oral CAR (ABC/DTG/3TC or DTG + the alternative non-abacavir backbone) for at least 100 Weeks, or

- oral CAB 30 mg + RPV 25 mg once daily for a minimum of 4 weeks during OLI followed by IM injections of CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4, IM CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter) for at least 94 Weeks.

In exceptional circumstances, to address pre-planned missed IM CAB + RPV dosing visits, following consultation with the Medical Monitor, Investigators could provide daily oral CAB 30 mg and RPV 25 mg as a short-term "bridging" strategy for subjects who had begun CAB + RPV and who would miss a subsequent scheduled IM CAB + RPV injection. In certain circumstances (e.g., prior to steady state dosing and following a >4-week oral bridge) repeating the loading doses of IM CAB and RPV could be required.

Objectives

Primary objective: To demonstrate the non-inferior antiviral activity of switching to IM CAB + RPV every 4 weeks compared to continuation of CAR over 48 weeks in HIV 1 antiretroviral naïve subjects.

Outcomes/endpoints

The primary endpoint is the pproportion of subjects with a "virologic failure" endpoint as per FDA Snapshot algorithm at Week 48 (ITT-E Population). Virologic failure is defined as any of the following:

- Non-response as indicated by a less than a 1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA after 4 weeks of starting the Induction Phase, which is subsequently confirmed, unless the plasma HIV-1 RNA is < 400 c/mL (Induction Phase criteria).

- Rebound as indicated by two consecutive plasma HIV-1 RNA that are > 0.5 $\log_{10}$ c/mL increase in plasma HIV-1 RNA from the nadir value on study, where the lowest HIV-1 RNA value is ≥ 200 c/mL (Induction Phase criteria).

- Rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥ 200 c/mL after prior suppression to < 200 c/mL.

Randomisation and blinding (masking)

Randomisation 1:1 was stratified by subject's Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL) and sex at birth.

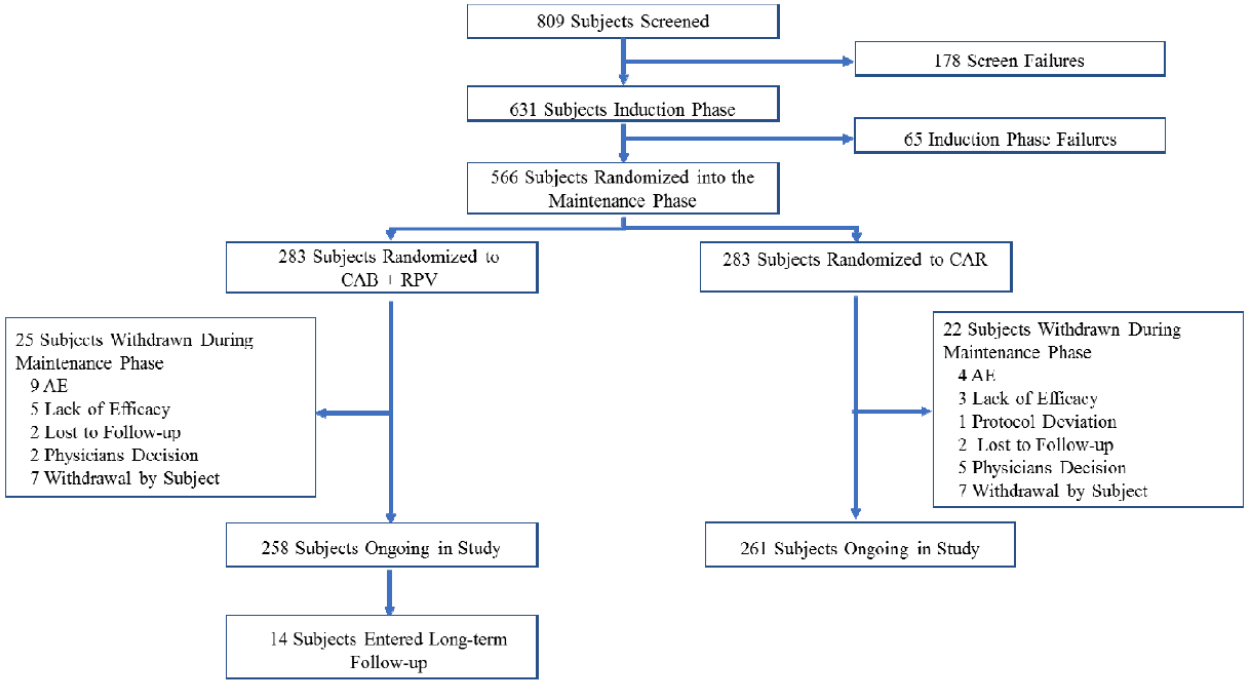
This study was open label.

Statistical methods

As this study (201584) and study 201585 were not sufficiently powered individually to rule out 4% virologic failure in excess, a 6% margin chosen in each study can be viewed as defining criteria for assessing the consistency acceptability of the study-specific results prior to integration of the studies in the pooled analysis, where a more stringent 4% margin is applied.

This study planned to randomise approximately 285 subjects per treatment group. Assuming the true proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL was 3% for the CAB + RPV treatment group and 2% for the CAR group, a non-inferiority margin of 6%, and a 2.5% 1-sided significance level, this provided approximately 97% power to show non-inferiority for the proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48.

Results



Data Source: Table 1.1 and Table 1.7
Note: Of the 65 Induction Phase failures 2 subjects were withdrawn prior to receiving study drug.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and ABC/DTG/3TC as CAR

Figure 8 Participant flow

Table 14 Summary of Subject accountability: Maintenance Phase conclusion Record (ITT-E Population)

	CAB + RPV (N=283)	CAR (N=283)
Subject Status		
Randomized	283	283
Ongoing, n (%)	258 (91)	261 (92)
Completed, n (%)	0	0
Withdrawn, n (%)	25 (9)	22 (8)
Primary[a]/subreason[b] for study withdrawal, n (%)		
AE	9 (3)	4 (1)
Lack of efficacy	5 (2)	3 (1)
CVF	5 (2)[e]	3 (1)
Protocol deviation	0	1 (<1)
Prohibited medication use	0	1 (<1)
Lost to follow-up	2 (<1)	2 (<1)
Physician decision	2 (<1)	5 (2)
Pregnancy	0	1 (<1)
Other[c]	2 (<1)	4 (1)
Withdrawal by subject	7 (2)	7 (2)
Frequency of visits	1 (<1)	4 (1)
Burden of travel or lack of access to travel	1 (<1)	0
Subject relocated	1 (<1)	1 (<1)
Intolerability of injections	2 (<1)	0
Subject was incarcerated	1 (<1)	0
Other, specify[d]	1 (<1)	2 (<1)
Outcome of AEs resulting in study withdrawal		
Fatal	0	0
Non-fatal	9 (3)	4 (1)

Data Source: Table 1.1 and Table 1.7

a. Subjects may have only 1 primary reason for withdrawal.
b. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than 1 subreason underneath a single primary reason. Subjects are not required to indicate subreasons.
c. CAB + RPV: 1 Subject needed at least 6 months anti-coagulation for thrombosis; 1 Subject was unreliable with appointments and frequently rescheduled (Investigator feared prolonged dosing interval with subsequent virologic failure). CAR: 2 Subjects noncompliance with study treatment and protocol procedures; 1 Subject ViiV Safety and Labelling Committee decision (subject had acute hepatitis E infection followed by continued cocaine use); 1 Subject did not show up or was late for visits.
d. CAB + RPV: pregnancy thoughts in near future; CAR: Relocation; Subject decision to stop CAR.
e. One subject did not meet CVF (Subject had low level viremia at Week 48: 128 c/mL, retest 10 days later 149 c/mL; Week 52: 229 c/mL; Long term follow-up Month 1 – prior to initiation of new ART: 109 c/mL).
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

During the Maintenance Phase, 9 subjects (3%) used oral bridging ranging from 4 to 61 days in duration to cover missed or delayed injection visits. The majority of subjects were able to resume CAB LA + RPV LA dosing. No cases of CVF or virologic blips were observed during the period of oral bridging or following resumption of CAB + RPV dosing.

Conduct of the study

Two quality issues impacting the efficacy data occurred throughout the study:

First, a quality issue at central laboratory was identified (Abbott HIV-1 Realtime assay contamination from April to June 2018). This contamination has caused false-positive results with HIV-1 RNA samples,

and therefore assay failures for Abbott Realtime assay runs, on 20, 23 and 24 April 2018. The samples tested between 15 and 26 April 2018 (i.e. determined to be within the period of potential contamination risk) with reported HIV-1 RNA results of ≥50 c/mL were retested in another laboratory using frozen plasma backup samples; results with a difference of more than 0.5 log copies/mL from the original result were updated with the retest result. No impact on subject safety or data integrity was incurred. There was 1 subject sample which fit the above retesting criteria. The retest result for this subject was <0.5 log copies/mL.

Secondly, another assay quality issue was reported regarding the Abbott RealTime HIV-1 RNA Assay (recall of certain lots of the Abbott RealTime HIV-1 Assay reagent, which was used to measure plasma HIV-1 RNA in this study). This quality issue caused a lack of precision in the lower end of the assay's quantification range, and results that were <40 c/mL using only these impacted lots were considered unreliable. Abbott Laboratories recommended that samples that were assayed using the impacted lots and with results <40 c/mL be retested. Results that were ≥40 c/mL using the same lots were not affected by this issue. Of 164 samples retested, 13 samples had a change in outcome in which HIV-1 RNA was ≥50 c/mL. There was one sample from Maintenance Phase (Day 1) with discordant results original HIV-1 RNA <50 c/mL, retest 58 c/mL). This subject remains on study and was fully suppressed <50 c/mL. Six sample discrepancies occurring at the Week -4 visit. A retest for HIV-1 RNA was required to determine if these subjects could continue into the Maintenance Phase of the study. Of the 6 subjects with HIV-1 RNA >50 c/mL at Week -4, 2 were excluded from the Per Protocol analyses, as the Day 1 HIV-1 RNA remained >50 c/mL (the other 4 subjects were not excluded as the Day 1 HIV-1 RNA was <50 c/mL).

Baseline data

Demographic characteristics were generally similar between treatment groups. Although the majority of subjects were male, the study exceeded the goal to enroll at least 20% female subjects. Most subjects were aged 18 to <50 years of age (88%) with a median (range) of 34 (18 to 68) years. The predominant race was White-White/Caucasian/European heritage.

Table 15 Demographic characteristics

Demographic Characteristic	CAB + RPV (N=283)	CAR (N=283)
Age (y), n		
Mean	35.9	36.0
SD	10.17	9.82
Median	34.0	34.0
Min.	19	18
Max.	68	68
Age group (y), n (%)		
<35	143 (51)	145 (51)
35 to <50	107 (38)	109 (39)
≥50	33 (12)	29 (10)
Sex at birth, n (%) [a]		
Female	63 (22)	64 (23)
Male	220 (78)	219 (77)
Race, n (%)		
White	216 (76)	201 (71)
Non-White	67 (24)	80 (28)
American Indian or Alaska Native	3 (1)	6 (2)
Asian-Central/South Asian Heritage	2 (<1)	1 (<1)
Asian-East Asian Heritage	1 (<1)	2 (<1)
Asian-Japanese Heritage	8 (3)	12 (4)
Asian-South East Asian Heritage	1 (<1)	0
Black or African American	47 (17)	56 (20)
Native Hawaiian or Other Pacific Islander	1 (<1)	0
White-Arabic/North African Heritage	5 (2)	3 (1)
White-White/Caucasian/European Heritage	211 (75)	198 (70)
Multiple	4 (1)	3 (1)
Missing	0	2 (<1)
Ethnicity, n (%)		
Hispanic or Latino	28 (10)	40 (14)
Not Hispanic or Latino	255 (90)	243 (86)
BMI (kg/m^2) at Induction Baseline (Week -20)		
Mean	25.109	24.934
SD	4.4190	4.8797
Median	24.100	24.000
Min.	17.30	12.60
Max.	44.90	47.40

Data Source: Table 1.22

a. Reported gender was also collected. Two individuals who were male at birth identified themselves as female at study enrolment.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

At Induction Baseline (Week -20), the viral load and prevalence of each HIV-1 subtype was similar between treatment groups, with 20% of subjects with HIV-1 RNA >100.000 c/ml and respectively 61% and 15% of subjects with HIV-1 subtype B and A. The frequencies of current and past medical conditions, the HIV risk factors and the baseline cardiovascular risk assessments were similar in both treatment groups. As regards hepatitis status, 18 (6%) subjects in the CAB + RPV group and 9 (3%) subjects in the CAR group were tested positive for HCV only. One additional subject in the CAB + RPV group was tested positive for HBV and HCV.

At Maintenance Baseline (Day 1), CDC stages of HIV infection were similar in both treatment groups, with 70% of subjects at Stage 1. Median CD4+ cell count was comparable between treatment groups at Induction Baseline and Maintenance Baseline.

Numbers analysed

Table 16 Randomised population and number analysed.

	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	Total (N=566) n (%)
Randomized Population	283 (100)	283 (100)	566 (100)
ITT-E Population	283 (100)	283 (100)	566 (100)
PP Population	278 (98)	282 (>99)	560 (99)
Safety Population	283 (100)	283 (100)	566 (100)
PK Population[a]	278 (98)	0	278 (49)
CVF Population	4 (1)	3 (1)	7 (1)
Long Term Follow-up Population[b]	14 (5)	0	14 (2)

Data Source: Table 1.1

a. PK analysis was only conducted for the CAB + RPV group.

b. Subjects in the CAR group were not required to enter Long Term Follow-up

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC

Outcomes and estimation

Week 48

Table 17 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Maintenance Phase) Snapshot Analysis (ITT-E and PP Populations)

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	283	6/283 (2.1)	-0.4 (-2.8, 2.1)	-0.4 (-2.8, 2.1)
CAR	283	7/283 (2.5)		
PP Population				
CAB + RPV	278	6/278 (2.2)	-0.3 (-2.8, 2.2)	-0.3 (-2.8, 2.2)
CAR	282	7/282 (2.5)		

Data Source: Table 2.1 and Table 2.2

a. Difference: proportion on CAB + RPV - proportion on CAR

b. Based on CMH stratified analysis adjusting for the following Baseline stratification factors: sex at birth (male, female) and Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL)

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

Table 18 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (Maintenance Phase) – Snapshot Analysis – (ITT-E and PP Populations)

Treatment	N	Number of HIV-1 RNA <50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	283	265 / 283 (94)	0.4 (-3.7, 4.4)	0.4 (-3.7, 4.5)
CAR	283	264 / 283 (93)		
PP Population				
CAB + RPV	278	260 / 278 (94)	0.3 (-3.9, 4.4)	0.3 (-3.8, 4.4)
CAR	282	263 / 282 (93)		

The proportion of subjects with confirmed virologic failure (CVF; 2 Consecutive Plasma HIV-1 RNA Levels ≥200 c/mL After Prior Suppression to <200 c/mL) at Week 48 in the CAB + RPV group was 1.4% (4 subjects) and in the CAR group was 1.1% (3 subjects) through Week 48.

At Week 48, median (IQR) increases from Day 1 to Week 48 in CD4+ cell counts of 45.5 (-60, 141) cells/mm3 for CAB + RPV and 80.0 (-32, 193) cells/mm3 for CAR were observed. The mean and median CD4+/CD8+ ratio through Week 48 was similar in both treatment groups.

Considering the rate of subjects with HIV-1 RNA ≥50 c/ml and the rate of subjects with CVF at Week 48, and the applicant's choice of a 6% non-inferiority margin, the switch from oral DTG+2 NRTIs to CAB+RPV LA IM in virologically-suppressed subjects is non-inferior to the oral regimen. The other efficacy endpoints and the PP analysis confirm the non-inferiority. Although the 6% non-inferiority margin is debatable, the non-inferiority is still demonstrated with a 4% margin.

Week 96

At Week 96, 3.2% of subjects in each group (CAB + RPV group and CAR group) had viral load ≥50 c/mL (both ITT-E and PP Populations).

Ancillary analyses

Subgroups analyses

There were no statistically significant differences in treatment effect for each randomisation stratification factor and in any Baseline or demographic subgroup examined:

Table 19 **Treatment by Strata Tests of Homogeneity for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Maintenance Phase) - Snapshot Analysis - (ITT-E Population)**

Analysis Strata		Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed	Difference in Proportion (95% CI)[a]
Sex at birth	Female	CAB + RPV	63	3/ 63 (4.8)	3.2 (-4.3, 12.0)
		CAR	64	1/ 64 (1.6)	
	Male	CAB + RPV	220	3/220 (1.4)	-1.4 (-4.7, 1.6)
		CAR	219	6/219 (2.7)	
	P-value for test of homogeneity[b]				0.179
Induction Baseline (Week -20) HIV-1 RNA (c/mL)	<100,000	CAB + RPV	227	4/227 (1.8)	-0.4 (-3.6, 2.5)
		CAR	227	5/227 (2.2)	
	≥100,000	CAB + RPV	56	2/ 56 (3.6)	0.0 (-9.2, 9.2)
		CAR	56	2/ 56 (3.6)	
	P-value for test of homogeneity[b]				0.907

Data Source: Table 2.4

a. Difference: CAB + RPV - CAR (unadjusted). 95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic.

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

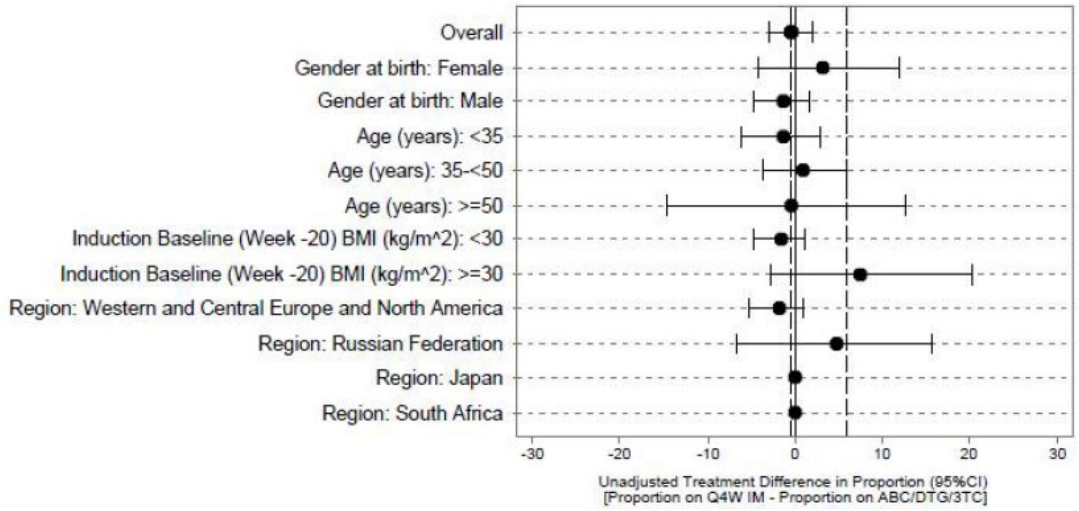
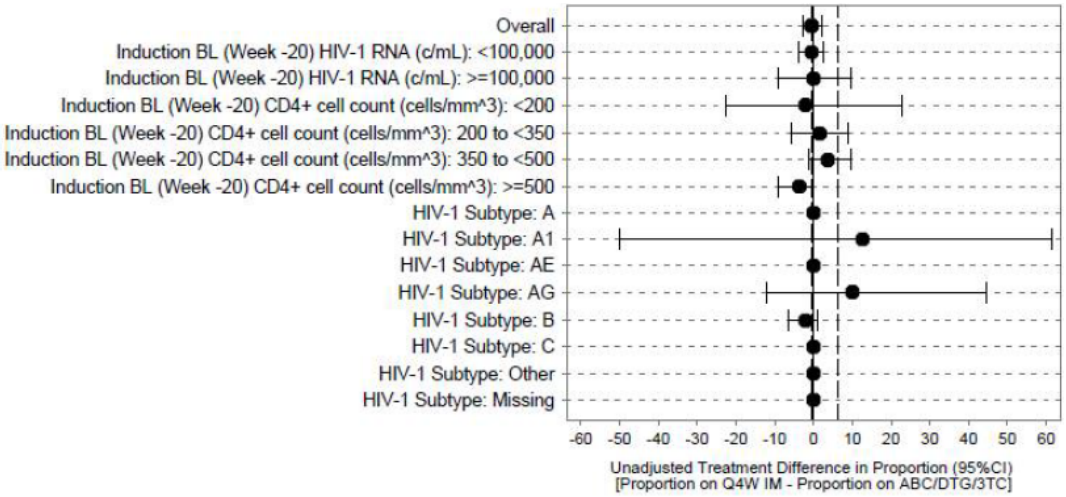


Figure 9 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Selected Demographic Subgroups in Study 201584 (FLAIR) (Maintenance Phase) - Snapshot Analysis



Data Source: Post-hoc Figure 2.12
Note: the dashed reference line on the right at 6% represents the none inferiority margin.
Note: the dashed reference line on the left represents the overall difference in proportion of CAB + RPV to CAR
Note: 95% CI were calculated using the normal approximation for overall, and using an unconditional exact method with inverted 1-sided tests based on the score statistic for the subgroups.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

Figure 10 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Selected HIV Disease Characteristic Subgroups in Study 201584 (FLAIR) (Maintenance Phase) - Snapshot Analysis

Of note, antiviral efficacy is numerically lower with CAB+RPV LA IM than oral CAR at Week 48 in obese subjects (BMI ≥30) (rate of virologic failure: 3/40 [7.5%] vs 0/37) and in HIV subtypes A1 and AG (and in general in subtype A) (pooled rate of virologic failure: 4/18 [22.2%] vs 1/20 [5%]).

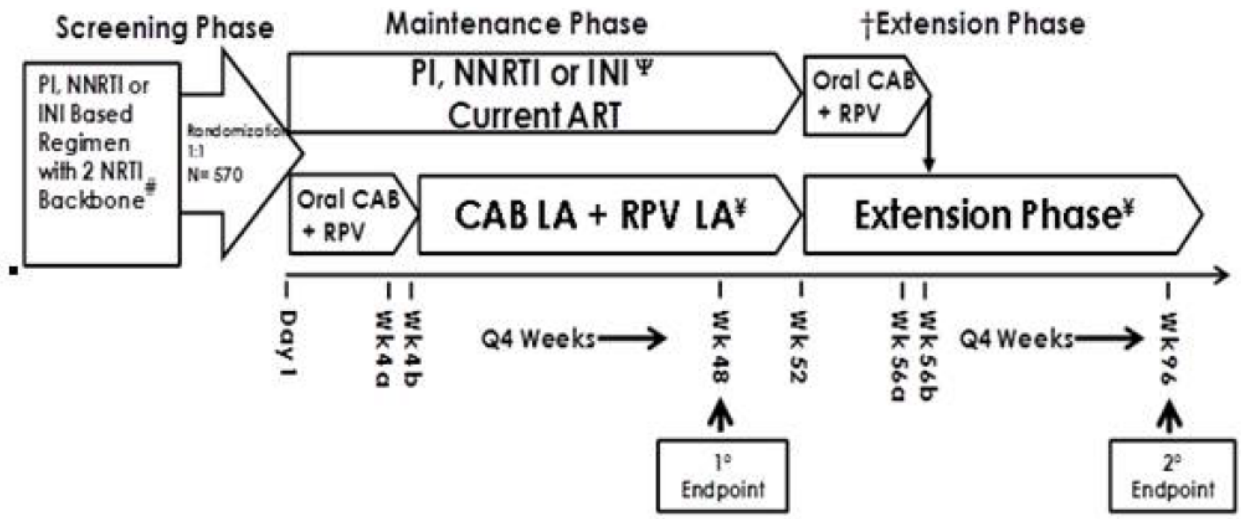
Resistance analyses

The rate of clinical virologic failure is low, with 4 and 3 subjects respectively in the CAB+RPV arm and CAR arm through Week 48. In the CAB+RPV group, 3 subjects had subtype A1 and came from Russia sites. The fourth subject had an oral CAB +RPV treatment interruption at Week 4a (result of positive pregnancy test later confirmed as false) and never received any CAB + RPV injections. Among the 3 CVF subjects in the CAR group, none of whom had any treatment emergent NRTI or INI RAMs. From Week 48 to Week 96, there was one additional clinical virologic failure in each group; one occurred at week 48 in the randomised CAB/RPV LA arm and one occurred at week 64 in a subject on the CAR arm.

Study 201585 (ATLAS study)

Methods

This is a Phase III, multi-phase, randomised, open label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1 virologically suppressed adult subjects on a stable ARV regimen.



N=570, randomized 1:1 to each group and stratified by Baseline 3rd agent class and sex at birth.

Must be on uninterrupted current regimen (either the initial or second CAR regimen) for at least 6 months prior to Screening (See Protocol Section 5.1 and Section 5.2). Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: 1 within the 6 to 12-month window, and 1 within 6 months prior to Screening. No history of virologic failure. No evidence of viral resistance based on the presence of any resistance-associated major INI or NNRTI mutation (except K103N) from prior genotype assay results. No current or prior history of etravirine use.

ΨINI based regimen excluded abacavir/dolutegravir/lamivudine (TRIUMEQ), and INI therapy was capped at approximately 40% of study enrolment for CAR

† Optional Extension Phase to CAB + RPV at Week 52 for subjects randomized to CAR

¥ Subjects who withdrew from the CAB + RPV group had to go into the 52-week LTFU Phase

Figure 11 ATLAS study

Study Participants

Included subjects were HIV-1 infected men or women aged 18 years or greater, on uninterrupted current regimen (either the initial or second ARV regimen) for at least 6 months prior to Screening, with HIV-1 RNA <50 c/ml in the 12 months prior to Screening.

Exclusion criteria included notably any switch to a second line regimen due to virologic failure, presence of any major known INI or NNRTI resistance-associated mutation (except for K103N), pregnancy, active CDC stage 3 disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy or CD4+ cell count <200 cells/mm^3), moderate to severe hepatic impairment, HBV infection (asymptomatic chronic HCV infection is allowed), creatinine clearance <50 ml/min, high risk of seizures, significant suicide risk, need for chronic anti-coagulation, current or prior use of etravirine and current use of tipranavir/ritonavir or fosamprenavir/ritonavir.

Treatments

Subjects were randomised to receive either:

- oral current ARV regimen (CAR) for 52 Weeks, or

- oral CAB 30 mg + RPV 25 mg once daily for 4 weeks during the oral lead-in Phase followed by IM injections of CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4, IM CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter) for at least 48 Weeks.

In exceptional circumstances, to address pre-planned missed IM CAB + RPV dosing visits, following consultation with the Medical Monitor, Investigators could provide daily oral CAB 30 mg and RPV 25 mg as a short-term "bridging" strategy for subjects who had begun CAB + RPV and who would miss a subsequent scheduled IM CAB + RPV injection. In certain circumstances (e.g., prior to steady state dosing and following a >4-week oral bridge) repeating the loading doses of IM CAB and RPV could be required.

The CAR included 2 NRTIs plus:

- INI with the exception of ABC/DTG/3TC (either the initial or second CAR regimen);

- NNRTI (either the initial or second CAR regimen);

- Boosted PI (or atazanavir [ATV] unboosted) (had to be either the initial CAR regimen or 1 historical within-class switch was permitted due to safety/tolerability).

Objectives

Primary objective: to demonstrate the non-inferior antiviral activity of switching to intramuscular CAB + RPV compared to continuation of current first line antiretroviral regimen (CAR) over 48 weeks in HIV-1 infected ART-experienced subjects.

Outcomes/endpoints

The primary endpoint is the proportion of subjects who met the Snapshot virologic failure criteria, defined as plasma HIV-1 RNA ≥ 50 c/mL, at Week 48.

Randomisation and blinding (masking)

Randomisation 1:1 was stratified by baseline third agent class (PI, INI, or NNRTI), and sex at birth.

This study was open label.

Statistical methods

As this study (201585) and study 201584 were not sufficiently powered individually to rule out 4% virologic failure in excess, a 6% margin chosen in each study can be viewed as defining criteria for assessing the consistency acceptability of the study-specific results prior to integration of the studies in the pooled analysis, where a more stringent 4% margin is applied.

This study planned to randomise approximately 285 subjects per treatment group. Assuming the true proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL was 3% for the CAB + RPV treatment group and 2% for the CAR group, a non-inferiority margin of 6%, and a 2.5% 1-sided significance level, this provided approximately 97% power to show non-inferiority for the proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48.

Results

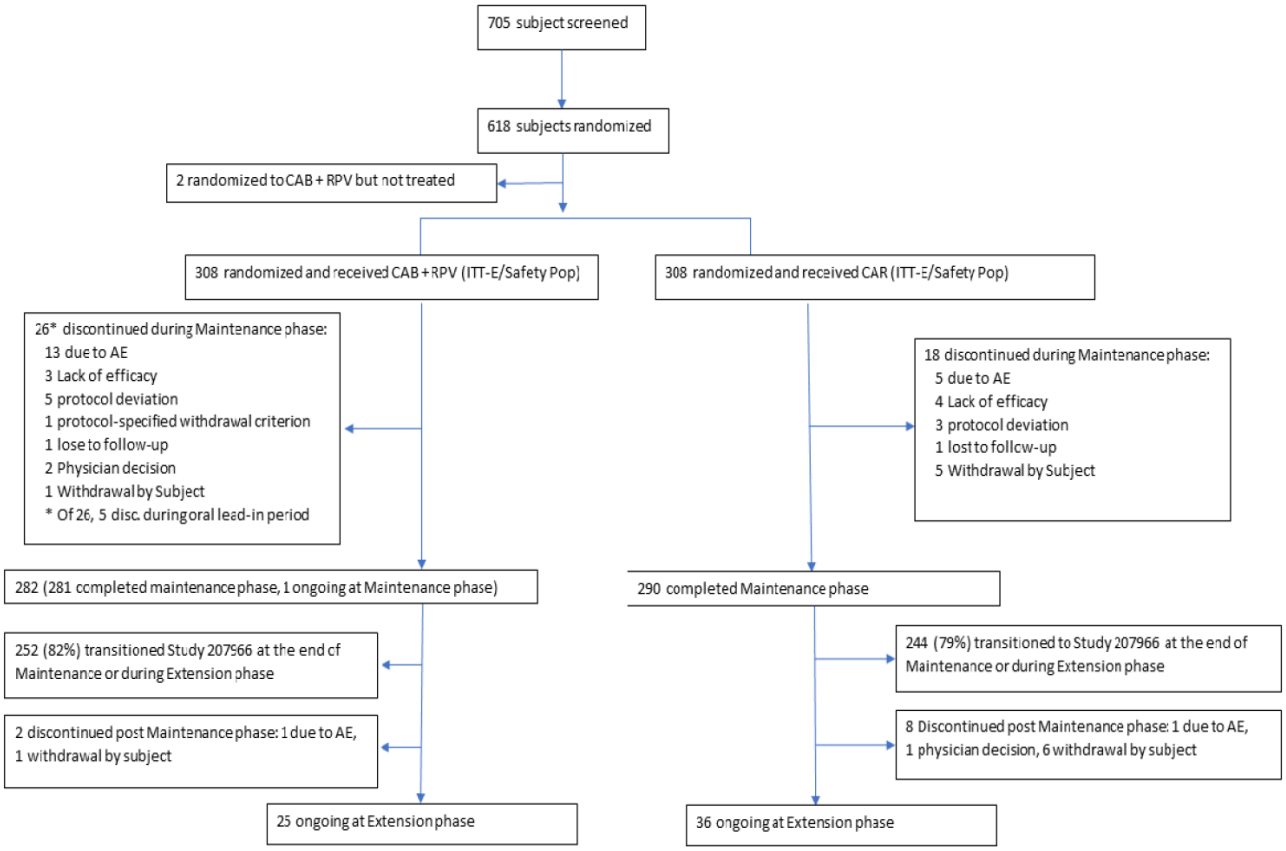


Figure 12 Participant flow

Table 20 **Summary of Subject Accountability: Maintenance Phase Conclusion Record (ITT-E Population)**

	CAB + RPV (N=308)	CAR (N=308)
Subject Status, n (%)		
Ongoing	1 (<1)	0
Completed	281 (91)	290 (94)
Withdrawn	26 (8)	18 (6)
Primary[a]/Subreason[b] for Study Withdrawal, n (%)		
Adverse Event	13 (4)	5 (2)
Lack of Efficacy	3 (<1)	4 (1)
Protocol defined virological failure	3 (<1)	4 (1)
Protocol Deviation	5 (2)	3 (<1)
Non-compliance with study treatment	1 (<1)	0
Non-compliance with protocol procedures	2 (<1)	2 (<1)
Pregnancy	2 (<1)	1 (<1)
Protocol-specified Withdrawal Criterion Met	1 (<1)	0
Subject met the GSK-defined liver chemistry stopping criteria	1 (<1)	0
Lost to Follow-up	1 (<1)	1 (<1)
Physician Decision	2 (<1)	0
Pregnancy (subject adhered to highly effective methods of contraception as per inclusion criteria 5)	2 (<1)	0
Withdrawal by Subject	1 (<1)	5 (2)
Frequency of visits	0	3 (<1)
Subject relocated	1 (<1)	0
Subject withdrew consent solely due to very busy work schedule	0	1 (<1)
The patient is not able to comply with the protocol's visits due to her working schedule	0	1 (<1)
Outcome of Adverse Events Which Led to Study Withdrawal, n (%)		
Fatal	0	1 (<1)
Non-fatal	13 (4)	4 (1)

Data Source: Table 1.7.

a. Subjects may have only 1 primary reason for withdrawal.

b. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than 1 subreason underneath a single primary reason. Subjects are not required to indicate subreasons.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

7 subjects (2%) used oral bridging ranging from 4 to 29 days in duration to cover missed or delayed injection visits. Each subject who utilised oral bridging retained virologic suppression during the oral bridging period and for subsequent study visits through the current reporting period.

Conduct of the study

Two quality issues impacting the efficacy data occurred throughout the study:

First, a quality issue at central laboratory was identified (Abbott HIV-1 Realtime assay contamination from April to June 2018). This contamination has caused false-positive results with HIV-1 RNA samples, and therefore assay failures for Abbott Realtime assay runs, on 20, 23 and 24 April 2018. The samples tested between 15 and 26 April 2018 (i.e., determined to be within the period of potential contamination risk) with reported HIV-1 RNA results of ≥50 c/mL were retested in another laboratory using frozen plasma backup samples; results with a difference of more than 0.5 log copies/mL from the original result were updated with the retest result. No impact on subject safety or data integrity was incurred. There

were 2 subject samples which fit the above retesting criteria (see below results of Subject A at week 48 and Subject B at week 60).

	HIV-1 RNA c/mL	
Visit	Original result	Retest result
Week 48	805	1151
Week 60	71	<40

Secondly, another assay quality issue was reported regarding the Abbott RealTime HIV-1 RNA Assay (recall of certain lots of the Abbott RealTime HIV-1 Assay reagent, which was used to measure plasma HIV-1 RNA in this study). This quality issue caused a lack of precision in the lower end of the assay's quantification range, and results that were <40 c/mL using only these impacted lots were considered unreliable. Abbott Laboratories recommended that samples that were assayed using the impacted lots and with results <40 c/mL be retested. Results that were ≥40 c/mL using the same lots were not affected by this issue. Of 268 samples retested, only one subject had a change in outcome original HIV-1 RNA <40 c/mL at Week 4, retest 70 c/mL). This subject continues in the Extension Phase of the study and remains fully suppressed <50 c/mL).

Baseline data

Demographic characteristics were generally similar between treatment groups (at the exception of the rate of subjects above 50 years old (21% in CAB+RPV group vs 31% in CAR group):

Table 21 **Demographic Characteristic**

Demographic Characteristic	CAB + RPV (N=308)	CAR (N=308)
Age (y), n		
Mean	41.6	43.2
SD	9.99	11.43
Median	40.0	43.0
Min.	21	18
Max.	74	82
Age Group (y), n (%)		
<35	80 (26)	80 (26)
35-<50	162 (53)	132 (43)
≥50	66 (21)	96 (31)
Sex, n (%)		
Female	99 (32)	104 (34)
Male	209 (68)	204 (66)
Race, n (%)		
White	214 (69)	207 (67)
Non-White	94 (31)	101 (33)
American Indian or Alaska Native	8 (3)	8 (3)
Asian-Central/South Asian Heritage	1 (<1)	0
Asian-East Asian Heritage	13 (4)	8 (3)
Asian-South East Asian Heritage	8 (3)	5 (2)
Black or African American	62 (20)	77 (25)
Native Hawaiian or Other Pacific Islander	0	1 (<1)
White-Arabic/North African Heritage	2 (<1)	2 (<1)
White-White/Caucasian/European Heritage	212 (69)	205 (67)
Multiple	2 (<1)	2 (<1)
Ethnicity, n (%)		
Hispanic or Latino	35 (11)	34 (11)
Not Hispanic or Latino	273 (89)	274 (89)
BMI (kg/m²) at Baseline		
Mean	26.203	26.742
SD	5.1022	5.7692
Median	25.500	25.500
Min.	15.30	17.80
Max.	50.90	57.70

The distribution of CD4+ cell counts at Baseline was comparable in both treatment groups, with 74% of subjects with baseline CD4 above 500 cells/mm^3. HIV risk factors were similar in both treatment groups.

The historic of antiretroviral therapy at screening was similar in both treatment groups, in terms of duration (≈ 65 months) and nature of antiretroviral therapy (NRTIs + PI: 17%, NRTIs + NNRTI: 50%, NRTIs + INI: 33%).

Overall, the population of this ATLAS study is more diversified than those in FLAIR study, with higher and significant proportions of women (>30%), subjects above 50 years old (20-30%) and heterosexual contact (45%) than in FLAIR study. However, subjects were less immunocompromised in this study (8% of subjects with CD4 levels <350 cells/mm3) than in FLAIR study (30%).

Numbers analysed

Table 22 **Number of patients analysed**

Population	No Treatment (N=87)	CAB + RPV (N=310)	CAR (N=308)
All Subjects Screened	87 (100%)	310 (100%)	308 (100%)
Randomized	NA	310 (100%)	308 (100%)
Safety[a]	NA	308 (99%)	308 (100%)
Intent-to-Treat Exposed[b]	NA	308 (99%)	308 (100%)
Per-Protocol	NA	294 (95%)	292 (95%)
Extension Switch[c]	NA	NA	173 (56%)
Long-Term Follow-up[d]	NA	23 (7%)	3 (<1%)
PK[e]	NA	308 (99%)	165 (54%)

Data Source: Table 1.1

a. Subjects were included in the Safety Population if they took at least one dose of study treatment.
b. Intent-to-Treat Exposed comprised of all randomized subjects who received at least one dose of study treatment.
c. The Extension Switch population consisted of all randomized subjects from the CAR group who received at least 1 dose of CAB and/or RPV during the Extension Phase of the study.
d. Subjects who were withdrawn after receiving at least one CAB+RPV injection needed to enter long-term follow-up phase. For the CAR group, the 3 subjects were withdrawn post switching to CAB+RPV.
e. The PK population for the CAR group represents subjects that switched to CAB + RPV starting at Week 56b in the Extension Phase. PK was not collected for subjects on CAR treatment during the Maintenance Phase.

In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

Outcomes and estimation

Week 48:

Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA >/=50 c/mL at Week 48 (Maintenance Phase) – Snapshot Analysis – (ITT-E and PP Populations)

Table 23

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	308	5 / 308 (1.6)	0.6 (-1.1, 2.4)	0.6 (-1.2, 2.5)
CAR	308	3 / 308 (1.0)		
PP Population				
CAB + RPV	294	4/294 (1.4)	0.3 (-1.4, 2.1)	0.3 (-1.4, 2.1)
CAR	292	3/292 (1.0)		

Data Source: Table 2.1 and Table 2.2

a. Difference: Proportion on CAB + RPV - Proportion on CAR.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: sex at birth (Male, Female) and Baseline third agent class (PI, NNRTI, INI).

Note: 95% CIs were calculated using the normal approximation method.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

Summary of Study Outcomes (Plasma HIV-1 RNA of 50 c/mL as cutoff) at Week 48 (Maintenance Phase) – Snapshot Analysis – (ITT-E Population)

Table 24

Outcome	CAB + RPV (N=308)	CAR (N=308)
HIV-1 RNA <50 c/mL	285 (92.5)	294 (95.5)
HIV-1 RNA ≥50 c/mL	5 (1.6)	3 (1.0)
Data in window not below threshold	1 (0.3)	1 (0.3)
Discontinued for lack of efficacy	3 (1.0)	2 (0.6)
Discontinued for other reason while not below threshold	1 (0.3)	0
Change in background therapy	0	0
No Virologic Data	18 (5.8)	11 (3.6)
Discontinued study due to AE or Death[a]	11 (3.6)	5 (1.6)
Discontinued study for other reasons[b]	7 (2.3)	6 (1.9)
On study but missing data in window	0	0

Data Source: Table 2.4.

a. One death occurred in the CAR group, which was not study drug related. Details are provided in Section 7.3.

b. Other reasons for discontinuation included pregnancy (n=5), lost to follow up (n=2), non-compliance with treatment (n=1), and withdrawal by subject due to frequency of visits (n=4) and relocation (n=1) (Data Source: Listing 4, Listing 11).

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

The proportion of subjects with CVF in the CAB + RPV group was 1.0% (3 subjects) and in the CAR group was 1.3% (4 subjects) through Week 48. The treatment difference (95% CI) in the Kaplan-Meier estimates of the proportion without efficacy related discontinuation was 0.3% (-1.4%, 2.0%).

Median (range) increases from Day 1 at Week 48 in CD4+ cell counts of 4.0 (-536 to 801) cells/mm^3 for CAB + RPV and of 13.5 (-1043 to 521) cells/mm^3 for CAR were observed. The mean and median CD4+/CD8+ ratio through Week 48 was similar in both treatment groups.

Considering the rate of subjects with HIV-1 RNA ≥50 c/ml and the rate of subjects with CVF at Week 48, and the applicant's choice of a 6% non-inferiority margin, the switch from an effective oral tritherapy to CAB+RPV LA IM Q4W in virologically-suppressed subjects is non-inferior to the pursue of

the oral regimen. The other efficacy endpoints and the PP analysis confirm the non-inferiority. Although the 6% non-inferiority margin is debatable, the non-inferiority is still demonstrated with a 4% margin.

Week 96:

At Week 96, 51 subjects remained ongoing in the Extension Phase. Numbers of subjects in each treatment group changed throughout the Extension Phase primarily due to transitioning to Study 207966:

Table 25 **Subject disposition at Week 96**

	CAB + RPV N=308	Extension Switch to CAB + RPV N=308
Withdrawn during Maintenance Phase Through Week 52, n	26	18[a, b]
Withdrawn During Extension Phase, n	4	8
Ongoing at Week 96, n	23	28
Transitioned to Study 207966[c], n	253	251[a]
Completed Maintenance Phase, Did Not Transition to Study 207966, and Did Not Enter Extension Phase, n	2	5

At Week 96, 23/23 (100%) subjects in the CAB + RPV group had viral load <50 c/mL and 28/29 (97%) subjects in the Extension Switch to CAB + RPV group had viral load <50 c/mL. No additional subjects had CVF during the Extension Phase between Week 48 and Week 96 endpoints in either treatment group.

Ancillary analyses

Subgroups analyses

There were no statistically significant differences in treatment effect for each randomisation stratification factor and in any Baseline or demographic subgroup examined:

Treatment by Strata Tests of Homogeneity for Proportion of Subjects with Plasma HIV-1 RNA >/=50 c/mL at Week 48 (Maintenance Phase) - Snapshot Analysis – (ITT-E Population)

Table 26

	Analysis Strata	Treatment	N	Number of HIV-1 RNA≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Sex at birth	Female	CAB + RPV	99	2/ 99 (2.0)	2.0 (-1.7, 7.1)
		CAR	104	0/104	
	Male	CAB + RPV	209	3/209 (1.4)	0.0 (-3.0, 2.9)
		CAR	204	3/204 (1.5)	
	p-value for~test of homogeneity[b]	0.321			
Baseline third agent class	PI	CAB + RPV	51	1/ 51 (2.0)	2.0 (-5.0, 10.6)
		CAR	54	0/ 54	
	INI	CAB + RPV	102	0/102	-2.0 (-7.1, 1.8)
		CAR	99	2/ 99 (2.0)	
	NNRTI	CAB + RPV	155	4/155 (2.6)	1.9 (-1.3, 5.9)
		CAR	155	1/155 (0.6)	
	p-value for~test of homogeneity[b]	0.177			

Data Source: Table 2.39

Note: PI = Protease Inhibitors, INI = Integrase Inhibitors, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitors.

a. Difference: Proportion on CAB + RPV - Proportion on CAR. 95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic.

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

Table 27 **Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA >/=50 c/mL at Week 48 by Select Subgroup (Maintenance Phase) - Snapshot Analysis - (ITT-E Population)**

	Analysis Strata	Treatment	N	Number of HIV-1 RNA≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Age (years)	<35	CAB + RPV	80	0/80	-1.3 (-6.9, 3.6)
		CAR	80	1/80 (1.3)	
	35 to <50	CAB + RPV	162	4/162 (2.5)	1.7 (-2.0, 5.6)
		CAR	132	1/132 (0.8)	
	≥50	CAB + RPV	66	1/66 (1.5)	0.5 (-4.6, 7.4)
		CAR	96	1/96 (1.0)	
Race	White	CAB + RPV	214	3/214 (1.4)	0.4 (-2.2, 3.2)
		CAR	207	2/207 (1.0)	
	Non-White	CAB + RPV	94	2/94 (2.1)	1.1 (-3.6, 6.7)
		CAR	101	1/101 (1.0)	
	Black/African American	CAB + RPV	62	2/62 (3.2)	1.9 (-4.3, 10.0)
		CAR	77	1/77 (1.3)	
	Non-Black/African American	CAB + RPV	246	3/246 (1.2)	0.4 (-2.0, 2.8)
		CAR	231	2/231 (0.9)	
Baseline CD4+ cell count (cells/mm^3)	<350	CAB + RPV	23	0/ 23	-3.7 (-19.0, 11.4)
		CAR	27	1/27 (3.7)	
	350 to <500	CAB + RPV	56	2/56 (3.6)	3.6 (-2.9, 12.4)
		CAR	57	0/57	
	≥500	CAB + RPV	229	3/229 (1.3)	0.4 (-2.1, 3.1)
		CAR	224	2/224 (0.9)	

Resistance analyses

The rates of CVF were low in both treatment groups through Week 48: 3 subjects in the CAB + RPV group and 4 subjects in the CAR group. Similar to FLAIR study, the 3 cases of confirmed virologic failure under CAB+RPV IM regimen with treatment emergence of RPV and/or CAB resistance had subtype A, and two of them came from Russia (the third came from France).

Health outcomes

At Week 48, subjects on the CAB + RPV group reported a substantial improvement in overall treatment satisfaction with CAB + RPV compared with their daily oral treatment at study entry (scoring a mean of 29 points from a maximum of 33 points).

Perception of injection (PIN) data suggest that subjects' acceptability of the injectable monthly dosing of CAB + RPV and the amount of bother experienced from ISRs improved over time from Week 5 up to Week 48.

Table 28 Summary and Statistical analysis in PIN dimension Scores per Visit-LOCF

Domain	Visit	n	Mean	SD	Median	Q1-Q3	Min- Max	p-value
Acceptability of ISRs	Week 5	296	2.10	1.028	2.00	1.00, 3.00	1.0, 5.0	
	Week 41	300	1.62	0.861	1.00	1.00, 2.00	1.0, 5.0	< 0.001
	Week 48	303	1.56	0.800	1.00	1.00, 2.00	1.0, 5.0	< 0.001
Bother of ISRs	Week 5	296	1.58	0.511	1.50	1.17, 1.83	1.0, 3.3	
	Week 41	300	1.37	0.435	1.17	1.00, 1.50	1.0, 3.5	Not Done
	Week 48	303	1.37	0.433	1.17	1.00, 1.50	1.0, 3.5	Not Done
Leg movement	Week 5	296	1.98	0.986	1.75	1.25, 2.50	1.0, 5.0	
	Week 41	300	1.47	0.749	1.00	1.00, 1.75	1.0, 5.0	Not Done
	Week 48	303	1.40	0.656	1.00	1.00, 1.50	1.0, 5.0	Not Done
Sleep	Week 5	296	2.00	0.958	1.75	1.25, 2.50	1.0, 5.0	
	Week 41	300	1.45	0.740	1.00	1.00, 1.75	1.0, 5.0	Not Done
	Week 48	303	1.44	0.685	1.00	1.00, 1.75	1.0, 5.0	Not Done

Data Source: Table 7.3
Note: PIN score for Acceptability of ISRs: 1= totally, 2= very, 3= moderately, 4= a little, 5= not at all acceptable.
Note: Bother of ISRs, leg movement, and sleep were scored as 1= not at all, 2= a little, 3= moderately, 4= very, 5= extremely bothered.

Study 207966 (ATLAS-2M)

Methods

This is a Phase III, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1, virologically-suppressed adult subjects. This was a multicentre study conducted in 13 countries: Argentina, Australia, Canada, France, Germany, Italy, Republic of Korea, Mexico, Russian Federation, South Africa, Spain, Sweden and United States.

The majority of subjects were enrolled from the ongoing 201585 Study (ATLAS study) with additional subjects on standard of care (SOC). Eligible subjects were randomised (1:1) to receive either CAB +

RPV Q8W or CAB + RPV Q4W for at least 100 weeks. Randomisation was stratified by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks).

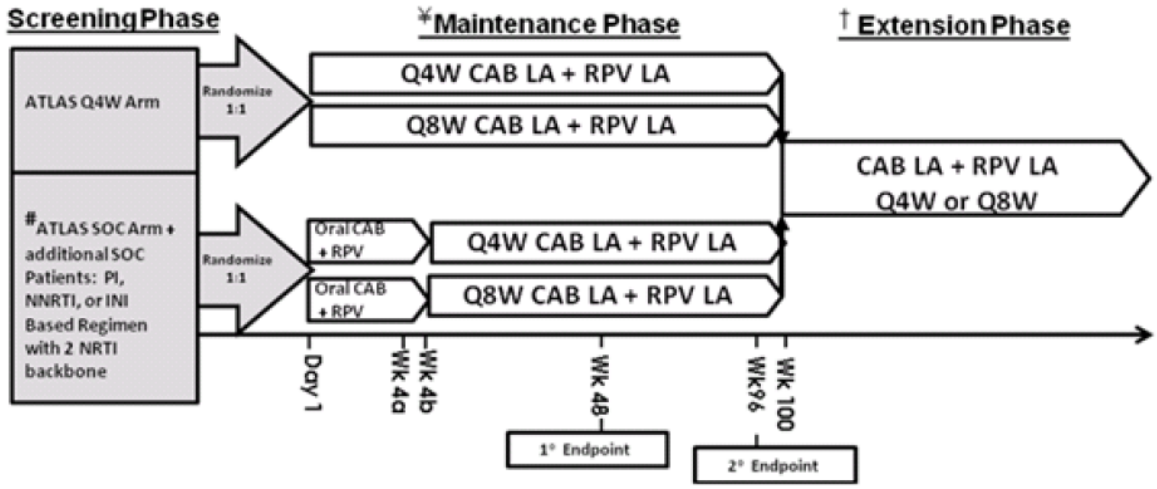
Two groups of subjects were randomised:

- Group 1: Subjects randomised from current ART SOC therapy, including those enrolled to the CAR arm of Study 201585 (following completion of the Week 52 visit at minimum), received oral therapy with CAB 30 mg + RPV 25 mg once daily at Baseline for 28 days (±3 days) followed by IM CAB + RPV Q8W or IM CAB + RPV Q4W thereafter.

- Group 2: Subjects entering Study 207966 from Study 201585 and currently receiving IM CAB + RPV Q4W were randomised 1:1 to either continue IM CAB + RPV Q4W or transition to IM CAB + RPV Q8W.

The IM CAB + RPV Q4W regimen consists in IM CAB 400 mg + RPV 600 mg every 4 weeks.

The IM CAB + RPV Q8W regimen consists in IM CAB 600 mg + RPV 900 mg every 8 weeks.



SOC subjects not transitioning from the Study 201585 were to be on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening. Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening was required. Subjects were excluded if they had a history of virologic failure; evidence of viral resistance based on the presence of any resistance-associated major INI, or NNRTI mutation (except K103N) from prior genotype assay results; or current or prior history of etravirine use.

†Optional Extension Phase to continue randomized IM CAB + RPV (CAB LA + RPV LA in the diagram) Q4W or Q8W at Week 100

¥Subjects who withdraw from IM regimen must go into 52-week LTFU if randomized regimen is not yet locally approved and commercially available.

Figure 13 ATLAS 2M

Results

Since the D120 AR, the Week 48 results became available. At the time of the data cut for this 48 Week data summary, the number of subjects ongoing in the Maintenance Phase was similar in both treatment groups (Q8W: 486 subjects [93%]; Q4W: 481 subjects [92%]).

Table 29 Summary of Subject Accountability: Maintenance Phase Conclusion Record (ITT-E Population)

	Q8W (N=522)	Q4W (N=523)
Subject Status		
Ongoing, n (%)	486 (93)	481 (92)
Completed, n (%)	0	0
Withdrawn, n (%)	36 (7)	42 (8)
AE	12 (2)	13 (2)
Lack of efficacy	9 (2)	3 (<1)
Protocol Defined CVF	8 (2)	2 (<1)
Insufficient viral load response	1 (<1)	1 (<1)
Protocol deviation	1 (<1)	1 (<1)
Prohibited medication use	0	1 (<1)
Non-compliance with study treatment	1 (<1)	0
Non-compliance with protocol procedures	1 (<1)	0
Protocol specified withdrawal criteria met	1 (<1)	3 (<1)
Pregnancy	1 (<1)	3 (<1)
Lost to follow-up	2 (<1)	0
Physician decision	5 (<1)	1 (<1)
Patient has developed resistance to rilpivirine [a]	1 (<1)	0
Subject had pulmonary tuberculosis, on long term follow-up	1 (<1)	0
Physician discretion with reason=positive pregnancy test with no confirmation of intrauterine pregnancy	1 (<1)	0
Subject was taking zidovudine lamivudine efavirenz abacavir atazanavir ritonavir before study start and was randomized in error but later early withdrawn during oral lead in phase	1 (<1)	0
The overall status of the subject including subject's significant cardiovascular history	0	1 (<1)
Subject required long term anticoagulant therapy	1 (<1)	0
Withdrawal by subject	6 (1)	21 (4)
Anxiety related to suicidality assessment	0	1 (<1)
Subject relocated	0	5 (<1)
Due to business subject cannot continue to participate in the study	0	1 (<1)
New safety updates a concern for patient wanting to have a baby in the future	0	1 (<1)
Subject was incarcerated	0	1 (<1)
Subject planning to become pregnant	1 (<1)	0
Burden of travel or lack of access to travel	0	1 (<1)
Subject wanted to switch to a non-integrase inhibitor regimen due to potential weight gain side effect	1 (<1)	0
Burden of procedures	1 (<1)	3 (<1)
Intolerability of injections	1 (<1)	4 (<1)
Frequency of injections	0	1 (<1)
Frequency of visits	3 (<1)	6 (1)
Depressive syndrome and pain at site injection	0	1 (<1)
Family problems	0	1 (<1)
Problems with work due to study schedule and injection site reactions; no other visits will be done	0	1 (<1)
The patient will move to other country	0	1 (<1)
Outcome of AEs resulting in study withdrawal		
Fatal	0	0
Non-fatal	12 (2)	13 (2)

Demographic characteristics were generally similar between the 2 treatment groups.

At Week 48, the proportion of subjects with plasma HIV-1 RNA ≥50 c/ml (Snapshot Algorithm) was similar between treatment groups, with the upper bound of 95% CI for the adjusted treatment difference

between Q8W and Q4W less than the pre-defined non-inferiority margin of 4%. Results for the PP population were similar to those for the ITT-E Population.

Table 30 **Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Maintenance Phase) Snapshot Algorithm**

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
Q8W	522	9 / 522 (1.7)	0.8 (-0.6, 2.2)	0.8 (-0.6, 2.2)
Q4W	523	5 / 523 (1.0)		
PP Population				
Q8W	516	7 / 516 (1.4)	0.4 (-0.9, 1.7)	0.4 (-0.9, 1.7)
Q4W	514	5 / 514 (1.0)		

Nevertheless, more subjects discontinued due to lack of efficacy in the Q8W group (Q8W: 6 [1.1%]; Q4W: 2 [0.4%]) while less subjects in this group had no virologic data (Q8W: 21 [4.0%]; Q4W: 29 [5.5%] due to fewer discontinuations related to AE, death, or for other reasons.

Table 31 **Summary of Study Outcomes (Plasma HIV-1 RNA 50 c/mL Threshold) at Week 48 (Maintenance Phase) Snapshot Algorithm (ITT-E Population)**

Outcome	Q8W (N=522) n (%)	Q4W (N=523) n (%)
HIV-1 RNA <50 c/mL	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL	9 (1.7)	5 (1.0)
Data in window not below threshold	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reason while not below threshold	0	1 (0.2)
Change in background therapy	0	0
No virologic data	21 (4.0)	29 (5.5)
Discontinued study due to AE or death[a]	9 (1.7)	13 (2.5)
Discontinued study for other reasons[b]	12 (2.3)	16 (3.1)
On study but missing data in window	0	0

Data Source: Table 2.3.

a. 2 deaths were reported: 1 in Maintenance Phase and another during Screening (subject did not receive study drug).

a. Q8W: lost to follow up, 2 subjects; withdrawal by subject, 4 subjects; protocol deviation, 1 subject; Investigator decision, 4 subjects, lack of efficacy, 1 subject. Q4W: protocol specified withdrawal criteria met (pregnancy), 3 subjects; withdrawal by subject, 12 subjects; protocol deviation, 1 subject (Data Source: Listing 4, Listing 11).

According to the randomisation strata (prior exposure to CAB + RPV), the test of evidence against homogeneity of the treatment difference was not statistically significant for prior exposure to CAB + RPV (p=0.346). However, the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 is higher for subjects with prior exposure to CAB + RPV between 1 to 24 weeks but is similar between both groups for subjects without prior exposure to CAB + RPV or with prior exposure > 24 weeks.

Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 by Randomization Strata (Maintenance Phase) - Snapshot Algorithm - (ITT-E Population)

Table 32

Analysis Strata	Weeks	Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Prior Exposure to CAB + RPV)	0	Q8W	327	5/ 327 (1.5)	0.0 (-2.2, 2.2)
		Q4W	327	5/ 327 (1.5)	
	1-24	Q8W	69	3/ 69 (4.3)	4.3 (-1.3, 12.3)
		Q4W	68	0 / 68	
	>24	Q8W	126	1/ 126 (0.8)	0.8 (-2.2, 4.4)
		Q4W	128	0 / 128	
P-value for Test of Homogeneity[b]					0.346

Data Source: Table 2.4.

a. Unadjusted Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W. 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 will be used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

The proportion of Snapshot virologic failures was numerically higher in the Q8W arm compared with the Q4W arm in female subjects (5/137 [3.6%] and 0/143 [0%] in females vs 4/385 [1.0%] and 5/380 [1.3%] in males, respectively) and in subjects with BMI ≥30 kg/m2 (6/113 [5.3%] in the Q8W group and 2/98 [2.0%] in the Q4W group for BMI ≥30 kg/m2 vs 3/409 [0.7%] in the Q8W group and 3/425 [0.7%] in the Q4W group for BMI <30 kg/m2).

The proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 was similar for both treatment groups:

Table 33 **Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (Maintenance Phase)-Snapshot Algorithm**

Treatment	N	Number of HIV-1 RNA <50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
Q8W	522	492 / 522 (94)	0.8 (-2.2, 3.7)	0.8 (-2.1, 3.7)
Q4W	523	489 / 523 (93)		
PP Population				
Q8W	516	491 / 516 (95)	1.0 (-1.8, 3.7)	1.0 (-1.7, 3.7)
Q4W	514	484 / 514 (94)		

Data Source: Table 2.8, Table 2.9.

a. Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W.

b. Based on CMH stratified analysis adjusting for the following Baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

Mean and median CD4+ cell counts remained stable from Baseline in both treatment groups over time. Mean and median change from Baseline in CD4+ cell counts were similar between treatment groups when analysed by subgroups.

The CAB and RPV Cmin measured in these subjects with HIV-1 RNA ≥50 c/ml are comparable to the values for the overall population matched for strata of prior exposure at that same visit and includes identification of subjects with RAMs.

Table 34 Summary of CAB and RPV Plasma Concentrations at the SVF Visit for Subjects with CVF Compared to Overall Population at Corresponding Study Visit

Regimen	SVF Visit	Prior exposure to CAB + RPV	CAB (μg/mL)		RPV (ng/mL)	
			CVF Subject at SVF Visit	Population GM (CVb%) [min, max][a]	CVF Subject at SVF Visit	Population GM (CVb%) [min, max][a]
Q8W	8[b]	1-24wk	1.1	1.65 (63) [0.272, 11.7]	74	51.4 (42) [15.4, 148]
	16[c]	0	0.65	1.41 (58) [0.085, 4.12]	14.2	46.2 (41) [13.6, 178]
	16[b,d]	0	1.35	1.41 (58) [0.085, 4.12]	34.8	46.2 (41) [13.6, 178]
	16	0	0.921	1.41 (58) [0.085, 4.12]	34.2	46.2 (41) [13.6, 178]
	24[b]	0	1.57	1.44 (62) [0.025, 4.45]	108	49.5 (44) [13.9, 145]
	24[b]	0	1.82	1.44 (62) [0.025, 4.45]	44.3	49.5 (44) [13.9, 145]
	24[b]	1-24 wk	1.45	1.62 (54) [0.565, 6.20]	132	57.1 (47) [21.5, 163]
	48	1-24 wk	1.44	1.77 (63) [0.239, 4.95]	78.5	77.6 (50) [22.2, 196]
Q4W	16[e]	0	1.28	2.13 (46) [0.602, 12.4]	101	57.8 (49) [16.7, 302]
	32	0	1.99	2.69 (51) [0.025, 8.46]	52.9	75.8 (44) [12.2, 341]

Data Source: Listing 29, Listing 30, Table 4.5, Table 4.6.

a. Matched for strata of CVF
b. Major NNRTI RAMs at Baseline
c. CVF but not snapshot failure, achieved <50 c/mL at Week 20 Visit
d. Major INSTI RAMs at Baseline
e. G190Q at Baseline associated with high level resistance to RPV, not defined as RAM

In comparison to the CAB and RPV Cmin measured in subjects with virologic success, no suboptimal exposition of CAB and RPV seems associated with these virologic failures.

Resistance analyses

Confirmed virologic failure (CVF) was defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. CVF up to Week 48 was uncommon with 10 subjects meeting CVF criteria: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Eight subjects met CVF criteria at or before the Week 24 timepoint.

Table 35 Cumulative Proportion of Subjects Meeting CVF by Visit Up to Week 48 (Maintenance Phase) (ITT-E Population)

SVF Timepoint[a]	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Week 8	1 (0.2)	0
Week 16	4 (0.8)	1 (0.2)
Week 24	7 (1.3)[b]	1 (0.2)[c]
Week 32	7 (1.3)	2 (0.4)
Week 48	8 (1.5)	2 (0.4)

Data Source: Table 2.23.

a. First of the 2 consecutive HIV-1 RNA levels ≥200 c/mL
b. In the Week 24 analysis of the Q8W arm there were 6 CVFs at the Week 24 visit because one additional CVF was initially captured as 'insufficient viral response'
c. In the Week 24 analysis of the Q4W arm there were 2 CVFs at the Week 24 visit because one CVF was identified at Week 32 but was already included in the Week 24 analysis database.

Note: This summary is the proportion of CVFs up to the analysis visit.
Note: Only visits during which at least 1 new CVF occurs are shown.

NNRTI RAM and INI RAM were present at baseline for respectively 6 and 5 subjects in the Q8W group, and 1 and 0 subject in the Q4W group. This could explain the higher number of CVF subjects in the Q8W group.

The NNRTI and INSTI RAM that have emerged from baseline to the SVF timepoint were K101E (n=3), E138E/K (n=1), V179V/I (n=1) and M230L (n=1) for NNRTI RAM, and Q148Q/R or Q148R (n=4), N155N/H or N155H (n=5) and E138E/K (n=1) for INI RAM. These RAM are known to be associated with decreased RPV or CAB susceptibility.

Summary of main efficacy results

Title: A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability ofLong-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naive Adult Participants		
Study identifier	201584 (FLAIR)	
Design	Phase III, multi-phase, randomised, open label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1, ART-naïve adult subjects.	
	Duration of Induction phase:	20 weeks
	Duration of Maintenance phase:	100 weeks
Hypothesis	Non-inferiority	
Treatments groups	CAB + RPV	Oral CAB + RPV during 4 weeks then CAB LA + RPV LA N=283
	Comparator	ABC/DTG/3TC N=283

Endpoints and definitions	Primary endpoint	- Proportion of subjects with a "virologic failure" endpoint as per FDA Snapshot algorithm at Week 48 (ITT-E Population) - Proportion of subjects with plasma HIV-1 RNA ≥50 c/ml at Week 48 (ITT-E Population)	
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: n= 566 Per protocol:n=560 Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	CAB+RPV	ABC/DTG/3TC
	Number of subjects	283	283
	Subjects with HIV-1 RNA ≥50 c/ml at Week 48 (ITT-E) (%)	**6 (2.1%)**	**7 (2.5%)**
	Subjects with confirmed virologic failure at Week 48 (ITT-E) (%)	4 (1.4%)	3 (1.1%)
	Subjects with HIV-1 RNA <50 c/ml at Week 48 (ITT-E) (%)	265 (93.6%)	264 (93.3%)
Effect estimate per comparison	Primary endpoint (ITT-E analysis)	Comparison groups	CAB+RPV – ABC/DTG/3TC
		Adjusted difference in proportion	**-0.4**
		variability statistic	**-2.8, 2.1**
		P-value	<0.01
	Primary endpoint (PP analysis)	Comparison groups	CAB+RPV – ABC/DTG/3TC
		Adjusted difference in proportion	-0.3
		variability statistic	-2.8, 2.2
		P-value	<0.01

Title: A Phase III, randomized, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI-, NNRTI-, or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed	
Study identifier	201585 (ATLAS)

Design	Phase III, multi-phase, randomised, open label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1 virologically suppressed adult subjects on a stable ARV regimen.		
	Duration of Maintenance phase:	52 weeks 44 weeks	
Hypothesis	Non-inferiority		
Treatments groups	CAB + RPV	Oral CAB + RPV during 4 weeks then CAB LA + RPV LA N=308	
	Comparator	Current ARV Regimen (CAR): 2 NRTI + 1 PI, NNRTI or INI N=308	
Endpoints and definitions	Primary endpoint	Proportion of subjects who met the Snapshot virologic failure criteria, defined as plasma HIV-1 RNA ≥ 50 c/mL, at Week 48 (ITT-E Population)	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: n= 616 Per protocol:n=586 Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	CAB+RPV	CAR
	Number of subject	308	308
	Subjects with HIV-1 RNA ≥50 c/ml at Week 48 (ITT-E) (%)	**5 (1.6%)**	**3 (1.0%)**
	Subjects with HIV-1 RNA <50 c/ml at Week 48 (ITT-E) (%)	285 (92.5%)	294 (95.5%)
Effect estimate per	Primary endpoint (ITT-E analysis)	Comparison groups	CAB+RPV – CAR
		Adjusted difference in proportion	**0.6**
		variability statistic	**-1.2, 2.5**
		P-value	<0.01
	Primary endpoint (PP analysis)	Comparison groups	CAB+RPV – CAR
		Adjusted difference in proportion	0.3
		variability statistic	-1.4, 2.1
		P-value	<0.01

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

Pooled data

A pool of the pivotal Phase 3 results was performed:

Table 36 **Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, and Pooled Data (ITT-E)**

Treatment [a]	Number of Virologic Failures/Total Assessed (%)	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV	6/283 (2.1)	-0.4 (-2.8, 2.1)	-0.4 (-2.8, 2.1)
CAR	7/283 (2.5)		
201585			
CAB + RPV	5/308 (1.6)	0.7 (-1.1, 2.4)	0.7 (-1.2, 2.5)
CAR	3/308 (1.0)		
Pooled Data			
CAB + RPV	11/591 (1.9)	0.2 (-1.3, 1.7)	0.2 (-1.4, 1.7)
CAR	10/591 (1.7)		

Table 37 **Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, and Pooled Data (PP)**

Treatment [a]	Number of Virologic Failures/Total Assessed (%)	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV	6/278 (2.2)	-0.3 (-2.8, 2.2)	-0.3 (-2.8, 2.2)
CAR	7/282 (2.5)		
201585			
CAB + RPV	4/294 (1.4)	0.3 (-1.4, 2.1)	0.3 (-1.4, 2.1)
CAR	3/292 (1.0)		
Pooled Data			
CAB + RPV	10/572 (1.7)	0.0 (-1.5, 1.5)	0.0 (-1.5, 1.5)
CAR	10/574 (1.7)		

Data Source: ISE/ISS Table 2.03

a. In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
b. Difference: Proportion on CAB + RPV (Q4W IM) – Proportion on CAR (unadjusted).
c. Based on CMH stratified analysis adjusting to Baseline viral load and Gender for Study 201584; adjusting to 3rd ART class and Gender for Study 201585; and adjusting to 10 strata for pooled analysis.

For the pooled analysis, CVF rates for both the CAB + RPV arm and the CAR group was 7/591 (1.2%).

The rates of virological failure are low and similar between both studies, which is consistent with their similar population. The pooled analysis confirms the non-inferiority of once-monthly CAB + RPV vs the continuation of an effective ARV regimen, considering a 4% non-inferiority margin.

Post-hoc analysis

A multivariable logistic regression analysis of pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M) was performed to examine the influence of baseline viral load, participant characteristics, dosing regimen,

and post-baseline plasma drug concentrations on confirmed virologic failure (CVF). This analysis included data from 1039 HIV-infected adults with no prior exposure to CAB+RPV, including 13 subjects 1.25%) with CVF at Week 48.

Four covariates were significantly associated (P<0.05 for each adjusted odds ratio) with increased risk of CVF: RPV-RAM at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), C_t RPV at 4 weeks following initial injection dose, BMI≥30 kg/m2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF.

No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI≥30 kg/m2:

Baseline Factors (number)	Virologic Successes (%)[2]	Confirmed Virologic Failure (%)[3]
0	694/732 (94.8)	3/732 (0.41)
1	261/272 (96.0)	1/272 (0.37)[4]
≥2	25/35 (71.4)	9/35 (25.7)[5]
TOTAL (95% Confidence Interval)	980/1039 (94.3) (92.74%, 95.65%)	13/1039 (1.25) (0.67%, 2.13%)

[1] HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)
[2] Based on the FDA Snapshot algorithm of RNA <50 copies/mL.
[3] Defined as two consecutive measurements of HIV RNA >200 copies/mL.
[4] Positive Predictive Value (PPV) <1%; Negative Predictive Value (NPV) 98%; sensitivity 8%; specificity 74%
[5] PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%

Since the applicant originally only claimed a Q4W regimen this study was considered supportive, it is now viewed as pivotal in support of the Q8W regimen newly claimed within the timeframe of the procedure.

2.5.1. Discussion on clinical efficacy

Dose selection

The doses of CAB and RPV were selected based on the Phase II studies (LATTE study for oral CAB and RPV, and LATTE-2 study for CAB LA and RPV LA).

Data from LATTE study suggest that an oral bitherapy CAB + RPV seems effective to obtain and maintain an adequate virologic suppression. Based on the Week 96 data, better results may be expected with CAB 30 mg or 60 mg than with CAB 10 mg, although no statistically significant difference was observed between these 3 CAB groups. However, a numerically higher rate of discontinuation due to AE is observed in the CAB 60 mg arm vs the other CAB arms. PK data have shown a relatively dose-proportional CAB exposure (AUC, Cmax and C0) between 10 mg and 60 mg, although a slight less-than-proportional increase was highlighted between 30 mg and 60 mg. Therefore, the selection of an oral CAB dose at 30 mg is endorsed and was approved in EMA Scientific Advice.

For the IM LA formulations of CAB and RPV, dose regimen were selected by the applicant using POPPK simulations and taking in to account i) the ability to reach target concentration early in treatment, ii) the ability to maintain mean C_T above that obtained with oral CAB 10 mg once daily during treatment (CAB trough concentrations ≥1.35 µg/mL), and iii) the lower total number of injections per visit. This is endorsed, although a higher PK target, corresponding to C_T with oral CAB 30 mg, could have been considered. However, the applicant considers that maintaining a target at approximately the level of the

30 mg oral dose is not needed in Maintenance, as viral suppression and short-term tolerability have been established during Induction.

The selected IM dose regimen (Q4W and Q8W) were then tested and supported in study LATTE-2. According to the EMA Scientific advice, the applicant has firstly selected the Q4W dose regimen for the Phase 3 studies and the MA application.

Since the D120 AR, the alternative Q8W dose regimen was added to the proposed posology, given that the Week 48 results of the Phase 3 study ATLAS-2M are now available. With this Q8W regimen, a 20 to 40% decrease of CAB/RPV predose concentrations are observed in comparison to the Q4W regimen. As regards CAB exposure, the lower concentrations measured (≈1.3 µg/ml) are equivalent to those measured in the oral CAB 10 mg group in the Phase 2 study LAI116482. Reassuringly, the virological impact in this group was similar to that in the CAB 30 mg group (i.e. the recommended posology of oral CAB tablets). Furthermore, this CAB Ct is approximately 8-fold above the protein adjusted IC90 (CAB PA-IC90 ≈ 0.16 µg/ml).

Design and conduct of clinical studies

The pivotal Phase 3 studies, FLAIR and ATLAS studies, were designed and powered to statistically demonstrate the non-inferiority of the CAB+RPV strategy (i.e. oral CAB 30 mg + RPV 25 mg QD during 1 month, followed by injection of IM CAB LA 600 mg + RPV LA 900 mg, and then IM CAB LA 400 mg + RPV LA 600 mg every 4 weeks thereafter) for switch from current oral antiretroviral regimen (CAR) in virologically-suppressed subjects. These studies were broadly similar in terms of design and objective (both studies assessing the rate of virological failure after 48 weeks of switch). Their open label design is endorsed since the use of placebo (notable placebo injections) would increase the risk of non-adherence and bias the evaluation and the potential interest of the monthly injections of ART. It is noted that the applicant has defined a virologic failure with a limit HIV-1 RNA value at 200 c/ml, but the standard criteria "confirmed viral load ≥50 c/ml" is also to be considered for a robust efficacy analysis.

The studies were open-label, which is considered acceptable given that the pharmaceutical form (suspension for injection) is not considered appropriate for a double-dummy design. The primary endpoint is an objective measurement (based on plasma HIV-1 RNA measurement), which will not be influenced by the open-label design.

The design of each open label randomised pivotal FLAIR and ATLAS studies, the pooling of these studies results, the non-inferiority margin of the individual studies (6%) and of the pooled studies (4% pooling enabling a more reliable efficacy estimate) were agreed by the EMA scientific advices.

These studies were well performed, although some protocol deviations (including GCP non-compliance in one site and quality issues on the HIV-1 assay (see GCP comments above) were observed throughout these studies. As regards the HIV-1 assay contamination, the applicant's explanation on the origins of this contamination, and its strategy to retest the positive samples during the contamination window, are acceptable. The robustness and integrity of the efficacy data could be considered preserved. In FLAIR study, a higher number of protocol deviations with the CAB+RPV IM regimen in comparison to the CAR regimen may suggest that this new injectable form of ART may be challenging to manage, with more requirements than a standard daily oral ART regimen, notably for the compliance of the monthly administrations and the study procedures associated with this treatment.

Patient population

A total of 1182 patients were included and treated within these Phase 3 studies (591 patients with CAB+RPV and 591 comparative patients with their current oral ARV regimen), conferring an adequate power for the interpretation of efficacy data. In both studies, baseline characteristics (notably CD4 level,

HIV subtype, CDC stage, HIV risk factor and medical conditions) were well balanced between both arms. The included population is mainly represented by asymptomatic Caucasian MSM without immunologic deficiency, although it is noted that efforts were made to include a significant proportion of women (25-30%), in comparison to the last clinical studies in HIV medicines. However, the proportion of subjects with low CD4 levels (<350 cells/mm^3) is low (<10%), and African people is poorly represented, with only few centres in South Africa in both studies. Finally, according to their exclusion criteria, studies participants should not have any evidence of primary resistance to NNRTIs (except for K103N which is allowed), or any known resistance to INIs from historical resistance test results, which should be reflected in the indication in Vocabria SmPC. Of note, prior to randomisation, subjects were stably suppressed for at least 6 months in ATLAS study, while it was for a median of 16.10 weeks in FLAIR study.

A particularity of this procedure is to propose an oral formulation of CAB and RPV to i) assess tolerability of this bitherapy before starting the long acting formulations, and ii) ensure the continuity of treatment with an oral bridging in case of missing injection. For this last indication, very few efficacy data are available (only 8 missed injections with oral bridging across studies).

In addition to these two pivotal studies, the applicant has submitted data from a pooled analysis of these studies and from an ongoing Phase 3 study (ATLAS 2M) comparing the current monthly regimen (Q4W) with an every 2 months regimen (Q8W). The pooling of the pivotal studies is endorsed given the included population and similar design of these studies. ATLAS 2M study was performed to assess an alternative dose regimen with larger intervals between each injections (CAB 600 mg + RPV 900 mg every 8 weeks). While a debatable 6% non-inferiority margin was selected for ATLAS and FLAIR versus combined ARV, a reduced non inferiority margin of 4% is selected for this study comparing two schedules regimen of the combination CAB+RPV LA, which is endorsed.

Additionally, the combination of CAB+RPV IM is also currently developed in parallel for a future PrEP indication, but data were not available nor required for this current MA application.

Efficacy data and additional analyses

Q4W regimen

According to the efficacy endpoints in studies FLAIR and ATLAS, the bitherapy CAB+RPV Q4W (i.e. oral doses during 1 month then monthly IM administrations) is non-inferior to a standard tritherapy (2 NRTI + 1 PI/NNRTI or INI) in virologically-suppressed subjects. Few cases of virological failure were observed throughout these studies, in both treatment arms. The difference in the percentages of patients with loss of virologic suppression (HIV RNA $\geq$50 copies/ml) at 48 weeks (pooling data of studies FLAIR and ATLAS) was 0.2 (95% CI: -1.4, 1.7), with results well below the pre-defined 4% non-inferiority margin and with consistency on the ITT and PP analyses.

However, when focusing on subgroup analysis, concerns may be raised on some subgroups of subjects:

- In both studies, the rate of virological failure was numerically higher in women treated by CAB+RPV than with the current oral ARV regimen (CAR) (pooled results: 5/162 vs 1/168 in women treated by CAB+RPV and CAR, respectively). This discrepancy was not observed with male subjects. In addition, in the pop PK modelling, categorisation of Cmin-LD by gender showed that the median was lower in females than males by 31%. However, the number of CVF cases remains low and consistent with the other switch studies for HIV medicines. Therefore, a gender effect of CAB+RPV seems unlikely but cannot be excluded.

- A trend of higher rate of virological failure with CAB+RPV is observed in subjects with BMI ≥30: in FLAIR study, 3 subjects/40 treated with CAB+RPV experienced virological failure, vs 0 subject/37 treated with CAR. Data according to BMI in ATLAS study were not provided in the CSR, but this trend is recovered in the pooled analysis. No conclusion can be raised given the low number of subjects in these subgroups.

In addition, the PKPOP analysis has shown that subjects with BMI ≥30 kg/m2 had 31% lower median Cmin-LD than those with BMI <30 kg/m2. When considered the subgroups BMI and gender, the trend of rate of virological failure with CAB+RPV is observed only in the subgroup of women with BMI ≥30, which could traduce a mixed gender and PK effect. Of note, based on the difference between individual observed and predicted CAB Ct, female and BMI ≥30 were not associated to a higher within-subject variability, and the hypothesis that misplaced injections are more frequent in patients with a high BMI value and consequently leads to higher risk of virological failure is not supported by this PK analysis.

- In the pooled analysis, an efficacy concern could also be raised in Russian subjects, with an over representation of Russian subjects among the patients who experienced a virological failure in the CAB+RPV group (6/101 Russian subjects [6%]) in comparison to the CAR group (2/98 Russian subjects [2%]). All Russian subjects came from different study centres, which rules out the hypothesis of a clinical practice problem, but all had HIV-1 subtype A (A1 or AG). However, the *in vitro* activity of CAB and RPV in the subtype A did not differ to the other HIV-1 subtypes. Therefore, there may be external factors, notably the circulation of HIV variants with certain viral mutations (such as L74I), that may have an impact on outcome in Russian subjects.

Q8W regimen

Based on ATLAS-2M study, the Q8W regimen (i.e. CAB/RPV 600/900 mg IM every two months) is non inferior to Q4W (monthly injections) regimen, both regimens being overall associated with a low rate of virologic failure (<2%). These results are consistent with data from FLAIR and ATLAS studies.

Although non inferiority has been established between the Q4W and Q8W regimen in the ATLAS2M study, it is unclear at this stage to what extent both regimens could be regarded as equally appropriate and therefore being both equally proposed in section 4.2 as currently claimed by the applicant.

Indeed, first the amount of data in support of the Q4W is significantly higher as compared to that for the Q8W.

The rate of subjects with HIV-1 RNA ≥50 c/ml at Week 48, and especially the rate of confirmed virologic failure (CVF), is numerically higher in the Q8W group (8 subjects) than in the Q4W group (2 subjects).

Table 38 Subjects with HIV-1 RNA ≥50 c/ml

	FLAIR		**ATLAS**		**LATTE-2**			**ATLAS-2M**	
SVF Time Point	CAB+RPV **Q4W**	CAR	CAB+RPV **Q4W**	CAR	CAB+RPV **Q8W**	CAB+RPV **Q4W**	CAB oral	CAB+RPV **Q8W**	CAB+RPV **Q4W**
Week 4	0	0	0	0	1	0	0	0	0
Week 8	1	1	1	0	0	0	1	1	0
Week 12	0	1	1	0	0	0	0	0	0
Week 16	0	1	0	0	0	0	0	3	1

Week 20	1	0	0	2	0	0	0	0	0
Week 24	0	0	1	0	0	0	0	3	0
Week 28	1	0	0	0	0	0	0		
Week 32	0	0	0	1	0	0	0	0	1
Week 40	0	0	0	1	0	0	0		
Week 48	1	0	0	0	1	0	0	1	0
Week 96	0	1	0	0	0	0			
Any time point	**4/283** (1.41%)	**4/283** (1.4%)	**3/308** (0.97%)	**4/308** (1.30%)	**2/115** (1.74%)	**0/115** (0%)	**1/56** (1.79%)	**8/522** (1.5%)	**2/523** (0.4%)

Moreover, the CAB exposure with the Q8W regimen may be considered borderline. Based on model prediction, the Q4W dose regimen was predicted to induce CAB exposure above the target of 1.35 µg/mL after ~1 year of treatment in 99.6% of subjects, while this would be 84% of subjects with the Q8W regimen.

In the Q8W regimen, most of the CVF (7/8) have occurred during the first 24 weeks of treatment. In addition, most of subjects experiencing CVF had no prior exposure to CAB + RPV, with a somewhat lower Cmin exposures during the first months of therapy with this Q8W regimen. This could suggest an inadequate CAB and/or RPV exposure at the beginning of treatment or differential resistance pattern at baseline.

The applicant argues that the Q8W regimen and the Q4W regimen are equally effective. The SAG input was requested on how they view the level of evidence in support of the Q8W, the SAG experts were confident that both regimens could be equally considered for the management of patients based on the clinical demonstration available (see SAG minutes).

In order to identify pejorative risk factors for CVF the applicant has performed multivariable analyses of pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M), including data from 1039 HIV-infected adults with no prior exposure to CAB+RPV. Through Week 48 in these studies, 13/1039 (1.25%) participants had CVF while receiving cabotegravir and rilpivirine. Albeit having some limitations resulting from the few CVF to substantiate correlations, based on the multivariable analyses the applicant has identified that the Q8W regimen might not be optimal in patients having cumulative risk factors of virologic failure, i.e. at least 2 of the following baseline factors: rilpivirine resistance mutations identified by proviral resistance testing, HIV-1 subtype A6/A1, or BMI>30 mg/m2. According to the SAG, the prescribers must be informed throughout a warning in the SmPC that such baseline factors may have an impact on the virologic response to CAB+RPV, in order to select candidates for dual LA Q8W regimen with further minimisation of the risk of virologic failure. These points have been introduced along the SmPC (4.2, 4.4, 5.1).

Additional expert consultation

A SAG meeting was held September 8 for the Vocabria and Rekambys parallel applications. The following, identical questions were asked to the SAG members for both applications and are presented with the (preliminary) answers by the experts. The outcome of the SAG was adopted during the September 2020 CHMP meeting.

1.-To what extent do the SAG experts consider that the level of evidence supports the applicant claim that both the Q4W and Q8W dosing regimens could be equally proposed in the product information?

The group considered that there is enough evidence to support Q8W dosing taking into account that there were not significant differences between Q8W and Q4W regimens in the different studies. Therefore, it can be concluded that both regimens seem to have comparable efficacy.

However, it was also highlighted that there are still some concerns regarding the subgroup of patients on Q8W dosing who showed more risk of virological failure (VF). In the multivariate analysis performed to explore variables associated with increased risk of confirmed virological failure (CVF), the main baseline factors associated with virologic outcome risk factors were:

- having a BMI> 30 kg/m2pre-existing major RPV RAMs that were no identified in the genotype
- subtype A 1/6

Several measures were proposed to minimise this risk:

To start a Q4W regimen in those patients who could have higher risk of VF as it was described before. In these cases, switching to a Q8W dosing could be considered afterwards in patients who reach and maintain undetectability with this regimen.

The experts also proposed adding a clarification in the SmPC explaining the risk factors which could contribute to developing a VF. In this case, the SmPC labelling would be useful for the clinicians to decide on the preferred regimen for every patient. In addition, the current wording of the indication already prevents from prescribing this treatment to patients who present or have past evidence of viral resistance to NNRTI or INI which may minimise the risk.

Wording of the indication (section 4.1):

Vocabria/Rekambys injection is indicated, in combination with rilpivirine/cabotegravir injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.

Finally, the experts consider that the patients' wishes should also be taken into consideration.

In conclusion, Q8W and Q4W seem to be equally effective. However, special considerations should be given to patients who might have higher risk of virological failure on Q8W considering the current data.

2 .-Could the SAG experts suggest appropriate tools to increase adherence to scheduled dosing?

Adherence is an extremely complex and heterogeneous topic that can change between patients, centres, etc, across Member states. Therefore, it is very difficult to make a universal recommendation that could apply to all patients.

However, it was also highlighted that new issues can emerge with this new regimen, especially, considering the very long half-life of both drugs after injection and therefore, measures should be in place to ensure the close monitoring of the patients.

Some strategies such as peer support, an increased frequency of the visits to the clinic at the beginning of treatment, the facilitation of the medication supply to the patients, reminder tools such as mobiles, text messages, actions intended to minimise local reactions due to injections, etc., could be of help. Overall, the experts remarked that there is no unique tool for all the patients and the strategies should be tailored in every case.

In conclusion, adherence is a key element and should be reinforced, however, there is not a unique tool to ensure good adherence to treatment. Hence, measures should be adapted to the centres, resources, patients' characteristics etc.

3.-Could the SAG experts discuss to what extent they are confident that a post approval study could enable substantiating the potential impact of inadequate handling of the LA regimen in real life setting (in terms of risk of virological failure and emergence of resistance to the dual INI and NNRTI classes)?

The experts recommend that a non-interventional post approval study on this CAB+RPV LA regimen is necessary to complement the data from existing registries. Such a study will substantiate real life settings since the clinical trials supporting the dossier were performed in very selected study populations. This post marketing study will be pivotal to monitor adherence and collect data on virological suppression, using appropriate threshold (i.e. plasma HIV-1 RNA levels <50 c/mL instead of <200 c/mL) to avoid waiting for virological failure while on CAB+RPV LA regimen. In addition, patient and physician preferences/selection criteria for long acting therapy should be recorded as well as comorbidities and co-medications.

The experts strongly recommend for such a post approval study to be performed whilst acknowledging that challenges in getting reliable data on resistance will occur.

2.5.2. Conclusions on the clinical efficacy

Overall, it can be concluded that the efficacy of CAB LA, when used in combination with RPV LA, has been established. The main uncertainties are the representativeness of the enrolled subjects for the patients to be treated after licensure, the development of resistance mutations in the few cases with virologic failure, and the appropriateness of the regimen as currently proposed, to keep the virus suppressed during the initial months after initiation of CAB + RPV long-acting.

The switch from a standard oral tritherapy to the bitherapy with CAB LA+RPV LA (as part of a monthly regimen [Q4W] or a 2 months regimen [Q8W]) in virologically-suppressed subjects is not associated with significantly higher rates of virologic failure based on the two large non inferiority phase III studies (FLAIR and ATLAS studies), the design of which was validated through EMA scientific advice (including the non inferiority margin). Furthermore, the ATLAS-2M study could support the use of a Q8W regimen which remains non-inferior to the Q4W regimen.

- The LA formulation with its long half-life enabling an every 4 weeks frequency of administration or every 8 weeks administration is primarily designed for convenience purpose, to get rid of the constraints

of a daily oral administration of a multitherapy and to potentially achieve a better adherence. At this stage the indication is confined to adult patients in line with the clinical data in support but given the challenging adherence in adolescents a future extension of indication in this population is awaited. The lack of oral daily intake could be an advantage for people traveling frequently, provided they could manage for the IM route.

- As for the oral fixed dose combination Juluca (dolutegravir-riplivirine), the combined use of CAB+RPV LA is only validated for virologically suppressed patients and is not demonstrated as being adequate to achieve undetectability in antiretroviral naive patients (although off label could be expected) or in antiretroviral experienced patients.

- The oral lead in regimen was a safeguard during clinical trials to ensure tolerance before introducing the long-lasting IM formulation.

Decision to introduce this new LA regimen should take into consideration that compliance to the LA IM injections is essential (which may be challenging whether patient did not support them), considering that CAB and RPV plasmatic concentrations slowly decrease until approximately one year and may lead to subtherapeutic concentrations and consequently to RAM emergence in case of missed doses or stop injections. The risk of selection (and potential transmission) of dual class resistance in case of treatment interruption without immediate suppressive regimen given the very long half-life of both products is a source of particular concern. Particular statements have been introduced in the SmPC/PL to warn on the need for adequate selection of patients and on the risk of resistance in case of delay in introducing a fully suppressive treatment after discontinuation. Post approval investigation in the real-life setting is critical for further scrutiny on this first LA regimen having in mind the potential individual and collective risks it carries.

Ultimately the applicant has agreed with the CHMP requested conservative wording for the indication.

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (see sections 4.2,4.4 and 5.1).

According to the SAG experts, both Q4W and Q8W regimen could be supported. In the multivariate analysis performed to explore variables associated with increased risk of confirmed virological failure, the main baseline factors associated with virologic outcome risk factors were BMI> 30 kg/m^2; pre-existing major RPV RAMs that were no identified in the genotype; and subtype A 1/6.

However, it was also highlighted that there are still some concerns regarding the subgroup of patients on Q8W dosing who showed more risk of virological failure (VF). In the multivariate analysis performed to explore variables associated with increased risk of confirmed virological failure (CVF), the main baseline factors associated with virologic outcome risk factors were:

- having a BMI> 30 kg/m2
- pre-existing major RPV RAMs that were no identified in the genotype
- subtype A 1/6

Several measures were proposed to minimise this risk:

- To start a Q4W regimen in those patients who could have higher risk of VF as it was described before. In these cases, switching to a Q8W dosing could be considered afterwards in patients who reach and maintain undetectability with this regimen.

- The experts also proposed adding a clarification in the SmPC explaining the risk factors which could contribute to developing a VF. In this case, the SmPC labelling would be useful for the clinicians to decide on the preferred regimen for every patient. In addition, the current wording of the indication already prevents from prescribing this treatment to patients who present or have past evidence of viral resistance to NNRTI or INI which may minimise the risk.

Finally, two paragraphs in the SmPC section 4.4 were required in order to minimise the risk of virological failure:

- a warning box as regards the risk of resistance following treatment discontinuation:

> Risk of resistance following treatment discontinuation
>
> To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of Vocabria when dosed monthly and no later than two months after the final injection of Vocabria when dosed every 2 months.

- a warning reflecting the increased risk of virologic failure in case of cumulative baseline risk factors:

> Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ⩾30 kg/m2. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ⩾30 kg/m2 or HIV 1 subtype A6/A1 (see section 5.1)

The CHMP considers the following measures necessary to address issues related to efficacy:

Description	**Due date**
The MAH will conduct a prospective cohort study (COMBINE-2 study) to collect data from patients in order to assess clinical effectiveness, adherence, durability and discontinuations after initiating the cabotegravir and rilpivirine long acting regimen. The study will also monitor for resistance and response to subsequent antiretroviral regimens among patients who switched from cabotegravir and rilpivirine long acting regimen to another regimen The MAH will submit interim study results annually and the final results of the study by September 2026.	September 2026
The MAH will conduct a real-world five-year Drug Utilisation Study (DUS). This observational cohort study will aim to better understand the patient population receiving cabotegravir long acting injection and/or rilpivirine long acting injection containing regimens in routine clinical practice. The study will assess usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. The MAH will submit interim study results annually and the final results of the DUS by September 2026.	September 2026

2.6. Clinical safety

Patient exposure

In the Phase 3 studies:

Table 39 Summary of Extent of Exposure During the Maintenance Phase in Studies 201584 and 201585 and Pooled Data (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
Overall Exposure, n (%)						
n	282	283	308	308	590	591
<2 weeks	2 (<1)	0	1 (<1)	0	3 (<1)	0
2 to <4 weeks	0	0	1 (<1)	0	1 (<1)	0
4 to <8 weeks	1 (<1)	3 (1)	3 (<1)	1 (<1)	4 (<1)	4 (<1)
8 to <12 weeks	3 (1)	3 (1)	0	1 (<1)	3 (<1)	4 (<1)
12 to <16 weeks	0	0	6 (2)	1 (<1)	6 (1)	1 (<1)
16 to <20 weeks	3 (1)	2 (<1)	5 (2)	1 (<1)	8 (1)	3 (<1)
20 to <24 weeks	2 (<1)	5 (2)	1 (<1)	4 (1)	3 (<1)	9 (2)
24 to <28 weeks	1 (<1)	1 (<1)	3 (<1)	0	4 (<1)	1 (<1)
28 to <32 weeks	1 (<1)	0	0	2 (<1)	1 (<1)	2 (<1)
32 to <36 weeks	1 (<1)	2 (<1)	0	1 (<1)	1 (<1)	3 (<1)
36 to <40 weeks	1 (<1)	0	0	0	1 (<1)	0
40 to <44 weeks	0	0	3 (<1)	3 (<1)	3 (<1)	3 (<1)
44 to <48 weeks	3 (1)	11 (4)	1 (<1)	0	4 (<1)	11 (2)
48 to <52 weeks	2 (<1)	35 (12)	4 (1)	53 (17)	6 (1)	88 (15)
52 to <64 weeks	148 (52)	130 (46)	280 (91)	241 (78)	428 (72)	371 (63)
64 to <76 weeks	104 (37)	91 (32)	0	0	104 (18)	91 (15)
>=76 weeks	10 (4)	0	0	0	10 (2)	0
Overall Exposure (Days)						
n	282	283	308	308	590	591
Mean	429.2	395.5	358.1	356.6	392.0	375.2
SD	88.83	85.01	69.45	42.74	86.84	69.15
Median	435.0	393.0	374.0	364.0	382.0	366.0
Q1	407.0	390.0	372.0	364.0	372.0	364.0
Q3	488.0	449.0	380.0	366.0	434.0	393.0
Min	3	29	7	45	3	29
Max	551	512	417	394	551	512

Data Source: ISS/ISE Table 3.03.

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
CAB + RPV: From Day 1, subjects started oral CAB 30 mg + RPV 25 mg once daily for 4 weeks. At Week 4b, subjects had the 1st CAB LA + RPV LA IM dose. After Week 4b, the IM injection was performed at every 4 weeks.
Overall Exposure for CAB LA + RPV LA arm = (Date of last IP injection + 35 days) - Oral lead-in CAB + RPV Start Date + 1 day.

The majority of subjects in Study 201585 transitioned to Study 207966 (ATLAS-2M) after completing Maintenance Phase at Week 52, therefore the extent of exposure represented in these data is higher in Study 201584.

In the Phase 2 studies, the median time of exposure to CAB + RPV in Study 200056 (LATTE 2) for the oral CAB arm was 700 days (~100 weeks). The median number of CAB LA + RPV LA injections was 25 and 46 for the Q8W and Q4W treatment arms, respectively. In Study LAI116482 (LATTE), median time of exposure to oral CAB was 1177 days (168 weeks) and median exposure to oral RPV was 505 days (72 weeks).

Overall, 1865 HIV-1 infected patients were treated with CAB LA + RPV LA, including 1228 with the Q4W regimen. Almost all subjects (n=542; 92%) treated with CAB + RPV IM in the 2 Phase 3 pivotal studies were exposed for at least 1 year.

Adverse events

Table 40 **Overview of all Adverse Events During the Maintenance Phase, Pooled Phase III Studies (Safety Population)**

	201584		201585		Pooled	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Any AE	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	445 (75)
Any Grade 3/4/5 AE	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)
Any drug related AE	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Any Grade 3/4/5 drug related AE	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)
Any AEs leading to withdrawal	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)
Fatal SAEs related to study treatment	0	0	0	0	0	0

Data Source: ISS/ISE Table 3.05.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

During the Maintenance Phase, injection site reaction (ISRs) were the most common AEs reported in the CAB + RPV group. Non-ISR AEs were reported in 86% of subjects in the pooled CAB + RPV group and in 75% of subjects in the pooled CAR group:

Table 41 **Overall Summary of Non-ISR Adverse Events During the Maintenance Phase for Pooled Data (Safety Population)**

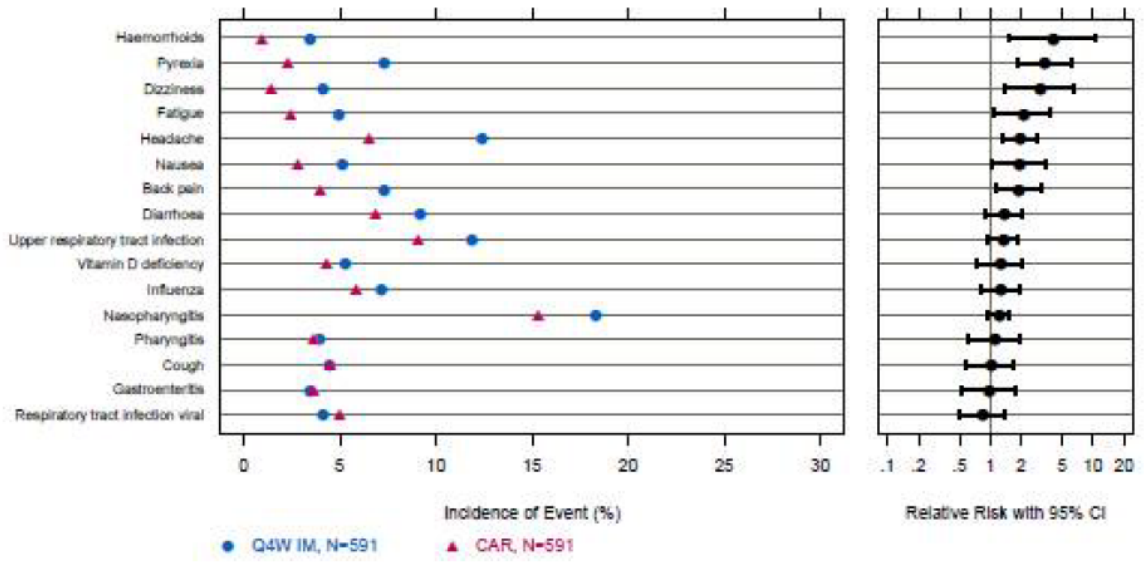
	201584		201585		Pooled	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Any AE	246 (87)	225 (80)	264 (86)	220 (71)	510 (86)	445 (75)
Any Grade 3/4/5 AE	22 (8)	11 (4)	25 (8)	24 (8)	47 (8)	35 (6)
Any drug related AE	79 (28)	28 (10)	87 (28)	8 (3)	166 (28)	36 (6)
Any Grade 3/4/5 drug related AE	4 (1)	0	4 (1)	1 (<1)	8 (1)	1 (<1)
Any AEs leading to withdrawal	8 (3)	4 (1)	9 (3)	5 (2)	17 (3)	9 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)
Fatal SAEs related to study~ treatment	0	0	0	0	0	0

Common AEs

In the pooled Phase III studies (201584 and 201585), the most commonly reported non-ISRs AEs occurring in ≥5% of subjects in either treatment group were generally similar, although higher rates of AEs were reported in the CAB + RPV group for haemorrhoids, pyrexia, dizziness, fatigue, headache, nausea, diarrhea, and back pain.

Table 42 **Most Common Adverse Events (Reported in >=5% of Subjects in Any Treatment Group) by Preferred Term during the Maintenance Phase for Study 201584, Study 201585, and Pooled Data (Safety Population)**

	201584		201585		POOLED			
Preferred Term, n (%)	CAB + RPV (N=283)[a]	CAR (N=283)[a]	CAB + RPV (N=308)[a]	CAR (N=308)[a]	CAB + RPV (N=591)[a]	AE Rate per 100 Subject Years[b]	CAR (N=591)[a]	AE Rate per 100 Subject Years[b]
ANY EVENT	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	542.03	445 (75)	221.25
Injection site pain	227 (80)	0	231 (75)	0	458 (77)	231.27	0	0.00
Nasopharyngitis	56 (20)	48 (17)	52 (17)	42 (14)	108 (18)	20.31	90 (15)	29.51
Upper respiratory tract infection	38 (13)	28 (10)	32 (10)	25 (8)	70 (12)	12.32	53 (9)	17.27
Headache	39 (14)	21 (7)	34 (11)	17 (6)	73 (12)	13.07	38 (6)	12.36
Diarrhea	32 (11)	25 (9)	22 (7)	15 (5)	54 (9)	9.43	40 (7)	12.81
Injection site nodule	44 (16)	0	37 (12)	0	81 (14)	14.51	0	0.00
Influenza	25 (9)	20 (7)	17 (6)	14 (5)	42 (7)	7.19	34 (6)	10.87
Injection site induration	38 (13)	0	30 (10)	0	68 (12)	12.28	0	0.00
Back pain	22 (8)	13 (5)	21 (7)	10 (3)	43 (7)	7.36	23 (4)	7.40
Pyrexia	22 (8)	4 (1)	21 (7)	9 (3)	43 (7)	7.42	13 (2)	4.22
Vitamin D deficiency	23 (8)	13 (5)	8 (3)	12 (4)	31 (5)	5.30	25 (4)	8.14
Respiratory tract infection viral	13 (5)	12 (4)	11 (4)	17 (6)	24 (4)	4.03	29 (5)	9.45
Cough	10 (4)	12 (4)	16 (5)	14 (5)	26 (4)	4.40	26 (4)	8.50
Injection site swelling	23 (8)	0	23 (7)	0	46 (8)	8.00	0	0.00
Nausea	16 (6)	11 (4)	14 (5)	5 (2)	30 (5)	5.13	16 (3)	5.15
Pharyngitis	15 (5)	9 (3)	8 (3)	12 (4)	23 (4)	3.86	21 (4)	6.80
Fatigue	7 (2)	8 (3)	22 (7)	6 (2)	29 (5)	4.93	14 (2)	4.52
Gastroenteritis	15 (5)	11 (4)	5 (2)	10 (3)	20 (3)	3.36	21 (4)	6.79
Dizziness	15 (5)	3 (1)	9 (3)	5 (2)	24 (4)	4.05	8 (1)	2.58
Hemorrhoids	16 (6)	3 (1)	4 (1)	2 (<1)	20 (3)	3.36	5 (<1)	1.61
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	3.86	0	0.00



Note: Common AEs are those reported with ≥5% in any treatment group in the individual studies.
Data Source: ISS/ISE Figure 3.01.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Figure 14 **Plot of Common Non-ISR AEs and Relative Risk for CAB + RPV vs. CAR for Phase III Pooled Studies (Safety Population)**

AEs by Grade

The majority of events reported in the Phase III programme had an intensity of Grade 1 or Grade 2 for both treatment groups. No Grade 5 events were reported in the pooled Phase III studies (201584 and 201585) for subjects receiving CAB + RPV; 1 Grade 5 (fatal) AE of methamphetamine overdose occurred in the CAR group (Study 201585), which was reported as unrelated to study treatment.

Overall, a higher proportion of subjects who switched to CAB + RPV had Grade 3 to 4 AEs compared with subjects who continued CAR (11% compared with 6%). Fifty (8%) subjects had Grade 3 events in the CAB + RPV group and 29 (5%) subjects had Grade 3 events in the CAR group. Sixteen (3%) subjects had Grade 4 events in the CAB + RPV group and 5 (<1%) subjects had Grade 4 events in the CAR group. This difference between treatment groups may be partially attributable to the higher incidence of acute viral hepatitis, ISRs, and AEs of lipase abnormalities and CPK and AST elevations in the CAB + RPV group.

The most common Grade 2 to 4 non-ISR AEs reported during the Maintenance Phase were headache (3% CAB + RPV vs. 2% CAR), diarrhoea (3% CAB + RPV vs. 1% CAR), nasopharyngitis (3% CAB + RPV vs. 1% CAR), and back pain (3% CAB + RPV vs. <1% CAR).

Drug-related AEs

In the pooled Phase III studies (201584 and 201585), the most frequently reported, Grade 2 to 4, drug-related, non-ISR AEs in the CAB + RPV group were headache (5 subjects [<1%]), diarrhoea (5 subjects [<1%]), fatigue (4 subjects [<1%]) and pyrexia (4 subjects [<1%]).

Table 43 Most Common Drug-Related Adverse Events (Reported in >=1% of Subjects in Any Treatment Group) by Preferred Term during the Maintenance Phase for Study 201584, Study 201585, and Pooled Data (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
ANY EVENT, n (%)	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Injection site pain	221 (78)	0	227 (74)	0	448 (76)	0
Injection site nodule	43 (15)	0	36 (12)	0	79 (13)	0
Injection site induration	37 (13)	0	29 (9)	0	66 (11)	0
Injection site swelling	22 (8)	0	22 (7)	0	44 (7)	0
Headache	14 (5)	4 (1)	11 (4)	0	25 (4)	4 (<1)
Injection site erythema	12 (4)	0	12 (4)	0	24 (4)	0
Pyrexia	13 (5)	0	11 (4)	0	24 (4)	0
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	0
Nausea	4 (1)	6 (2)	11 (4)	0	15 (3)	6 (1)
Fatigue	4 (1)	5 (2)	11 (4)	0	15 (3)	5 (<1)
Injection site bruising	6 (2)	0	10 (3)	0	16 (3)	0
Injection site warmth	8 (3)	0	6 (2)	0	14 (2)	0
Asthenia	7 (2)	0	6 (2)	0	13 (2)	0
Body temperature increased	8 (3)	0	4 (1)	0	12 (2)	0
Myalgia	4 (1)	1 (<1)	6 (2)	0	10 (2)	1 (<1)
Dizziness	4 (1)	1 (<1)	5 (2)	0	9 (2)	1 (<1)
Injection site hematoma	4 (1)	0	6 (2)	0	10 (2)	0
Abnormal dreams	4 (1)	0	3 (<1)	2 (<1)	7 (1)	2 (<1)
Anxiety	4 (1)	1 (<1)	4 (1)	0	8 (1)	1 (<1)
Insomnia	0	0	8 (3)	1 (<1)	8 (1)	1 (<1)
Diarrhea	5 (2)	1 (<1)	2 (<1)	0	7 (1)	1 (<1)
Creatinine renal clearance decreased	2 (<1)	3 (1)	2 (<1)	0	4 (<1)	3 (<1)
Malaise	5 (2)	0	2 (<1)	0	7 (1)	0
Influenza like illness	0	0	5 (2)	0	5 (<1)	0
Pain	1 (<1)	0	4 (1)	0	5 (<1)	0
Chills	0	0	4 (1)	0	4 (<1)	0
Depression	3 (1)	0	0	1 (<1)	3 (<1)	1 (<1)
Vitamin D deficiency	3 (1)	1 (<1)	0	0	3 (<1)	1 (<1)

Serious adverse events and deaths

Seven deaths were reported during the pooled Phase III studies (Study 201584 and Study 201585) and Phase II studies. All were considered by the investigators to be unrelated to study drug with the exception of a case of sudden death attributed to myocardial infarction by the investigator despite no post-mortem report or data suggesting MI (in Study 200056) where the investigator could not rule out the possibility of relationship to study drug. In addition, 1 death (acute pancreatitis) was reported during the Phase III study 207966 (ATLAS-2M) through the Week 24 data cut-off. Pancreatitis was considered by the investigator as possibly related to the study drugs so the death might have been related to study drugs. A second death (cerebral haemorrhage) was reported in study 207966 considered as not-drug related since it occurred before the patient received the study product. After the data-lock point for the initial

submission, 2 other deaths have been reported in study LAI116482 (cardiac arrest during surgery, gastrointestinal haemorrhage) but are poorly documented.

During the Maintenance Phase in the pooled Phase III studies (201584 and 201585), 31 subjects in the CAB + RPV group had a total of 37 SAEs and 26 subjects in the CAR group had a total of 33 SAEs. The incidence of subjects developing at least 1 SAE was low and similar between treatment groups in the Maintenance Phase (CAB + RPV 5%; CAR 4%). The most frequently reported SAEs were Hepatitis A (reported in 4 subjects in the CAB + RPV group and 2 subjects in the CAR group), colitis (reported in 1 subject in the CAB + RPV group and 2 subjects in the CAR group), anal abscess (reported in 0 subjects in the CAB + RPV group and 2 subjects in the CAR group), and anogenital warts (reported in 1 subject in the CAB + RPV group and 2 subjects in the CAR group). Two of these SAEs were considered study drug-related (right knee monoarthritis and suicidal ideation).

In the study 207966, 30 SAEs were reported through Week 24 (Q8W, 15/522 [3%]; Q4W; 15/523 [3%]). Three drug-related SAEs were considered drug-related: site abscess (Q8W group), allergic reaction (hypersensitivity preferred term) (Q4W group), and acute pancreatitis (Q8W group, cf death subjects). For both the injection site abscess and allergic reaction SAEs, study drug was withdrawn, and the subjects recovered. The injection site abscess was considered possibly related to RPV because the gluteal abscess appeared on the same site where RPV was administered by IM injection.

In response to D120 LOQ, 6 new SAEs have been reported in FLAIR (n=2), LATTE-2 (n=2) and ATLAS-2M (n=2) considered as not drug-related except 2 SAE related to partial IV administration of RPV LA. For the case of delusion reported, the causal relationship of study drugs cannot be ruled out considering that psychiatric side effects are common with NNRTIs and INSTIs.

Adverse events of interest

ISRs

Table 44 Summary of Subject-level Characteristics of ISR Adverse Events in the Pooled Phase III Studies, Maintenance Phase (CAB + RPV Group; Safety Population)

	201584 (N=283) n (%)	201585 (N=308) n (%)	POOLED (N=591) n (%)
Number of Subjects with Injection	278 (98)	303 (98)	581 (98)
Number of Subjects with ISR Event	239 (86)	250 (83)	489 (84)
Any Grade			
Grade 1 Events	222 (80)	215 (71)	437 (75)
Grade 2 Events	101 (36)	110 (36)	211 (36)
Grade 3 Events	11 (4)	11 (4)	22 (4)
Grade 4 Events	0	0	0
Grade 5 Events	0	0	0
Not applicable	1 (<1)	0	1 (<1)
Maximum Grade or Intensity			
Mild or Grade 1	135 (49)	137 (45)	272 (47)
Moderate or Grade 2	93 (33)	102 (34)	195 (34)
Severe or Grade 3	11 (4)	11 (4)	22 (4)
Maximum Duration, days			
1-7	133 (48)	158 (52)	291 (50)
8-14	51 (18)	44 (15)	95 (16)
>14	53 (19)	48 (16)	101 (17)
Not applicable	2 (<1)	0	2 (<1)
Event Characteristics			
Serious	0	0	0
Drug-related	233 (84)	244 (81)	477 (82)
Severe or Grade 3/4	11 (4)	11 (4)	22 (4)
Leading to Withdrawal/Investigational Product Withdrawn	2 (<1)	4 (1)	6 (1)
Outcome			
Recovered/Resolved	236 (85)	249 (82)	485 (83)
Recovering/Resolving	9 (3)	2 (<1)	11 (2)
Not Recovered/Not Resolved	7 (3)	2 (<1)	9 (2)
Recovered/Resolved with Sequelae	12 (4)	13 (4)	25 (4)

Note: All percentages based on the number of subjects with at least one injection. For Any Grade, Event Characteristics and Outcome, the sum in a column may be greater than number of subjects, because each event is assessed independently, so a subject can be counted in more than one category.

Overall, both CAB and RPV injections seems well tolerated throughout the studies, even though pain associated to IM injections was very commonly reported. Less than 5% of subjects experienced Grade 3 or more ISR AEs, and the proportion of subjects who withdraw from study due to ISRs is very low (<1%). Of note, although pain was the main ISR AE reported, a non-negligible rate of nodules and induration (≈15%) was observed. The few cases reported as "recovered with sequelae" relate mostly to "injection site pain" with a large interval for the duration. No significant differences in ISRs between CAB and RPV were observed. No trends were observed for an association between needle length and incidence, type, or severity of ISRs for either CAB or RPV.

Hepatotoxicity

In the pooled Phase III studies (201584 and 201585), 14 subjects met liver stopping criteria (LSC) (11 in the CAB+RPV group, 3 in the CAR group). All of the subjects who met LSC had acute viral hepatitis. There were no cases of DILI. Five subjects each had 1 AE potentially associated with hepatotoxicity in

the Maintenance Phase of the Phase III studies (CAB + RPV, 4 [<1%], CAR, 1 [<1%]). These events included hepatic cirrhosis (Grade 3; CAR group), hepatic steatosis (Grade 2; CAB + RPV group), hepatic toxic (Grade 1; CAB + RPV group), hepatocellular injury (Grade 4; CAB + RPV group), and non-alcoholic steatohepatitis (Grade 1; CAB + RPV group). None of the AEs were considered to be related to study treatment or to represent DILI.

In the Phase III study 207966, there was 1 report of DILI possibly related to CAB + RPV according to the Hepatic Adjudication Committee. Four other subjects (2 subjects in each arm) have met LSC. Three of them had acute viral hepatitis (B, C and E), and the remaining had a DILI possibly due to another prohibited treatment (Melanotan II).

In the Phase II studies, 4 subjects receiving oral CAB met LSC for which no alternative aetiology has been identified. One additional subject from a clinical pharmacology study also met LSC for which no alternative aetiology has been identified. These five subjects receiving oral CAB were adjudicated by hepatic experts to have suspected drug induced liver injury (DILI) or hepatotoxicity. Three of these subjects were on oral CAB 30 mg once daily and the remaining two were on oral CAB 60 mg. Severe hepatotoxicity with significant liver dysfunction or liver failure has not been observed. The degree of ALT elevation in these subjects was either Grade 3 or Grade 4. Aminotransferase elevations in these subjects have been transient and reversible.

Hepatotoxicity and risk of DILI will be kept under close scrutiny through a dedicated PASS study as agreed by the applicant.

Hypersensitivity reactions (HSR)

In the Phase II and the 2 pivotal Phase III studies, no cases of HSR have been observed following exposure to CAB during the CAB + RPV development programme. No subjects were excluded from treatment with CAB LA and RPV LA because of suspected HSR during the OLI.

In the Phase III study 207966, a Grade 3, drug-related, allergic reaction was reported as a SAE and resulted in withdrawal of the subject from the study. This case is not considered by the Sponsor to be a delayed-type hypersensitivity reaction.

In response to D120 LOQ, no cases suggestive of HSR have been reported except one grade 3 allergic reaction after injection of both CAB+RPV attributed by the applicant to partial IV drugs study administration. Considering that both NNRTIs and INSTIs are known to induce HSR, and the favourable outcome with antiallergic drug, hypersensitivity cannot be ruled out in this case and should be closely monitored in PSUR.

Rash

In the pooled Phase III studies, no Grade 3 or Grade 4 rashes observed. Rash AESIs (i.e., identified using key words "rash", "eruption", "photosensitivity", or "urticaria") were reported in 23 subjects in the CAB + RPV group and 14 subjects in the CAR group. No rash AESIs were considered serious, 10 rash AESI reports were considered to be drug-related (9 CAB + RPV, 1 CAR), and none led to withdrawal of study drug. Most resolved without drug discontinuation before the following injection.

QT prolongation

The QTc study with oral CAB did not highlight an effect of CAB on QT prolongation.

In response to the D120 LOQ, it has been observed a few occurrences of QTcF>500 ms and increases >60 ms from baseline in the phase 2 and phase 3 studies without evidence of a correlation with RPV or CAB plasma concentrations. All the events resolved despite CAB+RPV continuation. It should be kept in

mind that high exposure to RPV is associated to QT prolongation. For CAB, there are no evidence of an increased risk of QT interval prolongation.

Psychiatric AEs

In the pooled Phase III studies (201584 and 201585), depression, anxiety and suicidal ideation had a higher incidence in subjects with histories of these disorders:

Table 45 Summary of Pooled Phase III Post Baseline Depression, Anxiety, or Suicidal Ideation AEs by Prior History of Disease

	Prior History		No Prior History	
	CAB + RPV	CAR	CAB + RPV	CAR
Depression[a]	3/86 (3%)	5/82 (6%)	13/505 (3%)	9/509 (2%)
Anxiety[b]	8/66 (12%)	7/88 (8%)	18/525 (3%)	13/503 (3%)
Suicidal Ideation[c]	2/23 (9%)	0/26 (<1%)	2/568 (<1%)	5/565 (<1%)

a. Includes Depression, Depressed mood, Adjustment disorder with depressed mood, Major depression.
b. Includes Anxiety, Anxiety disorder, Panic attack, Acute stress disorder, Nervousness, Stress, Tension.
c. Includes Suicidal ideation, Intentional self-injury, Suicide attempt, Suicidal behavior, Depression suicidal.
Data Source: ISS/ISE Table 3.151; 201584 Table 3.105; 201585 Table 3.100.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

There was no significant difference on suicidal ideation and depression between treatment groups.

4 (<1%) subjects in the CAB + RPV group and 5 (<1%) subjects in the CAR group had AEs of suicidal ideation or behaviour. 1 subject in the CAB + RPV group had an AE of suicidal depression that was considered to be related to study drug and was subsequently discontinued from the study. Two AEs in the CAR group were Grade 3; these 2 subjects had no prior history of suicidal ideation. One of the Grade 3 AEs of suicidal ideation was considered serious (SAE) and related to study drug. This subject also experienced Grade 3 AEs of anxiety and depression. 2 subjects in the CAR group had SAEs of suicidal ideation (n=1) and suicide attempt (n=1). 3 subjects withdrew from study drug due to AEs of suicidal ideation (n=1, CAR group), suicide attempt (n=1, CAR group), and depression suicidal (n=1, CAB + RPV group).

16 (3%) subjects in the CAB + RPV group and 14 (2%) subjects in the CAR group reported depression. 5 subjects in the CAB + RPV group had depression AEs that were considered study drug related. Most of the AEs of depression were Grade 1 or 2. One subject in the CAR group with no prior history of depression had a Grade 3 AE of depression that was considered to be related to study drug and led to discontinuation from the study.

27 (5%) subjects in the CAB + RPV group and 20 (3%) subjects in the CAR group had AEs related to anxiety. Most AEs reported were Grade 1 or 2. AEs of anxiety were considered to be related to study drug in 10 other subjects (8 CAB + RPV; 2 CAR). There were no SAEs of anxiety. 1 subject in the CAB + RPV group and 1 subject in the CAR group withdrew from study due to AEs of anxiety or anxiety disorder.

Across the Phase 2 and 3 studies, no serious psychiatric events such as bipolarity and psychosis were considered related with CAB.

Sleep disorders were observed throughout the clinical development of CAB, with a higher incidence of insomnia. Across the pooled Phase III studies (201584 and 201585), 38 (6%) subjects in the CAB + RPV group and 21 (4%) subject in the CAR group had AEs of sleep disorders. Most of these AEs were insomnia, which was reported in 22 (4%) subjects in the CAB + RPV group and 8 (1%) subjects in the CAR group. All of the sleep disorder AEs were Grade 1 or Grade 2 intensity. In 15 subjects in the CAB + RPV group

and 4 subjects in the CAR group, AEs of sleep disorder were considered to be related to study drug. No SAEs and no withdrawals due to AEs of sleep disorders were reported.

Seizures

Across the Phase III pivotal studies, 6 (1%) subjects in the CAB + RPV group and 2 (<1%) subjects in the CAR group had AEs potentially associated with seizures. None of these events were considered to be associated with seizure, were not serious, and did not lead to withdrawal. Most were Grade 1 or 2 (1 Grade 3 event of seizure occurred in the CAR group in Study 201585) and all were considered not related to study treatment with CAB + RPV with 1 exception of an event of syncope with a verbatim term "vasovagal syncope-not cardiac".

Weight gain

Overall, a trend towards slight weight gain was observed in the Phase II and III trials for subjects in the CAB + RPV group vs CAR group (median change 1.5 kg vs. 1.0 kg for the CAR group at Week 48 in the Phase 3 studies)

Rhabdomyolysis

No rhabdomyolysis case related to CAB+RPV was reported. In the Phase III pivotal studies, Grade 3 and 4 elevations of CK were observed in 47 (8%) subjects in the CAB + RPV group through 48 weeks of treatment, compared with 26 (4%) subjects in the CAR group. These CK elevations were transient, asymptomatic and generally associated with subjects reporting strenuous exercise and/or weightlifting.

More subjects in the CAB + RPV group had AEs of myalgia compared with those in the CAR group (24 [4%] subjects vs. 8 [1%] subjects, respectively). 1 AE of myalgia (CAB + RPV group) led to study drug discontinuation. 1 subject in the CAB + RPV group had a Grade 2 AE of myositis associated with Grade 4 CK elevation and the myositis was considered related to treatment.

Pancreatitis

Across the Phase III pivotal studies, 3 (<1%) subjects in the CAB + RPV group (n=4 events) and no subjects in the CAR group had AEs potentially associated with pancreatitis. None of these AEs led to study drug discontinuation. Most of the clinical laboratory assessments for lipase elevations were Grade 1 or Grade 2.

In the Phase III study 207966, there was a single report of acute pancreatitis in a subject in the Q8W group (see section "Deaths"). The investigator considers the pancreatitis possibly related to study drugs as they are unable to exclude a causative association. Despite the long latency period and possible confounders, as pancreatitis have been observed with other INSTI or NNRTIs, the relationship to the study drugs cannot be ruled out.

No cases of pancreatitis were reported in the Phase II studies.

As a conservative approach the fatal case of pancreatitis will be reported in the section 4.8 stating that the causality cannot be ruled out.

Renal disorders

Overall, cystatin-c levels did not suggest worsening of eGFR, glomerular disease, or proximal tubule dysfunction. In the pooled Phase III studies (201584 and 201585), 2 (<1%) subjects in the CAB + RPV group and 3 (<1%) subjects in the CAR group had AEs related to creatinine abnormalities. The 2 cases in the CAB + RPV group were non-serious, not considered drug-related and not leading to withdrawal.

In the Phase III study 207966, an AE of creatinine renal clearance decreased occurred in 1 (<1%) subject in the Q8W group and 4 (<1%) subjects in the Q4W group. All of the events of creatinine renal clearance decreased were Grade 1 or 2 in severity. Two AEs of creatinine renal clearance decreased in the Q4W group were considered drug related. None of the AEs of creatinine renal clearance decreased led to discontinuation from the study.

In the Phase II studies, there were two serious reports potentially associated with impact on creatinine during treatment with CAB + RPV (Grade 4 acute kidney injury and Grade 4 renal failure). Both were not considered related to study drug (cardiogenic/septic shock and suicide attempt, respectively).

Laboratory findings

In the pooled Phase III studies (201584 and 201585), the majority (389/521 [74.7%] in the CAB + RPV group and 413/515 [80.2%] in the CAR group) of the post-baseline emergent clinical chemistry abnormalities were Grade 1 or Grade 2 in intensity. No clinically relevant differences were observed overall in subjects with at least 1 Grade 3 or Grade 4 post-baseline emergent abnormalities between the CAB + RPV and CAR groups.

Table 46 **Summary of Maximum Post-Baseline Emergent Clinical Chemistry Abnormalities during Study 201584, Study 201585, and Pooled Data (Safety Population)**

	201584		201585		POOLED	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Grades 1 to 4	249 (88)	244 (86)	272 (88)	271 (88)	521 (88)	515 (87)
Grades 2 to 4	168 (59)	157 (55)	190 (62)	197 (64)	358 (61)	354 (60)
Grades 3 to 4	69 (24)	45 (16)	63 (20)	57 (19)	132 (22)	102 (17)
Grade 1	81 (29)	87 (31)	82 (27)	74 (24)	163 (28)	161 (27)
Grade 2	99 (35)	112 (40)	127 (41)	140 (45)	226 (38)	252 (43)
Grade 3	51 (18)	30 (11)	37 (12)	43 (14)	88 (15)	73 (12)
Grade 4	18 (6)	15 (5)	26 (8)	14 (5)	44 (7)	29 (5)

Data Source: ISS/ISE Table 3.123.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In the Phase III study 207966, the W24 results are as follows:

Table 47 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Abnormalities for All Parameters During Study 207966 (Safety Population)

	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Grades 1 to 4	214 (41)	216 (41)
Grades 2 to 4	150 (29)	156 (30)
Grades 3 to 4	25 (5)	24 (5)
Grade 1	64 (12)	60 (11)
Grade 2	125 (24)	132 (25)
Grade 3	22 (4)	18 (3)
Grade 4	3 (<1)	6 (1)

Briefly, the laboratory abnormalities in the Phase 3 pivotal studies are as follows:

Liver parameters

Table 48 Summary of Subjects Meeting Hepatobiliary Abnormality Criteria at any Post-Baseline Visit During Maintenance Phase for Study 201584, Study 201585, and Pooled Data (Safety Population)

	201584		201585		POOLED	
Laboratory Criteria[a,b]	CAB + RPV (N=282) n (%)	CAR (N=281) n (%)	CAB + RPV (N=308) n (%)	CAR (N=307) n (%)	CAB + RPV (N=590) n (%)	CAR (N=588) n (%)
ALT >=3xULN and BIL >=2xULN[c,d]	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Hepatocellular injury[e]	12 (4)	5 (2)	4 (1)	0	16 (3)	5 (<1)
Hepatocellular injury[e] and BIL >=2xULN[c,d]	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
ALT >=3xULN - <5xULN	4 (1)	2 (<1)	1 (<1)	0	5 (<1)	2 (<1)
ALT >=5xULN - <10xULN	5 (2)	1 (<1)	1 (<1)	0	6 (1)	1 (<1)
ALT >=10xULN - <20xULN	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
ALT >=20xULN	3 (1)	1 (<1)	2 (<1)	0	5 (<1)	1 (<1)
BIL >=2xULN[c]	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Time from First Dose to First ALT Elevation >=3xULN (days)						
n (%)	12 (4)	5 (2)	5 (2)	1 (<1)	17 (3)	6 (1)
Mean	159.3	222.8	195.0	56.0	169.8	195.0
SD	114.06	108.77	123.01		114.06	118.75
Median	175.5	252.0	148.0	56.0	175.0	196.0
Min, Max	6, 379	81, 335	70, 377	56, 56	6, 379	56, 335

a. Subjects may be counted in more than one category.
b. ALT: alanine aminotransferase; ALP: alkaline phosphatase; BIL: total bilirubin; INR: International Normalized Ratio; ULN: upper limit of normal.
c. If direct bilirubin is available (on the same date as Total Bilirubin), then direct bilirubin as a portion of total bilirubin must be >=35% when total bilirubin is >=2xULN, in order to satisfy the criteria.
d. Bilirubin value is on or up to 28 days after ALT value.
e. Hepatocellular injury is defined as ((ALT/ALT ULN)/(ALP/ALP ULN)) >=5 and ALT >=3xULN. ALT and ALP values must occur on the same day.

Data Source: ISS/ISE Table 3.135.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Renal function

Table 49 Summary of Chemistry Changes from Baseline in Creatinine and Cystatin C during the Maintenance Phase for Pooled Study 201584 and Study 201585 Data (Safety Population)

Treatment	N	Actual Relative Time	n	Mean	SD	Median	Q1	Q3	Min.	Max.
Creatinine (umol/L)										
CAB + RPV	591	Baseline	591	83.8	16.961	83.1	71.6	95.5	43	149
		Week 48	512	-3.5	11.790	-3.5	-11.5	3.6	-42	83
CAR	591	Baseline	591	81.6	16.575	81.3	69.0	91.1	39	151
		Week 48	554	2.8	59.075	0.9	-5.3	5.3	-50	1376
Cystatin C (mg/L)										
CAB + RPV	591	Baseline	589	0.7	0.144	0.8	0.7	0.8	0	1
		Week 48	542	0	0.113	0	-0.1	0	0	0
CAR	591	Baseline	585	0.7	0.148	0.7	0.7	0.8	0	1
		Week 48	552	0	0.118	0	-0.1	0.1	0	0

Data Source: ISS/ISE Table 3.118.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Creatine kinase

Table 50 Summary of Maximum Post-Baseline Intensity CK (IU/L) Elevations in Phase III Studies, Maintenance Phase (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Grade 1	37 (13)	19 (7)	23 (7)	18 (6)	60 (10)	37 (6)
Grade 2	9 (3)	19 (7)	6 (2)	12 (4)	15 (3)	31 (5)
Grade 3	13 (5)	4 (1)	9 (3)	9 (3)	22 (4)	13 (2)
Grade 4	10 (4)	10 (4)	15 (5)	3 (<1)	25 (4)	13 (2)

Lipase

Table 51 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Abnormalities for Lipase (U/L) during the Maintenance Phase (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Grade 1	20 (7)	24 (8)	30 (10)	25 (8)	50 (8)	49 (8)
Grade 2	24 (8)	23 (8)	22 (7)	20 (6)	46 (8)	43 (7)
Grade 3	14 (5)	7 (2)	9 (3)	3 (<1)	23 (4)	10 (2)
Grade 4	4 (1)	1 (<1)	6 (2)	5 (2)	10 (2)	6 (1)

Data Source: ISS/ISE Table 3.123.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Lipase will be added to the section 4.8.

Lipids

Table 52 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Values for Lipid Parameters during the Maintenance Phase (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV (N=308) n (%)	CAB (N=308) n (%)	CAB + RPV (N=591) n (%)	CAR (N=591) n (%)
Cholesterol (mg/dL)						
Grade 1	30 (11)	18 (6)	39 (13)	14 (5)	69 (12)	32 (5)
Grade 2	15 (5)	8 (3)	10 (3)	17 (6)	25 (4)	25 (4)
Grade 3	0	0	0	1 (<1)	0	1 (<1)
Grade 4	0	0	0	0	0	0
Triglycerides (mg/dL)						
Grade 1	14 (5)	24 (8)	20 (6)	25 (8)	34 (6)	49 (8)
Grade 2	3 (1)	5 (2)	6 (2)	6 (2)	9 (2)	11 (2)
Grade 3	2 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
Grade 4	0	0	0	0	0	0

Data Source: ISS/ISE Table 3.123.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Table 53 Grade 3 and 4 Maximum Post-Baseline Emergent Clinical Chemistry Values (Selected parameters)

Lab Parameter	Study 201584		Study 201585		Pooled data	
	Q4 IM N=283	ABC/DTG/3TC N=283	Q4W IM N=308	CAR N=308	Q4W IM N=591	CAR N=591
Alanine aminotransferase (IU/L)						
Grade 3	4 (1%)	1 (<1%)	1 (<1%)	0	5 (<1%)	1 (<1%)
Grade 4	3 (1%)	2 (<1%)	3 (<1%)	1 (<1%)	6 (1%)	3 (<1%)

Grade 3 to 4	7 (2%)	3 (1%)	4 (1%)	1 (<1%)	11 (2%)	4 (<1%)
Aspartate aminotransferase (IU/L)						
Grade 3	5 (2%)	2 (<1%)	6 (2%)	0	11 (2%)	2 (<1%)
Grade 4	4 (1%)	2 (<1%)	1 (<1%)	0	5 (<1%)	2 (<1%)
Grade 3 to 4	9 (3%)	4 (1%)	7 (2%)	0	16 (3%)	4 (<1%)
Bilirubin (μmol/L)						
Grade 3	0	0	0	0	0	0
Grade 4	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)
Grade 3 to 4	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)
Direct Bilirubin (μmol/L)						
Grade 3	14 (5%)	2 (<1%)	6 (2%)	8 (3%)	20 (3%)	10 (2%)
Grade 4	0	0	0	0	0	0
Grade 3 to 4	14 (5%)	2 (<1%)	6 (2%)	8 (3%)	20 (3%)	10 (2%)
LDL cholesterol (mmol/L)						
Grade 3	4 (1%)	0	3 (<1%)	3 (<1%)	7 (1%)	3 (<1%)
Grade 4	0	0	0	0	0	0
Grade 3 to 4	4 (1%)	0	3 (<1%)	3 (<1%)	7 (1%)	3 (<1%)
Lipase (U/L)						
Grade 3	14 (5%)	7 (2%)	9 (3%)	3 (<1%)	23 (4%)	10 (2%)
Grade 4	4 (1%)	1 (<1%)	6 (2%)	5 (2%)	10 (2%)	6 (1%)
Grade 3 to 4	18 (6%)	8 (3%)	15 (5%)	8 (3%)	33 (6%)	16 (3%)
Phosphate (mmol/L)						
Grade 3	11 (4%)	6 (2%)	10 (3%)	14 (5%)	21 (4%)	20 (3%)
Grade 4	0	0	0	0	0	0
Grade 3 to 4	11 (4%)	6 (2%)	10 (3%)	14 (5%)	21 (4%)	20 (3%)
Triglycerides (mmol/L)						
Grade 3	2 (<1%)	1 (<1%)	1 (<1%)	0	3 (<1%)	1 (<1%)
Grade 4	0	0	0	0	0	0
Grade 3 to 4	2 (<1%)	1 (<1%)	1 (<1%)	0	3 (<1%)	1 (<1%)

There was a numerical difference (higher incidence) for the CAB + RPV group versus the comparator group with respect to the occurrence of Grade 3 or 4 elevations for the following parameters; Alanine aminotransferase; Aspartate aminotransferase; Creatine kinase and Lipase.

Haematology

Overall, the changes from Baseline in haematology values for the pooled Phase III studies (201584 and 201585) were not clinically relevant.

Safety in special populations

In the 201584 and 201585 pooled analysis, the AE profile for CAB + RPV was comparable across age, sex, and race.

The HCV co-infected subjects in the CAB + RPV arm did not develop signs or symptoms of DILI during their study participation. Although the number of subjects is limited, the hepatic safety profile of CAB in asymptomatic HCV co-infected subjects seems not worsened.

No safety data are available in subjects with renal or hepatic impairment. In response to D120 LOQ, the applicant provided a comparison of safety profile with CAB+RPV between patients with (50 and <90 mL/min/1.73m^2) and without (≥ 90 mL/min/1.73m^2) renal impairment at baseline did not identified any trends or clustering of AEs in patients with mild renal impairment at baseline. No data have been provided in patients with mild hepatic impairment, based on PK data available, no dose adjustment is expected.

Discontinuation due to AES

In the pooled Phase III studies (201584 and 201585), 22 (4%) subjects in the CAB + RPV group and 9 (2%) subjects in the CAR group experienced non-ISR AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase:

Table 54 **Summary of Non-ISR Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Drug During the Maintenance Phase in Study 201584 and Study 201585 (Safety Population)**

	201584		201585		POOLED	
System Organ Class Preferred Term	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
Number of Subjects with any event, n (%)	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)
General disorders and administration site conditions						
Asthenia	0	0	1 (<1)	0	1 (<1)	0
Discomfort	1 (<1)	0	0	0	1 (<1)	0
Fatigue	0	1 (<1)	0	0	0	1 (<1)
Infections and infestations[a]						
Hepatitis A	2 (<1)	0	2 (<1)	0	4 (<1)	0
Acute hepatitis B	2 (<1)	0	1 (<1)	0	3 (<1)	0
Acute hepatitis C	1 (<1)	0	0	0	1 (<1)	0
Secondary syphilis	1 (<1)	0	0	0	1 (<1)	0
Nervous system disorders						
Headache	0	0	2 (<1)	0	2 (<1)	0
Amnesia	0	1 (<1)	0	0	0	1 (<1)
Disturbance in attention	0	1 (<1)	0	0	0	1 (<1)
Dizziness	0	1 (<1)	0	0	0	1 (<1)
Dysarthria	0	1 (<1)	0	0	0	1 (<1)
Memory impairment	0	0	1 (<1)	0	1 (<1)	0
Gastrointestinal disorders						
Diarrhea	1 (<1)	0	1 (<1)	0	2 (<1)	0
Nausea	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Colitis	0	0	0	1 (<1)	0	1 (<1)
Vomiting	1 (<1)	0	0	0	1 (<1)	0
Psychiatric disorders						
Anxiety	0	0	1 (<1)	0	1 (<1)	0
Anxiety disorder	0	0	0	1 (<1)	0	1 (<1)
Depression	0	0	0	1 (<1)	0	1 (<1)
Depression suicidal	0	0	1 (<1)	0	1 (<1)	0
Suicidal ideation	0	0	0	1 (<1)	0	1 (<1)
Suicide attempt	0	1 (<1)	0	0	0	1 (<1)
Investigations						
Blood creatinine increased	0	0	0	1 (<1)	0	1 (<1)
Liver function test abnormal	0	0	1 (<1)	0	1 (<1)	0
Transaminases increased	1 (<1)	0	0	0	1 (<1)	0
Renal and urinary disorders						
Renal failure	0	1 (<1)	0	0	0	1 (<1)
Renal impairment	0	0	0	1 (<1)	0	1 (<1)
Hepatobiliary disorders						
Hepatocellular injury	0	0	1 (<1)	0	1 (<1)	0
Hyperbilirubinemia	0	0	1 (<1)	0	1 (<1)	0
Injury, poisoning and procedural complications						
Overdose	0	0	0	1 (<1)	0	1 (<1)
Musculoskeletal and connective tissue disorders						
Myalgia	0	0	1 (<1)	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Adenocarcinoma of colon	1 (<1)	0	0	0	1 (<1)	0

Additionally, 1 subject in the CAB + RPV group (Study 201585) was discontinued due to meeting the protocol-defined liver stopping criteria, which was not considered as an AE leading to withdrawal.

6 subjects withdrew during the Maintenance Phase due to 10 ISRs including injection site pain (n=8; 6 AEs were Grade 2, 2 AEs were Grade 3), injection site nodule (n=1, Grade 2), and injection site swelling (n=1, Grade 2). All of the ISR AEs were considered to be related to study drug. Two additional subjects withdrew from Study 201584 citing intolerability of injections but did not name a specific ISR AE term that led to withdrawal.

During the OLI period of the Maintenance Phase, 6 subjects (3 in each study) withdrew due to AEs. The AEs that occurred in Study 201584 were acute hepatitis C (Grade 2), hepatitis A (Grade 4), and transaminases increased (Grade 3), probably related to chronic hepatitis C infection, illicit drug use and inorganic solvent abuse. None of these AEs were considered to be related to study drug. AEs leading to withdrawal in Study 201585 were asthenia (Grade 1), myalgia (Grade1), headache (Grade 3), and depression suicidal (Grade 2). All 4 AEs were considered to be related to study drug.

In study 207966 (ATLAS-2M), the rate of AEs leading to withdrawal was similar between the Q8W arm (8/522 [2%]) and the Q4W arm (10/523 [2%]) through Week 24. The most frequently reported, non-ISR AE leading to withdrawal was fatigue (Q8W, 1/522 [<1%]; Q4W, 2/523 [<1%]). No AEs leading to withdrawal occurred at a frequency of ≥1% in either treatment group. Three (<1%) subjects on Q8W and 4 (<1%) subjects on Q4W reported ISRs that led to withdrawal.

Safety related to drug-drug interactions and other interactions

N/A

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety profile of CAB+RPV is based on the pooled phase III studies, studies 201584 and 201585. A comprehensive review of safety data gathered in phase II studies is lacking. To put in perspective, it is noted that longer follow up are expected from the ongoing phase III studies FLAIR and ATLAS.

The safety analysis for CAB + RPV LA was based on the Week 48 data of the pooled phase III studies, FLAIR and ATLAS. Relevant safety findings of Phase II-b and Phase III-b studies are included, as well as relevant Week 96 data of the pooled phase III studies that became available after the start of the application procedure.

In pooled phase III studies, a higher frequency of AEs has been reported in the CAB+RPV treatment arm compared to CAR treatment arm. Considering the design of these both studies, a higher rate of AEs is not unexpected in these open-label studies and in subjects switching to this new regimen in comparison to subjects continuing their current oral ARV treatment, which is supposed to be well tolerated.

Apart from the ISRs, the more frequent AEs reported and drug-related with CAB+RPV, in comparison to the CAR regimen, are gastrointestinal disorders (nausea and diarrhoea), nervous system disorders and psychiatric disorders (headache, fatigue and asthenia, dizziness, abnormal dreams, anxiety, insomnia and malaise). Other more frequent AEs (myalgia and pyrexia) might be associated with the injection formulation of CAB+RPV.

Regarding AE leading to withdrawal, in pooled phase III studies, most AEs leading to withdrawal are viral hepatitis as planned in the study protocols. For the other AEs leading to withdrawal, no specific pattern was identified.

The salient aspects of the safety profile of CAB+RPV are:

-Injection Site reactions:

ISRs AES were expected with CAB and RPV administered by intramuscular injection. Most ISRs are grade 1 or 2 with less than 1% of ISRs in phase III studies classified as grade 3 (or 4) and less than 1% of ISRs leading to ME withdrawal. Most ISRs reported are pain but there have been also nodule, induration, swelling, erythema and pruritus reported at a significant frequency. Most ISRs in phase III studies resolved within 14 days with a median duration of 3 days but 17% of subjects experienced ISRs lasting more than 14 days. Otherwise, duration of ISRs have been analysed globally for all ISRs. A more detailed analysis of the duration and outcome for pain and other ISRs has been provided by the applicant together with a review of the sequelae reported after ISRs reported in 4% of subjects.

Similar results regarding the severity, type and outcome of local ISRs have been found in phase II study 200056.

Unfortunately, the ISRs (type, frequency, outcome) have not been analysed according to the location of the injection because this information was not recorded. The comparison of ISRs in groups QW4 and QW8 in study found similar results with regards to severity and duration of local ISRs but a higher frequency of nodule and injection site discomfort in group QW4.

In phase III studies, 1.5 inch 23 gauge needles have been recommended to investigators to administer CAB and RPV LA. The proposed SmPC for Vocabria recommend now the use of 1 ½ inches 23 gauge needle since the local safety of CAB and RPV injections likely based on the clinical experience gained during phase II/III studies. However, a statement has been added for HCP in the SmPC who should take into account the BMI of the patient to ensure that the needle length is sufficient to reach the gluteus muscle.

-Hepatotoxicity:
Overall elevated liver enzymes meeting liver stopping criteria were numerically more frequent with cabotegravir than with CAR (dolutegravir) in the phase III studies. Alternative diagnosis mainly viral hepatitis explains the majority of these AEs. No cases of DILI among patients experiencing liver abnormalities and liver stopping criteria have been identified by the independent hepatic adjudication committee in these 2 studies. However, some cases of steatohepatitis have been reported of grade 1 or 2. All have been considered as not-drug-related.

A total of 6 cases of DILI have been reported with CAB+RPV in phase I/II studies and ATLAS-2M study. All the cases of DILI have been reported with oral CAB with or without RPV, at two different dosages for CB 30 mg (n=4) and 60 mg (n=2). None of these cases included any symptoms notably signs suggesting hypersensitivity (HS). All these cases have been detected following close liver monitoring, every 4 weeks. No new cases of liver disorder have been identified in the Safety Update report.

The review of hepatotoxicity reported with CAB+RPV in clinical programme until now did not identify any raise additional safety concerns. The review of the causes of liver chemistry changes identified pre-existing hepatic steatosis and non-alcoholic steatohepatitis, imbalance of acute viral hepatitis in the arm CAB+RPV without clear explanation. At this stage, a warning for hepatotoxicity is recommended as proposed by the applicant since these safety data for CAB+RPV might be falsely reassuring and "hepatoxicity" should be considered as a identified risk.

-Hypersensitivity: No AEs suggestive of HSR have been identified in the clinical programme for CAB+ RPV administered orally or by IM injection for HIV infection. And the case of HSR reported in study ATLAS-2M is reasonably not a type I hypersensitivity reaction. However, hypersensitivity is a class-effect

of integrase inhibitors (and NNRTIs) and listed in the SmPC for all these products. A warning in the Vocabria PI as proposed by the applicant is necessary.

-Psychiatric disorders: No SAE related to suicidal behavior nor any completed suicide has been reported with CAB+RPV in the phase III studies, suicidal ideation has been reported with a frequency "uncommon" and similar than in group CAR (Triumeq). Moreover, suicidal behavior notably in patients with pre-existing history of mental illness together with depression are listed in the SmPC for all Integrase inhibitors since it is considered as a class-effect. Suicidal ideation should be listed in the PI for CAB+RPV. Depression and anxiety were reported at a frequency "common" and similarly in groups CAR and CAB+RPV with very few cases serious or severe. Sleep disorders were reported throughout the clinical development of CAB+RPV, with a higher incidence compared to the patients receiving other cART. The most frequent sleep disorders reported were insomnia reported at a frequency "common". Most AEs did not lead to study drug discontinuation. This is consistent with the known safety profile of the other INI,

Ten treatment-emergent deaths were reported in the Phase 2 and 3 studies, including 8 deaths in the CAB+RPV treatment group. These deaths were considered unrelated to CAB+RPV except in one case (myocardial infarction) where the causal relationship cannot be excluded. However, for 2 of them ("cardiac arrest during surgery" and "death with unknown cause") the causal relationship to CAB+RPV cannot be excluded at this stage. More information is needed if possible. The exact cause of these deaths is unknown.

For the other AEs of interest:

Rash, mainly grade 1 or 2, has been commonly reported with CAB+RPV with no study drug withdrawal for rash reported.

A total of 6 seizures have been reported with CAB+RPV in the clinical programme submitted. None were drug related.

No cases of rhabdomyolysis have been reported with CAB+RPV. Myalgia and increase in CPK have been reported commonly.

One case of severe acute pancreatitis, possibly drug-related, has been reported with CAB+RPV. In the ATLAS-2M study, one subject died of pancreatitis that could be drug-related. As a conservative approach the fatal case of pancreatitis will be reported in section 4.8 stating that the causality cannot be ruled out.

The laboratory abnormalities identified at day 80 are common, mild and asymptomatic bilirubin elevations without transaminase elevation which reflect the competition between CAB and unconjugated bilirubin because of the common clearance pathway through UGT1A1, ALT/AST elevations mostly attributed to viral hepatitis with an imbalance in the CAB+RPV treatment group, CK elevations of all grades attributed to exercise but more frequent in CAB+RPV treatment group, and lipase elevations with more grade 3/ 4 with CAB.

Pregnancy: a total of 16 pregnancy cases have been reported in the CAB+RPV clinical programme including 3 cases with exposure to CAR, 2 cases with exposure to CAB+RPV via semen, and 11 cases with i*n utero* exposure to CAB+RPV. The review of the outcome of these pregnancies did not identify any safety concern. Overall data on use during pregnancy are too limited to conclude on the risk associated with *in utero* exposure to CAB+RPV.

Medication errors (ME): a total of 18 medication errors have been reported in the pooled phase III studies conducted with CAB+RPV including 14 ME related to wrong dosage and 3 ME presumed to be related to partial IV administration of the study product leading to AE (1 allergy-like reaction, 1 lack of efficacy, 1 vaso-vagal reaction). In response to D120 LOQ additional cases of accidental partial IV administration of CAB and/or RPV have been identified after an immediate reaction post-injection or in subjects with

elevated RPV or CAB concentrations shortly after receiving RPV or CAB LA leading to milder AEs. A statement in section 4.2 on the need of care to avoid inadvertent injection into a blood vessel has been added. Nevertheless, the MEs represent a significant potential risk for CAB+RPV considering the co-existent of different formulation (oral, IM) and dosage (400 and 600 mg).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

See clinical efficacy.

2.6.2. Conclusions on the clinical safety

Based on the safety data from pooled phase I and III studies, partially phase II studies, cabotegravir administrated with RPV seems to have an acceptable level of safety for the indication proposed. The salient aspects of the safety profile of CAB+RPV are the injection site reactions. In common with the INI class, the other risks identified are hepatotoxicity, hypersensitivity and psychiatric disorders notably depression, anxiety, sleep disorders commonly reported. Already at this stage of development suicidal behaviour was reported which is to be underlined when having in mind that CAB is structurally close to DTG known to induce suicidal attempt/ ideation particularly in patient with history of psychiatric disorders. The use of CAB+RPV during pregnancy is a missing information. The risk of medication error, notably the use of the wrong dosage and inadvertent IV administration, is a potential risk identified.

The CHMP considers the following measures necessary to address issues related to safety:

Description	**Due date**
The MAH will conduct a prospective cohort study (COMBINE-2 study) to collect data from patients in order to assess clinical effectiveness, adherence, durability and discontinuations after initiating the cabotegravir and rilpivirine long acting regimen. The study will also monitor for resistance and response to subsequent antiretroviral regimens among patients who switched from cabotegravir and rilpivirine long acting regimen to another regimen The MAH will submit interim study results annually and the final results of the study by September 2026.	September 2026
The MAH will conduct a real-world five-year Drug Utilisation Study (DUS). This observational cohort study will aim to better understand the patient population receiving cabotegravir long acting injection and/or rilpivirine long acting injection containing regimens in routine clinical practice. The study will assess usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. The MAH will submit interim study results annually and the final results of the DUS by September 2026.	September 2026

2.7. Risk Management Plan

Safety concerns

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

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug Utilisation, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA Planned	Describe CAB LA and/or RPV LA containing regimens usage patterns Assess adherence, durability and discontinuation of CAB+ RPV regimen and the ARV regimen after switching from CAB+RPV Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who are on CAB+RPV regimen and were suppressed at regimen initiation Monitor for resistance and next treatment response among individuals who switched off CAB LA and/or RPV LA (where data is available)	Medication errors including treatment non-compliance	Final protocol submission Estimated Study start Estimated Study completion Estimated Final report Regular updates	31 December 2020 EMA approval of protocol and CAB+RPV LA commercially available 31 December 2025 30 September 2026 Yearly interim reports presenting the progress and status of the study will be submitted and discussed in the PBRER/PSUR
Category 3- Required additional pharmacovigilance activities				
A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients	Monitor for hepatotoxicity, Estimate the number of patients discontinuing CAB based ARV regimen due to adverse events, and adverse events related to hepatic events	Hepatotoxicity	Final protocol submission Estimated Study start	31 December 2020 EMA approval of protocol and CAB+RPV LA commercially available 31 December 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
initiating CAB containing antiretroviral regimen Planned			Estimated Study completion Estimated Final report	 31 March 2027
European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC): Planned	To assess maternal and foetal outcomes following CAB use during pregnancy	Use in pregnancy	Final protocol submission Estimated Study start Interim Report 1 Interim Report 2 Interim Report 3 Final report	31 December 2020 EMA approval of protocol and CAB+RPV LA commercially available 25 pregnancies 100 Pregnancies 200 Pregnancies 12 months after third analysis
Antiretroviral Pregnancy Registry Planned	Assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy.	Use in pregnancy	Final protocol submission Estimated Study start Interim Report 1 Interim Report 2 Interim Report 3 Final report Regular updates	31 December 2020 EMA approval of protocol and CAB+RPV LA commercially available 25 pregnancies 100 Pregnancies 200 Pregnancies 12 months after third analysis A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the CAB PBRER

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8. • PL section 2 & 4 • Recommendation for liver chemistry monitoring are included in SmPC section 4.4 • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional Pharmacovigilance activities:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen Final study report due: March 2027
Medication errors including treatment non-compliance	**Routine risk minimisation measures:** • SmPC section 4.2, 4.4 • PL section 2 & 3 • Administered by Healthcare Professional. • Different packaging colours and logo for each phase of treatment. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** Drug Utilisation, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA Final study report due: September 2026
Use in Pregnancy	**Routine risk minimisation measures:** • SmPC section 4.6. • PL section 2 • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** Antiretroviral Pregnancy Registry (APR) Final report: 12 months after 200 pregnancies recorded European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Final report: 12 months after 200 pregnancies recorded

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 is acceptable.

2.8. Pharmacovigilance

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.

Periodic Safety Update Reports submission requirements

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 alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18-3-2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of cabotegravir with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers cabotegravir to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vocabria (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;*
- *It has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];*
- *It has an obligation to conduct post-authorisation efficacy studies [REG Art 9(4)(cc), Art 10a(1)(b), DIR Art 21a(f), Art 22a(1)(b)];*

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

While untreated HIV-1 infection remains a life-threatening disease, for years it has become a chronic disease with combined antiretroviral therapy being early introduced to prevent pejorative impact of immune deficiency (notably including opportunistic infections in patients with CD4<200/mm3).

The goal of ARV therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. Thanks to combined antiretroviral therapies [mostly consisting in tritherapy with one main agent [boosted protease inhibitor (PI), integrase inhibitor (INI) or non nucleoside transcriptase inhibitor (INNTI)] and a backbone regimen [with two nucleoside reverse transcriptase inhibitors (NRTI)] nowadays available high level of viral suppression (>90% of patients with HIV RNA <50 copies/ml) can be achieved in HIV infected patients.

3.1.2. Available therapies and unmet medical need

Simplified regimen has become an issue for particular investigation in such a chronic disease. This notably pertains to the so called virologically suppressed patients (HIV RNA <50 copies/ml), i.e. once the undetectability has been adequately (durably) obtained in patients with a standard multitherapy, several simplified approaches to reduce the treatment burden are being tested so as to sustain at long term this undetectability. While monotherapy and less frequent administration of the multitherapy (4 days a week, as currently tested in the ANRS Quatuor clinical trial/ 4D regimen) remains to be validated, the oral once daily single-tablet 2-drug regimen with dolutegravir (INI) and rilpivirine (NNRTI) as fixed dose combination, Juluca was approved in 2018 (EU and US) as the first simplified maintenance regimen in virologically suppressed patients.

It is also noteworthy that even in non virologically suppressed patients, i.e., patients in first line regimen, treatment naïve patients, a simplified regimen consisting of a bitherapy (and not a tritherapy) has been first recently (July 2019) approved; Dovato a fixed dose combination with dolutegravir (INI) and lamivudine (NRTI).

In virologically suppressed patients, ViiV healthcare is now proposing a new approach for the maintenance simplified regimen in virologically suppressed patients, with Vocabria (cabotegravir) consisting in a parenteral administration (IM, long acting) every 4 or 8 weeks. Cabotegravir is a new representative of the known pharmacological class of INI, with a chemical structure very close to dolutegravir. In line with its clinical development, Vocabria IM is to be used in combination with rilpivirine IM long acting every 4 or 8 weeks as well. A parallel centralised procedure is in review process with harmonised timelines.

Vocabria is not aimed at answering an unmet medical need but rather proposed for convenience to get rid of the constraint of a daily oral administration of a combined antiretroviral regimen.

For Vocabria IM route, the applicant has ultimately endorsed in response to the CHMP request the following therapeutic indication:

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA

<50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (see sections 4.2, 4.4 and 5.1).

In addition to this IM route, Vocabria has been developed as an oral route to be used under restricted conditions:

- Before introducing the long acting IM route, to test the tolerance
- In case of missing IM doses or pre-planned interruption

It has therefore not been developed to be part *of a long term* combined antiretroviral regimen in first line therapy.

It has to be underlined that the indications are currently confined to adult patients, i.e. while adherence is particularly challenging in adolescent patients, this population is not yet targeted in the claimed indication.

Finally, it is worth mentioning that Vocabria is also currently being developed for the HIV prevention (PrEP), out of the scope of the current Marketing Authorisation Application.

3.1.3. Main clinical studies

The dose-response relationship for antiviral activity of cabotegravir was assessed in HIV-1 infected subjects in the Phase I/IIa proof-of-concept 10 days monotherapy studies ITZ111451 and ITZ112929.

The dose regimen of cabotegravir was assessed throughout two Phase IIb studies in HIV-1 infected subjects (LAI116482 [LATTE study] and 200056 [LATTE-2 study]).

The clinical efficacy of the dual maintenance regimen with cabotegravir LA in combination with rilpivirine LA both administered every 4 weeks is based on the 48 weeks data from two large open label randomised controlled pivotal Phase III switch studies in HIV-1 infected subjects (201584 [FLAIR study, N=566] and 201585 [ATLAS study, N=616]). In addition, Week 48 data from an additional Phase III study (207966 [ATLAS-2M study]), comparing the 4W regimen versus an alternative 8W dose regimen, are available.

These studies were broadly similar in terms of design and objective (both studies assessing the rate of virological failure after 48 weeks of switch). Both studies were designed as non-inferiority studies versus a continuation arm with the current oral antiretroviral regimen (CAR: ABC/DTG/3TC in the FLAIR study and 2 NRTIs + 1 PI, NNRTI or INI in the ATLAS study). Of note, prior to randomisation, subjects were stably suppressed for at least 6 months in ATLAS study, while it was for a median of 16.10 weeks in FLAIR study.

A total of 1182 patients were included and treated within these Phase 3 studies (591 patients with CAB+RPV and 591 in the control arms consisting of patients with their current oral ARV regimen), conferring an adequate power for the interpretation of efficacy data.

The design of each open label randomised pivotal FLAIR and ATLAS studies, the pooling of these two study results, the non-inferiority margin of the individual studies (6%) and of the pooled studies (4% pooling enabling a more reliable efficacy estimate) were agreed by the EMA scientific advices.

As a particularity of this clinical development, an oral formulation of CAB and RPV therapy (one Vocabria tablet [30 mg] and one rilpivirine tablet [25 mg] once daily during one month) was to be used to ensure the tolerance of this bitherapy before to start the long acting formulations [as part of the Oral lead in phase (OLI)].

Moreover, this oral CAB and RPV was recommended as a bridging therapy: if a patient plans to miss a scheduled injection visit by more than 7 days, oral formulations may be used to replace up to 2 consecutive monthly injection visits. The first dose of oral therapy should be taken approximately one month after the last injection dose of Vocabria or rilpivirine. This proposal was supported by POPPK analysis (with a target value of Cmin at 0.65 µg/ml).

3.2. Favourable effects

The performance of cabotegravir IM to sustain the virologic suppression in combination with rilpivirine IM, could be substantiated by:

- The approx. 2 log decrease vs placebo in the 10 days monotherapy, as observed with other INI (dolutegravir and bictegravir) monotherapy studies
- No relevant DDI between cabotegravir and rilpivirine was seen, which is supportive for using these two ARV in combination

More importantly, the non-inferiority of the virologic suppression under cabotegravir IM and rilpivirine IM was demonstrated versus the continuation of the combined antiretroviral regimen in the control arm of the two large randomised controlled pivotal FLAIR and ATLAS studies. Indeed, in virologically-suppressed subjects, the difference in the percentages of patients with loss of virologic suppression (HIV RNA $\geq$50 copies/ml) at 48 weeks (pooling data of studies FLAIR and ATLAS) was 0.2 (95% CI: -1.4, 1.7), with results well below the pre-defined 4% non-inferiority margin for pooled studies and with consistency on the ITT and PP analyses.
In addition, the applicant has newly provided as part of the response to the D120 LOQ the 48 weeks efficacy data of the ATLAS 2M comparing an Q4W to a Q8W regimen in virologically suppressed patients. The every 2 months regimen (Q8W) was shown to be non-inferior to the Q4W regimen in this study. The difference in the percentages of patients (Q8W - Q4W regimen) with loss of virologic suppression at 48 weeks was 0.8 (95% CI: -0.6, 2.2), with results below the pre-defined 4% non-inferiority margin and with consistency between the ITT and PP analyses and with the results of FLAIR and ATLAS studies.

3.3. Uncertainties and limitations about favourable effects

Patient population

The wording of the therapeutic indication as initially proposed by the applicant was not considered acceptable since not adequately conservative. Indeed, patients with baseline NNRTI resistance mutations (except for K103N which was allowed) or INI resistance mutations were excluded from participation in the pivotal studies. The applicant ultimately revised the indication in response to the CHMP concern.

Subgroup analyses.

Somewhat higher virological failure rates were observed in some demographic categories, i.e. females, subjects with high BMI, subjects from Russian Federation. This was observed in both studies, as well as in the pooled analysis and also in ATLAS-2M study. Baseline disease characteristics associated with a somewhat worse outcome were infection with HIV-1 Subtype A1 or AG. It cannot be ruled out that external factors, such as HIV subtype or the circulation of HIV variants with certain viral mutations (such as L74I), may have an impact on outcome.

Virologic failure and resistance development.

Virologic failure rates were low in the clinical studies, and adherence to the visit schedule was high. As stated in a recent publication (Oliveira and al, Retrovirology 2018), the development of Q148R/K with CAB can result in high level of cross resistance to all INI. It is nevertheless expected that rescue in patients loosing virologic suppression under the dual LA maintenance therapy will be managed by boosted protease inhibitors. In response to the D120 issues to be addressed, the applicant agreed to conduct a drug utilisation study (DUS). This prospective observational cohort study will aim to better understand the patient population receiving CAB+RPV LA regimen in routine clinical practice, usage patterns and post marketing clinical effectiveness of this regimen. One of the key endpoints of the DUS is to assess durability and discontinuation of CAB+RPV regimen and the ARV regimen after switching from CAB+RPV. Non-adherence to the dosing schedule, the clinical effectiveness (i.e. proportion patients experiencing virologic failure) will also be assessed, and every effort will be made to monitor resistance in patients who switched off CAB+RPV regimen. It is important that patients should be switched to an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of CAB + RPV LA. If not adequately treated with an appropriate oral ARV regimen, patients will be at high risk of virologic failure, due to prolonged exposure to subtherapeutic levels of CAB and RPV, and subsequent resistance development. The risk of selection (and potential transmission) of dual class resistant virus is a source of particular concern with the use of this dual LA regimen. A prospective cohort study (COMBINE-2) is proposed in collaboration with the NEAT ID network. The study will test for resistance and will monitor for emergence of resistance among those who discontinue the CAB+RPV LA regimen and have virologic failure while on subsequent ARV regimen.

Further, according to the HIV SAG the currently proposed text in the SmPC suffices to allow proper patient selection (adequate observance), and no additional measures such as patient alert card, an electronic or mobile app reminder system for patients to manage properly discontinuation of treatment for the safe and effective use of this first novel injectable regimen can be mandatory in all European countries. Tools should be decided at the national level depending on the Health system organisation.

Limitations of the clinical data in support of the Q8W regimen

In response to the D120, the applicant has proposed, next to the Q4W regimen, to also include the Q8W regimen as a treatment option. In ATLAS-2M study, the rate of subjects with HIV-1 RNA ≥50 c/ml at Week 48, and especially the rate of confirmed virologic failure (CVF), is numerically higher in the Q8W group (8 subjects) than in the Q4W group (2 subjects). Most of them (10/14 subjects, including 7/10 subjects experiencing CVF) had no prior exposure to CAB + RPV.

This could suggest an inadequate CAB and/or RPV exposure at the beginning of treatment or differential resistance pattern at baseline. The applicant was requested to discuss an optimised dosing regimen that could start with Q4W dosing until therapeutic concentrations of CAB and RPV have been reached e.g. by monthly dosing at least for the first 6 months followed by Q8W dosing. The applicant did not further discuss the possibility of starting with a Q4W regimen for at least 6 months before switching to a Q8W regimen, but provided simulations for switch from Q4 to Q8 week regimen and vice versa. Reassuringly, the RPV concentrations remain below the levels that have been associated with QT prolongation. Steady state concentrations are decreasing after switch from Q4W to Q8W regimen, however, prediction intervals are overlapping, and the concentrations remain above the PAIC90 values. The input of the HIV SAG on questions pertaining to this newly introduced Q8W was requested. The experts considered that there is enough evidence to support Q8W dosing taking into account that there were not significant differences between Q8W and Q4W regimens in the different studies. Therefore, it can be concluded that both regimens seem to have comparable efficacy. However, it was also highlighted that there are still some concerns regarding the subgroup of patients on Q8W dosing who showed more risk of virological failure (VF). For patients who could have higher risk of VF it was remarked that starting with the Q4W

regimen should be considered to minimise the risk of virological failure. In these cases, switching to a Q8W dosing could be considered afterwards in patients who reach and maintain undetectability with this regimen.

Based on the multivariable analyses the applicant has identified risk factors of virologic failure, i.e. at least 2 of the following baseline factors: rilpivirine resistance mutations identified by proviral resistance testing, HIV-1 subtype A6/A1, or BMI>30 mg/m2. This information has been incorporated in section 5.1 of the SmPC plus an additional warning in section 4.4 (with cross reference to section 5.1).

Limitations of the clinical data in support of the oral bridging

There are currently limited clinical data in support of the oral bridging with CAB + RPV in view of the limited number of patients by study who used oral bridging (only 16 missed injections with oral bridging across FLAIR (n=9) and ATLAS (n=7) studies). This will be further substantiated in post-approval.

3.4. Unfavourable effects

Besides the hepatotoxicity, cutaneous reactions, psychiatric adverse events (already including suicidal ideation) in common with other representatives of the INI class, the safety profile of CAB LA is characterised by injection site reactions. ISRs AES were expected with CAB and RPV administered by intramuscular injection. Most ISRs are grade 1 or 2 with less than 1% of ISRs in phase III studies classified as grade 3 (or 4) and less than 1% of ISRs leading to ME withdrawal. Most ISRs reported are pain but there have been also nodule, induration, swelling, erythema and pruritus reported at a significant frequency. Most ISRs in phase III studies resolved within 14 days with a median duration of 3 days but 17% of subjects experienced ISRs lasting more than 14 days. Moreover "sequelae" were reported in 4% of subjects mainly relating to prolonged injection site pain.

CAB is glucuruno- conjugated and could potentially lead to increased bilirubin by competition with the transporter. However, only mild hyperbilirubinemia is reported so far without clinical manifestations.

3.5. Uncertainties and limitations about unfavourable effects

Design. Although an open-label switch design is acceptable, the interpretation of the safety results is not as straight forward as it would have been in case a double-blind trial design had been used, as reporting rates of adverse events can be influenced by knowledge of the allocated treatment. Also, subjects who have been randomised to the comparator arm continued on a treatment that they already tolerated; hence less adverse events are expected in this arm than in the CAB + RPV arm. Imbalances between the treatment groups in the incidence of AEs reported for several SOCs were observed. These were mainly introduced by the occurrence of injection side reactions in the CAB + RPV group.

3.6. Effects Table

Table 55 Effects Table for Vocabria

Indication: *Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral*

resistance to, and no prior virological failure with agents of the NNRTI and INI class (see sections 4.2, 4.4 and 5.1).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Reference
Favourable Effects						
Virologic failure in virologically-suppressed subjects, Week 48 **(ITT-E)**	HIV-1 RNA ≥50 copies/mL at Week 48	n/N (%)	11/591 (1.9%)	10/591 (1.7%)	Difference in percentages (95% CI): 0.2 (-1.4, 1.7) Trend to higher rate of virologic failure in females, Russian subjects and subjects with BMI ≥30	Pooled studies 201584 and 201585
Virologic failure in virologically-suppressed subjects, Week 48 **(PP)**	HIV-1 RNA ≥50 copies/mL at Week 48	n/N (%)	10/572 (1.7%)	10/574 (1.7%)	Difference in percentages (95% CI): 0.0 (-1.5, 1.5)	Pooled studies 201584 and 201585
Virologic success in virologically-suppressed subjects, Week 48 **(ITT-E)**	HIV-1 RNA <50 copies/mL at Week 48	n/N (%)	550/591 (93%)	558/591 (94%)	Difference in percentages (95% CI): -1.4 (-4.1, 1.4)	Pooled studies 201584 and 201585
Virologic failure in virologically-suppressed subjects, Week 48 **(ITT-E)**	HIV-1 RNA ≥50 copies/mL at Week 48	n/N (%)	Q8W regimen 9/522 (1.7%)	Q4W regimen 5/523 (1.0%)	Difference in percentages (95% CI): 0.8 (-0.6, 2.2)	Study 207966 (ATLAS-2M)
Virologic failure in virologically-suppressed subjects, Week 48 **(PP)**	HIV-1 RNA ≥50 copies/mL at Week 48	n/N (%)	Q8W regimen 7/516 (1.4%)	Q4W regimen 5/514 (1.0%)	Difference in percentages (95% CI): 0.4 (-0.9, 1.7)	Study 207966 (ATLAS-2M)
Health outcomes	HIV Treatment Satisfaction change Version (HIVTSQc) at Week 48	score	29.6	25.5	Difference in mean score (95% CI): 4.1 (2.8, 5.5) (p<0.001)	Study 201584
Unfavourable Effects						
AEs	Any event	n/N (%)	561/591 (95%)	445/591 (75%)	Not necessarily related to study drugs. AEs including ISRs in the CAB+RPV group only. Open-label switch study design may explain this imbalance.	Pooled studies 201584 and 201585
	SOC infections	%	65%	57%		
	SOC GI disorders	%	31%	20%		
	SOC musculoskeletal and connective tissue disorders	%	23%	15%		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Reference
	SOC nervous system disorders	%	22%	12%		
	SOC investigations	%	13%	8%		
	SOC psychiatric disorders	%	12%	9%		
	SOC skin and subcutaneous tissue disorders	%	14%	9%		
AEs related to study drug	According to investigator	n/N (%)	481/591 (83%)	36/591 (6%)	AEs including ISRs in the CAB+RPV group only.	Pooled studies 201584 and 201585
	Most frequently reported, Grade 2 to 4, non-ISRs	N	Headache (5), diarrhea (5), fatigue (4), pyrexia (4)	CLcreat decreased (2), blood cholesterol increased (2), renal failure (2)		
SAEs	Overall SAEs	n/N (%)	31/591 (5%)	26/591 (4%)	Higher rate of viral hepatitis in the CAB+RPV group. Two SAEs considered drug-related by investigator: knee monoarthritis (CAB+RPV group) and suicideal ideation (control group: EFV/TDF/FTC)	Pooled studies 201584 and 201585
Injection site reactions (ISRs)	Including pain, nodule, induration, swelling, erythema, pruritus, abscess, cellulitis	n/N (%)	489/591 (84%)	N/A	22 (4%) ISRs Grade 3, none Grade 4, non serious. 17% of subjects with duration of ISRs >14 days. 6 (1%) ISRs leading to withdrawal.	Pooled studies 201584 and 201585
Hepatotoxicity	Liver stopping criteria	n/N (%)	11/591 (2%)	3/591 (<1%)	Mostly due to viral hepatitis (10 in the CAB+RPV group, 3 in the control group). Not considered drug-related. No DILI. However, in the other clinical Phase II/III studies, 6 cases of DILI reported with oral CAB with or without RPV.	Pooled studies 201584 and 201585
Psychiatric AEs	Suicidal ideation	n/N (%)	4/591 (<1%)	5/591 (<1%)	One subject in the CAB + RPV group had suicidal depression considered to be related to study drug and was subsequently discontinued from the study. Other AEs Grade 1-2.	Pooled studies 201584 and 201585
	Depression	n/N (%)	16/591 (3%)	14/591 (2%)	Mostly Grade 1-2. 5 subjects in the CAB+RPV groups are considered drug-related by investigator.	
Neurologic AEs	Seizures-related AEs	n/N (%)	6/591 (1%)	2/591 (<1%)	Not considered associated with seizure, not serious, not leading to withdrawal, not considered drug-related.	Pooled studies 201584 and 201585

Abbreviations: AEs: adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

While Vocabria LA in combination with Rekambys LA is not expected to answer an unmet medical need, it is proposed for convenience to remove the constraints of an oral daily administration of combined antiretroviral regimen. Moreover, this maintenance regimen is a NRTI-sparing regimen, with expectations that NRTI-associated long-term toxicities can be reduced or avoided.

Although there are some uncertainties regarding the use of the long-acting formulation of RPV in clinical practice, it has been shown that, if used according to the proposed SmPC, RPV LA together with CAB LA is able to keep HIV-1 viral load suppressed in the majority of patients (>93%) with low rates of virologic failure (<2.2%).

It is questionable if the population included in these clinical studies is representative of the patients that may be treated in clinical practice. It can be expected that the future patient population may also include subjects with, for a variety of reasons, difficulties to adhere to the monthly injections, and even more to every two months injections. Therefore, it is considered important to ensure that patients understand the need of strict adherence to the monthly/every two months injections, especially during the initial period before steady-state exposures are reached, and that they understand that due to the long-acting properties of this regimen, a so called drug holiday (a period during which a patient does not take his/her medication) should at all times be avoided due to the slowly waning exposures that result in subtherapeutic CAB and RPV levels that will surely result in the selection of resistance-associated mutations. Overall, while this regimen is NOT advisable for patients with adherence issues to oral therapy, as might initially be thought, there is a need to clearly warn physicians on the adequate selection of candidates to this dual LA regimen. Patients and their treating physicians should be aware that after discontinuation of treatment with CAB + RPV LA, an oral antiviral regimen is definitely needed as concentrations of these agents may remain in the circulation for several years, increasing the risk of resistance.

The SmPC/PL have been revised to address those issues and post authorisations measures have been proposed as part of the RMP (DUS).

The input of a HIV SAG was received to notably ensure that adequate safeguards have been put in place to minimise the risk of emergence of resistance associated with treatment discontinuation/issues of adherence of this LA regimen. Input of the SAG was also requested on the extent both Q4W and Q8W can equally be considered. The experts remarked that the Q8W and Q4W seem to be equally effective. However, special considerations should be given to patients who might have higher risk of virological failure on Q8W considering the current data. Further, adherence was considered a key element and should be reinforced, however, there is not a unique tool to ensure good adherence to treatment. Hence, measures should be adapted to the centres, resources, patients' characteristics etc. Finally, the experts recommend that a non-interventional post approval study on this CAB+RPV LA regimen is necessary to complement the data from existing registries. Such a study will substantiate real life settings since the clinical trials supporting the dossier were performed in very selected study populations. This post marketing study will be pivotal to monitor adherence and collect data on virological suppression, using appropriate threshold (i.e. plasma HIV-1 RNA levels <50 c/mL instead of <200 c/mL) to avoid waiting for virological failure while on CAB+RPV LA regimen. In addition, patient and physician preferences/selection criteria for long acting therapy should be recorded. The experts

strongly recommend for such a post approval study to be performed whilst acknowledging that challenges in getting reliable data on resistance will occur.

The applicant has committed to perform two post approval studies to keep scrutiny on the adequate use of this first LA regimen (to be used in combination with Rekambys LA regimen with parallel and linked Marketing Application) and responding to the CHMP/PRAC concerns, a DUS under the umbrella of Eurosida as a PASS and a COMBINE-2 study as a PAES under the umbrella of the NEAT, both capture information on adherence and resistance, but the DUS as a PASS will be more directed towards collecting information on medication errors and usage pattern. The SAG input has been taking into account for the threshold of viral load to capture the loss of virologic suppression (i.e. 50 copies/ml). Both non interventional studies are aimed at further substantiating the benefit/risk ratio of the drug (given the potential individual risk and collective risk through transmission of dual NNRTI and INI resistance in case of inadequate handling) in a real life setting and thus will be imposed.

3.7.2. Balance of benefits and risks

As stated in therapeutic guidelines, the primary concern when switching should be to sustain and not to jeopardise virologic suppression. To that purpose, it is critical to be conservative in delineating the targeted population for maintenance therapy. Thus, the applicant has revised the indication of Vocabria IM as proposed in the D150 MO:

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (see sections 4.2, 4.4 and 5.1).

Although there are some uncertainties regarding the use of the long-acting formulation of Vocabria in clinical practice, it has been shown that, if used according to the proposed SmPC, Vocabria LA together with RPV LA is able to keep HIV-1 viral load suppressed in the majority of patients (>93%) with low rates of virologic failure (<2.2%). As the safety profile of Vocabria is acceptable, it can be concluded that from a *clinical perspective*, the balance of benefits and risks for Vocabria is positive, provided adequate post-authorisation follow-up.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Vocabria 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 Vocabria is favourable in the following indication:

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human

Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (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 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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The MAH will conduct a prospective cohort study (COMBINE-2 study) to collect data from patients in order to assess clinical effectiveness, adherence, durability	September

and discontinuations after initiating the cabotegravir and rilpivirine long acting regimen. The study will also monitor for resistance and response to subsequent antiretroviral regimens among patients who switched from cabotegravir and rilpivirine long acting regimen to another regimen The MAH will submit interim study results annually and the final results of the study by September 2026.	2026
The MAH will conduct a real-world five-year Drug Utilisation Study (DUS). This observational cohort study will aim to better understand the patient population receiving cabotegravir long acting injection and/or rilpivirine long acting injection containing regimens in routine clinical practice. The study will assess usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. The MAH will submit interim study results annually and the final results of the DUS by September 2026.	September 2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that cabotegravir is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

Description of the Post-authorisation measures

Post-authorisation measure (s)	Motivation
Proposed post-authorisation measure 1 with proposed classification:	Motivation/Background information on measure, including due date:
1. COMBINE-2 for CAB+RPV LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance (**Category 1 PAES**)	*Motivation* To gather further information about the clinical effectiveness and the development of resistance associated with this new injectable HIV treatment regimen (CAB/RPV LA). *Background information on measure* The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen.

Post-authorisation measure (s)	Motivation
	The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class will be eligible for inclusion. *Due dates* Final protocol submission: 31 December 2020 Estimated Study start: EMA approval of protocol and CAB+RPV LA commercially available Estimated Study completion: December 2025 Final report: September 2026 (with prior annual reports to be submitted and yearly updates)
Proposed post-authorisation measure 2 with proposed classification:	Motivation/Background information on measure, including due date:
2. Drug Utilisation, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating ARV regimen of CAB+RPV (**Category 1 PASS**)	*Motivation* To gather further information about the safety concern "Medication errors including treatment non-compliance" associated with this new injectable HIV treatment regimen (CAB/RPV LA). *Background information on measure* Describe CAB LA and/or RPV LA containing regimens usage patterns. Assess adherence, durability and discontinuation of CAB+ RPV regimen and the ARV regimen after switching from CAB+RPV. Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who are on CAB+RPV regimen and were suppressed at regimen initiation. Monitor for resistance and next treatment response among individuals who switched off CAB LA and/or RPV LA (where data is available). *Due dates* Final protocol submission:

Post-authorisation measure (s)	Motivation
	31 December 2020 Estimated Study start: EMA approval of protocol and CAB+RPV LA commercially available Estimated Study completion: December 2025 Estimated Final report: September 2026 (with prior annual reports to be submitted and yearly updates)

* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS)