15 October 2020
EMA/CHMP/455298/2020
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Rekambys

International non-proprietary name: rilpivirine

Procedure No. EMEA/H/C/005060/0000

## Note

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

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# List of abbreviations

| | |
|---|---|
| ACCEPT | chronic treatment acceptance questionnaire |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| AR | adverse reaction |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| BMI | body mass index |
| CAB | cabotegravir |
| CAR | continued/current antiretroviral regimen |
| CI | confidence interval |
| CK | creatine kinase |
| CPP | Critical Process Parameters |
| CQA | Critical Quality Attribute |
| CSF | cerebrospinal fluid |
| CVF | confirmed virologic failure |
| DILI | drug-induced liver injury |
| DSC | differential scanning calorimetry |
| DTG | Dolutegravir |
| DVS | dynamic vapor sorption |
| EC | European Commission |
| ECG | electrocardiogram |
| EFV | Efavirenz |
| FDA | (USA) Food and Drug Administration |
| FDC | fixed-dose combination |
| FT-IR | Fourier Transformed Infra Red spectrometry |
| GCP | good clinical practice |
| GMP | good manufacturing practice |
| HAART | highly active antiretroviral therapy |
| HBV | hepatitis b virus |
| HCV | hepatitis c virus |
| HIV(-1) | human immunodeficiency virus (type 1) |
| HIVTSQc | HIV treatment satisfaction questionnaire (change) |
| HIVTSQs | HIV treatment satisfaction questionnaire (status) |
| ICH | International Council for Harmonisation |
| IM | intramuscular |
| INSTI | integrase strand transfer inhibitor |
| IR | Infra red spectroscopy |
| ISR | injection site reaction |
| ITT-E | intent-to-treat exposed |
| LA | long-acting injectable, extended release suspension for injection, or prolonged release suspension for injection |
| LDPE | low-density polyethylene |
| LSC | liver stopping criteria |
| LSLV | last subject last visit |
| MS | mass spectrometry |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NSAID | nonsteroidal anti-inflammatory drugs |
| OLI | oral lead-in |
| P-338 | poloxamer-338 |
| PARs | proven acceptable ranges |
| PE | polyethylene |
| Ph. Eur. | European Pharmacopoeia |
| PI | protease inhibitor |
| PIN | perception of injection |
| PK | pharmacokinetic(s) |
| PopPK | population PK |
| PP | per protocol |

| | |
|---|---|
| ppm | part per million |
| PSD | Particle size distribution |
| Q4W | every 4 weeks; monthly |
| Q8W | every 8 weeks; bimonthly |
| qd | once daily |
| QTc | QT interval corrected for heart rate |
| QTTP | quality target product profile |
| RAM | resistance-associated mutation |
| RH | relative humidity |
| RPV | rilpivirine |
| SOC | standard of care |
| TGA | thermogravimetric analysis |
| TTC | threshold of toxicological concern |
| UHPLC | ultra high pressure liquid chromatography |
| ViiV | ViiV Healthcare Company |
| XRD | X-Ray Diffraction |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Janssen-Cilag International N.V. submitted on 26 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Rekambys, 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 26 April 2018.

The applicant applied for the following indication: "Rekambys is indicated, in combination with 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) and have no known or suspected resistance to either rilpivirine or cabotegravir (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/0039/2019* 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 indicated the active substance rilpivirine contained in the above medicinal product to be considered as a known active substance.

### *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 |
|---|---|---|
| 22 January 2015 | 919/1/FU/3/2014/I | *Dr Marion Haberkamp, Prof. Markku Pasanen* |
| 28 April 2016 | 2517/1/FU/1/2016/II | *Dr Hans Ovelgönne, Dr Filip Josephson* |
| 15 December 2016 | 919/1/FU/4/2016/I | *Prof. Dieter Deforce, Dr Mair Powell* |
| 31 May 2018 | 919/1/FU/5/2018/II | *Dr Mair Powell, Dr Sheila Killalea* |

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

- *Drug substance and drug product specification parameters and acceptance criteria*
- *Drug substance/product registration stability studies*
- *Adequacy of the proposed in vitro dissolution method*
- *Poloxamer excipient*
- *Adequacy of the preclinical toxicology studies to support MAA*
- *Dose and dose regimen*
- *Design of the 2 planned 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*
- *Data requirement to remove the oral lead in dosing for both CAB and RPV at the time of MAA*
- *Clinical pharmacology studies*
- *Regulatory submission strategy*

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Bruno Sepodes

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<br>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 opinion for granting a marketing authorisation to Rekambys on | 15 October 2020 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The Applicant seeks the following therapeutic indication for Rekambys:

Rekambys is indicated, in combination with 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) and have no known or suspected resistance to either rilpivirine or cabotegravir (see section 5.1).

### 2.1.2. Epidemiology

HIV continues to be a major global public health issue, having claimed more than 32 million lives so far. In 2018, 770 000 people died from HIV-related causes globally. There were approximately 37.9 million people living with HIV at the end of 2018, with 1.7 million people becoming newly infected in 2018 globally. An estimated 0.8% [0.7-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. The WHO African Region is the most affected region, with 25.7 million people living with HIV in 2018. The African region also accounts for almost two-thirds of the global total of new HIV infections (WHO FACT sheet).

In 2017, 159 420 newly diagnosed HIV infections were reported in 50 of the 53 countries of the WHO European Region, which corresponds to a rate of 20.0 newly diagnosed infections per 100.000 population. Over the course of the last three decades, over 2.3 million people have been diagnosed and reported with HIV in the WHO European Region, including over 650.000 people in the EU/EEA. Overall, numbers of people diagnosed with HIV were highest in the East of the Region (51.1 per 100.000 population), lower in the West and the EU/ EEA (6.9 and 6.2 per 100.000, respectively) and lowest in the Centre (3.2 per 100.000) (HIV/AIDS surveillance in Europe 2018 – 2017 data, ECDC).

Key populations include men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and their clients, and transgender people. They are at increased risk of HIV irrespective of epidemic type or local context. There is no cure for HIV infection. However, effective antiretroviral (ARV) drugs can control the virus and help prevent transmission. Where treatment is available, HIV infection has become a manageable chronic disease.

### 2.1.3. Biologic features

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).

HIV-1 is a rapidly replicating virus, with an error-prone Reverse Transcriptase (RT). Mutations in the viral genome occur randomly when the virus replicates, with an estimated mutation rate of approximately

one nucleotide mutation per replicative cycle. Many HIV variants are simultaneously present in each infected individual, which is also described as "quasispecies". Resistance-associated mutations (RAMs) can rapidly be selected when there is selection pressure due to e.g. too low concentrations of antiviral drugs. Often, resistance to drugs in a certain ARV class results in cross-resistance to other drugs in that same class.

### 2.1.4. Clinical presentation, diagnosis

HIV infection is often diagnosed through rapid diagnostic tests (RDTs), which detect the presence or absence of HIV antibodies.

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. Recent estimates suggest that even in high-income settings, about 25-35% of people living with HIV starting ART have a CD4 cell count of less than 200 cells/$mm^3$. 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.

Initial laboratory testing should include 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 are well tolerated, and these regimens are therefore less likely to induce drug resistance mutations.

### 2.1.5. Management

Standard treatment for HIV-1 infection consists of a combination of 3 antiretroviral agents (ARV), from at least 2 different classes, and typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI class. This treatment works well to suppress HIV-1 viral load to undetectable levels, in the far majority of patients. However, viral resistance to any regimen can develop, due to e.g. poor adherence, too low exposure due to drug interactions, or low potency of the drug.

The most recent guideline of the European AIDS Clinical Society (EACS, version 9.1 issued October 2018) recommend the use of an INSTI as the preferred third agent in ART-naïve adult HIV-positive persons; with the added note that tailoring antiretroviral regimens for each individual is essential as other classes of third agents (e.g boosted PI) might be indicated in the presence of resistance or risk of poor adherence.

Currently, dual-therapy regimens are also available, e.g. Juluca (DTG+RPV) and Dovato (DTG+3TC). While Juluca is specifically indicated for use in virologically suppressed patients, Dovato may also be used in treatment naïve patients.

The main goal in any HIV-1 infected patient is reaching and maintaining full virologic suppression, i.e. having HIV-1 RNA load below the limit of detection of most commonly used assays (often <50 copies/mL blood).

## *About the product*

The current application concerns RPV LA, an extended-release (also called prolonged release) suspension for intramuscular (IM) injection formulation of the NNRTI rilpivirine.

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine is available as Edurant, (25 mg oral tablet formulation), and in combination products together with FTC+TDF (Eviplera), FTC+TAF (Odefsey), or with DTG (Juluca).

The following indication and posology are claimed for Rekambys:

Rekambys is indicated, in combination with 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) and have no known or suspected resistance to either rilpivirine or cabotegravir (see section 5.1).

Rekambys should always be co-administered with cabotegravir injection. Therefore, the cabotegravir injection Summary of Product Characteristics should be consulted.

*Oral lead-in*

EDURANT is recommended for approximately 1 month (at least 28 days) in virologically suppressed patients prior to the initiation of Rekambys to assess tolerability to rilpivirine. One EDURANT 25 mg tablet should be taken once daily with a meal and should be administered with one cabotegravir 30 mg tablet once daily.

*Initiation injection (3 mL dose)*

On the final day of oral lead-in, the recommended initiation injection dose of Rekambys in adults is a single 3 mL (900 mg) intramuscular injection. Rekambys and cabotegravir injections should be administered at separate gluteal injection sites during the same visit.

*Continuation injection (2 mL dose)*

After the initiation injection, the recommended continuation injection dose of Rekambys in adults is a single 2 mL (600 mg) monthly intramuscular injection. Rekambys and cabotegravir injections should be administered at separate gluteal injection sites during the same visit. Patients may be given injections up to 7 days before or after the date of the monthly 2 mL injection schedule.

**Recommended Dosing Schedule in Adult Patients:**

| Drug | Oral Lead-In During Month 1 | IM Initiation Injections At Month 2 | IM Continuation Injections Month 3 Onwards |
|---|---|---|---|
| Rilpivirine | 25 mg once daily | 3 mL (900 mg) | 2 mL (600 mg) monthly |
| Cabotegravir | 30 mg once daily | 3 mL (600 mg) | 2 mL (400 mg) monthly |

IM = Intramuscular injection.

The Applicant states that "*the overall objective of the CAB + RPV clinical program is to develop a novel, highly effective, well-tolerated 2-drug LA injectable regimen. Such a regimen allows for reduced dosing frequency compared with daily oral antiretrovirals (ARVs). With less frequent dosing, the daily reminder*

*of subjects' HIV status may be avoided, and associated stigma related to taking oral treatment regimens may thereby be lessened. Since all injections are given by health care professionals, such a regimen 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. In addition, this nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen avoids known NRTI-associated adverse reactions (ARs) and long-term toxicities. Moreover, given the parenteral route of administration, a 2-drug LA injectable regimen may result in fewer gastrointestinal adverse events (AEs), eliminates dosing restrictions with regard to food and will not have the drug-drug interactions (DDIs) observed with oral ARVs at the level of the gastrointestinal tract."*

If approved, this will be the first 2-drug LA injectable regimen for maintaining viral suppression (plasma HIV-1 ribonucleic acid [RNA] <50 copies [c]/mL).

## *Type of Application and aspects on development*

**Development programme**

The clinical development program consists of 2 randomized, controlled pivotal Phase III studies (201584 [FLAIR] and 201585 [ATLAS]), supported by 2 randomized, controlled Phase IIb studies (LAI116482 [LATTE] and 200056 [LATTE-2]). In addition, a Phase IIIb Study 207966 (ATLAS-2M) evaluating monthly (Q4W) and bimonthly (Q8W) dosing is ongoing.

The oral formulations were evaluated for both lead-in treatment to confirm tolerability prior to LA injections and for bridging therapy to cover planned missed injection visits.

The EMA guideline "Guideline on the clinical development of medicinal products for the treatment of HIV infection" (EMEA/CPMP/EWP/633/02 Rev. 3) does not include specific guidance regarding injectable therapies. Sponsors are rather encouraged to discuss plans for clinical development programmes in these cases with EU regulators, which has been complied with (see Scientific advice, below).

**Scientific advice**

The applicant requested regulatory advice on the development program from CHMP on several occasions.

The following Scientific Advice procedures contained Toxico-pharmacology related questions:

- **EMEA/H/SA/919/1/FU/3/2014/I:** in this follow-up advice, questions were asked concerning:

The non-clinical studies performed (additionally to the NC package for Edurant) for the registration of RPV LA. CHMP was in agreement, although Cmax and distribution after parenteral treatment versus oral treatment should be more thoroughly discussed at MAA.

- **EMEA/H/SA/919/1/FU/5/2018/II:** in this advice, questions were asked concerning:

The non-clinical (reprotoxicity) studies needed for poloxamer 338. CHMP agreed with the general toxicology programme. Considerations for bridging existing reprotoxicity data from poloxamer 188 to poloxamer 338 were provided.

The following Scientific Advice procedures contained Clinical Efficacy/Safety related questions:

**- EMEA/H/SA/2517/1/2013/III:** in this advice, questions were asked concerning:

The phase 2b clinical study (protocol), the appropriateness of the two phase 2B studies to provide sufficient evidence to support Phase 3, and the appropriateness of the pivotal studies to support the

future Marketing Authorisation Application. CHMP was in general agreement, although several comments were raised.

**- EMEA/H/SA/2517/1/FU/1/2016/II:** this was a follow-up to the advice provided by CHMP in April 2013. Questions were asked, concerning:

The selected dosage regimen and design of the phase 3 studies, the intention to pool the data from both studies, and the potential to remove the oral lead-in period. The CHMP responded that the currently proposed Q4W dose schedule was reasonably supported by phase II data, and proceeding with this regimen was considered justified, the design and pooling of the phase 3 studies were acceptable, and that removing the oral lead-in will be a review issue at the time of the application, to be discussed in light of the emerging safety profile of the regimen.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as a prolonged-release suspension for injection containing 600 or 900 mg of rilpivirine as the active substance. The active substance concentration is 300 mg/ml in both presentations. The product is intended for intramuscular (IM) injection.

Other ingredients are: poloxamer 338, citric acid monohydrate, glucose monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide (to adjust pH and ensure isotonicity) and water for injections.

Both strengths of Rekambys are packaged in clear 4-ml Type I glass vial, with a butyl elastomer stopper and an aluminium overseal with a plastic flip-off button, 1 syringe (0.2 ml graduation), 1 vial adaptor and 1 needle for injection (23 gauge, 1½ inch).

### 2.2.2. Active Substance

#### *General information*

The chemical name of rilpivirine is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl] amino]benzonitrile corresponding to the molecular formula $C_{22}H_{18}N_6$. It has a relative molecular mass of 366.43 and its structure is given in Figure 1:

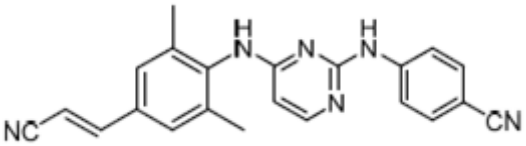



***Figure 1: Rilpivirine active substance structure.***

The chemical structure of rilpivirine was elucidated by a combination of high-resolution MS, IR and NMR spectroscopy. The solid state properties of the active substance were fully characterised by IR, XRD, DSC, TGA, and dynamic vapor sorption (DVS). IR spectroscopy and XRD were able to discriminate between the two polymorphic forms. DVS studies show that both Form I and Form II are not hygroscopic.

Rilpivirine appears as a white to slightly yellow crystalline non-hygroscopic powder. It is practically insoluble in aqueous media over a wide range of pH values. Its pKa is 5.6 (basic pyrimidine moiety) and its LogP>4.16.

Rilpivirine exhibits polymorphism. The active substance manufacturing process is designed to consistently yield the same polymorphic form. This form was observed in all active substance batches manufactured to date using the intended commercial synthetic process. Rilpivirine is an achiral molecule, with the E configuration for the cyanoethenyl double bond.

## *Manufacture, characterisation and process controls*

Rilpivirine is manufactured at four manufacturing sites, each responsible for different steps of the process.

Rilpivirine is manufactured in 8 steps, though a series of organic synthesis reactions, purification processes and irradiation. The proposed starting materials are acceptable and appropriate in-process controls have been put in place to assure active substance quality.

The manufacturing process steps 1 to 5 concern the synthesis of the intermediate R314585 'milled' (rilpivirine hydrochloride), which is the active substance of the approved commercial Edurant® tablets. Subsequently, rilpivirine hydrochloride (intermediate) is converted into free base, micronised and sterilised by gamma radiation. The specifications for the solvents and reagents, catalysts, and processing aids used in the active substance synthesis were provided and are acceptable. No solvent, reagent, catalyst or processing aid is used after step 6 of the process. No class 1 solvents have been used in the synthesis.

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.

The control strategy for the active substance is built upon the approved control strategy of the approved commercial manufacturing process for rilpivirine hydrochloride (R314585, TMC278) as described in the approved Edurant dossier. A criticality assessment of quality attributes is performed to define CQAs and non-CQAs (nCQA) in line with ICH Q8 and Q9 as well identify CPPs and critical to quality attributes of isolated intermediates (CQA of INT) and thereby propose a risk-based control strategy. A detailed discussion for the control strategy for Steps 6 to 8 was also provided including the Critical Quality Attributes (CQAs), the identification of the critical process steps and corresponding Critical Process Parameters (CPPs), and the selected Critical Control Points (CCPs) for each of the CQAs. The overall control strategy (including in-process controls, testing of starting material, monitoring of process parameters) and the risk mitigation measures are adequate to control the process leading to an active substance of consistent quality.

Based on the tests conducted, it was concluded that terminal sterilisation was not a viable option for the finished product. Therefore, an aseptic finished product manufacturing process was developed using active substance sterilised by gamma irradiation. Validation of the sterilisation step has been successfully completed on 3 consecutive full-scale batches at the commercial facilities. The validation batches were tested with the validated analytical methods and the release results, and the results

showed that all validation batches met the proposed specification limits. The validation report of the sterilisation method by gamma irradiation has been provided. The manufacturing process is considered appropriate, reproducible and validated.

The active substance is packaged in double, antistatic, low-density polyethylene (LDPE) bags (i.e., an inner and an outer bag); both the inner and the outer bag are appropriately closed and placed in a heat-sealed aluminium bag containing an oxygen scavenger. The primary packaging material (LPDE bags) is common for solid substances and complies with EU food legislation European Regulation 10/2011/EC.

The applicant discussed the suitability of the container closure system and package integrity. Upon irradiation, the active substance is stored into containers equipped with a rapid transfer port (RTP) for transferring the sterile substance to the finished product compounding isolator. Transport validation study, integrity test of the RTP container and container closure integrity tests were conducted to ensure that the sterility of the active substance is maintained during storage, transportation, physical and temperature stress.

## *Specification*

Rilpivirine active substance specification includes appropriate tests and limits for appearance (visual), identification (IR, UHPLC), assay (UHPLC), chromatographic purity (UHPLC), residue on ignition (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The specifications have been established in accordance with ICH Q6A and are acceptable.

The presence of mutagenic impurities in the active substance was assessed on the basis of the mechanistic understanding, and process capability to identify which pre-starting materials, reagents and by-products may be expected to be carried through as impurities to the active substance above the threshold of toxicological concern (TTC)-based allowable limit. In line with the ICH M7 guideline, mutagenicity assessment was performed for the potential impurities as well as for the active substance, starting materials, and intermediates.

No Class 1 or 3 compounds were found. All other structures were Class 5 and therefore controlled as non-mutagenic impurities. The level of identified Class 2 compounds in five active substance batches were consistently below 30 % of TTC, therefore, it has been concluded that they do not need to be controlled in the final active substance. Particle size distribution (PSD) and residual solvents are controlled on relevant intermediates and are not included in the active substance specification; this is acceptable.

A risk assessment was submitted on elemental impurities as per ICH Q3D, in which it was concluded that none of the elemental impurities assessed are expected to exceed the control threshold. Therefore, no control test is required in the active substance specification.

A risk evaluation concerning the presence of nitrosamine impurities in the product has been performed as requested. All the possible root causes as mentioned in the document "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) were taken into account. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product.

The analytical procedures have been sufficiently described. Non-compendial analytical methods have been successful validated according to ICH Q2 guidance. Satisfactory information and certificates of analysis of reference standards of active substance and its impurities have been presented.

Batch analysis data on ten commercial scale batches of rilpivirine, manufactured according to the commercial process by the proposed commercial manufacturing sites have been provided. In addition, the applicant provided batch analysis on 36 batches, various batch size, produced with previous synthetic methods, used for toxicology, clinical, development and stability studies. Overall, the results demonstrate that the active substance can be manufactured consistently and meeting the specification limits.

### *Stability*

Stability data on three production scale batches of active substance manufactured at the commercial sites and stored in the intended commercial packaging for up to 24 months under long term conditions 25°C / 60% RH and intermediate conditions 30°C / 75% RH and for up to 6 months under accelerated conditions 40°C / 75% RH, were provided according to the ICH guidelines. Samples were tested as per the release specification and in addition water content plus specified impurity. The methods of the additional two parameters have been provided in section 3.2.S.7.3 and are considered validated.

No trends can be observed in any of the provided stability batches; however, a slight increase of two impurities was observed under light exposure, which however remained within the specification and below 30% of TTC.

Photostability studies were performed on one production scale batch in line with ICH Option 2 and the results obtained indicate that the active substance is slightly sensitive to light resulting in the conversion of the active to its z-isomer.

Forced degradation studies were performed on one batch in order to demonstrate that the UHPLC method for related substances is stability indicating. The active substance was exposed to the following stress conditions: acidic, alkaline, thermal (dry heat and humid heat), oxidative stress, exposure to water, metal ions and exposure to light. The results indicated a minor degradation observed only under light exposure. Additionally, under alkaline conditions the hydrolysis of the nitrile group was observed which resulted in formation of a couple of impurities. On the basis of the results provided, the applicant concluded that the proposed UHPLC method for assay and related substances is stability indicating.

Considering the overall stability data, the proposed re-test period of 24 months for the active substance, when the active substance is packaged in the original package in order to protect from light and to maintain sterility, is acceptable.

## 2.2.3. Finished Medicinal Product

### *Description of the product and pharmaceutical development*

The finished product is an extended release suspension for injection containing 300-mg/ml micronised irradiated rilpivirine. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The product is intended for intramuscular (IM) injection. Two different strengths, 600 mg and 900 mg are obtained by filling in 4 ml glass vials to a fill volume allowing an extractable volume of 2.0 ml and 3.0 ml respectively. The vials are closed with rubber injection stopper and sealed with an aluminium cap.

The quality target product profile (QTPP) was defined and presented.

*Formulation development*
Rilpivirine free base was selected as active substance due to its low solubility. Therefore, the optimal form to meet the extended release target profile is an aqueous nanosuspension for intramuscular injection. The product is a nanosuspension for intramuscular injection and has a target pH of 7.0. Rilpivirine is practically insoluble in aqueous media. It exhibits good chemical stability in the solid state and in aqueous solution when protected from strong basic conditions. The robustness of the finished product milling step has been investigated with regard to the impact of particle size distribution of the active substance used. The particle morphology remains consistent at release and at the proposed shelf life of 24 months; thus, no control on morphology is necessary. This conclusion was supported by experimental data and is accepted.

With the exception Poloxamer 338, all other excipients are widely used materials in pharmaceutical formulation and in injectable formulations in particular, and are described in Ph. Eur. The selection of surfactant and determination of the minimal amount of Poloxamer 338 in formulation was justified. Overall the choice and function of excipients was duly justified. The compatibility between the active substance and the excipients was confirmed during long-term stability studies for clinical batches performed up to 36 months. The finished product remained physically and chemically stable when stored at 5 °C indicating a satisfactory compatibility between active substance and selected excipients.

Poloxamers, including Poloxamer 338, are described in the Ph. Eur. Whereas other poloxamers are occasionally used in formulations, including parenteral preparations, Poloxamer 338 has not been used before in parenteral preparations. Poloxamer 338 is therefore considered a novel excipient and full information has been provided in the dossier in line with the guidelines and summarised below.

The formulation development was satisfactorily described. The optimisation of the formulation was achieved with regard to physicochemical and pharmaceutical properties of the finished product.

The dissolution method used for the routine analysis of Rekambys was clearly presented and its development is considered appropriate. The discriminatory for batches with different particles size distribution is demonstrated. The biorelevance of the *in vitro* release method was examined by conducting an IVIVC study (TMC278-LAHTX-1002). In this study the effect of particle size on the *in vitro* and *in vivo* pharmacokinetics and the association between the *in vitro* release rate and *in vivo* pharmacokinetic behaviour were confirmed.

The development of the finished product manufacturing process has been described in sufficient detail. The manufacturing process was developed at a development site where the clinical supplies for phase 1 and phase 2 trials were manufactured. It was subsequently transferred to and scaled up at the commercial manufacturing site, where the batches for phase 3 clinical trials; primary stability and process validation were manufactured. The manufacturing equipment used for the different process steps of all the phase 3 clinical, primary stability and process validation/commercial batches was presented. A comparative table with development batch results and the commercial process validation batches manufactured at the commercial manufacturing site was provided.

The manufacturing process is aseptic. The justification for the aseptic manufacturing of the finished product using sterile active substance as input for the process is acceptable from the regulatory point of view since terminal steam sterilisation and gamma irradiation were shown to be not appropriate for the finished product and the particle size of the finished product suspension does not allow sterile filtration. Therefore, in line with the "Annex to Note for Guidance on Development Pharmaceutics – Decision Trees for the Selection of Sterilisation Methods (CPMP/QWP/054/98 Corr)" and Draft Guideline on the Sterilisation of the medicinal product, active substance, excipient and primary container

(EMA/CHMP/CVMP/QWP/BWP/850374/2015), the finished product needs to be manufactured through aseptic processing using sterile active substance as input for the process.

Elements of Quality by Design (QbD) such as the definition of a target product profile (QTPP) and associated finished product critical quality attributes (CQA), and risk-based approaches were utilised to help guide formulation and process development and develop a control strategy.

The applicant has developed a science-based criticality analysis approach, in line with ICH Q9, to determine the critical controls for the DP manufacturing process. An overview of the Criticality Analysis for the Finished product Manufacturing Process is provided. The critical quality attributes (CQAs) are derived from the Quality Target Product Profile (QTPP) and patient impact (safety, efficacy, and therapy compliance). The possible variables during various stages involved in manufacturing process were identified and the effect of the critical variables on the performance of the formulation were stated. The identified critical process parameters (CPPs) and the critical material attributes (CMAs) of the AS or excipients or a critical in-process control were evaluated against the risk of CQA failure. To obtain proven acceptable ranges (PARs) on the commercial equipment, process characterisation batches were manufactured and filled into vials at the commercial manufacturing site. Other elements of the control strategy include the manufacturing process design, finished DP release testing, and a compliant GMP quality system. Based on the outcome of this evaluation an acceptable risk-based control strategy is proposed.

Compatibility of the finished product with administration devices was satisfactorily demonstrated through the performance of in-use finished product–device compatibility studies where one batch was tested at beginning of shelf life and the second after 24 months storage at 5ºC. The results obtained are provided showing that the finished product batch at the beginning of shelf life remains physically and chemically stable in contact with the devices during in-use handling according to the instruction for use (IFU) in SmPC, i.e. that prior to administration, the vial should be brought to room temperature (not to exceed 25°C); that the vial may remain in the carton at room temperature for up to a maximum of 6 hours and that once in the syringe, the injection should be administered as soon as possible, but may remain in the syringe for up to a maximum of 2 hours (SmPC 6.3).

The finished product data generated to date demonstrate that batches consistently meet the sterility and bacterial endotoxins acceptance criteria at release and during stability studies. The control of sterility and bacterial endotoxins at finished product release and stability is acceptable.

The container closure system for Rekambys is standard for injectable formulations. It consists of a 4 ml clear Type I glass vial with a rubber injection stopper and aluminium seal. The aluminium seal does not come into contact with the dosage form. Suitable specifications and typical IR spectra for the rubber and coating of the stopper were presented and are in accordance with the general Ph. Eur. monographs. The sterilisation of the rubber stoppers and sterilisation/depyrogenation of the glass vials meet Ph. Eur. requirements.

The suitability of the selected material as container closure system was adequately confirmed by the stability studies, container closure integrity and extractable / leachable testing.

*Medical device*

The following CE marked medical device constituents are supplied in the medical kit:

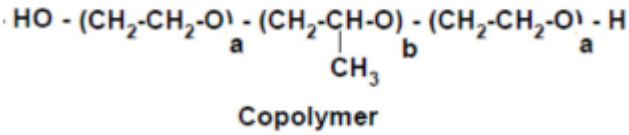
- One vial adapter
- One 23-Gauge x 1 ½-inch safety needle for intramuscular injection
- One 5-mL plastic syringe

These device constituents are commercially available devices and are provided in the medicinal product kit as pre-sterilised, individually pre-packaged items (supplied as such by their respective manufacturers).

Aspects related with manufacturers, CE mark, description, components in contact with finished product, design verification studies, functionality testing over time and risk management plan have been presented in the documentation and are found to be acceptable.

***Novel Excipient Poloxamer 338***

Poloxamer 338 has the chemical structure shown in Figure 2.




** "a" is 141 and "b" is 44.*

***Figure 2. Chemical structure of poloxamer 338***

The manufacturer of the novel excipient was stated.
Sufficient information has provided on the characteristics and the synthesis of poloxamer. The starting materials, catalysts and reagents used in the synthesis of poloxamer 338 were listed and the respective specifications are satisfactory. The maximum batch size has been defined.
The specification of Poloxamer 338 is considered acceptable.

Potential impurities and residual solvents were sufficiently discussed. Methods descriptions and brief information on validation was presented. USP reference standards are used.

Batch analytical data for 3 batches is provided. The parameters tested comply with the specification.

Poloxamer 338 is packaged into strong fibre or polyethylene drums. Each drum is lined with a single or a double polyethylene bag. All surfaces in contact with the products meet the requirements of the Ph. Eur. 3.1.3 for Polyolefins and/or FDA requirements.

Stability data of several batches is provided. The batches are stored in line with ICH stability conditions up to 36 months long term and 6 months accelerated, and tested for appearance, hydroxyl number, pH, and Molecular weight. No trends of significant changes are observed except for an out of specification result which was sufficiently explained. The proposed retest period of 36 months stored in tight containers is accepted.

## *Manufacture of the product and process controls*

The manufacturer of the finished product was stated. The finished product is aseptically manufactured through 12 steps and aseptically filled into glass vials. The commercial batch size has been clearly stated. The bulk solution may be used for filling vials of both strengths which is acceptable. Due to the aseptic processing step, the manufacturing process is regarded to be a non-standard process.

The critical steps of the finished product manufacturing process were defined. Considering this is an aseptic manufacturing process, the identified critical steps are considered acceptable. The acceptance criteria for bioburden prior to filtration is stated in accordance with the Note for Guidance on Manufacture of the Finished Dosage Form (NMT 10 CFU/100 ml).

No design spaces are claimed for the manufacturing process of the finished product.

The provided validation data on three commercial scale batches size showed good reproducibility with all presented data matching the specifications and in compliance with results obtained from finished product release testing. These imply that the manufacturing process is adequately controlled, reproducible and robust. Facility and equipment's validation reports for the aseptic process were provided.

Overall, the process for the manufacturing of Rekambys is described with appropriate details and process parameters and in-process controls as well as proposed holding times are supported by development studies and process validation.

## *Product specification*

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), resuspendability (visual), injectability (visual), identification (FT-IR UHPLC), assay (UHPLC), chromatographic purity (UHPLC), assay of T002592 (UHPLC), particulate matter (light obscuration), pH of solution (Ph. Eur.), particle size (laser diffraction), extractable volume (Ph. Eur.), *in vitro* release (paddle apparatus, UPLC/UV), uniformity of dosage units (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

Degradation product limits are in line with ICHQ6A and ICH Q3B and specified degradation products have been toxicologically qualified. Limits for genotoxic impurities were set based on the TTC concept of ICH M7 and are acceptable. Particle size and *in vitro* release limits were based on pivotal clinical batches and stability results. All other proposed limits are in line with Ph. Eur. and are considered appropriate to ensure the quality and performance of the product.

A risk evaluation concerning the presence of nitrosamine impurities in the product has been performed as requested. All the possible root causes as mentioned in the document "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) were taken into account. No risk was identified for the possible presence of nitrosamine impurities in the active substance or the related finished products. This can be accepted, based on the information provided by the applicant.

Based on the risk-based assessment as per the ICH Q3D guideline, testing of the finished product formulation for elemental impurities is not necessary as levels of elemental impurities from various sources are not expected to exceed the permitted daily exposure 30% threshold levels.

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 was provided for four commercial scale batches and six development batches. The data demonstrate that all parameters are well within their specifications and therefore indicate consistent manufacture of the finished product.

## *Stability of the product*

Stability data from six pilot scale batches of finished product (three of each strength) manufactured at the commercial site and stored for up to 24 months under long term conditions (5 ± 3ºC) and for up to 6 months under accelerated conditions (25 ± 2°C / 60 ± 5% RH) according to the ICH guidelines were provided. Stability samples were packaged in the commercial container closure system and were stored in upright and inverted position.

Samples were tested for appearance, resuspendability, injectability, assay, chromatographic purity assay of impurities, pH, *in vitro* release, sterility and particle size. The test methods used for primary stability testing are the same as for release, except for slightly different test methods for assay of active, chromatographic purity (HPLC) and particle size at early time points. The changes in test methods is justified by cross validation/comparability. No significant changes are observed for the tested parameters when the finished product is stored at long term condition 5°C through 24 months and at accelerated condition 25°C / 60%RH through 6 months and at light ICH unprotected condition. An increasing trend in particle size and a decrease in *in vitro* release was observed. At accelerated conditions, some out of specification results for *in vitro* release were observed. Nevertheless, the he finished product particle size and *in vitro* release remain within the proposed commercial specifications at the long-term condition 5°C (the commercial storage condition) for at least 24 months.
A photostability study in compliance with ICH Q1B has been completed and the results were provided. Although slightly higher results of one specified impurity and total degradation products were observed results are well within the specification limits.
Additional stability studies included, freeze/thaw cycling which showed a significant increase in particle size. Therefore, the product should not be frozen (SmPC 6.4).

Forced degradation studies under stress conditions were performed on a pilot batch under thermal stress, thermal acidic, thermal alkaline, oxidative, metal ions and neutral conditions. The proposed method for assay and chromatographic purity of the finished product was shown to be stability indicating.

Based on the overall stability data the proposed shelf-life of 2 years when stored in a refrigerator (2 - 8°C), as described in SmPC sections 6.3 and 6.4, can be accepted.

### *Adventitious agents*

None of the materials used for the manufacture of the drug product is of human or animal origin.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The manufacturing process for the finished product is non-standard and the required validation data has been provided. 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. Pharmacology

The Applicant provided sufficient Rilpivirine (RPV) data related to primary and secondary pharmacodynamics, safety pharmacology and PD drug interactions, showing that RPV has a high (*in vitro*) anti-viral activity against a wide range of HIV-1 variants without considerable cytotoxicity or off-target effects, nor clinically relevant safety issues with core vital systems. Anti-viral activity is retained for viral variants that typically emerged after failing EFV- or NVP-containing regimens. In addition, no antagonism was found when RPV was studied in combination with other anti-retroviral agents.

The provided data were originating from reports present in the Edurant dossier. Therefore, all reports (except for Report S-265744-EB-013-N, which contained a study mainly focussing on the activity of cabotegravir in combination with other anti-viral agents such as RPV) have been assessed previously. Considering similar patient exposures after (repeated) administration of oral RPV and IM RPV LA, the pharmacological profile of RPV LA is comparable to the approved oral RPV (Edurant). Thus, for the complete pharmacology profile of RPV is referred to the EPAR and the SmPC for Edurant and no additional non-clinical pharmacology studies with RPV LA are requested for the current application.

RPV is intended to be used in combination with cabotegravir. One *in vitro* study to test the anti-viral activity of cabotegravir in combination with other anti-viral drugs was provided, showing that RPV was additive with cabotegravir.

### 2.3.2. Pharmacokinetics

RPV is already available for oral administration, which has been approved as Edurant. For the authorisation of Edurant pharmacokinetic studies of RPV on distribution, metabolism and excretion were performed. These studies are not being re-assessed in this report. Where applicable, text from the EPAR of Edurant has been copied in the current assessment. Pharmacokinetic and toxicokinetic studies specifically performed with the final clinical formulation G001 containing 300 mg RPV base/mL suspension and poloxamer 338, are discussed below.

Methods of analysis

For the detection of rilpivirine, two radiolabeled ($^{14}C$ and $^{3}H$) RPV compounds were used. Tissue distribution was studied by quantitative whole-body autoradiography (QWBA) in male pigmented rats and pregnant female Sprague-Dawley rats. The concentration of radioactivity in the different tissues and biological fluids was determined by radioluminography or liquid scintillation counting. Metabolite profiles were determined by radio-high performance liquid chromatography (HPLC) and metabolite identification was done by a combination of liquid chromatography with tandem mass spectrometry (LC-MS/MS). RPV in plasma was determined by validated LC-MS/MS methods (heparin and EDTA plasma). These methods were also used and reviewed for the registration of Edurant and are therefore considered adequate.

For RPV LA development, in addition, an LC-MS/MS method was validated for the determination of RPV in minipigs (EDTA plasma). The method consisted of protein precipitation, followed by reversed phase HPLC coupled to tandem mass spectrometry. The method is considered adequate and had a validated range of 1 - 2000 ng/ml.

For Poloxamer 388, an LC-MS/MS method was validated for determination in rat and rabbit EDTA plasma. The assay consisted of a protein precipitation step followed by reversed phase HPLC coupled to tandem mass spectrometry. The acceptance criteria for this assay were expanded by 5% due to the complexity of this analyte. This is considered acceptable. LLOQ was 1 µg/ml.

Absorption

With regard to the long acting form of rilpivirine, several single-dose absorption studies were performed in rabbits and minipigs, mainly comparing different formulations. None of these studies was performed under GLP conditions.

Following a single IM administration of the final P338–containing formulation (G001), the initial release of RPV was quick, with Cmax reached within 24 hours in both species. However, it is noted that high inter-individual variability was observed. After the peak, plasma levels gradually declined during 2 days, after which plasma concentrations fluctuated until the end of the study in minipigs or until day 9-14 in rabbits, followed by a gradual decline.

IV studies were performed with RPV in 20% captisol in minipigs and RPV in PEG400/water in rabbits. Volume of distribution (Vdss) was large (4.9 L/kg) in minipigs, but very low in rabbits (0.32). Observed total clearance was low compared to hepatic blood flow in both species (753 ml/h/kg in minipigs and 0.03 ml/h/kg in rabbits). Half-life was 8-12 hours. Absolute bioavailability at 3 months after IM administration was 67% in rabbits and 35-62% in minipigs.

Repeated dose pharmacokinetic studies with the final clinical formulation G001 were performed in dogs (dosed on day 1 and day 15) and minipigs (every 2 weeks for 6 weeks or once per month for 9 months). In dogs, systemic exposure to RPV increased generally in a sub-proportional manner in males and females. In minipigs, only 1 dose level was administered. No accumulation was observed in females (1.6x), but in males exposure was up to 2.8 times higher after repeated dosing. In general, exposure was slightly higher in females than in males after the first dose, but not after repeated dosing.

Distribution

Based on the data from the Edurant submission, it was concluded that binding of rilpivirine to human, monkey, dog, rat, rabbit and mouse plasma proteins is high in all species (>99%) and is concentration-independent. Rilpivirine was highly bound to human albumin (99.5%) and to lesser extent to α1-acid glycoprotein (25-55%). In human plasma, the protein binding of rilpivirine appeared to be pH-dependent. The distribution of rilpivirine to red blood cells is limited in all species.

Additional studies with the final clinical formulation G001 were performed. Following a single IM dose of RVP in rats, two distinct concentration peaks were observed (between 4 and 24 h, and between 120 and 216 h). Subsequently, a slow first-order decline in plasma concentrations was observed. Blood to plasma concentration ratios (Cb:p) ranged from 0.34 to 0.66. Highest tissue concentrations were observed in kidney, adrenal gland, lung, pancreas and liver (tissue plasma ratios between 1.2 and 3.7). T1/2 plasma values ranged from 377 to 1089 h in rats. Also, in rabbits two concentration peaks were observed (<24h and between 3 and 9-14 days).

Absorption of radioactivity was rapid with the highest levels of radioactivity in all tissues at 4 h post-dose, except the uveal tract (24 h post-dose). This is in line with the high volume of distribution of rilpivirine and limited clearance. The highest tissue concentrations of radioactivity were observed in the uveal tract, liver and adrenal gland. There appeared to be binding to melanin in the pigmented parts of the eye, meninges, skin and uveal tract. Although the concentrations in these tissues are low, accumulation is expected since radioactivity is still present 14 days post-dose.

For the Edurant submission, it was shown that rilpivirine-related material crosses the placenta barrier in rats. The AUC0-8h for total radioactivity in the whole fetus was 0.64 times that in maternal blood. Placental transfer in humans is expected based on these results in rat. Concentrations of rilpivirine were quantifiable in blood samples from rat pups, demonstrating that pups were exposed to rilpivirine via the milk.

Metabolism

No studies were performed with the final clinical formulation G001, or the i.m. administration route. The following is based on the EPAR from Edurant. Rilpivirine is metabolised via Phase I and Phase II reactions and a large number of metabolites were detected in all species. The most important pathway is oxidation and hydroxylation and to a minor extent conjugation with glutathione and glucuronide. Overall, identified metabolites that were detected in human matrices were also detected in at least one animal species. However, a unique metabolite (M15) formed by N glucuronidation of rilpivirine, was observed in human plasma (8.7%) and faeces (0.6%). This metabolite is expected to be inactive and non-toxic due to the glucuronidation.

Rilpivirine metabolism, as well as the formation of all its metabolites, was mainly catalysed by CYP3A4. CYP1A1, CYP1A2, CYP1B1, CYP2C8/9/10, CYP2C18, CYP2C19, and CYP3A5 are also involved, but to a lesser extent. Also, CYP3A7 is involved in the metabolism of rilpivirine.

Reactive intermediate(s) of rilpivirine formed by phase I enzymes were scavenged by glutathione. Conjugation with glutathione was more dependent on the mu than the pi isoform of GST, although both isoforms were involved. GST mu and GST pi are subjected to genetic polymorphisms, leading to an absence or decreased isozyme activity. Thus, genetic polymorphisms of GST could influence the pharmacokinetics of rilpivirine in humans. However, conjugation with glutathione was a minor biotransformation route and therefore it is unlikely that GST will influence the pharmacokinetics of rilpivirine in humans.

*In vitro* and *in vivo* data indicate that gender differences might be present for the biotransformation of rilpivirine. In addition, interspecies differences in metabolism were observed both in vitro and *in vivo* (e.g. in rats the glutathione conjugation pathway was the predominant pathway whereas in dog and man, oxidation of RPV was the predominant one).

*In vitro* studies showed that RPV might be a very weak inducer of CYP1A2 and CYP2B6, and a moderate inducer of CYP2C19 and CYP3A4 in human hepatocytes. No conclusion could be drawn for CYP2E1 or GST.

*Ex vivo* studies in mice, rats and dogs were performed to examine the effect of RPV on hepatic enzyme activities. In mice and rats, RPV was an inducer of CYP4A forms, CYP3A forms and UDP-GT activity and in female rats also of CYP2B. In addition, RPV decreased GST activity in male mice, whereas in female rats an induction of GST activity was observed at high doses. In dogs, no clear effects were observed on CYP enzymes, UDP-GT or GST activity.

Incubations with P450 probe substrates in HLM showed that RPV was a potent inhibitor of CYP2C19 (70% inhibition) and CYP2E1 (86% inhibition), however, this could not be confirmed by subsequent studies. Although RPV is also an inhibitor of CYP2C8 and CYP2C9, this is not of clinical relevance, considering the human Cmax of RPV.

Excretion

No studies were performed with the final clinical formulation G001, or the i.m. administration route. The following is based on the EPAR from Edurant. The predominant route of elimination of radioactivity in all species following oral administration was via faeces (>85%), with a small contribution eliminated in urine (<6.2%). The majority of the eliminated radioactivity is unchanged rilpivirine (25-47% of the dose). In rats, biliary excretion is limited (18-25%).

Pharmacokinetic drug interactions

At therapeutic levels of rilpivirine, rilpivirine may inhibit the metabolism of clarithromycin (CYP3A4), sildenafil (CYP3A4), S-mephenytoin (CYP2C19) and norethindron (CYP2C19), but also, although less likely, the metabolism of sertraline (multiple CYPS, MAO, UGT), paroxetine (CYP2D6) and 17α ethinyloestradiol (Phase II metabolism).

The Pharmacokinetic Drug-Drug Interactions (DDI) of a.o. the combination of RPV LA with CAB LA will be assessed in the clinical AR.

Other pharmacokinetic studies

Several studies are performed with formulations other than the final clinical G001 Rilpivirine LA formulation. Since these studies are considered of less relevance for the pharmacokinetics of the final clinical formulation, they are not reviewed in depth. It is however noticed that, also with these formulations, the overall RPV exposure was slightly higher in female mice than in males. Mean Cmax values of RPV were higher after IM than after SC administration, but mean AUC0-day56 values were comparable. In addition, injection site-to-plasma ratios were higher with formulations of RPV LA in P338 compared to other solutions.

Several *in vitro* or *in vivo* studies were performed with T2592, the genotoxic impurity of RPV. *In vitro* studies in rat and human hepatocytes and subcellular liver fractions showed that oxidation and direct sulfate conjugation are the main metabolising steps, resulting in the release of thiocyanate. In rats administered a single IM injection of RPV LA with spiked levels of T2592, it was shown that T2592 is quickly metabolized to the sulfate metabolite and excreted via urine. It can thus be concluded that T2592 is rapidly metabolically cleared in the rat and most likely also in human.

Pharmacokinetics or toxicokinetics of P338 were examined in rats, rabbits and minipigs. Oral administration of P338 in female rats and rabbits at 1600 mg/kg did not result in measurable plasma concentrations in rats. In rabbits, concentrations were quantifiable up to 36h. In minipigs, a single IM administration of RPV LA (G001) at 600 mg (corresponding P338 dose 100 mg) resulted in peak plasma levels at 24-72h (compared to 48-72h in humans). The decrease in plasma concentration was mono-phasic. In male rats injected IM with P338, Cmax was reached more quickly (7h), followed by slow elimination. P338 was distributed to kidneys (kidney/plasma AUC0-529 h ratio: 1.1-fold), and to liver (liver/plasma AUC0-529 h ratio: 5-fold). Toxicokinetic studies were performed in rats and rabbits. Exposure of P338 increased less than dose-proportional to close to dose-proportional. No relevant accumulation occurred following repeated dosing and no relevant gender differences were observed.

## 2.3.3. Toxicology

For the authorisation of Edurant, the oral form of RPV has been examined in single and repeat-dose toxicity studies, genotoxicity, carcinogenicity, fertility, reproductive and embryo-fetal development, and pre-and postnatal development studies. These studies will not be re-assessed in this report. The main toxicology findings from Edurant are described in the following paragraph, as these findings are also applicable to the long-acting form of RPV (RPV-LA).

Liver toxicity associated with liver enzyme induction was observed in rodents. In dogs, cholestasis-like effects were noted. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily). In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. Rilpivirine has tested negative in the absence and presence of a metabolic activation system in the in vitro Ames reverse mutation assay and the in vitro clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

Studies specifically performed with the long-acting form of RPV (RPV-LA) include bridging toxicity and local tolerance studies, and studies performed with the excipient poloxamer 338 (P338). These studies are further described below.

A 4-week bridging repeat-dose toxicity study was performed in dogs with RPV-LA IM administration. Besides local swelling and edema in 1 low dose animal and all high dose animals at the injection site, no additional target organ toxicities were identified compared to studies with oral RPV administration. Increases seen in progesterone and 17α-hydroxyprogesterone are consistent with the known toxicity profile of RPV. The highest dose level of IM administration (1200 mg/injection, margin-of-exposure (MOE): 5) gave a systemic exposure similar to that obtained with the low dose level of oral administration (5 mg/kg/day, MOE: 6). In addition to the bridging repeat-dose toxicity study in dogs, 2 repeat-dose studies in minipigs were performed to mainly assess local tolerability of RPV-LA. Animals were treated with 600mg/injection IM every 2 weeks or once monthly in a 6-week and a 9-month study, respectively. Findings were mainly limited to the injection site and included erythema/edema and white eosinophilic deposits at the injection site. In addition, regional lymph nodes were swollen and were infiltrated with macrophages. In both species, RPV-LA via IM injection caused injection site reactions. This is also seen in the clinical data, and therefore a known side effect in humans. No systemic treatment-related toxicity was observed in minipigs; however, exposure margins were low (MOE: 0.5-0.6).

RPV base in different vehicle suspensions classified as a non-eye irritant in an in vitro Hen's egg chorioallantoic membrane (HET-CAM) test. After dermal application or SC injection administration, RPV base was a non-skin sensitizer in a mouse local lymph node assay. Acute local irritation of RPV base after IM and SC injection was assessed in rabbits and minipigs with different formulations, including the clinical formulation G001. Acute inflammatory responses were observed at the injection site, which were also observed in the bridging repeat-dose toxicity studies in dogs and minipigs.

The amount of N-Methylpyrrolidone (NMP) as a residual solvent in the RPV LA drug product is acceptable according to ICH Q3C (R7). Levels of other impurities (e.g. R600682 and R600683) have already been assessed during the authorisation of Edurant.

Genotoxicity and fertility, embryofetal development and pre- and postnatal development studies have been conducted with poloxamer 338 (P338), the excipient used in the final clinical formulation G001. P338 was also included as a vehicle in the 6-week and 9- month minipig repeat-dose toxicity studies. Increases in C-reactive protein (CRP) were seen in P338 as well as RPV-LA treated groups within 24 hours of injection but returned to baseline within 3 days. No other systemic or local toxicity related to P338 were observed in minipigs at 100mg/month (MOE: 19).

P338 demonstrated no genotoxic potential in in vitro mammalian and non-mammalian test systems. After IM administration, no effects on male and female fertility of rats, and embryofetal development in rats and rabbits were observed (rats up to 10mg/kg, MOE: 9-18; rabbits up to 5 mg/kg, MOE: 9). In a peri- and postnatal development study in rats, no effects of P338 on F0 females and F1 generation were observed with sufficient exposure levels (up to 10mg/kg, MOE: 12).

No combination repeat-dose toxicity studies with rilpivirine and cabotegravir have been conducted as the applicant did not expect any synergistic or additive toxicities. A single dose rat IM and a single dose monkey IM combination study showed no adverse effects of co-administration.

## 2.3.4. Ecotoxicity/environmental risk assessment

This medicinal product contains a known active substance (rilpivirine) and relates a new dosage, new pharmaceutical form and new route of administration. It is indicated in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. The posology comprises an intramuscular prolonged-release injection 30 mg /day (900 mg injection for 1

month). Following administration, unchanged rilpivirine will be predominantly excreted in feces (a mean of 25.5% of the dose). Only trace amounts (<1%) of unchanged substance were detected in urine.

ERA studies were included in the present application. They are in accordance with the CHMP guideline (EMEA/CHMP/SWP/4447/00 corr.1, June 2006).

Rilpivirine is considered not to be PBT, nor vPvB. A risk to the STP, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of rilpivirine.

## 2.3.5. Discussion on non-clinical aspects

The toxicological profile of RPV LA is generally acceptable and there are no major concerns precluding a MA from the non-clinical point of view. Nevertheless, before a final conclusion could be reached, some other concerns regarding the excipient P338, the RMP and ERA needed further addressed by the applicant.

With respect to the excipient:
P338 is considered a known excipient when used orally. However, the Applicant was requested to discuss with (publically) available non-clinical and/or clinical data the carcinogenic potential of P338 after exposure via i.m. injection. In their D120 response, the Applicant referred to the absence of carcinogenicity of poloxamer 188, which is in line with previous scientific advice. However, in the studies referred to by the Applicant, poloxamer 188 was administered orally or subcutaneously, but not intramuscularly. Moreover, the used poloxamer 188 dose was not provided nor discussed in relation to the current poloxamer 338. Therefore, the justification regarding the absence of carcinogenicity of poloxamer 338 after intramuscular administration provided by the Applicant was not considered sufficient. In their D180 response, no further relevant information was provided, since exposure data after short-term SC dosing only was provided, and this was not related to the carcinogenicity doses. Therefore, the applicant was asked to discuss the systemic exposure of P188 after oral dosing at doses relevant for the carcinogenicity studies conducted with P188 and relate this to clinical exposure after IM dosing with P338. The Applicant provided further information that indicated that P338 administered by the IM route at the proposed clinical concentrations is not considered to have carcinogenic potential. Poloxamer 338 is considered non-genotoxic based on a Good Laboratory Practice (GLP) Ames and in vitro mammalian chromosome aberration test. As both assays were negative, there are no indications for any mutagenic effect （Information on Toxicological Data: Lutrol F68. BASF, MEM/QM-D205, November 2000:1-9). This is considered acceptable.

With respect to the Risk Management Plan:
Injection site reactions were observed after IM administration of RPV in both dogs and minipigs. The Applicant was requested to include this finding as a non-clinical key safety finding in the RMP and to discuss the relevance of this finding for humans. In their D120 response, the Applicant added the RPV-LA administration-related local findings in dogs and minipigs and the clinical relevance of these safety findings to the revised RMP.

With respect to the Environmental Risk Assessment:
Regarding the bioconcentration study in fish (OECD 305, Burri, 2009; study nr. B79413, sponsor id: RMD1023, TMC278-TiDP6-NC325), the Applicant was requested to present BCF values that are normalised to a lipid content of 5% as per the ECHA R.11 guidance to which EMA/CHMP/SWP/44609/2010 Rev. 1 refers for PBT assessment, as well as the updated TG OECD 305 (2012). In their D120 response, the Applicant provided BCF values that had been recalculated and normalized to 5% lipid content. The mean BCF values for both dose levels (0.21 µg/L - 1.96 µg/L) were 196 and 169. Thus, the substance does not fulfil the bioaccumulation criterion (B).

### 2.3.6. Conclusion on the non-clinical aspects

RPV-LA was adequately evaluated with PK studies and bridging toxicology studies. The programme revealed no additional target organ toxicities compared to studies with oral RPV administration. In addition, no findings were observed in toxicology studies with excipient poloxamer 338.

## *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.

- **Tabular overview of clinical studies**

The clinical pharmacology characteristics of RPV LA were determined based on studies with the CAB + RPV regimen and studies with RPV LA alone. In addition, studies with oral RPV that determined the clinical pharmacology of RPV, and are relevant for RPV LA, are discussed (in short) where applicable, and study reports are resubmitted with this MAA.

In total 185 healthy subjects were included receiving the RPV LA formulation. In addition, in the CAB + RPV program, 1667 HIV infected subjects received the RPV LA formulation, next to 19 non-infected HIV subjects and 1873 HIV infected subjects received oral treatment (see table below).

**Table 1 Estimated cumulative subject exposure[a] from clinical studies.**

| | Number of Subjects | Exposure (person-years) |
|---|---|---|
| **RPV LA Injectable Nanosuspension Clinical Program (Janssen Conducted Studies)** | | |
| *Non-HIV-infected subjects*[b] | | |
| RPV LA Injectable Nanosuspension (G001) | 185 | - |
| **CAB LA + RPV LA Clinical Program (ViiV Conducted Studies)** | | |
| *HIV-infected subjects*[c] | | |
| RPV LA | 1,667 | 2,296 |
| RPV oral | 1,873 | 903 |
| *Non-HIV-infected subjects*[d] | | |
| RPV LA | 19 | - |

CAB: cabotegravir; LA: long-acting; RPV: rilpivirine.

a. Exposure and person-time were calculated up to the point of the subject's last dose administered or until 20 December 2018 for subjects still on treatment at that time. For injections, exposure can last for up to a year after the last injection.
b. Includes studies TMC278-TiDP15-C158, TMC278LAHTX1001 and TMC278LAHTX1002
c. Includes studies 201584, 201585, 200056, 207966 and LAI116482
d. Study LAI115428

In total,11 studies, including one sub-study of the LATTE-2 study, were submitted to support the clinical program. Next to the 7 studies listed in the table below, 3 Phase I studies in healthy volunteers were submitted, i.e. study TMC278-C158 (single and repeat dose study), study TMC278-LAHTX1001 (single dose study) and study TMC278-LAHTX1002 (single dose study).

**Table 2 Main studies submitted to support the clinical program.**

| Study | Study Design | Population | Treatment Details |
|---|---|---|---|
| 201584 (FLAIR)<br>Status: Ongoing; Week 48 CSR completed<br>LSLV Cut-off date: 30 Aug 2018 | 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 ART-naïve adult subjects | **Induction Phase (20 weeks):** Oral ABC/DTG/3TC FDC (NRTI substitution allowed)<br>**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<br>Control group: oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs)<br>**Extension Phase and beyond:** Details are provided in the CSR. |
| 201585 (ATLAS)<br>Status: Ongoing; Week 48 CSR completed<br>LSLV Cut-off date: 29 May 2018 | 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 ART-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<br>Control group: 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI.<br>**Extension Phase and beyond:** Details are provided in the CSR. |

| Study | Study Design | Population | Treatment Details |
|---|---|---|---|
| LAI115428<br>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):**<br>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<br>**Cohort 3 (4 months):**<br>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<br>Details of the run-in period, and Cohorts 1 and 4 (CAB LA alone) are described in the CSR. |
| LAI116181<br>Status: Completed; CSR completed | Open-label, repeat dose, three-period, single-sequence, Phase 1 drug-drug interaction trial:<br>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 |

## 2.4.2. Pharmacokinetics

Eleven pivotal studies (including 1 sub-study) in healthy subjects and in HIV-1 infected patients were submitted to support the pharmacokinetics of RPV LA formulation. In addition, pharmacokinetic data were included in a population pharmacokinetic analysis. The clinical pharmacology characteristics of RPV LA were determined based on studies with the CAB + RPV regimen and studies with RPV LA alone. Furthermore, studies with oral RPV (MAA Edurant) that determined the clinical pharmacology of RPV, and are relevant for RPV LA, were resubmitted with this MAA.

Analytical methods:

For the analysis of RPV in plasma, the applicant used LC-MS/MS as basic analytical method. The methods proved to be sensitive and robust for analysis of RPV. Validation results showed acceptable performance within the normal standard criteria. In addition, RPV is stable in plasma during a sufficiently long period. Data on incurred sample reanalysis proved that the analytical methods produced reproducible results. Cross-validations have been carried out showing comparable performance of the methods.

Absorption:

A population pharmacokinetic analysis (report 04R3RP) was carried out to describe the release characteristics of RPV after i.m. LA administration. In this analysis, 4 studies with intensive PK sampling (studies TMC278-C158, TMC278LAHTX1001, TMC278LAHTX1002, and LAI115428) were used to develop the reference POPPK model and conduct the covariate analysis. Thereafter data from one Phase II study (LATTE-2 (study 200056)) and 2 Phase III studies (ATLAS (study 201585) and FLAIR (study 201584))

were used for external validation of the POPPK model. This was followed by including the total combined datasets to update the POPPK model parameters.

After absorption from the i.m. injection site, RPV disposition was described by an open, one-compartment model with linear elimination. The population PK model was parameterized in terms of Vc and Kel. The absorption of RPV from the injection site was best described by 2 parallel absorption pathways: a fast absorption route describing the initial RPV peak and a second slow absorption route determining the terminal part of the RPV plasma concentration vs. time curve, reflecting the flip-flop kinetics after i.m. administration.

It was estimated that after i.m. administration of RPV LA, a total of 39.6% of the dose is absorbed fast into the systemic circulation while the remaining 60.4% of the dose is absorbed at a slower rate.

After administration of the LA formulation, tmax values are observed after about 72h. After single and multiple-dose, a comparable relative bioavailability (taking into account the difference in administered dose) was observed with an oral solution and with the commercial IR tablet formulation (Edurant).

Over the single dose range of 300 - 1200 mg AUC28d increased dose-proportional. A less than dose-proportional increase in AUC was observed over the dose range of 600 and 900 mg, when RPV was given as a second injection and in combination with CAB. To be noted, in principle 1 dose scheme is recommended, i.e. after oral administration lead-in period, RPV LA 900 mg should be given after 1 month, followed by monthly 600 mg LA doses, so possible non-linear pharmacokinetics are not considered relevant.

With the dosing regimen used in Phase III studies (i.e., a 900 mg initial injection followed by 600 mg Q4W continuation injections), approximately 80% of the RPV steady-state exposure is reached after 48 weeks (time of Phase III primary endpoint). After that, there is limited further accumulation, with RPV steady-state exposure reached after 2.2 years (79% after 48 weeks, 90% after 1.5 years and 95% after 2 years). No unexpected accumulation is observed after applying the SmPC recommended dose scheme. Steady-state was estimated to be reached after 2.2 years, and the accumulation ratio was estimated to be 4.2 for AUC.

After i.m. LA administration, RPV pharmacokinetics shows a moderate to high inter- or between-subject variability (CV) in AUC, Cmax and Ctrough ranging from 37 - 39%, 36 - 40% and 32 - 77%, depending on the assessed study. Intra-subject variability was not evaluated. As this is an i.m. administration and the popPK analysis did not show clear covariates which may explain a moderate to high inter- or between-subject variability, the rather high variability in pharmacokinetics may not be expected. However, after oral administration of RPV, inter-individual variability in pharmacokinetics (AUC and Cmax) was about 35% and population pharmacokinetic analysis indicated a variability of around 45% for Ctrough and AUCtau. Therefore, it seems that the variability is inherent to RPV pharmacokinetic variability and less to the administration pathway.

Failure in patients' adherent to the monthly injections may be essentially limited to misplaced injections resulting in suboptimal exposures and increased variability in exposure. However, in the ATLAS study, plasma concentrations of CAB and RPV were measured every 4 weeks (in the 4QW LA injection arm) there was no indication of misplaced injections based upon variability, as no increased within-subject variability in Ctrough values over time by gender and BMI (< and > 30 $kg/m^2$) was observed.

In the LATTE-2 study, the applicant evaluated a 4QW and a 8QW dosing scheme. The 4QW dosing scheme is relevant for this application. After administration of oral 25 mg o.d. RPV (with oral CAB) and prior to administration of the LA injections, the RPV Ctrough concentration was 65.1 ng/ml (95% CI 61.1 - 69.4), consistent with previous data for oral RPV in HIV-1 infected subjects (LATTE study).

Week 32 and 48 data indicated that RPV plasma still increased, for AUC from 61309 ng.h/ml to 71106 ng.h/ml, for Cmax from 111 ng/ml to 127 ng/ml and for Ctrough from 77.2 ng/ml to 92.1 ng/ml. Week 72 and 96 Ctrough data indicated still increasing levels (from 97.5 ng/ml to 104 ng/ml).

Twelve months after discontinuation of LA treatment (n=12), RPV concentrations ranged from about 2 to 108 ng/mL, and 6 subjects had RPV concentrations above the PA-IC90 of protein-binding adjusted IC90 of 12 ng/ml. Subjects who received oral treatment (25 mg RPV o.d + 30 mg CAB o.d) for 100 weeks and switching to the SPC recommended i.m. LA dosing regimen showed increased Ctrough levels from 41 ng/ml after 4 weeks first injection to 79 ng/ml at week 128.

The results of study 201585 (ATLAS study) and study 201584 (FLAIR study) were in line with the results of LATTE and LATTE-2. After the oral lead-in period with 25 mg RPV o.d. + 30 mg CAB o.d., 4 weeks after the first injection the Ctrough plasma decreased and steadily increased after subsequent injections. Ctrough RPV concentrations were above the PA-IC90 of protein-binding adjusted IC90 of 12 ng/ml after the oral lead-in, 4 weeks after the first injection and thereafter.

Following discontinuation of the RPV LA Q4W regimen (administered to steady-state), 87% of patients overall were predicted to have quantifiable plasma RPV concentrations (>BQL (1 ng/ml)) 3 year after the last i.m. injection and 5% of patients overall were predicted to have quantifiable plasma RPV concentrations (>BQL (1 ng/ml)) 4 years after the last i.m. injection.

The population estimates of AUC and Ctrough after the oral lead-in dosing are in line with those estimated for Edurant (study 08/TIB/003/1073a).

Based upon the estimated steady-state AUCtau after the oral lead-in, the relative bioavailability of the i.m. LA formulation is about 105%, and comparable Ctrough values are observed.

The 900 mg initial injection prevents that concentrations would drop below the PA-IC90 of protein-binding adjusted IC90 of 12 ng/ml.

These data confirm that Ctrough RPV concentrations were above the PA-IC90 of protein-binding adjusted IC90 of 12 ng/ml after the oral lead-in, 4 weeks after the first injection and thereafter.

The popPK analysis indicated that the estimated GMR of the AUCinf of RPV in Phase I studies, relative to the Phase III studies, was 1.44 with 90% CI of 1.36 - 1.52. This difference could be attributed to the difference in PK between healthy volunteers and HIV infected patients, as also observed for the oral formulations (Edurant dossier), in which a lower exposure was observed in HIV-infected patients compared to healthy volunteers. However, in comparison with Phase II studies, the popPK analysis also indicated a difference of 17.5%, so the difference cannot solely be explained due to a difference between healthy volunteers and patients.

Bioavailability/bioequivalence:

Based upon development LA formulations F004 and F006, showing issues with drug load, stability and/or a lack of a desired pharmacokinetic profile, LA formulation G001 was developed. Formulation G001 which was used in the Phase I, II and III studies and selected as the commercial formulation appeared to have an acceptable tolerability, stability and pharmacokinetic profile.

In the pivotal Phase II and III studies, all LA injections were administered intramuscularly in the gluteal. This is also the SmPC recommended injection site.

The results (study TMC278-TiDP15-C146) for the LA formulation F004 showed that the pharmacokinetic profile was generally comparable when the same dose was given via the IM or SC route. Similarly, the pharmacokinetic profile administered via the IMD route (deltoid muscle) was comparable with the IM (gluteus maximus) administration route, but the time to reach maximum plasma concentration was

slightly longer. The results (study TMC278-TiDP15-C150) for the LA formulation F006 indicated poor tolerability and a suboptimal PK profile resulting in low plasma concentrations.

It appeared that alterations in particle size distribution occur when stored at room temperature. By mimicking altered particle size distribution, results indicate that the LA formulation should not be stored at room temperature, this may result in a 57% decrease in exposure to RPV over 28 days after injection and 43% decreased exposure to RPV over 6 months after injection. Therefore, the LA formulation should be stored at 2°C to 8°C (as per current recommendation).

An IVIVC study (TMC278-LAHTX-1002) was carried out to evaluate the effect of particle size on the in vitro and in vivo pharmacokinetics of RPV. No level A IVIVC could be established, and setting of dissolution specifications based on IVIVC was not possible.

Monthly vs Q4W dosing:

Model-based simulations showed comparable exposures for the Q4W (13 doses/year) and monthly (12 doses/year) dosing. More than 99% of the subject achieved a Ctau of ≥12 ng/ml after the first i.m. dose and the doses thereafter. In addition, more than >95% of subjects achieved a Ctau ≥17.3 ng/ml (the 5th percentile of the observed concentrations 4 weeks after initial IM administration of RPV LA 900 mg) and the doses thereafter. These data support the proposed at least 28 days and/or monthly dose regimen.

Allowable injection window at specific injection visits:

Different scenarios were simulated, i.e.

- an oral lead-in of 25 mg once daily for 4 weeks, followed by a 900 mg initiation injection, two 600 mg RPV doses every 4 weeks, a 600 mg RPV dose 6 weeks (i.e. a 2-week delay in LA dose), thereafter followed by 600 mg Q4W continuation injections;

- an oral lead-in of 25 mg once daily for 4 weeks, followed by a 900 mg initiation injection, two 600 mg RPV doses every 4 weeks, a 900 mg RPV dose 12 weeks (i.e. an 8-week delay in LA dose)), thereafter followed by 600 mg Q4W continuation injections;

- an oral lead-in of 25 mg once daily for 4 weeks, followed by a 900 mg initiation injection, two 600 mg RPV doses every 4 weeks, 4 weeks after the last LA dose oral dosing of 25 mg RPV once daily for 4 weeks, followed by 600 mg Q4W continuation injections;

- an oral lead-in of 25 mg once daily for 4 weeks, followed by a 900 mg initiation injection, two 600 mg RPV doses every 4 weeks, 4 weeks after the last LA dose oral dosing of 25 mg RPV once daily for 8 weeks, a 900 mg RPV dose thereafter followed by 600 mg Q4W continuation injections.

Ctau values were maintained, i.e. >99% of subjects had a concentration of 12 ng/ml) in case the delay was 1, 2, 4, 8 or 12 weeks. However, the % of subjects decreased for the concentration >17.3 ng/ml, from 99.2% to 98.9% to 98.1% to 96.6% to 95.6% for a delay of the dose if 1, 2, 4, 8 and 12 weeks respectively. If instead the normal 600 mg dose a 900 mg dose was administered after an 8-week delay, the Ctau was restored and 99.6% of the subjects had a concentration >17.3 ng/ml.

According to the SmPC, adherence to the monthly injection schedule is strongly recommended. Patients who miss an injection visit should be clinically reassessed to ensure the resumption of therapy is appropriate. Dosing recommendations after a missed injection are given in the table below:

**Table 3 Dosing recommendations after a missed injection**

| Time since last injection | Recommendation |
|---|---|
| <2 months: | Continue with the monthly 2 mL injection dosing schedule as soon as possible. |
| ≥2 months: | Re-initiate the patient on the 3 mL dose, and then continue to follow the monthly 2 mL injection dosing schedule. |

This proposed recommendation seems acceptable, as Ctau values were maintained in case of less than a 2 month delay, i.e. >99% of subjects had a concentration of 12 ng/ml and a small decrease in % of subjects for obtaining a concentration of >17.3 ng/ml was observed from 99.2% to 96.6%. Applying a 900 mg LA dose in case the delay is more than 2 months, the Ctau was restored and 99.6% of the subjects had a concentration >17.3 ng/ml after this injection and subsequent injections with 600 mg LA.

Oral bridging to manage pre-planned dosing delays:

The SmPC recommends that if a patient plan to miss a scheduled injection by more than 7 days, oral therapy (EDURANT (25 mg) and cabotegravir tablets (30 mg) once daily) may be used to replace up to 2 consecutive monthly injection visits. The first dose of oral therapy should be taken approximately 1 month after the last injection dose of Rekambys. Simulated data showed that in such a case Ctau values are maintained (> 12 ng/ml and 17.3 ng/ml) and that the maximal plasma concentration during oral replacement is comparable to those observed in the TQT study C152, in which subjects received 25 mg q.d. orally. The RPV plasma concentrations during oral replacement therapy are not anticipated to be associated with a clinically relevant increase in QTcF.

Distribution:

The RPV typical value for the apparent volume of the central compartment (Vc/F) estimated by PopPK was 132 l, reflecting moderate distribution to peripheral tissues.

Animal data indicate that RPV distributes over the whole body, but high concentrations were observed in liver, adrenal gland, brown fat and kidney. In addition, RPV crosses the blood-brain barrier, but to a small extent, and crosses the placenta (Edurant application).

Blood to plasma ratio was 0.65-0.75, indicating limited distribution to blood cells. Plasma protein binding was on average 99.7%. RPV was extensively bound to albumin and to a lesser extent to alpha acid glycoprotein.

After administration of the RPV LA injection, in combination with CAB LA injection, low CSF RPV concentrations were observed, with median RPV CSF:plasma concentration ratio of 0.01. These concentrations appear still higher than the highest IC50 for wild type HIV-1 viruses of 0.081 ng/ml.

Metabolism:

RPV is metabolised by hydroxylation, oxidation, glucuronidation and conjugation with glutathione. At 14 days after the administration of a single oral dose of radiolabelled RPV, on average 85.1% ± 4.0% of the administered radioactivity had been excreted via the faeces. The average recovery in urine was 6.1% ± 2.1% with only trace amounts (≤ 0.03%) of unchanged RPV. The total radioactivity recovered was about 91.2 ± 5.1%. Only 60% of the excreted radioactivity was identified. The major loss in radioactivity appears to be caused by the fact that late faeces samples were not analysed for metabolites, some during extraction and some not identified. Unchanged drug was excreted in faeces and accounted for 25.5% of the dose on average (range 12.1-33.4%). No quantitative conclusion can be made on the

origin, but some of the unchanged drug may originate from poor absorption (solubility issue at higher doses). It can also not be excluded that biliary excretion of RPV exists as an elimination pathway.

In plasma, the unchanged drug accounted for a major part of the total radioactivity (76% based on Cmax and 51% based on AUClast). 59 - 84 % of the drug-related plasma exposure has been identified. Several metabolites were detected in plasma (glucuronides, direct and following oxidation, tricyclic and hydroxymethyl metabolite). Two metabolites were tested for antiviral activity M33 (hydroxymethyl-rilpivirine, which constituted 4-11% of parent exposure in plasma) had similar activity on wild type virus while metabolite 42 (oxidation at the pyrimidinyl moiety, main metabolite in faeces, 16% of dose) had 36 times lower activity. Neither is active on resistant strains.

No further metabolic profiling after i.m. LA administration was carried out. The metabolism of RPV is based upon data obtained after the IR formulation. This is acceptable, although after i.m. administration, the unknown first-pass metabolism after oral administration would not attribute to the overall metabolic profile.

RPV primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Elimination:

The apparent plasma clearance of RPV in HIV-infected subjects after LA injection was calculated to be 5.1 l/h.

After RPV LA i.m. administration RPV is characterized by absorption rate-limited elimination (flip-flop PK) and a long apparent half-life. The PopPK apparent terminal elimination half-life of RPV was estimated to be 200 days (28 weeks).

Special patient groups:

Based upon pharmacokinetic data and population pharmacokinetic analysis no clinically significant effect of body weight/body mass index, gender, race (White/Black) and ethnicity (Hispanic/non-Hispanic) on the pharmacokinetics is observed.

As RPV is almost completely eliminated non-renally, an impaired renal function is considered not to influence the pharmacokinetics of RPV significantly.

No study has been carried out with the LA formulation in patients with hepatic impairment. Based upon the pharmacokinetics observed after oral administration in patients with hepatic impairment, showing a non-clinically relevant effect on RPV pharmacokinetics only in subjects with mild hepatic impairment, no statistically significant impact on the RPV pharmacokinetics is expected after LA administration, also considering that the effect may be even less pronounced due to a lack of first-pass. Nonetheless the latter, in line with Edurant it is additional recommended that Rekambys should be used with caution in patients with moderate hepatic impairment. Furthermore, predicted steady state plasma concentrations in patients with severe hepatic impairment were comparable to orally administered RPV (25 mg q.d.), in line with the SmPC of Edurant, the SmPC recommends that no data are available in patients with severe hepatic impairment (Child-Pugh score C) and that therefore Rekambys is not recommended in these patients.

Age was identified as a significant covariate in the popPK analysis. Simulated single dose RPV LA pharmacokinetic data indicated a significant decrease in Cmax from 74.2 ng/ml at an age of 24 years to 43.2 ng/ml at an age of 65 years. No significant impact was observed on Ctau and AUCinf. After oral treatment, after the first i.m. injection, simulations predicted no impact of age on Cmax and Ctau, while AUCtau decreased by about 20% over the age range of 24 to 65 years. After the second i.m. injection, Cmax was about 20% lower, while no significant impact is observed for Ctau and AUCtau over the age range of 24 to 65 years. Furthermore, for subjects ≥ 65 years of age, the median and 90% prediction

interval of RPV plasma concentrations over time was comparable with those for subjects across the observed age range in FLAIR and ATLAS studies.
The difference in specifically the absorption of RPV may be due to the increase in the subcutaneous (fat) layer, which increases with increasing age, however as indicated before this has limited impact on the overall exposure, including Ctau after multiple injections.
Based on the provided data showing a limited impact on the overall exposure, including Ctau after multiple injections with respect to age, the recommended SmPC text in section 5.2, i.e. that no clinically relevant effect of age on the RPV exposure after intramuscular administration has been observed and that pharmacokinetic data for RPV in subjects of >65 years old are limited, is agreed.

Interactions:

Given that the pathways of metabolism and elimination of RPV are independent of formulation and route of administration, and RPV plasma concentrations achieved with the RPV LA monthly regimen are within the range of plasma concentrations observed with oral RPV 25 mg once daily, results from oral DDI studies can be extrapolated to RPV LA. As for the LA administration, the (unknown) first-pass effect is not applicable, even a less pronounced effect may be observed.

As RPV is a substrate for CYP3A, induction of CYP3A4 may result in lower RPV plasma concentrations. This is confirmed by simulated data of the effect of rifampicin and rifabutin. Increased clearance of RPV up to 5-fold after LA administration, resulted in decreased Ctau plasma concentrations below 17.3 ng/ml and 12 ng/ml. Administration of a higher RPV LA dose than the recommended dose (i.e. 1200 mg followed by 900 mg monthly) could not compensate this. Therefore, inducers of CYP3A4 are contraindicated, which is agreed.

In addition, simulated data showed that inhibition of CYP3A4 increased Cmax of RPV after LA administration. The effect was more pronounced at steady state, resulting in a 1.5-fold increase in RPV Cmax due to lopinavir/ritonavir and ketoconazole and a 2.3-fold increase in RPV Cmax due to darunavir/ritonavir. For ketoconazole and ritonavir-boosted lopinavir, the increase in RPV Cmax was not more than 1.79-fold, which is considered not clinically relevant regarding QT prolongation (Edurant application). For fluconazole, itraconazole, posaconazole and voriconazole a comparable or less pronounced effect is expected. Therefore, the SmPC recommends that RPV LA can be co-administered with these CYP3A4 inhibitors.

RPV will be co-administered with CAB. An interaction study with orally administered CAB and orally administered RPV showed that at steady state no interaction is observed between CAB and RPV. These results can be extrapolated to LA RPV.

Although ritonavir-boosted darunavir is not intended to be co-administered with Rekambys and CAB, the simulated increase in RPV Cmax of 2.3-fold is considered still within safety limits for QT prolongation. The latter also applies in the extreme case oral rilpivirine (25 mg q.d.) would be administered on top of rilpivirine LA treatment.

Additional data have been submitted for the potential of a drug interaction between dolutegravir and RPV. Dolutegravir is primarily metabolized via UDP-glucuronosyltransferase (UGT)1A1 with a minor component of CYP3A4. No interactions are expected and this is confirmed by this interaction study showing no clinically relevant interaction at steady state after oral administration.

The interactions have been sufficiently worded in the SmPC.

## 2.4.3. Pharmacodynamics

The PD and PK/PD development program were mainly based on the clinical pharmacology studies from the single entity development program for oral RPV, previously submitted with the MAA for oral RPV and summarized in the locally approved EDURANT prescribing information. The RPV LA + CAB LA in vivo clinical virology data were generated based on the Phase 3 ATLAS and FLAIR studies and the Phase 2b LATTE-2 and LATTE studies in addition to the Phase 3b study ATLAS-2M.

Based on earlier studies with Edurant, it is well known that the potency of rilpivirine is low compared to other agents in the same class. Also, exposure is known to be on the edge of efficacy. Several amino acid substitutions, when present at baseline, are known to affect the activity of rilpivirine (as also mentioned in section 5.1 of the Edurant and draft Rekambys SmPC): K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L.

The proposed therapeutic indication excludes use in subjects with NNRTI or IN class resistance.

Confirmed virologic failure (CVF), defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL, through Week 96 was rare in the studies and was distributed evenly between the groups (see table below). For LATTE-2, results until Week 160 are available. There were no additional PDVFs between the Week 48 and Week 160 analysis time points. For ATLAS-2M, results are shown until week 48.

**Table 4. Number of Subjects Meeting CVF Criteria by Visit**

| | **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%) |

In the pooled Week 48 analysis of the ATLAS and FLAIR studies, there were 7 subjects with confirmed virologic failure (CVF) in the CAB + RPV arm (7/591, 1.2%) and 7 subjects with CVF in the CAR arm (7/591, 1.2%). Six of the 7 CVFs on CAB + RPV had INI RAMs and 6/7 had RPV RAMs, of which 4 were treatment-emergent. Five of the 7 subjects had phenotypic resistance against RPV at the virologic failure time point. Among these 5 patients, phenotypic cross-resistance was observed against EFV (n=4), ETR (n=3), and NVP (n=4). Three of the 7 subjects developed dual resistance to CAB and RPV. The seventh subject with CVF never received an injection, and resistance testing was not performed. The only subject with PDVF and treatment-emergent mutations on CAB + RPV LA in the phase 2 study LATTE-2 had NNRTI RAMs K103N, E138G, K238T (RPV FC=3.3). In ATLAS-2M, 4/9 CVFs in the Q8W arm and Q4W arm combined had on-treatment NNRTI RAMs at the virologic failure time point.

The following emergent RT mutations were present at the virologic failure time point in subjects treated with CAB + RPV LA in ATLAS, FLAIR, LATTE-2 or ATLAS-2M:

- K101E (n=3, RPV fold change (FC)=2.6-4.7)
- E138A (n=1, RPV FC=2.4) *(E138E/A was present at baseline)*
- E138A/K/T (n=1, RPV FC=7.1)
- E138K (n=2, RPV FC=1.0-6.5)
- V108I+E138K (n=1, RPV FC=3.7) *(V108V/I+E138K was present at baseline)*
- K103N+E138G+K238T (n=1, RPV FC=3.3)
- K101E+M230L (n=1, RPV FC=17)
- K103N (n=1, RPV FC 2.4) *(K103K/N was present at baseline)*
- Y188L (n=1, RPV FC 6.8) *(Y188Y/F/H/L was present at baseline)*

The prevalence of each HIV-1 subtype is shown in table below. 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 5. Proportion with CVF by HIV-1 subtype**

**Table 7:Proportion with CVF by Subtype up to Week 48 in Phase 2/3/3b 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%) | NA | NA | 1/14 (7%) | 0/9 |
| **A1** | 3/8 (38%) | 1/17 (6%) | NA | NA | 2/30 (3%) | 0/30 |
| **AE** | 0/1 | 0/7 | NA | NA | 0/7 | 0/6 |
| **AG** | 1/10 (10%) | 1/10 (10%) | 1 | NA | 0/14 | 0/8 |
| **B** | 0*/174 | 0/162 | 1 | NA | 2/309 (0.6%) | 2/302 (0.7%) |
| **C** | 0/18 | 0/24 | NA | NA | 2/33 (6%) | 0/37 |
| **Other** | 0/19 | 0/27 | NA | NA | 1/37 (3%) | 0/46 |
| **Missing** | 0/7 | 0/51 | 0/32 | 0/10 | 0/78 | 0/85 |
| **Non-B** | 4/102 (4%) | 3/95 (3%) | NA | NA | 5/135 (3%) | 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

Source: Mod5.3.5.1/201584 W48 CSR, Mod5.3.5.1/201585 W48 CSR, Mod5.3.5.3/ATLAS-2M W48 CSR and Mod5.3.4.2/200056 W48 CSR

Two observations are to be made regarding the above table. First, the % mentioned in the ATLAS-2M Q8W A1 subgroup is incorrect, 2/30 is not 3% but 6.6%. Secondly, also in ATLAS-2M Q8W, the Non-B row should contain 6 rather than 5 subjects, equalling 4.4% rather than the mentioned 3%.

QTc

Two thorough QTc trials have been performed already during the development of Edurant: TMC278-TiDP6-C131 (C131), at RPV doses of 75 and 300 mg q.d., and TMC278-TiDP6-C152 (C152) at a RPV dose of 25 mg q.d. Both trials used a double-blind, double-dummy, randomized, placebo-controlled, and positive-controlled 3-way crossover design, respectively.

Based on these studies in healthy volunteers, it was concluded that RPV at the 25 mg q.d. dose does not prolong the QTcF interval. At supra-therapeutic RPV doses of 75 and 300 mg q.d., however, a dose- and plasma concentration-dependent prolongation of the QTcF interval was observed. The QTcF prolongation at both supra-therapeutic doses of RPV exceeded the ICH E14 threshold of clinical concern (i.e., the upper limit of the 90% CI of the mean maximum QTcF prolongation was above 10 ms). The mean time-matched change (90% CI) in QTcF versus placebo (time point with highest upper limit of 90% CI) was 2.0 (-1.0 - 5.0), 10.7 (6.1 - 15.3) and 23.3 (18.1 – 28.4) ms for RPV 25 mg q.d., 75 mg q.d. and 300 mg q.d., respectively. As the exposures obtained with the RPV-LA regimen as currently proposed are in the range of exposures seen with the 25 mg oral tablet, no QTcF interval prolongation is expected with Rekambys.

Pharmacodynamic interactions with other medicinal products or substances

No clinically significant drug-drug interactions were observed between RPV and CAB (DDI Study LAI116181). Also, no interactions were observed with tenofovir disoproxil fumarate, didanosine, rtv-boosted lopinavir, ketoconazole, sildenafil, atorvastatin, oral contraceptives containing norethindrone and ethinyl estradiol, methadone, paracetamol, chlorzoxazone, raltegravir, metformin, digoxin and rtv-boosted darunavir, although for the latter the increased RPV Cmax should be discussed in relation to a possible QT prolongation. RPV LA is contraindicated with strong CYP3A inducers because significant decreases in RPV plasma concentrations were observed with rifampicin and rifabutin. For more information, please refer to the PK section of this report.

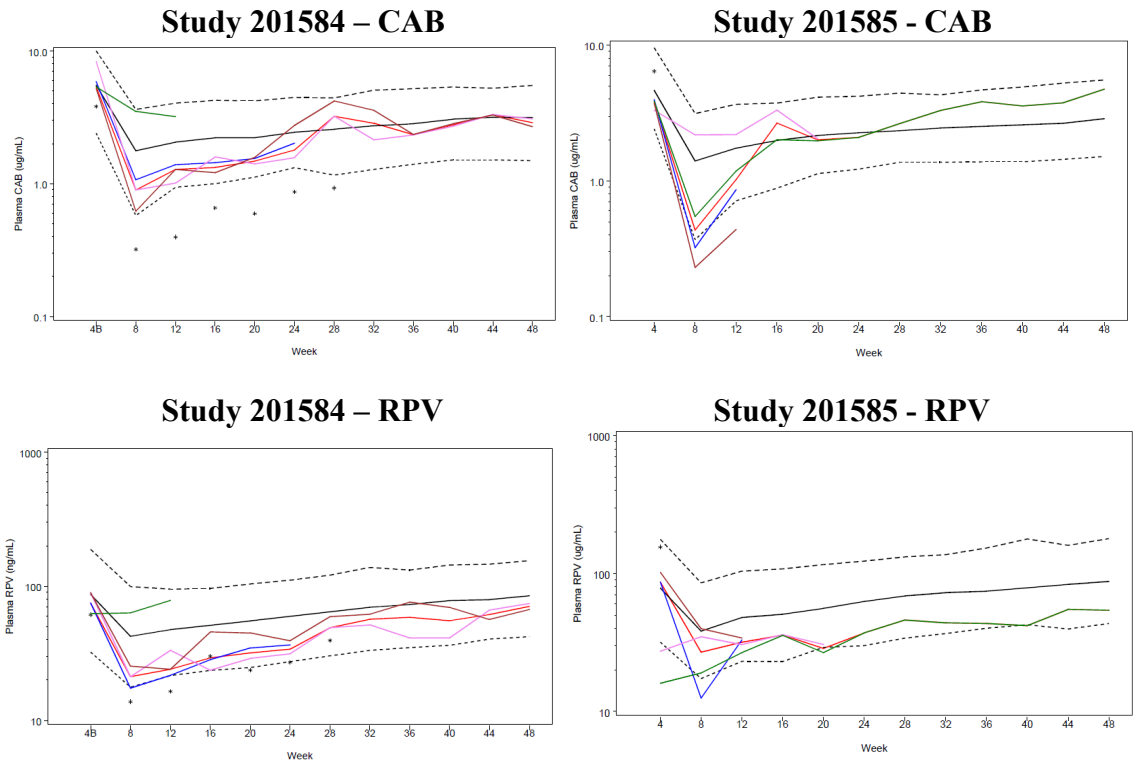
The applicant investigated the potential effect of concomitant drug use and concluded that there was no indication for the occurrence of AEs related to a potential increase in RPV exposure in subjects who were using concomitant medication that may have resulted in increased RPV exposure. The currently available

information is provided in section 4.5 of the SmPC, and the impact of concomitant medications will be further monitored post approval.

**Relationship between plasma concentration and effect**

Efficacy

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) (see figure below).




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

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

**Figure 3 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**

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

Safety

Throughout the development of RPV (oral and LA), there were, except for the QT prolongation mentioned above, no safety parameters found to be correlated with RPV plasma concentrations.

Plasma RPV Ctau Used to Guide Dose Recommendations

The time to achieve steady-state with RPV LA is about 2.2 years. According to the applicant, efficacious concentrations are already achieved following the initial IM injection. Although the oral lead-in was not required for the achievement of either therapeutic or steady-state dose levels, this is required to assess tolerability before the LA regimen is started. Recommendations for e.g., re-initiation of RPV LA after missed doses or oral bridging were based on simulations where ≥95% of patients keep a plasma RPV Ctau ≥17.3 ng/mL. A plasma RPV Ctau of 17.3 ng/mL is the 5th percentile of observed Ctau after the initial injection in the pooled Phase III studies, which showed non-inferiority to CAR. The 5th percentile of the popPK model-predicted RPV Ctau at this time point was similar, i.e. 18 ng/mL.

RPV LA doses should be administered monthly ± 7 days and adherence to the monthly injection dosing schedule is recommended. Doses administered beyond the 7-day window are considered missed doses and may result in <95% of patients achieving plasma RPV Ctau ≥17.3 ng/mL. If a patient misses a scheduled dose, the next dose should be given as soon as possible, then resume monthly dosing. A conservative approach was taken with regards to the selected time-frame (≥2 months since the last injection) in which a re-initiation dose of 3 mL instead of 2 mL is recommended.

If a patient plans to miss a scheduled injection by more than 7 days, oral bridging should be used to cover up to two missed injections, and injection dosing should be resumed on the same day oral dosing completes. In the Phase III development program, a total of 18 subjects (11 subjects in FLAIR and 7 subjects in ATLAS) received oral bridging for durations ranging from 3 days to approximately 2 months. All but 2 subjects were able to resume IM dosing and no cases of CVF were observed during a period of oral bridging or following resumption of IM dosing. Oral bridging is recommended for a duration of up to 2 months (i.e., 2 planned missed injection visits). If this period is anticipated to be extended to more than 2 months, a transition to standard of care ART is recommended.

Management of RPV LA Discontinuation

Alternative highly active antiretroviral therapy (HAART) should be initiated as soon as feasible, no later than one month following discontinuation of RPV LA, to maintain suppression of viral load and to reduce the chance of any RPV resistance emerging while concentrations are waning. It was not immediately clear how many subjects, across the full clinical development program, discontinued LA treatment and how these subjects were actually managed. The applicant clarified that a total of 71 (15, 25, and 31 in LATTE-2, FLAIR and ATLAS) subjects who received the LA regimen (either Q4W or Q8W in Latte-2) entered the long-term follow-up while virologically suppressed, of which 8 (2, 3, and 3 in LATTE-2, FLAIR and ATLAS) subjects entered the long-term follow-up with confirmed virologic failure. A maximum of 12 months follow-up information was provided, which is however considered too short for meaningful conclusions keeping the long half-life of both products in mind. Ideally, the applicant should follow-up patients who discontinue treatment until RPV and CAB concentrations are too low to result in potential selection of resistance mutations if a patient is not taking another appropriate antiviral regimen. The applicant initially proposed a 24-month follow-up, however a longer duration of follow-up is considered needed, at least until the residual levels are too low to induce selection pressure on the virus. The applicant accepted to extend the follow up of the patients for up to 5 years after discontinuation of the RPV LA + CAB LA regimen. Details will be included in the full study protocols for the proposed post-marketing Drug Utilization Study (DUS) and COMBINE-2 study, that will be submitted for review by December 2020. It remains to be seen 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). 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 centers, resources, patients' characteristics etc.

## 2.4.4. Discussion on clinical pharmacology

*Pharmacokinetics*

After absorption from the i.m. injection site, RPV disposition followed a fast absorption route describing the initial RPV peak and a second slow absorption route determining the terminal part of the RPV plasma concentration vs. time curve, reflecting the flip-flop kinetics after i.m. administration. tmax values are observed after about 72h. After single and multiple-dose, a comparable relative bioavailability (taking into account the difference in administered dose) was observed with the commercial IR tablet formulation (Edurant). After the oral lead-in period with 25 mg RPV o.d. + 30 mg CAB o.d., 4 weeks after the first injection the Ctrough plasma decreased and steadily increased after subsequent injections. The 900 mg initial injection prevents that concentrations would drop below the PA-IC90 of protein-binding adjusted IC90 of 12 ng/ml after the first injection. Steady-state was estimated to be reached after 2.2 years.

Different dosing scenarios, i.e. monthly vs Q4W dosing, allowable injection window at specific injection visits and oral bridging to manage pre-planned dosing delays were simulated, which supported the SmPC dosing recommendations In case oral rilpivirine (25 mg q.d. would be administered on top of rilpivirine LA treatment, the highest geometric mean ($5^{th}$, $95^{th}$ percentile) Cmax for this situation is 298 ng/ml (203, 425 ng/ml). This is just above the mean steady state Cmax levels of 247 ng/ml (148, 411 ng/ml; $5^{th}$, $95^{th}$ percentile) observed in the TQT study C152, in which subjects received 25 mg q.d. orally. Furthermore, the Cmax values are well below the 80% probability for a negative TQT study if the mean rilpivirine exposure expressed as Cmax would increase 1.85-fold (to 457 ng/ml) as compared to that observed in the rilpivirine 25 mg qd TQT study. Based upon these exposure data, no difference in QT interval is expected.

Based upon pharmacokinetic data and population pharmacokinetic analysis no clinically significant effect of body weight/body mass index, gender, race (White/Black) and ethnicity (Hispanic/non-Hispanic) on the pharmacokinetics is observed. Renal and hepatic impairment are considered not to have a clinically significant impact on RPV exposure, although a further discussion was requested for moderate hepatic impairment. Considering that the predicted steady state Cmax exposure in patients with severe hepatic impairment is comparable, in line with the SmPC of orally administered rilpivirine, the applicant proposed 'No data are available in patients with severe hepatic impairment (Child-Pugh score C); therefore Rekambys is not recommended in these patients', which is agreed.

Increased age led to a significant decrease in Cmax after single dose and no significant impact was observed on Ctau. Regarding AUC0-t, a decrease of about 25% was observed comparing a subject of 24 years to a subject of 65 years old. However, no impact was observed on AUCinf. In addition, after oral treatment, after first i.m. injection, simulations predicted no impact of age on Cmax and Ctau, while AUCtau decreased about 20% over the age range of 24 to 65 years. After the second i.m. injection, Cmax was about 20% lower, while no significant impact is observed for Ctau and AUCtau over the age range of 24 to 65 years. The difference in specifically the absorption may be due to the increase in the subcutaneous (fat) layer, which increases with increasing age. However, this has limited impact on the overall exposure, including Ctau after multiple injections. Based on the provided data showing limited impact on the overall exposure, including Ctau after multiple injections with respect to age, the proposed SmPC text in section 5.2, i.e. "No clinically relevant effect of age on the RPV exposure after intramuscular administration has been observed. Pharmacokinetic data for RPV in subjects of >65 years old are limited" is agreed.

Results from oral DDI studies can be extrapolated to RPV LA. As for the LA administration the (unknown) first-pass effect is not applicable, even a less pronounced effect may be observed. As RPV is a substrate for CYP3A, induction and inhibition of CYP3A4 may result in respectively lower and higher RPV plasma concentrations. CYP3A4 inducers are therefore contraindicated. Inhibitors appear to have a small to moderate effect on RPV plasma concentrations, of which the interaction with darunavir/ritonavir resulting in a possible 2.3-fold increase in RPV Cmax may be clinically relevant regarding QT prolongation. Although, it is acknowledged that Rekambys with CAB LA is a complete ARV regimen and it is not intended to be co-administered with darunavir/ritonavir treatment further clarifications were requested. The highest impact observed with a 2.3-fold increase in Cmax would be predicted to increase Cmax levels to 263 ng/ml. This is just above the mean steady state Cmax levels of 247 ng/ml (148, 411 ng/ml; $5^{th}$, $95^{th}$ percentile) observed in the TQT study C152, in which subjects received 25 mg q.d. orally. Furthermore, the Cmax values are well below the 80% probability for a negative TQT study if the mean rilpivirine exposure expressed as Cmax would increase 1.85-fold (to 457 ng/ml) as compared to that observed in the rilpivirine 25 mg qd TQT study. Based upon these exposure data, no difference in QT interval is expected.

*Pharmacodynamics*

The pharmacodynamic properties of rilpivirine are well known. For the long-acting formulation, no new PD studies have been performed, which is acceptable. RPV LA exposure is in the range of what has been observed with the marketed daily 25 mg oral RPV tablet and was consistent between ATLAS and FLAIR studies.

Several amino acid substitutions, when present at baseline, are known to affect the activity of rilpivirine (as also mentioned in section 5.1 of the Edurant and draft Rekambys SmPC ): K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L. The therapeutic indication excludes use in subjects with NNRTI or IN class resistance, in line with the population studied.

The number of subjects with confirmed virologic failure when treated with CAB+RPV LA has been consistently low across the main clinical studies (<1.75%), which is reassuring. Except for one subject with CVF at the Week 48 timepoint in FLAIR, all virologic failures occurred in the first 28 weeks of treatment.

In the pooled ATLAS and FLAIR studies, there were 7 subjects with confirmed virologic failure (CVF) in the CAB+RPV arm (7/591, 1.2%). Six of these 7 subjects had RPV RAMs at the time of failure, of which 4 were treatment-emergent. Five of the 7 subjects had phenotypic resistance against RPV at the virologic failure time point. The seventh subject with CVF never received an injection and resistance testing was not performed. Among the 5 subjects with phenotypic resistance, cross-resistance was observed against EFV (n=4), ETR (n=3), and NVP (n=4). Three of the 7 subjects developed dual resistance to CAB and RPV. The following RT mutations were present at the virologic failure time point in CAB+RPV LA Phase 3 studies: K101E (n=1, RPV fold change (FC)=2.6), E138A (n=1, RPV FC=2.4), E138A/K/T (n=1, RPV FC=7.1), E138K (n=2, RPV FC=1.0-6.5), and V108I+E138K (n=1, RPV FC=3.7). These are all known RAMs and no new RPV RAMs were identified. The only subject with PDVF and treatment-emergent mutations on CAB+RPV LA in the phase 2 study LATTE-2 had NNRTI RAMs K103N, E138G, K238T (RPV FC=3.3), as well as INI RAM Q148R (CAB FC=5.1). In ATLAS-2M, 4/9 CVFs in the Q8W arm and Q4W arm combined had on-treatment NNRTI RAMs at the virologic failure time point.

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, limits the conclusions that can be drawn.

Overall, the data indicate that treatment-emergent RPV RAMs develop frequently in patients with virologic failure, five of the 7 subjects (71%) with CVF in the pooled ATLAS and FLAIR studies had phenotypic resistance against RPV at the virologic failure time point. Despite the arguments put forward by the Applicant, the concerns regarding the implications of treatment emergent RPV and/or CAB RAMs have not been eased. This issue will be closely monitored after approval.

*PK/PD*

Exposure-response analyses revealed that the 11 subjects with CVF had exposures that are generally below the median. This is of interest and deserves further attention. For certain subjects (e.g. the subjects denoted with *** in study FLAIR (201584), exposure of both RPV as well as CAB is low (suggesting there may be a potential subject–related cause), whereas for other subjects (e.g. the subject denoted with the brown line in ATLAS (201585) this is applicable to only one of the two components (pointing more towards an accidental administration error).

In both pivotal studies, multivariable analysis indicated that RPV concentration (last available RPV through concentration in ATLAS, RPV week 8 through concentration in FLAIR) was retained as a statistically significant predictor of Week 48 HIV RNA ≥50 c/mL. This may suggest that RPV concentration after LA injection, as with the oral tablets, is on the edge of inducing efficacious RPV exposure. The number of subjects with virologic failure (n=11 across the two pivotal studies) is however limited. No specific PK/PD association was observed in LATTE-2.

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 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 is endorsed.

No relationships between RPV concentrations and safety parameters of interest were identified.

*Missed injections*

A main issue in clinical practice will be the management of missed visits and discontinuation. During the clinical studies, only a few subjects had missed visits, and the current recommendations are hence largely based on PK predictions rather than on clinical practice. Oral bridging with CAB + RPV tablets is recommended to cover up to 2 planned missed injection visits (i.e., a period of up to 2 months). If this period is anticipated to be extended to more than 2 months, a transition to standard of care ART is recommended.

Regarding discontinuation of the CAB + RPV LA treatment, it was not immediately clear how many subjects, across the full clinical development program, discontinued LA treatment and how these subjects were actually managed. A maximum of 12 months follow-up information was provided, which is however considered too short for meaningful conclusions keeping the long half-life of both products in mind. Ideally, the applicant should follow-up patients who discontinue treatment until RPV and CAB concentrations are too low to result in potential selection of resistance mutations if a patient is not taking another appropriate antiviral regimen. The warning in section 4.4 of the SmPC, "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 last every 1 month injection of Rekambys or two months after the last every 2 months injection of Rekambys. If virologic failure is suspected, an alternative regimen should be adopted as soon as possible" was added with this regard. Based on the in vitro and clinical drug-drug interaction profile, RPV is not expected to alter concentrations of other ARV medications including PIs, NNRTIs, NRTIs, INIs, entry inhibitors, and ibalizumab, which is reassuring especially keeping in mind the long half-life of RPV-LA.

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 centers, resources, patients' characteristics etc.

## 2.4.5. Conclusions on clinical pharmacology

In general, the pharmacokinetics of RPV LA have been sufficiently evaluated. No major issues have been identified. Several concerns were raised clarifying issues on applied analytical methods, lacking study reports, oral replacement therapy, the effect of age on RPV PK, hepatic impairment and interactions. (see also clinical safety).

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

## *2.5. Clinical efficacy*

The clinical development program consists of 2 randomized, controlled pivotal Phase III studies (201584 [FLAIR] and 201585 [ATLAS]), supported by 2 randomized, controlled Phase IIb studies (LAI116482 [LATTE] and 200056 [LATTE-2]). In addition, a Phase IIIb Study 207966 (ATLAS-2M) evaluating monthly (Q4W) and bimonthly (Q8W) dosing is ongoing.

**Table 6 Clinical development program-studies**

| **Study** | **Study Design, primary objective** | | **Numbers by Treatment Regimen** | **Primary (or main) endpoint** |
|---|---|---|---|---|
| | *Pivotal Studies* | | | |
| | | | | |
| **FLAIR**<br>HIV-1 infected <u>treatment-naive</u> subjects | Open-label, randomized study.<br><br>To demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC. | | **Induction Phase** (20 weeks):<br>Oral ABC/DTG/3TC FDC (NRTI substitution allowed)<br>**Maintenance Phase** (100 weeks):<br><u>CAB + RPV group</u> (N=283): 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<br><u>Control group</u> (N=283): oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs). | Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 |

| | | | | |
|---|---|---|---|---|
| **ATLAS**<br>HIV-1 infected <u>treatment-experienced</u> subjects | Open-label, randomized study.<br><br>To demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen. | | **Maintenance Phase** (52 Weeks):<br><u>CAB + RPV group</u> (N=308): 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<br><u>Control group</u> (N=308): 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI. | Proportion of subjects with a 'virologic failure' endpoint as per the Snapshot Algorithm at Week 48. |
| | *Additional Studies* | | | |
| **ATLAS-2M (ongoing)**<br>Subjects were enrolled from the ongoing ATLAS study with additional subjects receiving antiretroviral therapy (ART) standard of care (SOC) | Open-label, randomized, multicenter, parallel-group, noninferiority study.<br><br>To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks. | | **Maintenance Phase** (52 Weeks):<br><u>CAB + RPV Q4W group</u> (N=523): CAB LA 600 mg + RPV LA 900 mg loading dose, CAB LA 400 mg + RPV LA 600 mg Q4W (±7 days)<br><u>CAB + RPV Q8W group</u> (N=522): 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 Q8W (±7 days) | Proportion of subjects with HIV-RNA ≥50 c/mL as per FDA Snapshot algorithm at Week 48.<br><br>Week 24 results are included in the dossier, Week 48 results will be available Dec 2019 |
| **LATTE-2**<br>HIV-1 infected treatment-naive subjects | Phase IIb, randomized (2:2:1), multicentre, parallel group, open-label study.<br><br>To evaluate CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression. | | **Induction Phase** (20 weeks):<br>Oral CAB 30 mg + ABC/3TC once daily. With oral RPV 25 mg once daily for last 4 weeks<br>**Maintenance Phase** (96 weeks):<br><u>CAB + RPV Q4W group</u> (N=115): CAB LA 800 mg + RPV LA 600 mg loading dose, CAB LA 400 mg + RPV LA 600 mg Q4W<br><u>CAB + RPV Q8W group</u> (N=115): 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 Q8W<br><u>Control group</u> (N=56): Oral CAB 30 mg + ABC/3TC once daily | The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 32 |

| | | | | |
|---|---|---|---|---|
| **LATTE**<br>HIV-1 infected treatment-naive subjects | Phase IIb, dose-finding randomized (1:1:1:1), multicentre, parallel group, open-label study.<br><br>To select a dose of CAB for further evaluation as part of a two-drug combination ART regimen with RPV for 24 weeks, following a 24-week induction period of CAB with two NRTIs. | | **Induction Phase** (24 weeks):<br>CAB group (N=60, 60, 61): Oral CAB 10, 30, or 60 mg + ABC/3TC or TDF/FTC once daily<br>Control group (N=62): EFV + ABC/3TC or TDF/FTC<br>**Maintenance Phase** (72 weeks): CAB + RPV group (N=60, 60, 61): Oral CAB 10, 30, or 60 mg + oral RPV 25 mg once daily<br>Control group (N=62): EFV + ABC/3TC or TDF/FTC<br>**Open-Label Phase** (post 96 weeks): CAB 30 mg + RPV 25 mg | The proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 |

## 2.5.1. Dose response studies and main clinical studies

For RPV-LA, the aim was to achieve RPV plasma concentrations in the range of those observed with oral RPV 25 mg (Edurant) once daily in HIV-infected patients, hence no formal dose-finding studies have been conducted, which is accepted.

The combination of RPV with CAB has been investigated in Study LAI116482 (LATTE), *A Phase IIb, Dose Ranging Study of Oral GSK1265744 [Cabotegravir] in Combination with Nucleoside Reverse Transcriptase Inhibitors for Induction of HIV-1 Virologic Suppression Followed by an Evaluation of Maintenance of Virologic Suppression when Oral GSK1265744 is Combined with Oral Rilpivirine in HIV-1 Infected, Antiretroviral Therapy Naive Adult Subjects*.

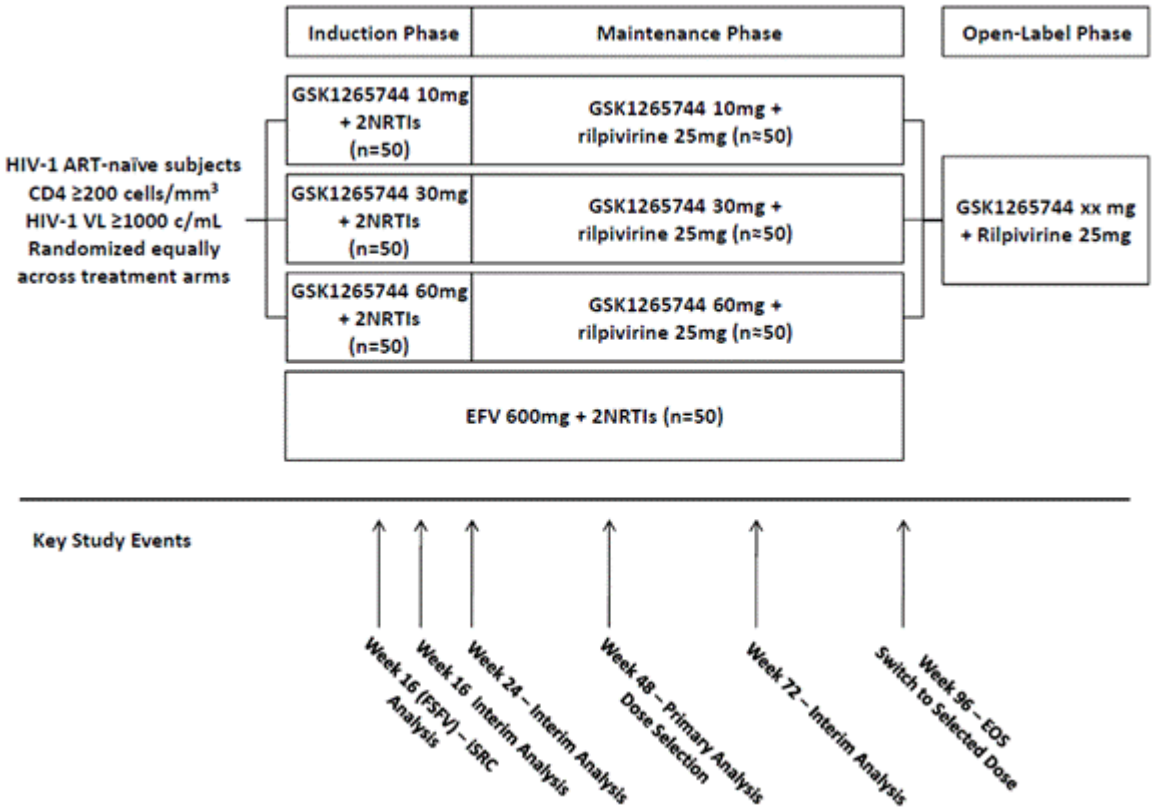


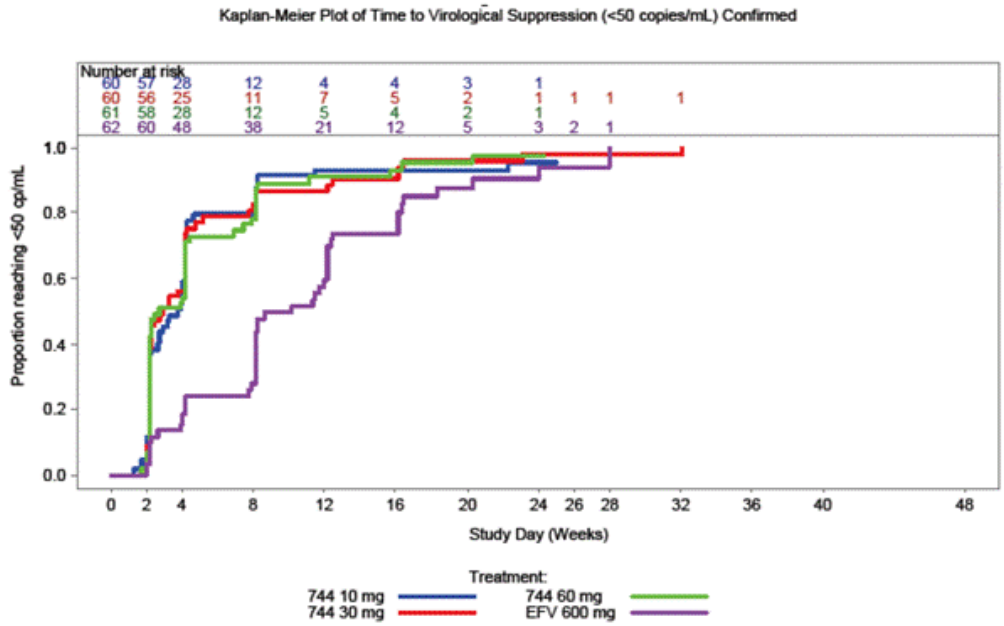

**Figure 4. Study schematic LATTE**

Based on the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48, it was concluded that all 3 CAB arms showed comparable efficacy (see table and figure below)). The response rate in the EFV control arm (71%) was similar to response rates seen in previously published studies and was slightly lower than the response rate through Week 48 in a similarly designed study, ING112276 (80%), due in part to a higher rate of AE related withdrawals. The time to virologic suppression (HIV-1 RNA <50 c/mL) was significantly shorter for the CAB arms compared to EFV (each p<0.001; log-rank test).

**Table 7. Proportion (95% CI) of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 - Snapshot (MSDF) Analysis (ITT-E Population) - LATTE**

| Visit | | GSK744 10 mg N=60 | GSK744 30 mg N=60 | GSK744 60 mg N=61 | GSK744 Subtotal N=181 | EFV 600 mg N=62 |
|---|---|---|---|---|---|---|
| Week 48 | n (%)<br>95% CI | 48 (80)<br>(70, 90) | 48 (80)<br>(70, 90) | 53 (87)<br>(78, 95) | 149 (82)<br>(77, 88) | 44 (71)<br>(60, 82) |

Data Source: Table 7.2
95% CIs are normal approximation confidence intervals.




Data Source: Figure 7.13

**Figure 5. Kaplan-Meier Plot of Time to Virological Suppression (<50 c/mL) – LATTE**

Overall, 11 subjects met the criteria for PDVF: 3 subjects on CAB 10 mg, 2 subjects on CAB 30 mg, 1 subject on CAB 60 mg, and 5 subjects on EFV. It was predefined that if comparable efficacy, safety and tolerability were observed across all three CAB doses at 16 and 24 weeks, the 30 mg dose was to be selected for further investigation. Overall, it was concluded that efficacy and safety results supported the selection of CAB 30 mg once daily for further evaluation. Dose selection was confirmed at Week 72.

Of note, this study provides the main body of evidence that the combination of oral RPV 25 mg + oral CAB 30 mg is efficacious in keeping HIV-1 suppressed for a prolonged period of time. The proposed SmPC recommends use of this dual regimen as an oral lead-in before initiation of injectable RPV + CAB (i.e. a period of 1 month), as well as to replace up to 2 consecutive monthly injection visits (oral bridging). While the oral lead-in has been included in other clinical studies (see below), resulting in ample experience for this short use, the LATTE study is the only study providing evidence that oral CAB + RPV can safely be used also > 1 month.

The combination of RPV-LA with CAB-LA was subsequently tested in Study 200056 (LATTE-2). This was a Phase IIb, randomized, multicentre, parallel-group, open-label, three-part study in HIV-1 infected ART-naive adults. The study enrolled 286 subjects, randomised 2:2:1 to receive an IM regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks for 96 weeks, an IM regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks for 96 weeks, or to continue on the oral Induction Period regimen of CAB 30 mg + ABC/3TC once daily for 96 weeks.

This study consists of a Screening Period, Induction Period, Maintenance Period, Extension Period and a Long-term Follow-up Period (withdrawn subjects only) (see figure below).

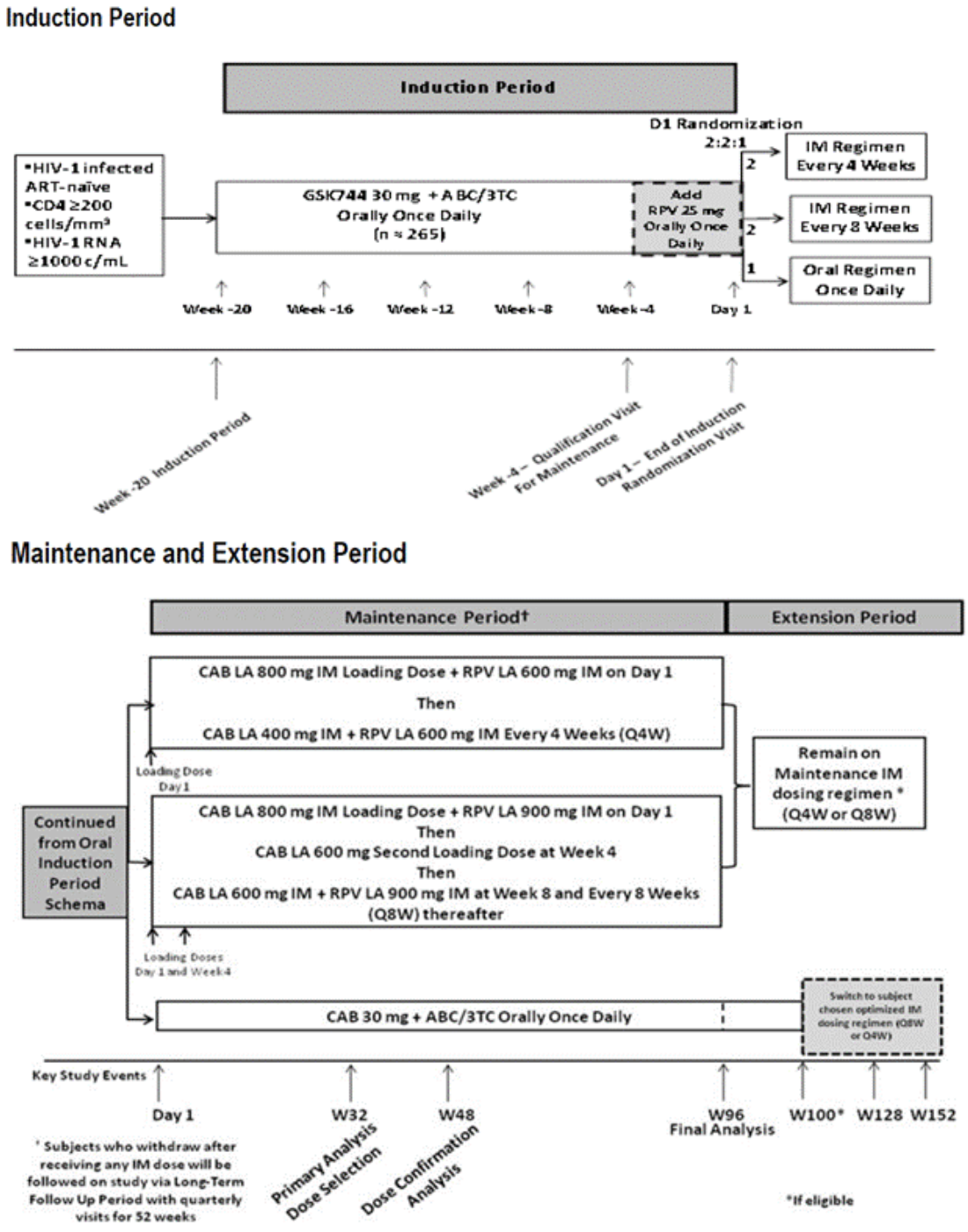



**Figure 6. Study design schematic LATTE-2**

Dosing for each arm was as follows:

- **IM injections every 4 weeks (Q4W)**

Day 1: CAB LA 800 mg + RPV LA 600 mg IM
Week 4: CAB LA 400 mg IM + RPV LA 600 mg IM, every 4 weeks for 96 weeks

- **IM injections every 8 weeks (Q8W)**

Day 1: CAB LA 800 mg + RPV LA 900 mg IM
Week 4: CAB LA 600 mg IM (second loading dose, no RPV)
Week 8: CAB LA 600 mg IM + RPV LA 900 mg IM, every 8 weeks for 96 weeks

- **Oral Control Arm**

  CAB 30 mg + ABC/3TC once daily for 96 weeks (or 104 weeks if continuing on to the Extension period)

While the Q4W arm is most representative of the commercial posology, the loading part of this regimen is (slightly) different from the recommended posology according to the draft Rekambys SmPC, which is:

Day 1: CAB LA 600 mg IM + RPV LA 900 mg IM
Week 4: CAB LA 400 mg IM + RPV LA 600 mg IM, every 4 weeks

In summary, for CAB the commercial loading dose (600 mg) is lower than the LATTE-2 Q4W loading dose (800 mg), while for RPV the commercial loading dose (900 mg) is higher than the LATTE-2 Q4W loading dose (600 mg).

The selection of these regimens was based on modelling and simulation. 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, and RPV exposure around 115 ng/mL. This is above the mean RPV Ctrough (80 ng/mL) and the mean Cavg (100 ng/mL) for RPV 25 mg once daily (Phase III). Based on these model predictions, the Q8W dose regimen was predicted to induce CAB exposure above the target of 1.35 µg/mL after ~1 year of treatment in 84% of subjects. For RPV, the mean steady-state Ctrough (~65 ng/mL) is predicted to be below the mean RPV Ctrough with oral RPV 25 mg although the range of model-predicted Ctrough is similar to the range of Ctrough with oral RPV 25 mg once daily.

Following the Week 32 analysis, neither IM regimen met the pre-defined stopping criteria, thus the Week 48 efficacy and safety analysis was used to further characterize and determine which of the IM dosing regimens would be carried forward to phase III. The Week 48 outcomes are provided below.

**Table 8. Summary of Study Outcomes (<50 copies/mL) at Week 48 – Snapshot (MSDF) Analysis (ITT-ME Population) – LATTE-2**

| Outcome | Q8W IM N=115 n (%) | Q4W IM N=115 n (%) | CAB 30 mg N=56 n (%) | Subtotal IM N=230 n (%) |
|---|---|---|---|---|
| **Virologic Success, n (%)** | 106 (92) | 105 (91) | 50 (89) | 211 (92) |
| **Virologic Failure, n (%)** | 8 (7) | 1 (<1) | 1 (2) | 9 (4) |
| Data in window not below threshold | 6 (5) | 1 (<1) | 0 | 7 (3) |
| Discontinued for lack of efficacy | 1 (<1) | 0 | 1 (2) | 1 (<1) |
| Discontinued for other reason while not below threshold | 1 (<1) | 0 | 0 | 1 (<1) |
| **No Virologic Data** | 1 (<1) | 9 (8) | 5 (9) | 10 (4) |
| Discontinued due to AE or Death | 0 | 6 (5) | 2 (4) | 6 (3) |
| Discontinued for Other Reasons | 1 (<1) | 3 (3) | 3 (5) | 4 (2) |

Data Source: Table 7.1002

Note: Pre-defined windows for virologic assessment at Week 48: -2 to +4 week window, followed by ± 6-week window if necessary to obtain data in window. Two subjects were classified as virologic success using the expanded 6-week window (Q4W n=2, Subject 448 and 453).

After further evaluation, the Q4W IM dosing regimen resulted in lower rates of virologic non-response with similar safety to Q8W, thus Q4W IM dosing was selected for use in the pivotal phase III studies. Q8W dosing remained under evaluation within LATTE-2 and is further investigated in ATLAS-2M. The selection of the Q4W regimen based on these data is endorsed.

The numerically higher number of subjects with virologic failure in the Q8W arm (n=8) vs. the Q4W arm (n=1) is in line with the model predictions of CAB and RPV exposures, which were below target levels with the Q8W dose regimen in a higher proportion of subjects than with the Q4W regimen. Selection of the Q4W dose regimen is justified also from this perspective.

At Week 160, 90% (Q8W IM arm) and 83% (Q4W IM) of subjects randomized to receive injectable dosing maintained virologic suppression (HIV-1 RNA <50 c/mL). The proportion of subjects with no virologic data in window was higher in the Q4W IM arm (17%) compared to the Q8W IM arm (5%), driven by discontinuations due to AE/death or for other non-virologic reasons. No new protocol-defined virologic failures (PDVFs) occurred between Week 48 and Week 160 in any of the two LA arms.

In conclusion, the selected dose and dosing frequency of RPV LA was based on maintaining plasma trough concentration at the end of the dosing interval at or above exposures following efficacious doses of oral RPV 25 mg once daily.

## Main studies

The MAA for RPV LA was originally based on the results of the ATLAS and FLAIR Phase III studies. During the assessment, results of the Phase IIIb ATLAS-2M study became available. Relevant results of this study have been added to the description of the main studies below.

### Study 201584 (FLAIR)

*A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-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: Week 48 - Primary Endpoint*

### Study 201585 (ATLAS)

*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: Week 48 - Primary Endpoint*

Since the D120 AR, Week 96 results of ATLAS and FLAIR studies became available. However, only a Week 96 clinical study report was provided for ATLAS.

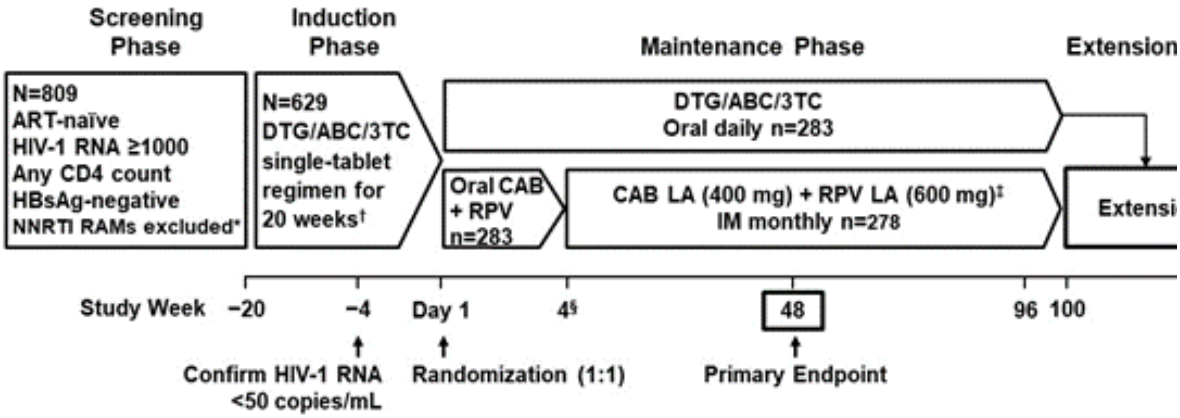
### Study 207966 (ATLAS-2M)

ATLAS-2M is an ongoing Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of IM CAB + RPV Q8W compared to IM CAB + RPV Q4W in HIV-1 infected adult subjects.

#### *Methods*

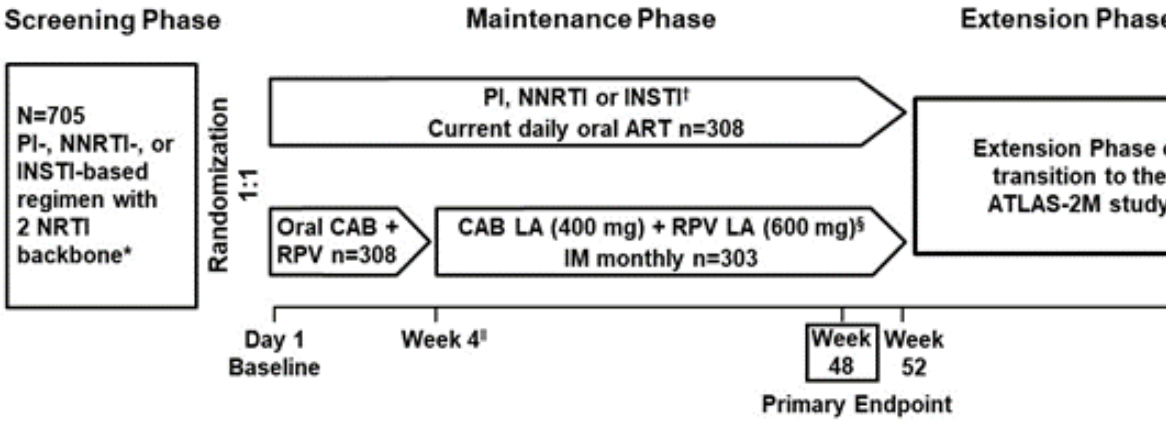
The design of the studies is depicted in the figures below (A. FLAIR, B. ATLAS, C. ATLAS-2M).

A.



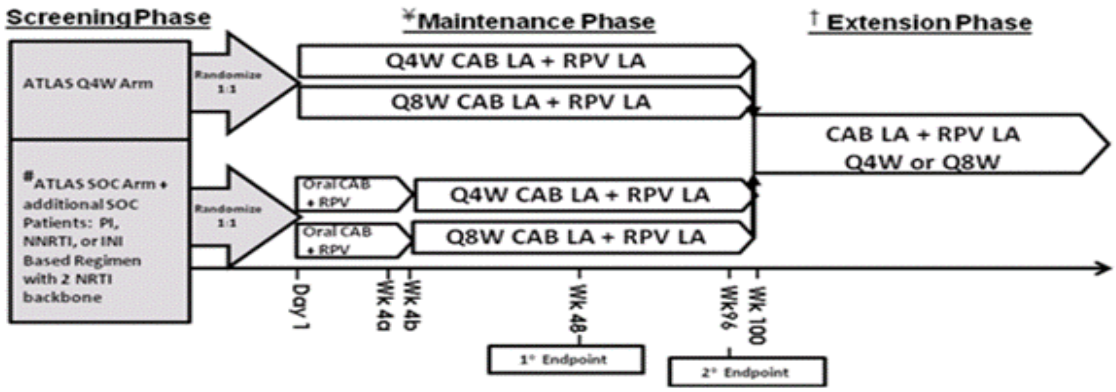

*NNRTI RAMS but not K103N were exclusionary; †DTG plus 2 alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive (n=30 as last re induction: n=2 discontinued during induction, n=14 randomized to CAB LA + RPV LA, n=14 randomized to DTG/ABC/3TC arm and continued on DTG plus 2 alternative non- in Maintenance Phase); ‡Participants who withdraw/complete CAB LA + RPV LA enter 52-week long-term follow-up; §Participants received initial loading doses of CAB LA 60 RPV LA 900 mg at Week 4. Beginning Week 8, participants received CAB LA 400 mg + RPV LA 600 mg injections every 4 weeks.

B.




*Uninterrupted ART 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrollment; Triume from study; ‡Optional switch to CAB LA + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB LA + RPV LA must comp 52 weeks of follow-up; ‖Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, part received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks.

3TC: lamivudine; ABC: abacavir; ART: antiretroviral therapy; ARV: antiretroviral; CAB: cabotegravir; DTG: dolutegravir; combination; FTC: emtricitabine; HBsAg: hepatitis B surface antigen; HIV-1: human immunodeficiency virus type 1; IM: intramuscular; INSTI: integrase strand transfer inhibitor; LA: long-acting; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; RPV: rilpivirine




# 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.

**C.**

**Figure 7. Study design FLAIR (201584) (A), ATLAS (2015085) (B), and ATLAS-2M (C).**

***Study Participants***

Study participants were HIV-1 infected (documented by Screening plasma HIV-1 RNA ≥1000 c/mL), ART-naive men or women aged 18 years or greater at the time of signing the informed consent. Subjects in FLAIR were antiretroviral-naïve, whereas subjects in ATLAS were required to be on an uninterrupted current regimen (either the initial or second ARV regimen) for at least 6 months prior to Screening. Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, had to occur due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for treatment failure (HIV-1 RNA ≥400 c/mL). Any evidence of primary resistance to NNRTIs (except for K103N which was allowed), or any known resistance to INIs from historical resistance test results [(IAS)–USA, 2015], were exclusionary.

Also, subjects with evidence of active CDC Stage 3 disease, known moderate to severe hepatic impairment, pre-existing physical or mental conditions, HBV/HCV infection, unstable liver disease, history of liver cirrhosis with or without hepatitis viral co-infection, or ALT ≥3 times ULN, or ongoing or clinically relevant pancreatitis, were excluded from participation in either study.

The majority of subjects in ATLAS-2M were enrolled from the ongoing ATLAS Study with additional subjects on standard of care (SOC) included in order to support a targeted total sample size of approximately 1020 subjects.

***Objectives***

The primary objective of FLAIR and ATLAS was to demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks compared to continuation of ABC/DTG/3TC (FLAIR) or CAR (ATLAS) over 48 weeks in HIV-1 antiretroviral naïve participants (FLAIR) and in HIV-1 infected antiretroviral therapy (ART)- experienced participants (ATLAS).

***Outcomes/endpoints***

The primary endpoint for both studies was the difference in the proportion of subjects with a 'virologic failure' endpoint (HIV-1 RNA ≥ 50 c/mL) as per FDA Snapshot algorithm in the CAB + RPV arm compared with the comparator arm at Week 48. The key secondary endpoint was the difference in proportion of subjects with Plasma HIV-1 RNA <50 c/mL in the CAB + RPV arm compared with the comparator arm at Week 48 using the FDA Snapshot algorithm. Additionally, the difference in proportion of subjects with confirmed virologic failure (CVF), defined as 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL, in the CAB + RPV arm compared with the comparator arm at Week 48 (ITT-E Population), is considered an important secondary endpoint.

***Randomisation and blinding***

Subjects were randomised 1:1 to each arm (CAB + RPV or CAR), facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG). In the FLAIR study the randomisation was stratified by participants' Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and sex at birth. In ATLAS the randomisation was stratified by baseline 3rd Agent class (PI, INI or NNRTI) and sex by birth.

As these were open-label studies, no blinding was required. Summaries of the study data were not available to sponsor staff prior to the planned Week 48 primary analysis.

In ATLAS-2M, randomization was stratified by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks). A total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W: 524 subjects; Q4W: 525 subjects).

***Statistical methods***

The Cochran Mantel Haenszel test stratified for the used stratification factors in the randomisation procedure is acceptable as the *primary efficacy analysis* method. The primary efficacy analysis was performed for the ITT-E population (all randomised subjects with at least one dose of study drug) and for the PP population (all subjects from the ITT-E population without protocol violations). The results of both analyses have equal importance and should show similar conclusions.

*Non-inferiority*: CAB LA + RPV LA will be declared non-inferior to CAR if the upper limit of the two-sided 95% confidence interval for the difference between the two groups in the proportion of participants with HIV-RNA ≥50 c/mL at Week 48 (defined by the US FDA snapshot algorithm) is below 6%.

The weighted chi-squared test to test *homogeneity* between the strata for each stratification factor with a significance level of 10% is acceptable.

The performed efficacy analysis for the *pooled studies* was based on Cochran Mantel Haenszel test and was adjusted for 10 strata (4 strata from FLAIR and 6 strata from ATLAS) without including a study effect. This is not considered an appropriate analysis for the pooled data and the results are therefore only considered explorative.

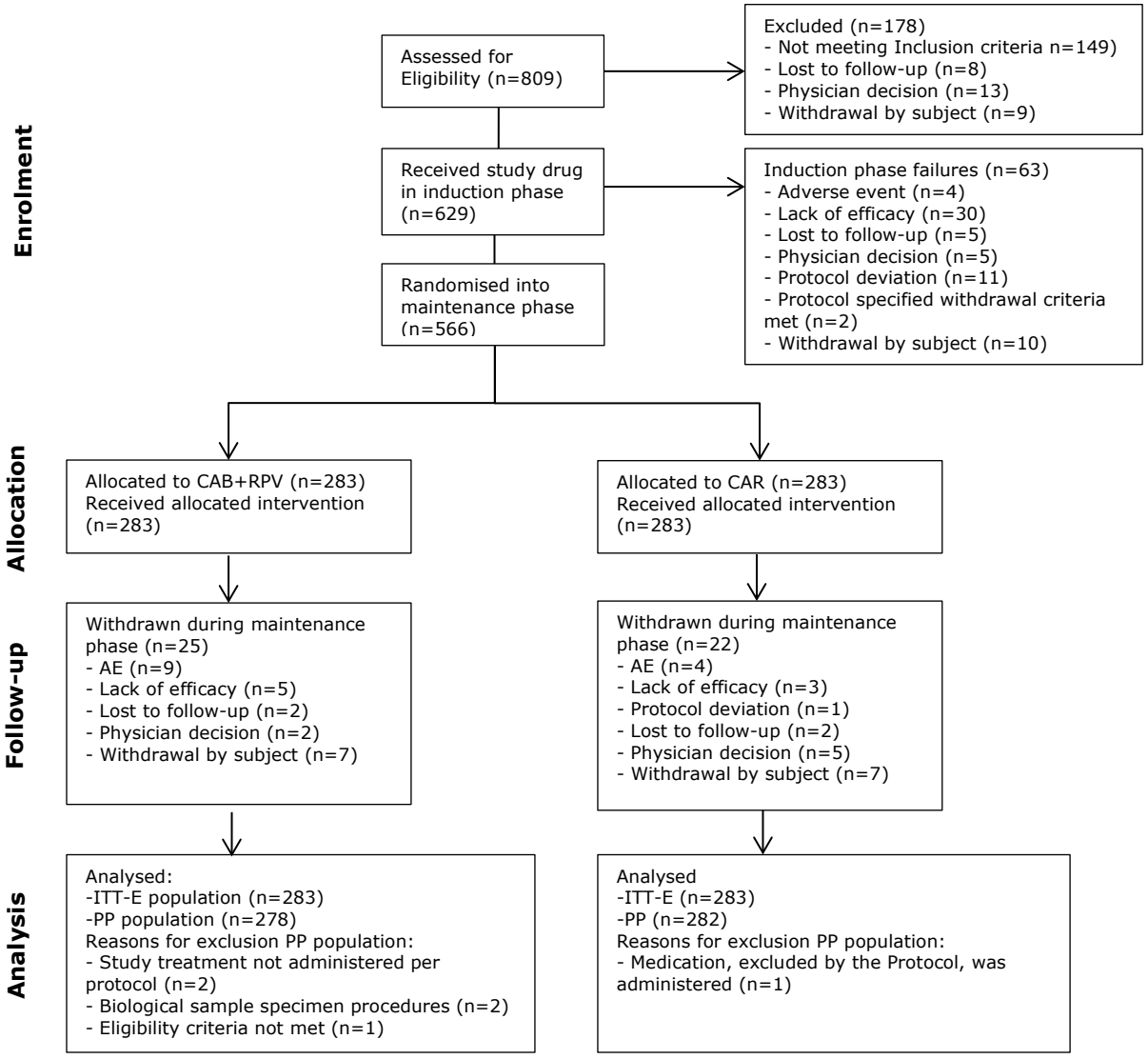
A planned *interim analysis* was performed by an independent data monitoring committee (IDMC) and was only set up for futility testing. As efficacy was not evaluated, no multiplicity adjustment is needed.

The *key secondary efficacy* parameter was analysed with the same method as used with the primary efficacy parameter. Non-inferiority could be claimed if the lower limit of the 95% confidence interval for the difference is above -10%

***Results***

***Participant flow***

**FLAIR (Study 201584)**




First subject first visit: 27 Oct 2016, ongoing study. Last subject last visit for Week 48 analysis: 30 Aug 2018. The data cut-off date for the Week 48 analysis was 18 October 2018.

Included countries (number of randomised subjects: number CAB + RPV arm vs number CAR arm; number of sites): Canada (23: 10 vs 13; 6); France (43: 22 vs 21; 8); Germany (44: 23 vs 21; 11); Italy (38: 14 vs 24; 5); Japan (20: 8 vs 12; 3); Netherlands (5: 2 vs 3; 4); Russian Federation (93: 54 vs 39; 13); South Africa (32: 15 vs 17; 8); Spain (157: 82 vs 75; 18); United Kingdom (25: 16 vs 9; 7); and the United States (86: 37 vs 49; 25).

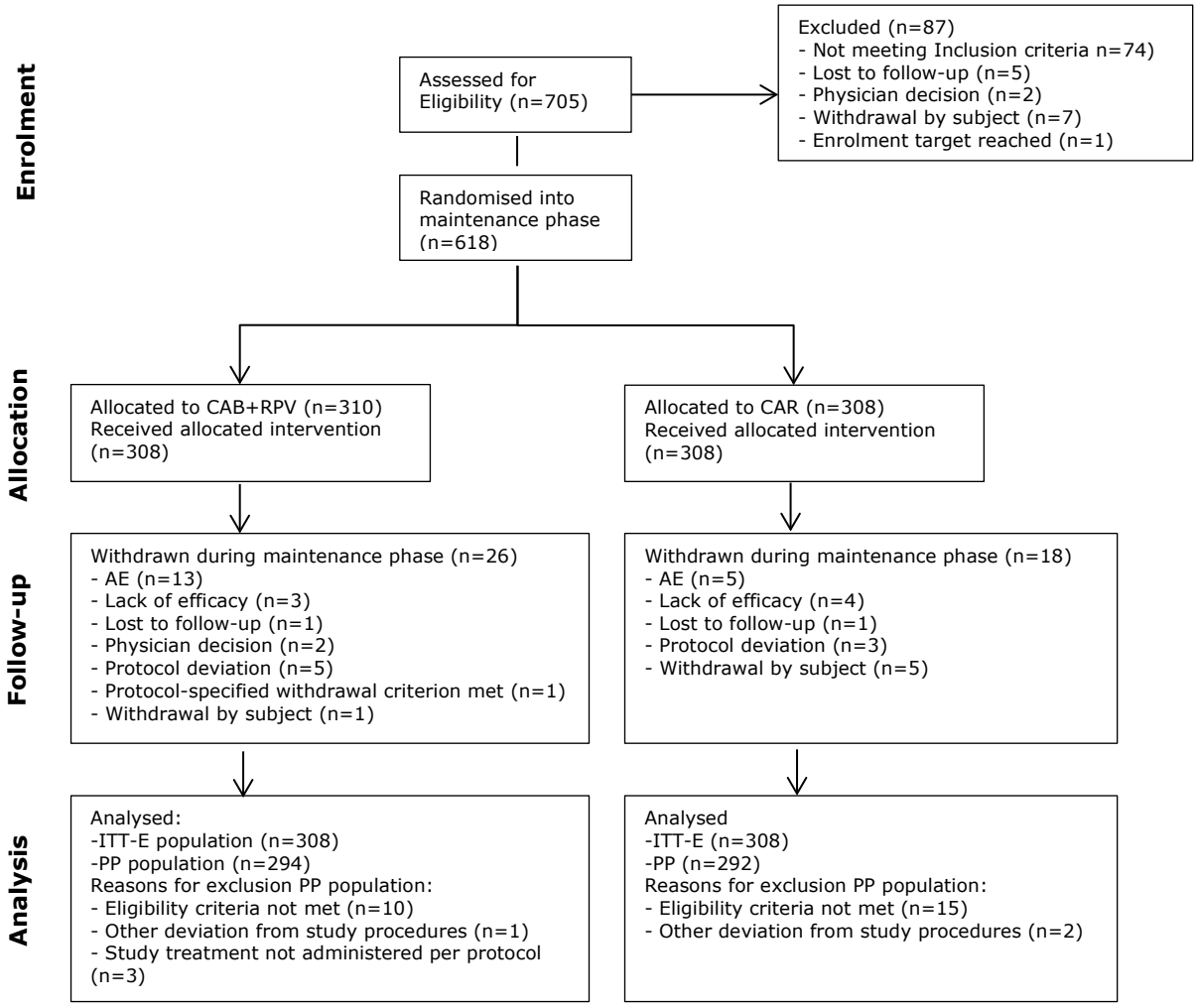



**Figure 8 ATLAS (Study 201585)**

First subject first visit: 28 Oct 2016, ongoing study. Last subject last visit for Week 48 analysis: 29 May 2018. The data cut-off date for the Week 48 analysis was 02 August 2018.

Included countries (number of randomised subjects: number CAB + RPV arm vs number CAR arm; number of sites): Argentina (16: 12 vs 4; 4); Australia (19: 13 vs 6; 4); Canada (34: 17 vs 17; 6); France (32: 17 vs 15; 8); Germany (49: 33 vs 16; 10); Italy (28: 10 vs 18; 2); Korea (19: 11 vs 8; 5); Mexico (10: 6 vs 4; 1); Russia (106: 47 vs 59; 13); South Africa (71: 34 vs 37; 9); Spain (62: 29 vs 33; 15); Sweden (16: 11 vs 5; 3); and United States (156: 70 vs 86; 36).

In both studies, there are several countries with an imbalance in the number of treated subjects between the two arms. The applicant did not include country as a stratification factor, because it would result in too many strata.

In both studies combined, 51 subjects in the CAB + RPV arms were withdrawn during the maintenance phase, vs. 40 in the CAR arms. Ten subjects (5 in each study) were withdrawn from the oral lead-in without receiving any injection. In FLAIR, this was due to hepatitis A virus (n=1); transaminitis (n=1, subject had positive hepatitis C antibody at Screening, and reported illicit drug use on study); hepatitis C virus (n=1); lost to follow-up (n=1) and confirmed virologic failure (n=1, following time off study treatment for false positive pregnancy test). In ATLAS, this was due to AEs (n=2, drug-related headache

and depression suicidal), protocol deviations (n=2), and physician decision due to pregnancy (n=1). Any subject who received at least a single dose of IM CAB and/or RPV and discontinued the regimen for any reason was expected to enter a 52-week Long-Term Follow-Up Phase. For FLAIR, of the 20 subjects that were eligible to enter Long-Term Follow-up at the time of the data cut for this report, 14 subjects entered the Long-Term Follow-Up Phase and 6 subjects withdrew prior to entering Long-Term Follow-Up. Reasons for not entering the Long-Term Follow-Up Phase were not collected. Of the 14 subjects who entered the Long-Term Follow-Up Phase, 13 subjects were ongoing in the Long-Term Follow-Up Phase and 1 subject had completed the Long-Term Follow-Up Phase. From ATLAS, 23 subjects in the CAB + RPV group (either from the Maintenance or Extension Phase) and 3 subjects in CAR group (from injection Extension Phase) entered LTFU. Eight of the 23 subjects have completed LTFU.

Important protocol deviations were reported more frequently in ATLAS (approximately 25% of subjects in each arm) than in FLAIR, and in FLAIR more frequently in the CAB + RPV arm (47 subjects [17%]) compared to the CAR group (14 subjects [5%]). No clear trend of events was noticeable. Several subjects were assigned to the wrong stratum, which could have affected the primary result (bias). Of the 22 mis-randomized subjects in ATLAS, the majority (18 of 22) are incorrect due to misclassification of third agent class. Thus, the main reason for the higher rate in ATLAS compared to FLAIR was due to possible mis-definition of ART class at entry by site or incorrect initial entry of ART and corrected during data monitoring prior to database release.

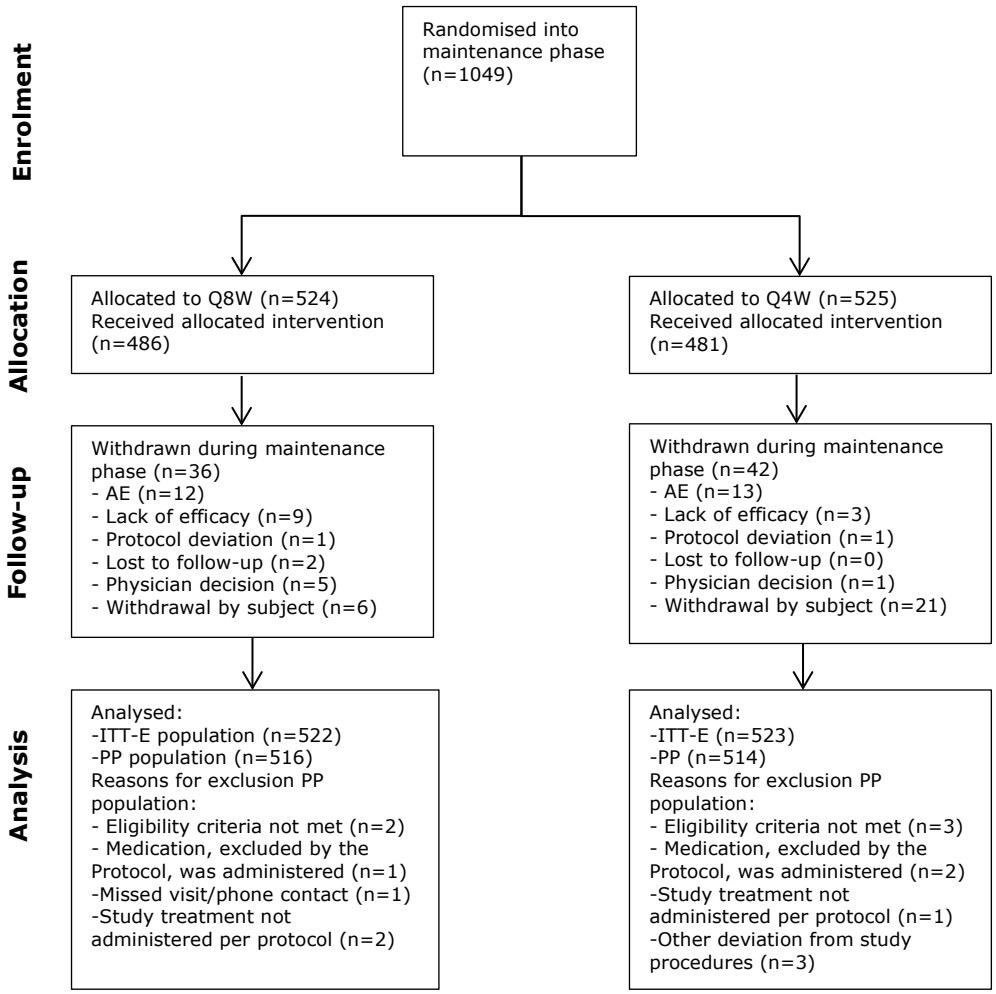



**Figure 9 ATLAS-2M (Study 207966)**

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. A total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W: 524 subjects; Q4W: 525 subjects). Four subjects were randomized but did not receive study treatment (2 subjects each in the Q8W and Q4W groups). The first subject was screened on 27-OCT-2017. The last subject last visit for the Week 48 analysis was 06-JUN-2019. This study is ongoing.

The proportion of subjects withdrawn during the Maintenance Phase was comparable between the 2 treatment groups (Q8W: 36 subjects [7%]; Q4W: 42 subjects [8%]). For the Q8W group, the most common reasons for withdrawal were AEs (12 subjects [2%]) and lack of efficacy (9 subjects [2%] of which 8 were CVF). For the Q4W group, the most common reasons for withdrawal were withdrawal by subject (21 subjects [4%]; mostly due to frequency of study visits or subject relocation) and AEs (13 subjects [2%]).

Similar numbers and types of important protocol deviations were recorded across treatment groups (Q8W: n=116 [22%]; Q4W: n=140 [27%]). Most of the important protocol deviations in both groups were related to assessments or time point completion (Q8W: n=34 [7%]; Q4W: n=38 [7%]) or informed consent (Q8W: n=38 [7%]; Q4W: n=55 [11%]).

***Baseline data***

Demographic and baseline disease characteristics were well balanced across treatment groups in the two studies (see the following 2 tables below). In FLAIR, ~20% of subjects had a baseline HIV-1 RNA load of ≥100.000 copies/mL. CD4 counts were ≥500 cells/mm3 in the far majority of subjects (70%). In ATLAS, subjects had been on treatment for a median of 52 months, which is also reflected in high CD4 counts and undetectable viral load (inclusion criterion). Prior ARV regimens included NNRTIs as 3rd agent in half of the cases, followed by INSTIs (~33% of subjects) and PIs (~17% of subjects). Overall, the study population of both studies consists of asymptomatic, otherwise healthy adult subjects. When comparing across studies, subjects enrolled in ATLAS were slightly older. More subjects were female, as compared to subjects enrolled in FLAIR, which was a pre-specified goal (20% in FLAIR and 25% in ATLAS).

For completeness, the Applicant was requested to provide the time since HIV-1 diagnosis (for both studies) and start of initial ARV treatment (for ATLAS only), but this information was unfortunately not available.

**Table 9. Summary of Demographic Characteristics for FLAIR and ATLAS study (Studies 201584, 201585) and Pooled Data (ITT-E Population)**

| | **FLAIR (201584)** | | **ATLAS (201585)** | | **Pooled** | |
|---|---|---|---|---|---|---|
| **Demographic Characteristic** | **CAB + RPV N=283** | **CAR N=283** | **CAB + RPV N = 308** | **CAR N = 308** | **CAB + RPV N = 591** | **CAR N = 591** |
| **Age (yrs)** | | | | | | |
| Mean | 35.9 | 36.0 | 41.6 | 43.2 | 38.9 | 39.8 |
| Standard Deviation | 10.17 | 9.82 | 9.99 | 11.43 | 10.46 | 11.28 |
| Median | 34.0 | 34.0 | 40.0 | 43.0 | 38.0 | 38.0 |
| Min | 19 | 18 | 21 | 18 | 19 | 18 |

| | FLAIR (201584) | | ATLAS (201585) | | Pooled | |
|---|---|---|---|---|---|---|
| **Demographic Characteristic** | **CAB + RPV N=283** | **CAR N=283** | **CAB + RPV N = 308** | **CAR N = 308** | **CAB + RPV N = 591** | **CAR N = 591** |
| Max | 68 | 68 | 74 | 82 | 74 | 82 |
| **Age, Groups (yrs)** | | | | | | |
| <35 | 143 (51) | 145 (51) | 80 (26) | 80 (26) | 223 (38) | 225 (38) |
| 35 to <50 | 107 (38) | 109 (39) | 162 (53) | 132 (43) | 269 (46) | 241 (41) |
| ≥50 | 33 (12) | 29 (10) | 66 (21) | 96 (31) | 99 (17) | 125 (21) |
| **Sex at Birth, n (%)** | | | | | | |
| Female | 63 (22) | 64 (23) | 99 (32) | 104 (34) | 162 (27) | 168 (28) |
| Male | 220 (78) | 219 (77) | 209 (68) | 204 (66) | 429 (73) | 423 (72) |
| **Height (cm) at Baseline [a]** | | | | | | |
| Mean | 173.6 | 173.5 | 172.2 | 172.5 | 172.9 | 173.0 |
| Standard Deviation | 9.61 | 8.89 | 9.41 | 10.46 | 9.52 | 9.74 |
| Median | 174.0 | 174.0 | 173.0 | 173.0 | 174.0 | 173.0 |
| Min. | 142 | 151 | 139 | 142 | 139 | 142 |
| Max. | 203 | 200 | 198 | 196 | 203 | 200 |
| **Weight (kg) [a]** | | | | | | |
| Mean | 75.72 | 75.11 | 77.69 | 79.50 | 76.75 | 77.40 |
| Standard Deviation | 14.569 | 15.668 | 15.901 | 17.877 | 15.297 | 16.984 |
| Median | 74.0 | 74.0 | 76.00 | 77.55 | 75.00 | 75.20 |
| Min | 46.0 | 36.0 | 41.2 | 48.2 | 41.2 | 36.0 |
| Max | 125.6 | 148.0 | 139.4 | 162.8 | 139.4 | 162.8 |
| **Body Mass Index ($kg/m^2$) at Baseline [a]** | | | | | | |
| Mean | 25.109 | 24.934 | 26.203 | 26.742 | 25.679 | 25.876 |
| Standard Deviation | 4.4190 | 4.8797 | 5.1022 | 5.7692 | 4.8144 | 5.4330 |
| Median | 24.100 | 24.000 | 25.500 | 25.500 | 24.900 | 24.800 |
| Min | 17.3 | 12.6 | 15.30 | 17.80 | 15.30 | 12.60 |
| Max | 44.9 | 47.4 | 50.90 | 57.70 | 50.90 | 57.70 |

| | FLAIR (201584) | | ATLAS (201585) | | Pooled | |
|---|---|---|---|---|---|---|
| **Demographic Characteristic** | **CAB + RPV N=283** | **CAR N=283** | **CAB + RPV N = 308** | **CAR N = 308** | **CAB + RPV N = 591** | **CAR N = 591** |
| **Ethnicity, n (%)** | | | | | | |
| Hispanic / Latino | 28 (10) | 40 (14) | 35 (11) | 34 (11) | 63 (11) | 74 (13) |
| Not Hispanic / Latino | 255 (90) | 243 (86) | 273 (89) | 274 (89) | 528 (89) | 517 (87) |
| **Race, n (%)** | | | | | | |
| American Indian or Alaskan Native | 3 (1) | 6 (2) | 8 (3) | 8 (3) | 11 (2) | 14 (2) |
| Asian-Central/South Asian Heritage | 2 (<1) | 1 (<1) | 1 (<1) | 0 | 3 (<1) | 1 (<1) |
| Asian-East Asian Heritage | 1 (<1) | 2 (<1) | 13 (4) | 8 (3) | 14 (2) | 10 (2) |
| Asian-Japanese Heritage | 8 (3) | 12 (4) | 0 | 0 | 8 (1) | 12 (2) |
| Asian-South East Asian Heritage | 1 (<1) | 0 | 8 (3) | 5 (2) | 9 (2) | 5 (<1) |
| Black or African American | 47 (17) | 56 (20) | 62 (20) | 77 (25) | 109 (18) | 133 (23) |
| Native Hawaiian or Other Pacific Islander | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 1 (<1) |
| White-Arabic/North African Heritage | 5 (2) | 3 (1) | 2 (<1) | 2 (<1) | 7 (1) | 5 (<1) |
| White-White/Caucasian/ European Heritage | 211 (75) | 198 (70) | 212 (69) | 205 (67) | 423 (72) | 403 (68) |
| Multiple | 4 (1) | 3 (1) | 2 (<1) | 2 (<1) | 6 (1) | 5 (<1) |
| **Race Subgroups, n (%)** | | | | | | |
| African American/African Heritage | 47 (17) | 56 (20) | 62 (20) | 77 (25) | 109 (18) | 133 (23) |
| Asian | 12 (4) | 15 (5) | 22 (7) | 13 (4) | 34 (6) | 28 (5) |
| White | 216 (76) | 201 (71) | 214 (69) | 207 (67) | 430 (73) | 408 (69) |
| Other | 8 (3) | 9 (3) | 10 (3) | 11 (4) | 18 (3) | 20 (3) |

Data Source: Mod5.3.5.3/209522 Output/Tab1.07

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

a. 201584 Baseline values = Induction Baseline (Week -20)

**Table 10. Summary of Baseline Characteristics for FLAIR and ATLAS study (Study 201584, Study 201585) and Pooled Data (ITT-E Population)**

| | FLAIR (201584) | | ATLAS (201585) | | Pooled | |
|---|---|---|---|---|---|---|
| | CAB + RPV (N=283) | CAR (N=283) | CAB + RPV (N=308) | CAR (N=308) | CAB + RPV (N=591) | CAR (N=591) |
| **Induction Baseline (Week -20) HIV-1 RNA c/mL, n (%)** | | | | | | |
| <1000 | 9 (3) | 5 (2) | NA | NA | NA | NA |
| 1000 to <10,000 | 64 (23) | 71 (25) | NA | NA | NA | NA |
| 10,000 to <50,000 | 95 (34) | 113 (40) | NA | NA | NA | NA |
| 50,000 to <100,000 | 59 (21) | 38 (13) | NA | NA | NA | NA |
| 100,000 to <200,000 | 30 (11) | 33 (12) | NA | NA | NA | NA |
| ≥200,000 | 26 (9) | 23 (8) | NA | NA | NA | NA |
| **Time from First HIV-1 RNA <50 c/mL until Maintenance Phase Start** | | | | | | |
| Median (Weeks) (IQR) | 16.10 (12.40, 16.10) | 16.10 (15.30, 16.30) | NA | NA | NA | NA |
| **Time Since First ART Until Maintenance Phase Start** | | | | | | |
| Time | 20 weeks [a] | 20 weeks [a] | 52 months [b] (IQR 33, 87) | 52 months [b] (IQR 33, 84) | | |
| **Baseline CD4+ (cells/mm$^3$)** | | | | | | |
| Median (IQR) | 624 (473, 839) | 625 (472, 799) | 654 (497, 816) | 653 (488, 844) | 645 (487, 824) | 641 (480, 821) |
| **Baseline CD4+ (cells/mm$^3$), n (%)** | | | | | | |
| <350 | 19 (7) | 27 (10) | 23 (7) | 27 (9) | 42 (7) | 54 (9) |
| ≥350 to <500 | 64 (23) | 60 (21) | 56 (18) | 57 (19) | 120 (20) | 117 (20) |
| ≥500 | 200 (71) | 196 (69) | 229 (74) | 224 (73) | 429 (73) | 420 (71) |
| **Derived Baseline CDC Classification, n (%)** | | | | | | |
| HIV infection stage 1 | 200 (71) | 196 (69) | 229 (74) | 224 (73) | 429 (73) | 420 (71) |
| HIV infection stage 2 | 78 (28) | 82 (29) | 78 (25) | 83 (27) | 156 (26) | 165 (28) |
| HIV infection stage 3 | 5 (2) | 5 (2) | 1 (<1) | 1 (<1) | 6 (1) | 6 (1) |
| **Induction Baseline (Week -20) Most Prevalent HIV-1 Subtype** | | | | | | |
| A | 46 (16) | 36 (13) | NA | NA | NA | NA |
| B | 174 (61) | 174 (61) | NA | NA | NA | NA |
| C | 18 (6) | 20 (7) | NA | NA | NA | NA |
| **Alternate Background NRTI at End of Induction Phase, n (%)** | | | | | | |
| 3TC and ABC | 1 (<1) | 1 (<1) | NA | NA | NA | NA |
| FTC/TAF | 3 (1) | 3 (1) | NA | NA | NA | NA |
| FTC/TDF | 9 (3) | 10 (4) | NA | NA | NA | NA |
| 3TC and TDF | 2 (<1) | 1 (<1) | NA | NA | NA | NA |
| **Baseline Third Agent Class, n (%)** | | | | | | |
| NNRTI | NA | NA | 155 (50) | 155 (50) | NA | NA |
| INSTI | NA | NA | 102 (33) | 99 (32) | NA | NA |
| PI | NA | NA | 51 (17) | 54 (18) | NA | NA |
| **Hepatitis B, n (%)** | | | | | | |
| Non-reactive | 282 (>99) [c,d] | 283 (100) [c] | 308 (100) | 308 (100) | NA | NA |
| **Hepatitis C, n (%)** | | | | | | |
| Non-reactive | 264 (93) | 274 (97) | 285 (93) | 277 (90) | NA | NA |
| Reactive | 19 (7) | 9 (3) | 23 (7) | 31 (10) | NA | NA |

Data Source: Mod5.3.5.1/201584 W48 CSR/Tab1.25, Tab1.29, Tab1.37, Tab1.42, and Tab1.43; Mod5.3.5.1/201585 W48 CSR/Tab1.19, Tab1.31, Tab1.32; Mod5.3.5.3/209522 Output/Tab1.08 and Tab1.09

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

a. Represents the 20-week Induction period for Study 201584
b. Median results are presented
c. Status at Induction Baseline (Week -20) for Study 201584
d. 1 subject was not excluded from the study because HBV result was non-reactive based on local labs.

***Numbers analysed***

The ITT-E population consisted of all randomly assigned subjects who received at least one dose of study drug. Subjects were assessed according to their randomized treatment, regardless of the treatment they received.

The PP population included all subjects in the ITT-E population with the exception of major protocol violators. In FLAIR, a total of 6 subjects were excluded from the PP Population. Reasons for exclusion from the PP Population were Study treatment not administered per-protocol (n=2 in CAB + RPV arm), Biological sample specimen procedures (n=2 in CAB + RPV arm), Medication, excluded by the Protocol, was administered (n=1 in CAR arm), and Eligibility criteria not met (n=1 in CAB + RPV arm). In ATLAS, a total of 30 subjects were excluded from the PP Population. Reasons for exclusion from the PP Population were Eligibility criteria not met (n=10 in CAB + RPV arm, n=15 in CAR arm), Study treatment not administered per-protocol (n=3 in CAB + RPV arm), and Other deviation from study procedures (n=1 in CAB + RPV arm, n=2 in CAR arm).

**Table 11 ITT-E population and PP population**

| | ITT-E population | | PP population | |
|---|---|---|---|---|
| | CAB+RPV | CAR | CAB+RPV | CAR |
| **FLAIR** | 283 | 283 | 278 | 282 |
| **ATLAS** | 308 | 308 | 294 | 292 |
| ***Pooled*** | *591* | *591* | *572* | *574* |

***Outcomes and estimation***

**Primary Efficacy Results: Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot Analysis)**

Both studies met their primary objective as the upper bound of the 95% CI for the adjusted treatment difference was below the non-inferiority margin of 6% for both analysis populations (Table 12,Table 19)

**Table 12. Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584 (FLAIR), Study 201585 (ATLAS), 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) | | |

Data Source: Mod5.3.5.3/209522 Output/Tab2.01

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 Control (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.

**Table 13. Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584 (FLAIR), Study 201585 (ATLAS), 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: Mod5.3.5.3/209522 Output/Tab2.03

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.

The Applicant was requested to re do the primary efficacy analyses, as the ITT-E primary efficacy analyses should include the randomised strata instead of the actual strata, and the PP primary efficacy analyses should additionally exclude all subjects with a mis-randomisation. Also the Homogeneity tests (see below) was re-done. The outcome of these analyses does not change the overall interpretation of the outcome of the studies.

One site (FLAIR Center Number 227256, ATLAS Center Number 227253, located in Free State, South Africa) was identified as having extensive and persistent GCP non-compliance issues. Two additional sensitivity analyses were requested: one in which the subjects enrolled at the GCP non-compliant site are counted as failures, and one in which the subjects enrolled at this site were excluded from the analysis. These sensitivity analyses were performed for the PP population (excluding the mis-randomised subjects) and ITT-E population (including the randomised strata) and did not change the overall interpretation of the studies.

Primary efficacy subgroup analyses were performed for each stratification factor used in the randomisation procedure. The consistency of the treatment effect between the strata for each stratification factor was tested by the weighted chi-squared test. All performed tests of homogeneity were non-significant (p-value ≥0.10). However, there seems to be a higher percentage of virologic failures for females in the CAB + RPV arm compared to the CAR arm (4.8% vs. 1.6% in FLAIR, 2.0% vs. 0% in ATLAS), which will be further discussed in "Ancillary analyses".

**ATLAS-2M**

Q8W CAB LA + RPV LA was noninferior to Q4W CAB LA + RPV LA in maintaining virologic suppression in HIV-1 infected subjects at Week 48, with few subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot Algorithm in either group for the ITT-E population. The upper bound of 95% CI for the adjusted treatment difference between Q8W and Q4W was 2.2%, which was 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 14 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) | | |

Data Source: Table 2.1, Table 2.2.

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).

Note: The 2 subjects with HIV-1 RNA ≥50 c/mL in the Q8W group were excluded from the PP Population for the following protocol deviations: 1 did not meet eligibility criteria and another did not have study treatment administered per protocol (Data Source: Listing 7, Figure 2.8).

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 15 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).

**Key Secondary Efficacy Endpoint (Proportion of subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm).**

In FLAIR and ATLAS once-monthly CAB + RPV was non-inferior to CAR based on the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48. The lower bound of 95% CI for the adjusted treatment difference between CAB + RPV and CAR was greater than the pre-defined non-inferiority margin of -10%. Snapshot outcomes at Week 48, based on the ITT-E population, are shown in the table below.

**Table 16. Snapshot outcomes at Week 48 (ITT-E)**

| Outcome | 201584 | | 201585 | | Pooled Data | |
|---|---|---|---|---|---|---|
| | CAB + RPV n (%) N=283 | CAR n (%) N=283 | CAB + RPV n (%) N=308 | CAR n (%) N=308 | CAB + RPV n (%) N=591 | CAR n (%) N=591 |
| HIV-1 RNA <50 c/mL | 265 (93.6) | 264 (93.3) | 285 (92.5) | 294 (95.5) | 550 (93.1) | 558 (94.4) |
| HIV-1 RNA ≥50 c/mL | 6 (2.1) | 7 (2.5) | 5 (1.6) | 3 (1.0) | 11 (1.9) | 10 (1.7) |
| Data in window not below threshold | 2 (0.7) | 2 (0.7) | 1 (0.3) | 1 (0.3) | 3 (0.5) | 3 (0.5) |
| Discontinued for lack of efficacy | 4 (1.4) | 3 (1.1) | 3 (1.0) | 2 (0.6) | 7 (1.2) | 5 (0.8) |
| Discontinued for other reason while not below threshold | 0 | 2 (0.7) | 1 (0.3) | 0 | 1 (0.2) | 2 (0.3) |
| Change in background therapy | 0 | 0 | 0 | 0 | 0 | 0 |
| No Virologic Data | 12 (4.2) | 12 (4.2) | 18 (5.8) | 11 (3.6) | 30 (5.1) | 23 (3.9) |
| Discontinued study due to AE or death | 8 (2.8) | 2 (0.7) | 11 (3.6) | 5 (1.6) | 19 (3.2) | 7 (1.2) |
| Discontinued study for other reasons | 4 (1.4) | 10 (3.5) | 7 (2.3) | 6 (1.9) | 11 (1.9) | 16 (2.7) |
| On study but missing data in window | 0 | 0 | 0 | 0 | 0 | 0 |

Data Source: Mod5.3.5.3/209522 Output/Tab2.05

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

An important secondary endpoint in both studies was the proportion of subjects with confirmed virologic failure (CVF), defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL, at week 48. Overall, 7/591 (1.2%) subjects in each arm met CVF criteria through Week 48 (see table below). Please refer to the PD section of this report for more information and discussion regarding virologic failures.

**Table 17. Cumulative Summary of Confirmed Virologic Failure by Visit in Studies 201584 (FLAIR), 201585 (ATLAS) and Pooled Data (ITT-E Population)**

| Time Point | FLAIR (201584) | | ATLAS (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 (%) |
| Week 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Week 8 | 1 (0.4) | 1 (0.4) | 1 (0.3%) | 0 | 2 (0.3) | 1 (0.2) |
| Week 12 | 1 (0.4) | 2 (0.7) | 2 (0.6) | 0 | 3 (0.5) | 2 (0.3) |
| Week 16 | 1 (0.4) | 3 (1.1) | 2 (0.6) | 0 | 3 (0.5) | 3 (0.5) |
| Week 20 | 2 (0.7) | 3 (1.1) | 2 (0.6) | 2 (0.6) | 4 (0.7) | 5 (0.8) |
| Week 24 | 2 (0.7) | 3 (1.1) | 3 (1.0) | 2 (0.6) | 5 (0.8) | 5 (0.8) |
| Week 28 | 3 (1.1) | 3 (1.1) | 3 (1.0) | 2 (0.6) | 6 (1.0) | 5 (0.8) |
| Week 32 | 3 (1.1) | 3 (1.1) | 3 (1.0) | 3 (1.0) | 6 (1.0) | 6 (1.0) |
| Week 36 | 3 (1.1) | 3 (1.1) | 3 (1.0) | 3 (1.0) | 6 (1.0) | 6 (1.0) |
| Week 40 | 3 (1.1) | 3 (1.1) | 3 (1.0) | 4 (1.3) | 6 (1.0) | 7 (1.2) |
| Week 44 | 3 (1.1) | 3 (1.1) | 3 (1.0) | 4 (1.3) | 6 (1.0) | 7 (1.2) |
| Week 48 | 4 (1.4) | 3 (1.1) | 3 (1.0) | 4 (1.3) | 7 (1.2) | 7 (1.2) |

Data Source: Mod5.3.5.3/209522 Output/Tab2.09
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: The summary is the proportion of CVF up to the analysis visit.
Note: 1 subject with CVF did not have resistance testing performed. This subject had a pause in oral therapy because of a false positive pregnancy, resulting in CVF and study withdrawal prior to initiating LA therapy.

Adherence to CAB + RPV dosing schedule was high, of 3577 injection visits in FLAIR, 98% of injections were given within the allowed ±7 days of the planned dosing visit day. Similarly, in ATLAS 98% of the 3343 injections were given within the allowed ±7 days of the planned dosing visit day.

A total of 65 visits in FLAIR, and 87 visits in ATLAS, occurred outside the allowed ±7 days. Of these, 18 occurred between -8 and -14 days, 42 occurred between +8 and +14 days and 5 visits occurred after more than 14 days. In the two studies combined, 9 injections were missed by subjects in the CAB + RPV group. Oral bridging was used to deliver CAB + RPV at 8 of the missing injection visits. One of the missed injections was not covered by oral bridging.

ATLAS-2M

Plasma HIV-1 RNA <50 c/mL at Week 48 Snapshot Algorithm

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

**Table 18 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.

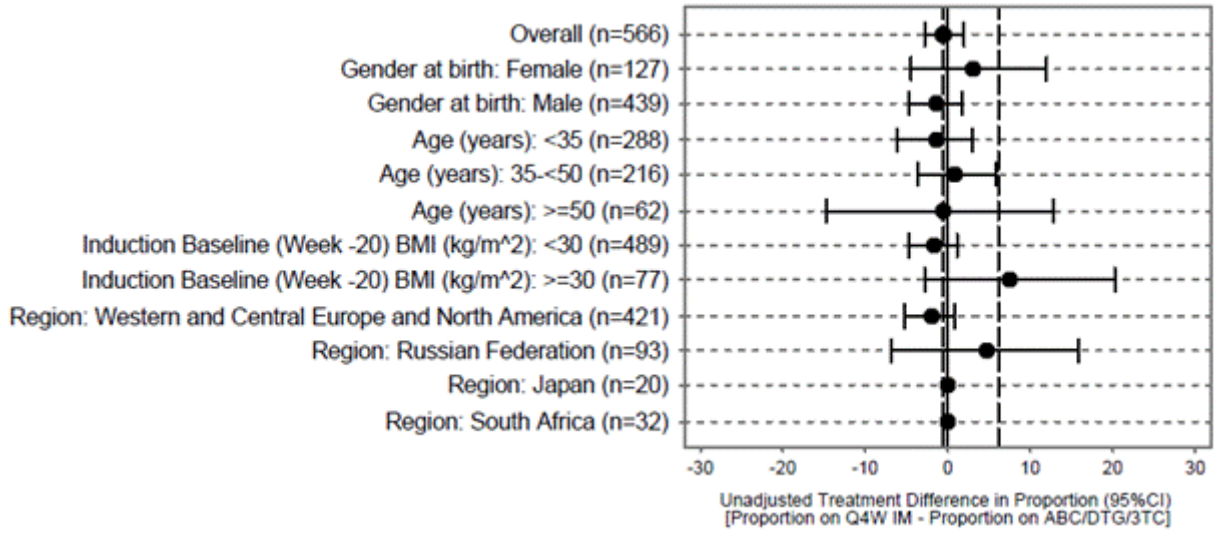
a. Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W.

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).

***Ancillary analyses***

Forest plots for selected subgroups, displaying the treatment difference estimate for each subgroup along with the associated 95% CI, are provided (Table 19,Figure 10,Figure 11).

**Figure 10. 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**



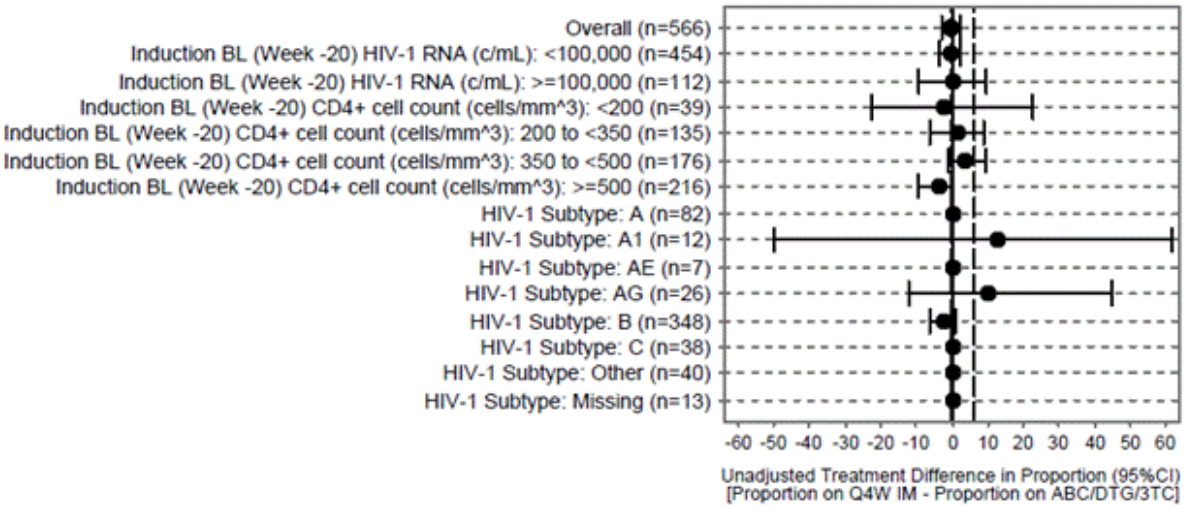

Data Source: Mod5.3.5.1/201584 W48 CSR/Fig2.11

Note: Q4W IM = CAB + RPV group, ABC/DTG/3TC = CAR

Note: The dashed reference line on the right at 6% represents the non-inferiority margin while the dashed reference line on the left represents the overall difference in proportion CAB + RPV - CAR (unadjusted).

Note: 95% CIs were calculated using the normal approximation for overall and using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic for the subgroups.

**Figure 11. 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**




Data Source: Mod5.3.5.1/201584 W48 CSR/Fig2.12
Note: Q4W IM = CAB + RPV group, ABC/DTG/3TC = CAR
Note: The dashed reference line on the right at 6% represents the non-inferiority margin while the dashed reference line on the left represents the overall difference in proportion CAB + RPV - CAR (unadjusted).
Note: 95% CIs were calculated using the normal approximation for overall and using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic for the subgroups.

**Table 19. Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 in Study 201585 (ATLAS) by Select Subgroup (Maintenance Phase) - Snapshot Analysis - (ITT-E Population)**

| Subgroups | Analysis Strata | Treatment | N | Number of Virologic Failures/ 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 - <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) | |

Data Source: Mod5.3.5.1/201585 W48 CSR/Tab2.40
Note: Results for countries, Baseline viral load, and Baseline CDC category are provided in Study 201585 Data Source Table 2.40
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.
a. Difference: Proportion on CAB + RPV - Proportion on CAR (unadjusted). 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.

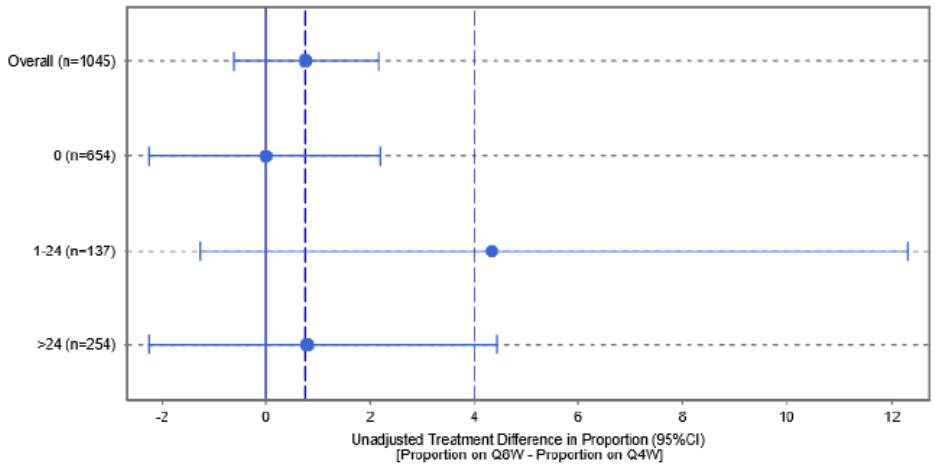
ATLAS-2M

Treatment differences for the primary endpoint for each randomization stratification stratum (prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks) is as follows:

**Table 20 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-IIT-E population.**

| 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.




Data Source: Figure 2.2.
Note: The dashed reference line on the right at 4% represents the non-inferiority margin. Note: The dashed reference line on the left represents the overall difference in proportion Q8W-Q4W (unadjusted). Note: 95% CIs were calculated using the normal approximation for overall, and using an unconditional exact method with two inverted one-sided tests based on the score statistic for the subgroups.

**Figure 12 Unadjusted Treatment Difference in proportion ( 95% CI) of subjects with HIV RNA ≥ 50 c/ml at week 48 by prior exposure to CAB+RPV. Snapshot Algorithm. ITT-E population**

The test of evidence against homogeneity of the treatment difference was not statistically significant for prior exposure to CAB + RPV (p=0.346), with CIs in each stratum largely overlapping with the CI for the overall treatment effect.

Treatment differences on the primary endpoint (proportion of subjects with HIV-1 RNA≥50 at Week 48 [Snapshot algorithm]) were generally consistent across the strata within the following subgroups: demographic factors (age, gender, race, BMI), Baseline CDC stage of disease, Baseline viral load, Baseline CD4+ lymphocyte count, and participating countries. 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).

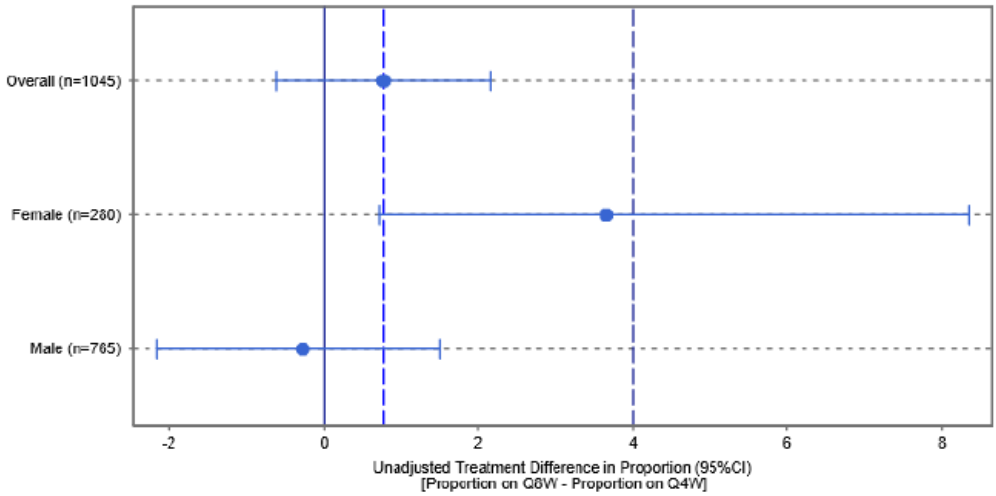
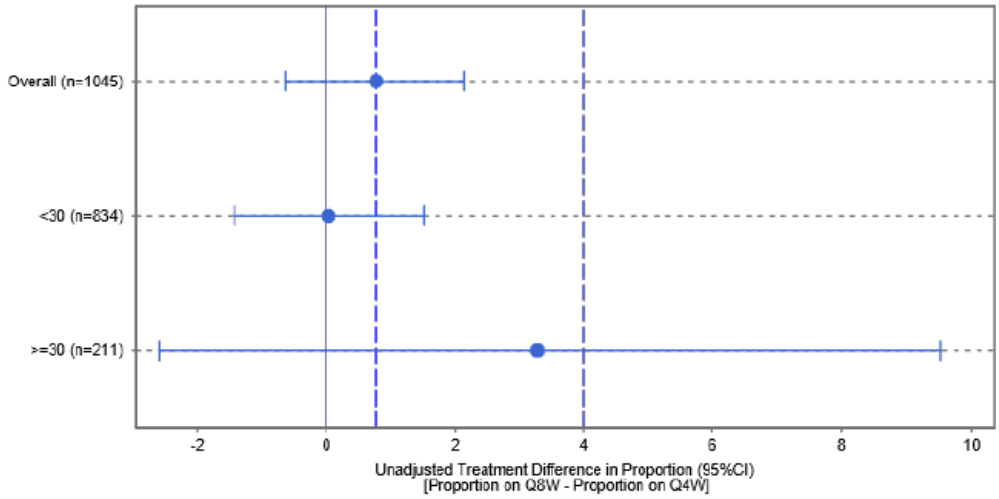



**Figure 13 Unadjusted Treatment Difference in proportion (95% CI) of subjects with HIV RNA ≥ 50 c/ml at week 48 by sex at birth. Snapshot Algorithm. ITT-E population**




Data Source: Figure 2.2.
Note: The dashed reference line on the right at 4% represents the non-inferiority margin. Note: The dashed reference line on the left represents the overall difference in proportion Q8W-Q4W (unadjusted). Note: 95% CIs were calculated using the normal approximation for overall, and using an unconditional exact method with two inverted one-sided tests based on the score statistic for the subgroups.

**Figure 14 Unadjusted Treatment Difference in proportion (95% CI) of subjects with HIV RNA ≥ 50 c/ml at week 48 by by baseline BMI (kg/m$^2$). Snapshot Algorithm. ITT-E population**

Secondary endpoints

Treatment differences for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 for each randomization stratum (prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks) is as follows:

**Table 21 Proportion of Subjects with Plasma HIV-1 RNA < 50 c/ml at week 48 by randomization strata (maintenance phase) Snapshot Algorithm. ITT-E population**

| Analysis Strata | Weeks | Treatment | N | Number of HIV-1 RNA <50 c/mL/ Total Assessed (%) | Difference in Proportion (95% CI)[a, b] |
|---|---|---|---|---|---|
| Prior Exposure to CAB + RPV) | 0 | Q8W | 327 | 306/ 327 (94) | 1.8 (-2.3, 6.0) |
| | | Q4W | 327 | 300/ 327 (92) | |
| | 1-24 | Q8W | 69 | 66/ 69 (96) | 0.1 (-8.3, 8.6) |
| | | Q4W | 68 | 65/ 68 (96) | |
| | >24 | Q8W | 126 | 120/ 126 (95) | -1.6 (-7.4, 3.7) |
| | | Q4W | 128 | 124/ 128 (97) | |
| P-value for Test of Homogeneity[c] | | | | | 0.550 |

Data Source: Table 2.10.
a. Unadjusted Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W.
b. 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.
c. 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.
Note: Randomization strata are rederived using the prior exposure to CAB + RPV in Study 201585, collected from eCRF.

The test of evidence against homogeneity of the treatment difference was not statistically significant for prior exposure to CAB + RPV (p=0.550).

Results for subgroups (age, gender, race, BMI, Baseline CDC stage of disease, Baseline viral load, Baseline CD4+ lymphocyte count, participating countries) were similar to those for the overall population and were similar between treatment groups.

- ***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 22 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.

**Global Health Outcomes**

Subjects receiving CAB + RPV injections reported a significant improvement in treatment satisfaction compared with daily oral antiretroviral therapy. When measured by HIV-TSQ, the HIV-Treatment Satisfaction Questionnaire, the difference in treatment satisfaction, by HIV-TSQc (change) in FLAIR at Week 48 was +4.1 (95% CI: 2.8, 5.5) and HIV-TSQs (status) in ATLAS at Week 44 was +5.7 (95% CI: 4.37, 7.0).

Based on the outcomes reported above, subjects seemed generally satisfied with the LA treatment regimen. This is reassuring.

***Summary of main efficacy results***

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

**Table 23. Summary of efficacy for trial 201584 (FLAIR)**

| | | | |
|---|---|---|---|
| **Title:** A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-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: Week 48 - Primary Endpoint | | | |
| Study identifier | 201584 (FLAIR), EudraCT 2016-001646-25 | | |
| Design | Open-label, randomized, multicentre, parallel-group study | | |
| | Duration of Run-in phase:<br>Duration of Oral Lead-in:<br>Duration of Main phase:<br>Duration of Extension phase: | | 20 weeks<br>4 weeks<br>96 weeks<br>After main phase, duration not specified |
| Hypothesis | Non-inferiority (maintenance of virologic suppression) | | |
| Treatments groups | CAB + RPV | | Cabotegravir + Rilpivirine, 100 weeks, n=283 |
| | ABC/DTG/3TC or DTG+2NRTIs | | Abacavir + Dolutegravir + Lamivudine (Triumeq), or Dolutegravir + 2 NRTIs if HLA-B57, 100 weeks, n=283 |
| Endpoints and definitions | Primary endpoint | HIV-1 RNA $\geq$ 50 c/mL | Difference in proportion of subjects with a 'virologic failure' endpoint (HIV-1 RNA $\geq$ 50 c/mL) as per FDA Snapshot algorithm in the CAB + RPV arm compared with the ABC/DTG/3TC arm at Week 48. |
| | Key Secondary endpoint | HIV-1 RNA $<$ 50 c/mL | Difference in proportion of subjects with Plasma HIV-1 RNA <50 c/mL in the CAB + RPV arm compared with the ABC/DTG/3TC arm at Week 48 using the FDA Snapshot algorithm. |
| | Secondary endpoint | CVF | Difference in proportion of subjects with CVF (2 consecutive plasma HIV-1 RNA levels $\geqslant$ 200 c/mL after prior suppression to <200 c/mL) in the CAB + RPV arm compared with the ABC/DTG/3TC arm at Week 48 (ITT-E Population). |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Intent to treat (ITT-E)<br>Week 48 | | |
| Descriptive statistics and estimate variability | Treatment group | CAB + RPV | ABC/DTG/3TC |
| | Number of subjects | 283 | 283 |
| | **Virologic failure (n/N (%))** | **6/283 (2.1%)** | **7/283 (2.5%)** |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint (ITT-E) | Comparison groups | CAB+RPV vs ABC/DTG/3TC |
| | | Adjusted difference in proportion | -0.4% |
| | | (95% CI) | (-2.8, 2.1) |
| Analysis population and time point description | Per Protocol (PP)<br>Week 48 | | |
| Descriptive statistics and estimate variability | Treatment group | CAB + RPV | ABC/DTG/3TC |
| | Number of subjects | 278 | 282 |
| | **Virologic failure (n/N (%))** | **6/278 (2.2)** | **7/282 (2.5)** |
| Effect estimate per comparison | Primary endpoint (PP) | Comparison groups | CAB+RPV vs ABC/DTG/3TC |
| | | Adjusted difference in proportion | -0.3 |
| | | (95% CI) | (-2.8, 2.2) |
| **Analysis description** | **Secondary Analyses** | | |
| Analysis population and time point description | Intent to treat<br>Week 48 | | |
| Descriptive statistics and estimate variability | Treatment group | CAB + RPV | ABC/DTG/3TC |
| | Number of subjects | 283 | 283 |
| | **Virologic success (n/N (%))** | **265/283 (94%)** | **264/283 (93%)** |
| Effect estimate per comparison | Key Secondary endpoint | Comparison groups | CAB+RPV vs ABC/DTG/3TC |
| | | Adjusted difference in proportion | 0.4% |
| | | (95% CI) | (-3.7, 4.5) |
| Descriptive statistics and estimate variability | Treatment group | CAB + RPV | ABC/DTG/3TC |
| | Number of subjects | 283 | 283 |
| | **CVF (n/N (%))** | **4/283 (1.4%)** | **3/283 (1.1%)** |
| Effect estimate per | Secondary endpoint | Comparison groups | CAB+RPV vs ABC/DTG/3TC |
| | | Difference in proportion | 0.3% |
| | | (95% CI) | ? |

**Table 24. Summary of efficacy for trial 201585 (ATLAS)**

| | |
|---|---|
| **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: Week 48 - Primary Endpoint | |
| Study identifier | 201585 (ATLAS), EudraCT 2016-001647-39 |

| | | | | |
|---|---|---|---|---|
| Design | Open-label, randomized, multicentre, parallel-group study | | | |
| | Duration of Oral lead-in:<br>Duration of Main phase:<br>Duration of Extension | | 4 weeks<br>48 weeks<br>After main phase, duration not specified | |
| Hypothesis | Non-inferiority (maintenance of virologic suppression) | | | |
| Treatments groups | CAB + RPV | | Cabotegravir + Rilpivirine, 48 weeks, n=308 | |
| | Current antiviral regimen (CAR) | | PI-, NNRTI-, or INSTI-based regimen with 2 NRTI backbone, 52 weeks, n=308 | |
| Endpoints and definitions | Primary endpoint | HIV-1 RNA ≥ 50 c/mL | Difference in proportion of subjects with a 'virologic failure' endpoint (HIV-1 RNA ≥ 50 c/mL) as per FDA Snapshot algorithm in the CAB + RPV arm compared with the CAR arm at Week 48. | |
| | Key Secondary endpoint | HIV-1 RNA < 50 c/mL | Proportion of subjects with Plasma HIV-1 RNA <50 c/mL in the CAB + RPV arme compared with the CAR arm at Week 48 using the FDA Snapshot algorithm. | |
| | Secondary endpoint | CVF | Proportion of subjects with CVF (2 consecutive plasma HIV-1 RNA levels ⩾200 c/mL after prior suppression to <200 c/mL) in the CAB + RPV arme compared with the CAR arm at Week 48 (ITT-E Population). | |
| **Results and Analysis** | | | | |
| **Analysis description** | **Primary Analysis** | | | |
| Analysis population and time point description | Intent to treat (ITT-E)<br>Week 48 | | | |
| Descriptive statistics and estimate variability | Treatment group | | CAB + RPV | CAR |
| | Number of subjects | | 308 | 308 |
| | **Virologic failure (n/N (%))** | | **5/308 (1.6%)** | **3/308 (1.0%)** |
| Effect estimate per comparison | Primary endpoint (ITT-E) | | Comparison groups | CAB+RPV vs CAR |
| | | | Adjusted difference in proportion | 0.7% |
| | | | (95% CI) | (-1.2, 2.5) |
| Analysis population and time point description | Per Protocol (PP)<br>Week 48 | | | |
| Descriptive statistics and estimate variability | Treatment group | | CAB + RPV | CAR |
| | Number of subjects | | 294 | 292 |
| | **Virologic failure (n/N (%))** | | **4/294 (1.4%)** | **3/292 (1.0%)** |
| Effect estimate per comparison | Primary endpoint (PP) | | Comparison groups | CAB+RPV vs CAR |
| | | | Adjusted difference in proportion | 0.3% |

| | | | |
|---|---|---|---|
| | | (95% CI) | (-1.4 2.1) |
| **Analysis description** | **Secondary Analyses** | | |
| Analysis population and time point description | Intent to treat<br>Week 48 | | |
| Descriptive statistics and estimate variability | Treatment group | CAB + RPV | CAR |
| | Number of subjects | 308 | 308 |
| | **Virologic success (n/N (%))** | **285/308 (93%)** | **294/308 (96%)** |
| Effect estimate per comparison | Key Secondary endpoint | Comparison groups | CAB+RPV vs CAR |
| | | Adjusted difference in proportion | -3.0% |
| | | (95% CI) | (-6.7, 0.7) |
| Descriptive statistics and estimate variability | Treatment group | CAB + RPV | CAR |
| | Number of subjects | 308 | 308 |
| | **CVF (n/N (%))** | **3/308 (1.0%)** | **4/308 (1.3%)** |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | CAB+RPV vs CAR |
| | | Difference in proportion | -0.3% |
| | | (95% CI) | ? |

**Table 25. Summary of efficacy for trial 207966 (ATLAS-2M)**

| Title: A Phase IIIb, Randomized, Multicenter, Parallel-group, Noninferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every 8 Weeks or Every 4 Weeks in HIV-1-infected Adults who are Virologically Suppressed | | | |
|---|---|---|---|
| Study identifier | Study 207966 (ATLAS-2M) | | |
| Design | Open-label, randomized, multicenter, parallel-group study | | |
| | Duration of Oral Lead-in: Duration of oral lead-in: 4 weeks (only applicable to subjects who were not transitioning from the ATLAS Study 201585)<br>Duration of Main phase: 96 Weeks<br>Duration of Extension phase: After main phase, duration not specified | | |
| Hypothesis | Non-inferiority (maintenance of virologic suppression) | | |
| Treatments groups | IM CAB + RPV Q8W | | Cabotegravir + Rilpivirine, 100 weeks, n=522 |
| | IM CAB + RPV Q4W | | Cabotegravir + Rilpivirine, 100 weeks, n=523 |
| Endpoints and definitions | Primary endpoint | To demonstrate non-inferior antiviral activity of Q8W vs Q4W dosing (HIV RNA ≥50 c/mL) | Proportion of subjects with plasma HIVRNA ≥50 copies/mL as per FDA Snapshot algorithm at Week 48 (ITT-E population) |

| | | | | |
|---|---|---|---|---|
| | Key Secondary endpoint | To demonstrate antiviral activity of Q8W vs Q4W dosing (HIV-1 RNA < 50 c/mL) | Proportion of subjects with plasma HIV-1 RNA <50 c/mL (c/mL) at Week 24, Week 48 and Week 96 using the FDA Snapshot algorithm (ITT-E population) | |
| | Secondary endpoint | CVF | Difference in proportion of subjects with CVF (2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) in the Q8W vs the Q4W arm at Week 48 (ITT-E Population) | |
| Database lock | 06-JUN-2019 | | | |
| **Results and Analysis** | | | | |
| **Analysis description** | **Primary Analysis** | | | |
| Analysis population and time point description | Intent to treat (ITT-E)<br>Week 48 | | | |
| Descriptive statistics and estimate variability | Treatment group | | IM CAB + RPV Q8W | IM CAB + RPV Q4W |
| | Number of subjects | | 522 | 523 |
| | **Virologic failure (n/N (%))** | | **9/522 (1.7%)** | **5/523 (1.0%)** |
| Effect estimate per comparison | Primary endpoint (ITT-E) | | Comparison groups | Q8W vs Q4W |
| | | | Adjusted difference in proportion | 0.8% |
| | | | (95% CI) | (-0.6, 2.2) |
| Analysis population and time point description | Per Protocol (PP)<br>Week 48 | | | |
| Descriptive statistics and estimate variability | Treatment group | | IM CAB + RPV Q8W | IM CAB + RPV Q4W |
| | Number of subjects | | 516 | 514 |
| | **Virologic failure (n/N (%))** | | **7/516 (1.4)** | **5/514 (1.0)** |
| Effect estimate per comparison | Primary endpoint (PP) | | Comparison groups | Q8W vs Q4W |
| | | | Adjusted difference in proportion | 0.4 |
| | | | (95% CI) | (-0.9, 1.7) |
| **Analysis description** | **Secondary Analyses** | | | |
| Analysis population and time point description | Intent to treat<br>Week 48 | | | |
| onDescriptive statistics and estimate variability | Treatment group | | IM CAB + RPV Q8W | IM CAB + RPV Q4W |
| | Number of subjects | | 522 | 523 |
| | **Virologic success (n/N (%))** | | **492/522 (94%)** | **489/523 (93%)** |
| Effect estimate per comparison | Key Secondary endpoint | | Comparison groups | Q8W vs Q4W |
| | | | Adjusted difference in proportion | 0.8% |

| | | | |
|---|---|---|---|
| | | (95% CI) | (-2.1, 3.7) |
| Descriptive statistics and estimate variability | Treatment group | IM CAB + RPV Q8W | IM CAB + RPV Q4W |
| | Number of subjects | 522 | 523 |
| | **CVF (n/N (%))** | **8/522 (1.5%)** | **2/523 (<1%)** |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | Q8W vs Q4W |
| | | Difference in proportion | 1.1% |
| | | (95% CI) | ? |

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

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, 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.

**Table 26 Baseline factors and virologic successes.**

| 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<br>(95% Confidence Interval) | 980/1039 (94.3)<br>(92.74%, 95.65%) | 13/1039 (1.25)<br>(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%

## Clinical studies in special populations

There is an ongoing study in children and adolescents, Study 208580 (MOCHA). This is a Phase I/II study of the safety, acceptability, tolerability, and pharmacokinetics of oral and long-acting injectable Cabotegravir and long-acting injectable Rilpivirine in virologically suppressed HIV-infected children and adolescents. As of the 29 Apr 2019 cut-off date, 4 of a planned total of 155 subjects have been enrolled.

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

| | 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** |

## 2.5.2. Discussion on clinical efficacy

Rekambys (RPV LA) is to be used only in combination with CAB LA. Two pivotal clinical studies have been performed with CAB + RPV LA versus a comparator regimen, the Phase III studies FLAIR (Study 201584) and ATLAS (Study 201585). Additionally, the results of a third pivotal trial became available during the assessment; the ongoing, randomised, open-label, Phase IIIb Study ATLAS-2M (Study 207966), comparing Q4W and Q8W dosing. Further support comes from a randomized, open-label, controlled, Phase IIb study LATTE-2 (Study 200056). The RPV LA development program has been formally discussed with CHMP at various milestones throughout development, and an agreement was reached regarding the key elements of the main studies.

**Dose selection**

For RPV-LA, the aim throughout the clinical development was to achieve RPV plasma concentrations in the range of those observed with oral RPV 25 mg once daily in HIV-infected patients. This means that the mean RPV concentration at the end of a dosing interval ($C_\tau$) was targeted to be approximately 77-80 ng/mL. Dose selection for the LATTE-2 regimen was based on this principle. The selected Q4W dose regimen was predicted to induce RPV exposure around 115 ng/mL after ~1 year of treatment, which is well above the RPV target. For the Q8W regimen, a somewhat lower mean steady-state Ctrough of ~65 ng/mL was predicted, but the range of model-predicted Ctrough was similar to the range of Ctrough with oral RPV 25 mg once daily.

Overall, it was concluded from the efficacy data of LATTE-2 that both the Q4W and Q8W dosing regimens of CAB LA + RPV LA demonstrated appropriate antiviral activity through 160 weeks of treatment in virologically suppressed patients. The Q4W IM dosing regimen resulted in lower rates of virologic non-response, with similar safety to Q8W, hence this regimen was selected for use in the pivotal phase III studies. Q8W dosing remained under evaluation within LATTE-2 and is further investigated in ATLAS-2M. The numerically higher number of subjects with virologic failure in the combined Q8W arms (n=9) vs. the Q4W arms (n=2) of LATTE-2 and ATLAS-2M is in line with the model predictions of CAB and RPV exposures, which were above target levels with the Q4W dose regimen in a higher proportion of subjects than with the Q8W regimen. Selection of the Q4W dose regimen would be justified also from this perspective.

Modelling and simulation indicated that a 900-mg IM loading dose (single 3-mL injection) on Day 1 rather than a 600-mg LA dose brings RPV plasma concentrations closer to steady-state values during the early phase. For CAB, both observed and model-predicted CAB concentrations indicated the first CAB LA dose initiation could be lowered from 800 mg to 600 mg while maintaining plasma concentrations during the early phase at levels.

An 'optimised' CAB + RPV regimen was subsequently used in the pivotal Phase III studies FLAIR and ATLAS and is currently recommended in the draft SmPC. This regimen is further supported by data from the Q4W arm of ATLAS-2M and by the lack of drug-drug interaction between RPV LA and CAB LA upon co-administration.

In conclusion, the dose and dosing frequency of RPV LA are based on maintaining plasma trough concentration at the end of the dosing interval at or above exposures known to be induced by oral RPV 25 mg once daily. What should be kept in mind though is that the 25 mg oral dose is on the edge of efficacy, but higher dosing has been associated with QT prolongation. Hence, the window of opportunity

is relatively small for this NNRTI. The appropriateness of the currently proposed posology will be further discussed with the results of the phase III studies below.

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. Additional concerns regarding occurrence of resistance with the Q8W regimen and further optimisation of the Q8W regimen, have been raised, and the appropriateness of this dosing regimen was discussed by a HIV SAG (see below). Overall, the experts considered that there is enough evidence to support Q8W dosing taking into account that there were no significant differences between Q8W and Q4W regimens in the different studies. Therefore, it can be concluded that both regimens seem to have comparable efficacy.

**Design and conduct of clinical studies**

FLAIR and ATLAS are both Phase III, randomized, multicenter, parallel-group, open-label studies evaluating the efficacy, safety, and tolerability of long-acting intramuscular Cabotegravir and Rilpivirine for maintenance of virologic suppression following switch from an Integrase inhibitor single-tablet regimen for 20 weeks (FLAIR) or current INI-, NNRTI-, or PI-based antiretroviral regimen (ATLAS) in HIV-1 infected antiretroviral therapy-naive (FLAIR) or experienced (ATLAS) adult participants. The clinical development of Rekambys is further supported by data from the Phase IIIb study ATLAS-2M, which is an open-label, randomised, non-inferiority study designed to assess the antiviral activity and safety of IM CAB + RPV Q8W compared to IM CAB + RPV Q4W in HIV-1 infected adult subjects. The majority of subjects in study ATLAS-2M were enrolled from the ongoing ATLAS Study with additional virologically suppressed subjects included in order to reach the targeted total sample size of approximately 1020 subjects. It should be noted that only 327 subjects in the Q8W arm did not receive prior treatment with CAB+RPV LA in the ATLAS study. Efficacy in these patients is most relevant if adding the Q8W regimen to section 4.2 is considered as it may take longer before these patients have reached therapeutic concentrations of CAB and RPV.

*Design*

The design of these studies has been discussed during scientific advice procedure EMEA/H/SA/2517/1/FU/1/2016/II and was considered acceptable by CHMP. Both studies consisted of an oral lead-in phase, which was mainly to investigate tolerability to each of the two components. In both studies combined, 10 subjects were withdrawn during the oral lead-in phase before receiving any injection. Reasons were, among others, AEs, lost to follow-up, confirmed virologic failure, protocol deviations, and physician decision. Overall, it can be concluded that the oral CAB + RPV regimen was well tolerated in most subjects. After the oral lead-in phase, subjects received a loading dose of CAB 600 mg IM and RPV 900 mg IM, followed by a maintenance dose of CAB 400 mg IM and RPV 600 mg IM every 4 weeks thereafter. The primary analysis time point was at Week 48.

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 safety analysis, as well as the results of some subjective parameters (mainly patient satisfaction questionnaires) should be interpreted with care.

*Patient population*

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%). However, the proportion of subjects with low CD4 counts (<350 cells/mm$^3$) is low (<10%), and African people are poorly represented, with only few centers in South Africa in both studies. It is,

however, questionable if the enrolled population is representative for the patients that will be treated in clinical practice. The applicant revised the therapeutic indication to exclude patients with INI and NNRTI class resistance. Given the public health matter of selection (and potential transmission) of dual class resistance in case of treatment interruption without immediate suppressive regimen, the applicant was requested to submit a proposal for a post-authorisation study looking at proportions stopping injection therapy, the effectiveness and adherence to subsequent oral therapy, and the resulting "real life" frequency of de novo INI and NNRTI class resistance. The Applicant proposes a five-year drug utilization study (DUS) to be conducted in a real-world context, as was already proposed for Cabotegravir. 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 duration 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. Submission of the DUS protocol is planned for Q42020. As data on resistance testing collected in the DUS may not be comprehensive, an additional prospective cohort study (COMBINE-2) is proposed in collaboration with the NEAT ID network. The NEAT ID study sites will test for HIV subtype in patients who experience virological failure. 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.

*Conduct of the studies*

Overall, the conduct of the studies was considered acceptable. There was however an imbalance in important protocol deviations between the CAB + RPV arm (n=47) and CAR arm (n=14) in FLAIR. In some cases, this was related to 'wrong study treatment/administration/dose', a category for which important protocol deviations were also reported in ATLAS.

In both studies, randomisations to wrong strata occurred (3 mis-randomisations in FLAIR and 22 mis-randomisations in ATLAS). The Applicant considered these mis-randomisations as solved by using the actual strata in the ITT-E analysis. However, these mis-randomisations should be considered protocol violations as the subjects assigned to the wrong stratum could have been randomised to another treatment in the correct stratum. This could have affected the primary result (bias). New ITT-E (including the randomised strata) and PP analyses (without the subjects with mis-randomisations) have been performed by the applicant and did not impact the overall outcome of the studies. The central randomisation resulted for some countries in an unexpected imbalance between the two treatment arms. More details for the randomisation procedure were requested to understand this imbalance. The maximum imbalance in the number of subjects between the two arms was 35% observed in Germany (33 vs 16 patients with 10 sites) and 26% observed in Italy (14 vs 24 patients with 5 sites) for the Atlas and Flair study, respectively. As for both trials the countries showed more or less comparable results with the overall primary treatment effect, the issue will not be further pursued.

One site, participating in both studies (FLAIR Center Number 227256, ATLAS Center Number 227253), was identified as having extensive and persistent GCP non-compliance issues. This included inadequate PI oversight with respect to overseeing study-related activities conducted at the site, informed consent being not dated, and significant deficiencies regarding source documentation practices. The Applicant states that data from the subjects enrolled at these sites was not compromised, and therefore these data were not excluded from the analyses. Due to the notion that there were "significant deficiencies regarding source documentation practices" this can without further information not be agreed with. The Applicant was requested to provide more information regarding the deficiencies at these sites, and, as a precautionary measure, provide for both studies two sensitivity analyses: one in which the subjects enrolled at the GCP non-compliant site are counted as failures, and one in which the subjects enrolled

at this site were excluded from the analysis. These analyses were provided and did not have an impact on the overall conclusions of the two studies.

As regards the HIV-1 assay contamination, the Applicant's strategy to retest the positive samples during the contamination window is acceptable. The Applicant explained that the contamination issue was most likely due to not frequent enough changing of gloves and emptying of the biohazard trash container in the extraction room. After identification of the issue, corrective measures were put in place and no subsequent issues have been reported. The back-up samples used for subsequent testing were not located in the Valencia lab and were not at risk of contamination, and transport to the replacement laboratory was done according to existing SOPs.

**Efficacy data and additional analyses**

*Main results*

As the pivotal studies are switch studies, conducted in subjects who are by-protocol virologically suppressed (on either their current antiviral regimen (ATLAS) or achieved with ABC/DTG/3TC during the induction phase (FLAIR)), before treatment with CAB + RPV was initiated, the primary endpoint is the comparison of the proportion of subjects who were classified as Snapshot virological failure at Week 48 in the CAB + RPV arm vs. the CAR arm. Both studies met their primary objective and showed consistent results (upper limit of 95% confidence interval for failure rate <2.5%, which is below the 4% non-inferiority margin). In both studies combined, 11/591 subjects (1.9%) in the CAB + RPV arm experienced Snapshot virologic failure, which was comparable to the number of subjects with Snapshot virologic failure in the CAR arm (10/591 (1.7%)). Similar results were obtained when looking at the PP population (10/591 subjects [1.7%] had Snapshot virologic failure in both arms).

The proposed analysis (Cochran Mantel Haenszel test) to analyse the pooled studies is adjusted for 10 strata (4 strata from FLAIR and 6 strata from ATLAS) and does not contain an adjustment for study. This is not considered an appropriate analysis for the pooled data. Therefore, the results of the pooled analyses will only be considered as explorative.

The key secondary endpoint, proportion of subjects with plasma HIV-1 RNA <50 c/mL, confirmed that CAB + RPV LA was non-inferior to treatment with an oral, 3-drug regimen (for both studies, the lower limit of 95% confidence interval for success rate was > -7% , ITT-E and PP populations, which is above the -10% non-inferiority margin). There was a slight imbalance between arms in the number of subjects who discontinued the study for other reasons. Based upon the additionally provided information, no efficacy or safety concerns were raised.

Estimated rates of confirmed virologic failure (CVF) in FLAIR, ATLAS, and the pooled analysis, were <1.5% in the CAB + RPV group and in the CAR group through Week 48. When CVF did occur in the CAB + RPV group, it was frequently associated with RT and/or INI mutations that decreased drug susceptibility to CAB and/or RPV. For both antivirals, 4/7 subjects with CVF had treatment-emergent RAMs, which were associated with 0.82 - 9.36-fold reduced susceptibility to CAB, and 0.97 - 7.09 fold reduced susceptibility to RPV. Please see the PD discussion of this report for more details.

Week 48 (primary endpoint) results of the ATLAS-2M have been provided during this procedure. The primary analysis showed that the Q8W regimen is non inferior to the Q4W regimen, with both regimens being overall associated with a low rate of virologic failure (<2%). These results are consistent with efficacy data from FLAIR and ATLAS studies. However, there are numerical trends that deserve to be underlined:

- 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 proportion of virologic failures was numerically higher in the Q8W arm compared with the Q4W arm in female subjects and in subjects with BMI ≥30 kg/m2. This tendency was also observed in ATLAS and FLAIR studies.

No difference was observed in the safety profile between the 2 study arms. The main benefit for the Q8W regimen as compared to the Q4W thus seems to be the reduced number of visits.

*Subgroup analyses*

In both studies, the rates of virologic failure was numerically higher in women treated with 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 in men. In addition, in the pop PK modelling, categorization of CAB Cmin-LD by gender showed that the median was 31% lower in females than in males. 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 virologic failure with CAB + RPV is observed in subjects with BMI ≥30: in FLAIR, 3/40 subjects in the CAB + RPV arm experienced virologic failure, vs. 0/37 subject in the CAR arm. Data according to BMI in ATLAS study were not provided in the CSR, but this trend is recovered in the pooled analysis. When considered the subgroups BMI and gender, the trend of rate of virologic failure with CAB + RPV is observed only in the subgroup of women with BMI ≥30, which could traduce a mixed gender and PK effect. It is acknowledged and agreed that the low overall number of events and the relative proportion of participants with similar factors and durable efficacy responses, limits the conclusions that can be drawn. On the basis of the totality of the evidence, the Applicants do not recommend any differential dosing or prescribing recommendation by gender, BMI, or a combination of those factors. However, as stated in Section 4.2 of the SmPC, the prescriber should consider a longer needle length to deliver the LA formulations to the gluteal muscle.

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 virologic 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 centers, 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. For more information and discussion, please refer to the PD section of this report.

No relevant differences were observed based on age, VL categories or CD4 count categories.

In order to identify predictive 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. This was further discussed by the SAG experts, who proposed several measures to minimize this risk:

- To start a Q4W regimen in those patients who could have higher risk of virologic failure (VL) 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 VL. 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 minimize the risk.
- Finally, the experts consider that the patients' wishes should also be taken into consideration.

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.

*Additional comments*

Across studies, it is of interest that all CVFs occurred in subjects with <48 weeks exposure to CAB + RPV LA. As the maximal exposure of CAB and RPV (steady-state) will only be reached after 44-72 weeks and 2.2 years of treatment, respectively, this may be due to suboptimal exposure in some subjects during the initial period of treatment. In this respect, it was considered informative to know whether there are any subject-specific factors that can be identified, either PK-, demographic-, disease-related, or something else, that are shared between the subjects who have experienced CVF in any of the CAB + RPV LA studies. The Applicant further analysed the impact of baseline factors, and concluded that there are no strong predictive factors identified that could be useful in selecting patients that less likely to benefit from treatment with these long-acting agents other than the presence of baseline RAMs that are already excluded in the therapeutic indication.

Out of window visits occurred infrequently (65/3577 visits (1.8%) and 87/3343 visits (2.6%) for FLAIR and ATLAS, respectively). Whether this can be extrapolated to the real-life setting remains to be determined, especially considering that the subjects enrolled in the pivotal studies are not fully representative for patients that may be treated in real life. This will be further investigated in a DUS.

## 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 (VL). 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 minimize this risk:

To start a Q4W regimen in those patients who could have higher risk of VL 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 VL. 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 minimize 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, centers, 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 minimize 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 centers, 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.

### 2.5.3. Conclusions on the clinical efficacy

Overall, it can be concluded that the efficacy of RPV LA, when used in combination with CAB LA, has been established with administration every 4 weeks. Additionally, efficacy of a Q8W dosing regimen has been demonstrated. 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. Further actions will be taken by the Applicant to address these issues post-authorization.

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

| |
|---|
| 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 anti-retroviral 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. |
| 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. |

## *2.6. Clinical safety*

### *Patient exposure*

In the pooled Phase III studies (FLAIR (Study 201584) and ATLAS (Study 201585)), the Safety Population consisted of 591 subjects randomized to CAB + RPV and 591 subjects randomized to CAR. Overall and for the individual studies, the number of subjects randomized and treated was similar across treatment groups. As described in section 3.3.6 on Clinical Efficacy, the pivotal Phase III studies consisted of a Screening Phase, an Induction Phase (FLAIR only), a Maintenance Phase and an Extension Phase. As part of the Maintenance Phase, an oral lead-in (OLI) phase, with a minimum duration of 4 to

5 weeks, was included to evaluate tolerability to the individual components. The Safety analysis focusses on the safety data from the Maintenance Phase.

The duration of exposure was 392 ± 86.84 and 375.2 ± 69.15 days for the CAB + RPV and CAR groups respectively (mean and SD). For the pooled phase III studies, most subjects were exposed from 52 to <64 weeks (72% and 63% of subjects in the CAB + RPV and the CAR group respectively).

The following sections describe the Week 48 safety data in the pooled Phase III studies. As Week 96 safety data of the Phase III studies became available during the second round of the application procedure, these have only been described in this overview if leading to new safety concerns. If considered relevant additional data from Phase II (LATTE or LATTE-2) and Phase IIIb (ATLAS-2M) have been described.

Together with the available data on the safety profile of EDURANT, the overall exposure can be considered sufficient to establish a safety profile for RPV LA.

## *Adverse events*

Pooled Phase III data

During the Maintenance Phase, more AEs were reported in the CAB + RPV group than in the CAR group (95% vs 75%) (see Table 27). Injection site reactions (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 75% of subjects in the pooled CAR group. The higher incidence of AEs in the CAB + RPV vs CAR group may partly be due to the open-label study design, in which the switch to a novel intervention could have induced anticipation of adverse events, while patients in the CAR group have already been using their medication for at least 6 months. More drug-related AEs (83% vs 6%) and Grade 3 to 5 AEs (11% vs 6%), were observed for CAB + RPV compared with CAR. The frequency of SAEs was similar across treatment groups (5% vs 4%).

**Table 27 Overview of all AEs During the Maintenance Phase, Pooled Phase III Studies**

| | 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: Mod5.3.5.3/209522 Output/Tab3.05.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

***Commonly reported AEs***

Adverse events reported in ≥5% of subjects in either treatment group are presented in the table below.

**Table 28 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 |

a.Number and percent of subjects with AE.
b.Number of subjects with AE per 100 subject years: 100*number of subjects with AE/subject years, where subject years = sum of subject duration of dosing in days (across all subjects)/365.25.
Data Source: Mod5.3.5.3/209522 Output/Tab3.17.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

There were imbalances between the groups in the incidence of AEs reported for several of the SOCs, most notably: infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, skin and subcutaneous tissue disorders, investigations, and psychiatric disorders. Several differences in individual AE PTs reported within these SOCs contributed to these results. The largest differences in numbers of subjects reporting events occurred for:

- Infections and infestations: nasopharyngitis (CAB + RPV 18% vs. CAR 15%) and upper respiratory tract infection (CAB + RPV 12% vs CAR 9%).
- Gastrointestinal disorders: diarrhoea (CAB + RPV 9% vs. CAR 7%) and nausea (CAB + RPV 5% vs. CAR 3%).

- Musculoskeletal and connective tissue disorders: back pain (CAB + RPV 7% vs. CAR 4%) and myalgia (CAB + RPV 4% vs. CAR 1%).
- Nervous system disorders: headache (CAB + RPV 12% vs. CAR 6%) and dizziness (CAB + RPV 4% vs. CAR 1%).
- Skin and subcutaneous tissue disorders: rash (CAB + RPV 3% vs. CAR 2%) and eczema (CAB + RPV 2% vs. CAR 1%).
- Investigations: blood creatine phosphokinase increased (CAB + RPV 3% vs. CAR 2%) and lipase increased (CAB + RPV 2% vs. CAR 1%).
- Psychiatric disorders: anxiety (CAB + RPV 4% vs. CAR 2%) and insomnia (CAB + RPV 4% vs. CAR 1%).

Statistical comparisons were conducted to evaluate potential associations of CAB + RPV treatment with the incidence of commonly reported AEs (≥5%). AEs occurring significantly more often in the CAB + RPV group were: ISRs (pain 77%, nodule 14%, induration 12%, swelling 8%, pruritus 4% in the CAB + RPV LA group vs. 0% in the CAR group), pyrexia (7% vs. 2%), headache (12% vs. 6%), fatigue (5% vs. 2%), and back pain (7% vs. 4%).

The majority of AEs reported in the Phase III studies had a severity of Grade 1 or 2 for both treatment groups. Notably, 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%). With the exception of ISRs (4% vs. 0%), differences between the treatment groups in Grade 3 and 4 AEs (PTs) were ≤1%.

***Drug related AEs***

Drug-related AEs reported in ≥1% of subjects in any individual study or pooled treatment group are shown in the table below. Drug-related AEs were more commonly reported in the CAB + RPV group than in the CAR group (83% vs. 6%). This difference is mainly driven by ISRs; excluding ISRs, 28% of the subjects in the CAB + RPV group and 6% of the subjects in the CAR group had at least 1 drug-related AE. Drug-related non-ISR AEs occurring in ≥2% of the subjects in either pooled treatment group were headache (4% vs. <1%), pyrexia (4% vs. 0%), nausea (3% vs. 1%), fatigue (3% vs. <1%), asthenia (2% vs. 0%), body temperature increased (2% vs. 0%), myalgia (2% vs. <1%), and dizziness (2% vs. <1%). Although many of these AEs have also been reported for EDURANT, it seems that there is a trend towards more influenza-like events, which may be attributable to the injections.

In both groups, most drug-related AEs were Grade 1 or 2. Grade 3 to 4, non-ISR, drug-related AEs occurred with similar frequency in both treatment arms (1% and <1% for CAB + RPV and CAR respectively). No Grade 5 drug-related AEs occurred in the Phase III studies.

The most frequently reported, Grade 2 to 4, drug-related, non-ISR AEs in the CAB + RPV group were headache, diarrhoea, fatigue and pyrexia (each occurring in <1% of subjects).

**Table 29 Most Common Drug-Related AEs (Reported in ≥1% 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) |
| Diarrhoea | 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) |

Data Source: Mod5.3.5.3/209522 Output/Tab3.26.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Oral lead-in phase ATLAS and FLAIR

An OLI phase of CAB + RPV was included in Studies 201584 and 201585 to evaluate tolerability to the individual components. The duration of the OLI varied by subject, with 4 to 5 weeks being the minimum duration. The median time of exposure of HIV-1 infected subjects to oral CAB + RPV during the OLI

period of the Maintenance Phase of pooled Studies 201584 and 201585 was 5.3 weeks. During the OLI for Studies 201584 and 201585, 187 (32%) subjects in the CAB + RPV group had at least one AE. The most frequently reported AEs during OLI were nasopharyngitis (n=16 [3%]) and headache (n=17 [3%]). Vitamin D deficiency was reported in 16 [3%] subjects during the OLI, however, it should be noted that vitamin D was only measured at Day 1, which was before the OLI was started and was reported at similar incidence in the CAB + RPV group and CAR group during the Maintenance Phase (5% and 4% of the subjects, respectively).

Phase II data

Overall, injection site pain (97% of subjects) was the most commonly reported AE in the randomized IM dosing arms. Other commonly reported ISRs included injection-site nodule (34% of subjects) and swelling (31% of subjects). The most commonly reported non-ISR events included nasopharyngitis (38%), diarrhoea (22%), and headache (22%) across both randomized IM dosing arms. There were no clear differences in incidence of AEs suggesting a regimen-specific trend.

The majority of events reported were Grade 2 or 3 in severity. The number of Grade 3 events was driven by General disorders and administration site conditions (18/50 Grade 3 events, 36%), Infections and infestations (9/50 Grade 3 events, 18%) and Psychiatric disorders (9/50 Grade 3 events, 18%).

Injection site pain (97%) was the most commonly reported drug-related AE in the randomized IM arms. Other commonly reported ISRs included injection-site nodule (33%) and swelling (31%). The most commonly reported non-ISR drug-related AEs included pyrexia (5%), headache (3%), fatigue (3%) and influenza-like illness (3%) across both IM dosing arms. AEs as reported in phase II studies showed a similar pattern, i.e. AEs mainly driven by injection site reactions.

ATLAS2M Phase III-b data

In the ongoing ATLAS-2M study (207966) results suggest that the overall safety profile of CAB + RPV Q8W dosing is similar to that observed with Q4W dosing, with AEs reported in 86% vs 88%, respectively. The rate of drug-related AEs was similar for both treatment arms, as can be appreciated from the table below. Injection site reactions were the most frequently reported drug-related AEs (70% vs. 72% in the Q4W and Q8W arm, respectively). The most frequently reported non-ISR drug-related AEs were pyrexia (Q8W, 18/522 [3%]; Q4W: 24/523 [5%]) and fatigue (Q8W, 6/522 [1%]; Q4W: 16/523 [3%]). Overall AEs were consistent in nature with those reported in phase III studies.

**Table 30 Summary of common drug related AEs (≥1%) in either treatment group during the maintenance phase**

| Preferred Term | Q8W (N=522) n (%) | Q4W (N=523) n (%) |
|---|---|---|
| Any drug-related event | 400 (77) | 399 (76) |
| Injection site pain | 364 (70) | 358 (68) |
| Injection site nodule | 54 (10) | 87 (17) |
| Injection site induration | 40 (8) | 37 (7) |
| Injection site discomfort | 34 (7) | 40 (8) |
| Injection site swelling | 32 (6) | 26 (5) |
| Injection site pruritus | 26 (5) | 24 (5) |
| Pyrexia | 19 (4) | 25 (5) |
| Injection site erythema | 12 (2) | 15 (3) |
| Asthenia | 12 (2) | 6 (1) |
| Injection site bruising | 10 (2) | 11 (2) |
| Headache | 10 (2) | 11 (2) |
| Dizziness | 10 (2) | 5 (<1) |
| Chills | 9 (2) | 6 (1) |
| Diarrhea | 8 (2) | 3 (<1) |
| Fatigue | 7 (1) | 19 (4) |
| Injection site warmth | 7 (1) | 7 (1) |
| Malaise | 7 (1) | 6 (1) |
| Body temperature increased | 7 (1) | 8 (2) |
| Injection site hematoma | 3 (<1) | 14 (3) |
| Nausea | 5 (<1) | 12 (2) |
| Pain | 5 (<1) | 10 (2) |
| Influenza like illness | 5 (<1) | 8 (2) |
| Back pain | 2 (<1) | 6 (1) |
| Insomnia | 1 (<1) | 6 (1) |

Data Source: Table 3.12.

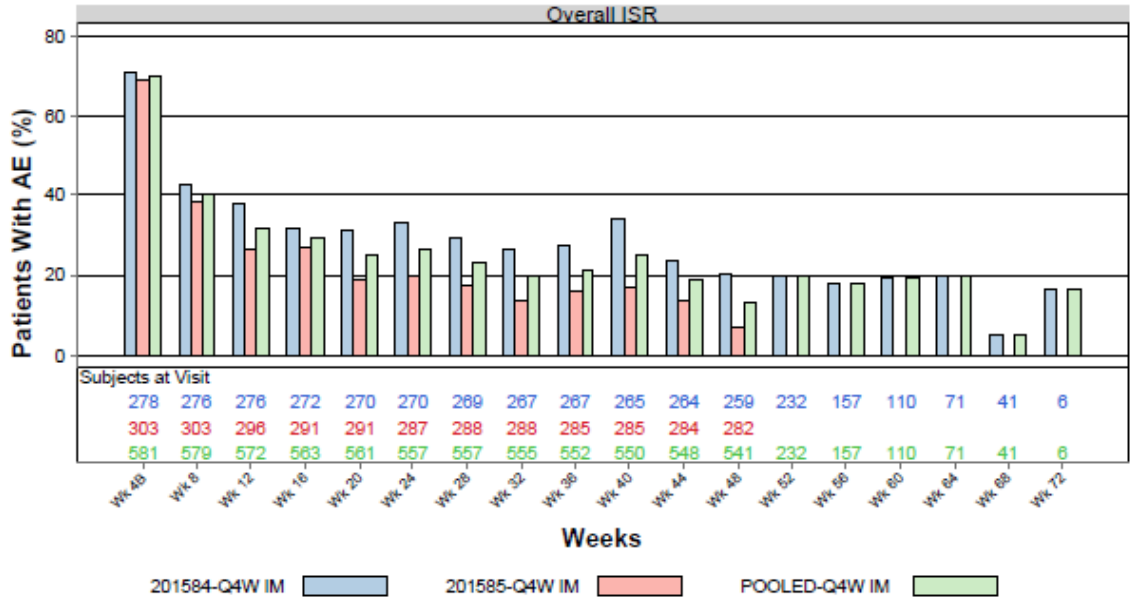
***Adverse events of special interest (AESIs)***

**Injection site reactions (ISRs)**

Pooled Phase III data

581 subjects received at least 1 injection of whom 489 (84%) subjects experienced ISRs. Most ISRs resolved within 14 days (94%), with a median duration of 3 days. The incidence and severity of ISRs decreased over time (see figure below). From this figure, a difference between the ATLAS and FLAIR study can be appreciated with less patients reporting ISRs in the ATLAS study, which the applicant describes being mainly driven by chance. As numerical differences are small (see Table 19 on common drug related AEs), this issue is not further pursued. Most ISRs were related to injection site pain (77%), nodule (14%), induration (12%), swelling (8%), erythema (4%), and pruritus (4%). Most subjects had AEs of Grade 1 (75%) or Grade 2 (36%). Only 6 subjects (1%) discontinued because of ISRs. No significant differences in ISRs between CAB and RPV injections were observed.

**Figure 15 Incidence of Overall ISR AEs for Phase III Studies**




Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Data Source: Mod5.3.5.3/209522 Output/Fig3.19.

Phase II and IIIb data

In Phase II study 200056 ISR results in the Q4W group were similar to but occurred with higher incidence than in the Phase III studies (98% vs. 84%).

Phase IIIb ATLAS-2M study

The overall frequency and severity of ISRs, as well as the rate of ISRs leading to withdrawal, were consistent with those observed for the pooled Phase III studies.

**Rash and hypersensitivity**

Pooled Phase III

In the pooled Phase III Studies there were no reports of severe rash. Grade 1 and 2 rash AEs were reported in 23 subjects (4%) in the CAB + RPV group and 14 subjects (2%) in the CAR group. Ten subjects were reported with rash AEs considered to be drug-related (9 CAB + RPV, 1 CAR); none led to the withdrawal of study drug. Drug-related hypersensitivity reactions occurred in 2 subjects (lip swelling and eosinophilia) in the CAB + RPV group). These AEs were Grade 1 or 2 in severity.

Phase II data

In the phase II LATTE-2 study, rash was reported in 7% of subjects. Most rashes were Grade 1 or 2. There was one non-serious Grade 3 rash considered related to study drug and leading to withdrawal.

Phase IIIb data

Rash events occurred in ≤2% of subjects in either treatment group.

Hypersensitivity reactions are considered an important potential risk for CAB + RPV, also because of prolonged drug retention following an IM injection and the inability to remove drug from circulation via means such as dialysis etc. 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, hypersensitivitv cannot be ruled out in this case. The applicant has committed to evaluate hypersensitivity reactions in future PSURs**.**

**QT interval prolongation**

It is known from EDURANT that QT prolongation may occur with supratherapeutic doses (75 and 300 mg doses were both associated with QT prolongation), while QT prolongation was not observed at the recommended dose of 25 mg. As shown in the section on PK/PD (Secondary Pharmacology Clinical AR), exposure for RPV LA is in line with exposure observed with oral RPV 25 mg once daily. Thus QT prolongation might not be expected and the fact that no thorough QT studies have been performed for RPV LA can be agreed.

Pooled Phase III studies

ECGs were collected pre-dose at day 1, Week 4b and Week 48. At Week 4b and at Week 48, a second ECG was performed 2 hours post-dose for subjects in the CAB + RPV group. In the pooled analysis, there were few QTc outliers (change from Baseline >60 msec or absolute QTc value >500 msec). A summary of change from Baseline in QTcF intervals is presented in Table 31. Higher rates of QT prolongation were observed in the CAB + RPV group compared with the CAR group. In these subjects, triplicate ECGs did not confirm a maximum change from Baseline corrected QT value >60 msecs and all subjects remained on study. All subjects had QTcF intervals of ≤500 msec.

For the pooled Phase III studies five subjects were reported with AEs potentially related to QT prolongation (4 in the CAB + RPV group, 1 in the CAR group). These AEs were 'Electrocardiogram QT prolonged' (3 subjects in the CAB + RPV group, 1 subject in the CAR group) and 'Electrocardiogram repolarization abnormality' (1 subject in the CAB + RPV group). Of the 4 AEs occurring in the CAB + RPV group, 2 were considered related to the study drug, none were considered serious or led to withdrawal, and QTcF interval was <500 msecs at Week 48. For more details please refer to the Clinical AR, section on Clinical Safety.

Pharmacokinetic/pharmacodynamic (PD) analyses were conducted for QTc in both Phase III studies. No clinically relevant relationships between RPV plasma concentrations and QTc changes from Baseline were identified (Clinical AR, section on Secondary Pharmacology).

Phase II studies

During Study 200056 (LATTE-2), one CAB + RPV related Grade 3 AE of QT prolongation was reported which led to study drug withdrawal. Additionally, one subject had an increase in QTc from Baseline >60 msec despite triplicate ECGs at Week 32 of the Maintenance Phase. The subject was withdrawn due to meeting ECG withdrawal criteria and sinus tachycardia. The event resolved.

During study LAI116482 (LATTE) one subject on oral CAB + RPV had a drug-related AE of ECG abnormal, which led to withdrawal.

Phase IIIb ATLAS-2M study

As of the data cut-off for the 24-week report, no AEs of QT prolongation had been reported.

**Table 31 Summary of QTcF Intervals Maximum Change from Baseline in the Maintenance Phase for Pooled Phase III Studies (Safety Population)**

| | 201584 | | 201585 | | POOLED | |
|---|---|---|---|---|---|---|
| **Actual Relative Time (Timepoint, msec) Category** | **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 (%)** |
| N | 188 | 181 | 208 | 193 | 396 | 374 |
| <=30 | 162 (86) | 171 (94) | 192 (92) | 186 (96) | 354 (89) | 357 (95) |
| >30 to <=60 | 24 (13) | 9 (5) | 13 (6) | 6 (3) | 37 (9) | 15 (4) |
| >60 | 2 (1) | 1 (<1) | 3 (1) | 1 (<1) | 5 (1) | 2 (<1) |

Data Source: ISS/ISE Table 3.146.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

The applicant concludes that there were few occurrences of QTcF >500 ms and increases >60 ms from baseline in the Phase 2 and Phase 3/3b studies and remarks that no correlation with RPV or CAB plasma concentrations was observed in these cases. All patients continued CAB+RPV therapy and repeat ECG measurements did not have subsequent increases of clinical concern. As plasma concentrations with the recommended RPV LA dosing schedule remain within the same range as plasma concentrations that are reached after oral dosing with Edurant, QT prolongation is not expected. Although no correlation was observed between QT prolongation and RPV concentration in the phase III studies, the effect of accidental iv administration with a subsequent high rise in plasma RPV concentration is not known. Thereto accidental IV administration must be evaluated in future PSURs, as the applicant has committed to perform.

**Neuropsychiatric events**

No completed *suicides* occurred during the pooled Phase III clinical studies. Four (<1%) subjects in the CAB + RPV group and 5 (<1%) subjects in the CAR group had AEs of *suicidal ideation* or behaviour. Most AEs were Grade 1 or 2. Results from self-administered suicidality assessments reflected a somewhat higher percentage of 5% for the CAB + RPV and 6% for the CAR group but no difference between treatment arms. In Phase II studies, 7 subjects were reported with SAEs of suicidal ideation or suicidal attempt with CAB + RPV treatment.

During the Phase III studies, 16 (3%) subjects in the CAB + RPV group and 14 (2%) subjects in the CAR group had AEs of *depression*. Five subjects in the CAB + RPV group had depression AEs that were considered study drug-related. Most AEs were Grade 1 or 2. Results for depression from Phase II studies (LAI116482 and 200056) were consistent with those observed in Phase III studies.

Across the Phase III studies, 27 (5%) subjects in the CAB + RPV group and 20 (3%) subjects in the CAR group had AEs related to *anxiety*. Most AEs were Grade 1 or 2. Anxiety AEs were considered study drug-related in 10 subjects (8 CAB + RPV; 2 CAR). Few subjects were reported with AEs that led to withdrawal (n=1 in Phase III and n=2 in Phase II). One subject had an SAE of anxiety in Phase II, which was not considered CAB + RPV related and did not lead to withdrawal.

Across the pooled Phase III studies, 7 (1%) subjects in the CAB + RPV group and 1 (<1%) subject in the CAR group had AEs related to *mood disorders*. All mood disorder AEs were Grade 1 or 2. Mood disorder AEs were considered study drug-related in 3 subjects in the CAB + RPV group. No SAEs or withdrawals due to mood disorder with CAB + RPV were reported in the Phase III and II studies.

There were no *bipolar disorder* AEs in the pooled Phase III studies and in the LATTE-2 study 200056. Adverse events associated with bipolar disorders were reported with CAB + RPV in the LATTE study LAI116482 (bipolar disorder: n=2; mania: n=1). This includes a SAE of mania considered not related.

Across the pooled Phase III studies, 1 (<1%) subject receiving CAB + RPV had an AE related to *psychosis* (paranoia, Grade 1). This AE was considered study drug-related but did not lead to withdrawal. In the LATTE-2 study, one Grade 3 psychiatric disorder was considered study drug-related and led to withdrawal.

Across the pooled Phase III studies, the incidence of *sleep disorder* AEs was numerically higher in subjects in the CAB + RPV group (38 (6%)) than in the CAR group (21 (4%)); AEs in 15 vs. 4 subjects were considered study drug-related. All were Grade 1 or Grade 2 in severity. There were no SAEs of sleep disorders with CAB + RPV during Phase III and II studies.

AEs were balanced between the treatment arms, except for sleep disorders, depression and anxiety, with higher rates in the CAB + RPV group. Psychiatric disorders are a known adverse event associated with several antiretroviral agents, including RPV and DTG. Depression, anxiety, abnormal dreams and insomnia have been added to the frequency table in section 4.8 as common ADRs to RPV LA. No new safety concerns were raised.

Phase IIIb data

Neuropsychiatric events occurring in >1% of the subjects were anxiety, depression and insomnia. Drug-related neuropsychiatric AEs were reported for 12 (2%) subjects in the Q8W group and 16 (3%) subjects in the Q4W group. Three neuropsychiatric SAEs were reported in the Q8W group (psychotic disorder, bipolar disorder and major depression). No SAEs occurred in the Q4W group. Three subjects in the Q4W group had AEs leading to withdrawal (depression (n=1 AE), insomnia (n=1 AE), sleep disorder (n=1 AE), and abnormal dreams (n=2 AEs).

**Hepatic safety**

Liver stopping criteria (LSC) were defined per the protocol as a threshold to discontinue drug treatment, regardless of the cause of liver chemistry changes. If LSC were met, an independent hepatic adjudication committee further evaluated the case to determine the cause of liver chemistry changes. LSC was the primary method for detection of DILI cases. Whilst these have not been observed during the pooled Phase III studies, DILI has been observed in patients receiving oral CAB. Elevated ALT values have been observed with exposure to CAB + RPV during Phase III studies. Aminotransaminase elevations in these subjects have been transient and reversible. Liver chemistry changes are presented in the section on laboratory findings.

Pooled Phase III studies

Of the 14 subjects with *liver stopping criteria*, 11 with liver stopping criteria were in the CAB + RPV group and 3 subjects were in the CAR group. All of the subjects who met LSC had viral hepatitis: 13 subjects had acute viral hepatitis, and one had chronic hepatitis C infection with substance abuse. Notably, more subjects receiving CAB + RPV (n=10) had acute viral hepatitis than those receiving CAR (n=3). The applicant describes that no underlying mechanism has been identified explaining the difference in the occurrence of viral hepatitis and concludes that it will possibly be induced by chance which is acknowledged.

A search was conducted for AESIs related to *hepatotoxicity* and 5 subjects each had 1 AE (CAB + RPV, 4 [<1%], CAR, 1 [<1%]). These events included hepatic cirrhosis (Grade 3; CAR group), hepatic steatosis (Grade 2; CAB + RPV group), toxic hepatitis (Grade 1; CAB + RPV group), hepatocellular injury (Grade 4; CAB + RPV group), and non-alcoholic steatohepatitis (Grade 1; CAB + RPV group). Hepatocellular injury occurred in a subject with acute hepatitis A in the ATLAS study, was considered serious and led to discontinuation of the study drug. None of the AEs was considered to be study drug-related or to represent DILI.

Phase I/II Studies

Five subjects receiving oral CAB from Phase 2b (LATTE, LATTE-2, n=4) and from a DDI study with rifabutin (205712, n=1) met LSC and alternative etiologies for aminotransferase elevations were not identified. These subjects were suspected to have had *DILI* as adjudicated by hepatology experts. Three of the five subjects were on oral CAB 30 mg once daily and the remaining two were on oral CAB 60 mg. Mild to moderate hepatotoxicity has been identified in these subjects, but severe hepatotoxicity with significant liver dysfunction or liver failure has not been observed. In these subjects, aminotransferase elevations were Grade 3 or 4 in severity and were transient and reversible.

During the LATTE study (LAI116482), AEs potentially associated with *hepatotoxicity* were not reported, except for cases identified by liver chemistry monitoring (transaminases increased, hepatitis, suspected DILI). During the LATTE-2 study (200056), hepatic fibrosis, ischaemic hepatitis, hepatic steatosis, hepatotoxicity, hypertransaminasemia, non-alcoholic fatty liver, and acute hepatitis were reported with treatment with CAB + RPV. None of these events was considered related to study treatment and they did not lead to withdrawal.

Phase IIIb study; ATLAS-2M

There was one possible case of DILI in a female subject who had received 28 days of oral CAB + RPV (Q4W group). This subject experienced an asymptomatic increase in liver biochemistry for which no cause was identified. The subject was withdrawn from the study after receiving 11 weeks of oral CAB + RPV. The subject commenced ABC/3TC/DTG and the ALT/AST returned to normal after 12 weeks.

Four patients (two in both study arms), met LSC; three of them had acute hepatitis and one of them had taken non-prescribed medication (Melanotan II) resulting in DILI. DILI was unlikely to be related to CAB + RPV as liver enzymes remained normal after study drugs had been restarted.

**Weight gain**

Pooled Phase III data

Weight gain is considered an AESI for CAB since it is an AR for the structurally related INSTI, DTG. Across the Phase III studies, 2 (<1%) subjects in the CAB + RPV group and no subjects in the CAR group had AEs potentially associated with weight gain. A median weight gain (min; max) of 1.50 kg (-27.5 kg; 40.9 kg) was observed with CAB + RPV compared with 1.0 kg (-28.0 kg; 39.0 kg) with CAR. This is consistent with a trend for weight gain during the Phase II clinical trials. Weight increase has been reported in the frequency table in section 4.8. No new safety concerns were raised.

Phase IIIb data

Four (<1%) subjects in the Q8W group and 2 (<1%) subjects in the Q4W group had an AE of weight increased. Weight increased was considered drug-related in 2 subjects in the Q8W group and 1 subject in the Q4W group. AEs of weight increased were Grade 1 or 2 and did not lead to withdrawal.

**Medication errors**

Dosing errors

Medication errors not associated with device malfunction occurred in 15 subjects. 14 subjects received the wrong dose and one subject received the right dose and drug but from the wrong study. Of the 14 subjects receiving the wrong dose, 8 involved an underdose and 6 an overdose. No AEs were directly attributable to these errors.

Device malfunctions

Seven device malfunctions were recorded; in 4 subjects it resulted in dosing errors causing underdosing, for which in 3 of the 4 subjects additional 'top-up' injections were given to compensate for the lost study drug.

Accidental IV administration

An acute exposure to higher than normal systemic drug levels happens if an injection is accidentally administered into a vein rather than a muscle. Transient high levels could lead to a safety risk from overexposure and could also lead to a risk of virologic failure, as systemic concentrations would decline more quickly than after an IM injection. Accidental IV administration associated with adverse outcomes is known to have occurred in 3 subjects during the CAB + RPV development program. One of these subjects (enrolled in LATTE-2), experienced confirmed virologic failure (CVF) without treatment-emergent resistance. The 2 other subjects (enrolled in ATLAS-2M) were reported with SAEs (allergic reaction and vasovagal reaction). Accidental IV administration is an important risk of the LA formulation for which follow up is required. The applicant has been requested to provide AEs for all subjects for whom potential intravenous administration could not be ruled out, based on e.g. Cmax. This analysis did not yield additional cases of QT prolongation (QT prolongation has previously been observed with supratherapeutic dosing in Edurant). The applicant has committed to carefully monitor and discuss medication errors in future PSURs and the Applicant has included the safety concern Medication errors in the RMP of RPV LA. The fact that partial IV administration could be associated with the occurrence of (serious) AEs has been reflected in section 4.4 of the SmPC.

## Serious adverse events and deaths

### Pooled Phase III studies

During the Maintenance Phase in the pooled Phase III studies, 31(5%) subjects in the CAB + RPV group had a total of 37 SAEs and 26 (4%) subjects in the CAR group had a total of 33 SAEs. The rate of SAEs is as can be expected in this patient population. The most frequently reported SAEs in the CAB + RPV vs. CAR groups were hepatitis A (4 vs. 2 subjects), colitis (1 vs. 2 subjects), anal abscess (0 vs. 2 subjects), and anogenital warts (1 vs. 2 subjects). Other SAEs were reported in $\leq$1 subject per treatment group. Two subjects experienced SAEs considered by the Investigator to be drug-related; one subject in the CAR group of the ATLAS study experienced a SAE of suicidal ideation and one subject in the CAB + RPV group of the FLAIR study experienced a SAE of right knee mono-arthritis. Regarding the case of mono-arthritis, the investigator considered that in the absence of a clear aetiology of the symptoms and given the subject had no prior medical history of arthritis, a causal relationship to study drugs could not be fully excluded. The applicant remarks that in the absence of other similar cases, the prolonged time to onset and the subject's lack of recurrence of symptoms on ongoing CAB+RPV the evidence for a causal relationship is not compelling which can be agreed. Two deaths were reported. Both were not considered by the investigator to be related to study drug treatment: one subject receiving CAR died during the Induction Phase of the FLAIR study due to a reported homicide and one subject receiving CAR died during the Maintenance Phase of the ATLAS study due to a methamphetamine overdose.

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.

**Oral lead-in phase ATLAS and FLAIR**

Four subjects in the CAB + RPV group had SAEs during the OLI period, none of which were considered drug-related: enterocolitis, pyrexia, hepatitis A, and abortion missed [nonviable pregnancy was terminated]. Study drug was discontinued due to the SAEs of enterocolitis and hepatitis A. Study drug withdrawal was not applicable for the SAEs of pyrexia and abortion missed. The SAE of pyrexia was considered a Jarisch-Herxheimer reaction secondary to treatment of syphilis with IM penicillin G, which was started after study drug discontinuation and which required hospitalization.

***Phase II data***

Through 160 weeks of treatment, 38 (17%) subjects reported a SAE in Study 200056. The majority of events were single occurrences with no demonstrated trends per study arm. One SAE was considered to be study drug-related by the investigator. This was a SAE of myocardial infarction that occurred in a patient with cardiovascular risk factors (BMI of 40 kg/m2 and hypertension) and after 3 years of CAB + RPV use. This SAE resulted in death. The investigator could not exclude a causal relationship with the study drugs. Two other deaths were not considered study drug-related; one patient died of refractory epilepsy after recreational drug use and the other patient died due to a road traffic accident.

***Phase III-b data***

Few SAEs were reported through Week 24 of the ATLAS-2M study (3% in both study arms). Overall, the SAE with the greatest frequency was pneumonia (<1% in both study arms). Three drug-related SAEs were reported through Week 24:

- One subject presented with a gluteal abscess on the same site where RPV IM was administered
- One subject, who previously received CAB + RPV oral dosing and injections without any problems, developed a hypersensitivity reaction after administration of RPV LA. This subject experienced a severe reaction of tingling in the throat, tongue and lips, shortness of breath and nausea and transient cyanosis immediately after the administration of IM RPV LA (CAB LA was not administered due to the onset of the event), that resolved within 1 hour. Notably, the post-dose RPV PK was consistent with partial IV administration. An allergic reaction could not be excluded.
- One subject with a history of a post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and who previously participated in the ATLAS study and received CAB + RPV LA for 17 months, presented with severe acute pancreatitis 2 weeks after the Week 16 visit. This subject was hospitalized and experienced cardiopulmonary arrest 2 days after admission. He required prolonged intensive care admission during which he experienced multiple serious complications, also reported as SAEs. The initial event of pancreatitis was considered possibly related to the study drugs by the investigator. Since pancreatitis has been observed with other NNRTIs, to the risk of pancreatitis is added to section 4.8 of the SmPC.

***Serious adverse events and deaths reported in ongoing studies***

Review of safety data of ongoing studies from the time point of the initial safety analyses reported above up to 29 April 2019 was performed for the Phase III studies FLAIR (201584) and ATLAS (201585), and the Phase II studies LATTE-2 (200056) and LATTE (LAI116482). Information with regard to deaths and SAEs considered as at least possibly related to the study drugs is summarized below. The Phase IIIb ATLAS-2M study was not part of the search but relevant SAEs are described below.

In the FLAIR and the ATLAS study, no additional deaths or drug-related SAEs were reported.

In the LATTE-2 study (Q4W CAB + RPV), one subject died. This subject had diabetes and mild dyslipidemia and had been in the study for over 4 years. The cause of death was reported as 'cocaine toxicity' with atherosclerotic heart disease being a contributory cause. The investigator does not suspect

a causal relationship to study drugs. Additionally, one SAE of depression, at least possibly related to the study drugs, occurred.

In the LATTE study, 2 deaths had been reported since the data cut-off, one from gastrointestinal haemorrhage and one from cardiac arrest. Neither were considered related to the study drugs. Three SAEs considered at least possibly related to the study drugs were reported, including one SAE of depression with suicidal ideation, one SAE of major depression/suicide attempt and one SAE of seizure (at least possibly related but to which -according to the investigator- the subject's use of crystal meth may have been a contributory factor).

In the Atlas-2M study, there was one SAE reported after the data lock point. This involved a female subject who previously participated in the ATLAS study. At Week 40, the subject developed acute symptoms of vasovagal reaction immediately after receiving injections of RPV (given first) + CAB (second). She felt dizzy, had a heavy sensation on her chest, reported severe abdominal cramping radiating to the left of her back. Examinations revealed a sudden drop in heart rate from 71 bpm to 65 bpm, and blood pressure from 123/79 mmHg to 68/22 mmHg. No alteration in consciousness was observed and the subject did not experience injection site pain, nausea, sweating, rashes, wheezing, or cyanosis. The subject received oxygen and an intravenous infusion with normal saline. Within 10 minutes after the onset of the symptoms, the subject had recovered. The ECG was normal. The oxygen saturation, ECG, blood chemistry and complete blood count were normal, except for a Grade 1 anaemia (which was longstanding). The RPV plasma concentration after study drug administration was 14-fold higher than expected which was consistent with a partial IV administration of RPV. Importantly, an additional case of partial IV administration of RPV occurred, which has been further discussed under Medication errors.

## Laboratory findings

### *Chemistry*

Results of the clinical laboratory findings in the pooled Phase III studies demonstrate that the majority of subjects (74.7% in the CAB + RPV group and 80.2% in the CAR group) had post-Baseline emergent clinical chemistry abnormalities of Grade 1 or Grade 2 (see table below)). There is a higher incidence of Grade 3-4 abnormalities in the CAB + RPV group, largely attributable to elevations in alanine aminotransferase; aspartate aminotransferase; creatine kinase and lipase. Liver enzyme abnormalities have been included in the SmPC. The applicant describes that creatine kinase elevations are exercise related. Creatine kinase elevations do not increase over time during the Phase III trials, which is reassuring. The occurrence of lipase elevations however, is e reflected in the SmPC, also see below (section on Lipase).

**Table 32 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: Mod5.3.5.3/209522 Output/Tab3.123.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

***Liver function***

Elevated ALT has been observed with exposure to CAB + RPV during the development program. Details on subjects experiencing AEs related to hepatotoxicity have been described under AESI hepatotoxicity.

The severity of liver enzyme abnormalities in the pooled Phase III studies is provided below.

**Table 33 Summary of Maximum Post-Baseline Intensity of ALT 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 (%) |
| Grade 1 | 28 (10) | 22 (8) | 38 (12) | 28 (9) | 66 (11) | 50 (8) |
| Grade 2 | 9 (3) | 4 (1) | 4 (1) | 4 (1) | 13 (2) | 8 (1) |
| 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%) |

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.

Additionally, a summary of hepatobiliary abnormalities during the Maintenance Phase in the Phase III studies is provided in Table 34. This table indicates that hepatocellular injury occurred in 18 subjects in the CAB + RPV group vs. 6 subjects in the CAR group.

**Table 34 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.

The primary method for detection of DILI during the CAB+RPV HIV treatment programme is evaluation of cases where subjects met protocol-defined liver stopping criteria (LSC). This was determined by liver chemistry elevations, predominantly alanine aminotransferase (ALT) which the applicant considered most specific for liver injury. Details about liver chemistry stopping/monitoring criteria can be found in the respective protocols. During ATLAS and FLAIR, transaminase elevations (ALT and AST) were

observed with CAB+RPV: 11 subjects met LSC, 1 subject met LMC. All subjects who met LSC had acute viral hepatitis, except for one subject who had concurrent substance abuse. One subject met liver monitoring criteria due to alcohol use and was noted to have Gilbert's syndrome prior to meeting LMC. The hepatic adjudication committee reviewed all these cases. No cases of DILI were identified. Four out of these 12 subjects in the pooled Phase 3 Studies receiving CAB+RPV had ALT ≥3xULN and total bilirubin ≥2 x ULN. All these subjects had acute viral hepatitis. When subjects receiving CAB+RPV are assessed on the basis of degree of ALT elevation (see table below) it can be seen that most subjects with ALT≥5 x ULN (threshold for clinically important ALT elevation) had alternative explanations for the elevated ALT, primarily due to acute viral hepatitis. Although a number of subjects (n=5) had ALT elevation ≥ 3 ULN and <5 x ULN, these subjects continued on study treatment and did not discontinue. Two of these subjects had explanations for the ALT elevation: in one case due to muscle damage and in another case due to recent acute Hepatitis C.

**Table 35 Summary of Subjects receiving CAB+RPV with Post-Baseline Emergent ALT Elevations (≥3 x ULN) in Pooled Phase 3 studies**

| Subject ID Study ID | Treatment Group | Study Phase | ALT | AST | Total Bilirubin | Resolved? | Withdrew from study? | Type of criteria | Reason for Meeting Liver Monitoring/ Stopping Criteria |
|---|---|---|---|---|---|---|---|---|---|
| **Summary of CAB+RPV Subjects with Maximum Post-Baseline Emergent Increases in ALT >=3 x ULN but <5 x ULN in Phase III Studies (Maintenance Phase)** | | | | | | | | | |
| Subject 1 | CAB+RPV | MP-LA Week 28 | 3.9xULN | 2.7xULN | WNL | Y | N | NA | Transient ALT elevation. Continued study treatment. |
| Subject 2 | CAB+RPV | MP-LA Week 56 | 4xULN | 10.9xULN | WNL | Y | N | NA | Transient episode of ALT elevation associated with concurrent CK elevation 47.7 x ULN. Continued study treatment |
| Subject 3 | CAB+RPV | MP-LA Week 52 | 4xULN | 1.7xULN | WNL | Y | N | NA | Elevated ALT. Resolved within 1 month (prolonged). Elevated Total bilirubin and direct bilirubin starting 08 May 2018. Continued study treatment. Remained on ATLAS after W52. |
| Subject 4 | CAB+RPV | MP-LA Week 24 | 4.4xULN | 1.6xULN | WNL | Y | N | NA | Acute Hepatitis C at Week 21. Transient episodes of ALT elevation. Continued study treatment. |
| Subject 5 | CAB+RPV | MP-LA Week 24 | 4.6xULN | 2xULN | WNL | Y | N | NA | Transient episodes of ALT elevation. Continued study treatment |
| **Summary of CAB+RPV Subjects with Maximum Post-Baseline Emergent Increases in ALT ≥5 x ULN but <10 x ULN in Phase III Studies (Maintenance Phase)** | | | | | | | | | |
| Subject 6 | CAB+RPV | MP-LA Week 52 | 6.5xULN | 4.4xULN | WNL | Y | N | LMC | HCV reactive at screen. Transient episodes of ALT elevation. Continued study |
| Subject 7 | CAB+RPV | MP-LA Week 24 | 7.4xULN | 6.7xULN | 1.7xULN | Y | N | LMC | Never met liver stopping criteria. Alcohol use 2 days before study visit; AE of direct bilirubin increased (known Gilbert's) |
| Subject 8 | CAB+RPV | a. MP-LA Week 44 | 8.1xULN | 5.3xULN | 1.5xULN | Y | Y | LSC | Acute hepatitis B |
| Subject 9 | CAB+RPV | MP-LA Week 16 | 8.6xULN | 4.8xULN | 8xULN | Y | Y | LSC | Acute Hepatitis A |
| Subject 10 | CAB+RPV | MP-oral Week 4 | 8.8xULN | 3.1xULN | 1.5xULN | Y | Y | LSC | Acute hepatitis A |
| **Summary of CAB+RPV Subjects with Maximum Post-Baseline Emergent increases in ALT ≥10 x ULN < 20 ULN in Phase III Studies (Maintenance Phase)** | | | | | | | | | |

| Subject ID Study ID | Treatment Group | Study Phase | ALT | AST | Total Bilirubin | Resolved? | Withdrew from study? | Type of criteria | Reason for Meeting Liver Monitoring/ Stopping Criteria |
|---|---|---|---|---|---|---|---|---|---|
| **Summary of CAB+RPV Subjects with Maximum Post-Baseline Emergent Increases in ALT >=3 x ULN but <5 x ULN in Phase III Studies (Maintenance Phase)** | | | | | | | | | |
| Subject 11 | CAB+RPV | MP – LA Week 36 to 40 | 14.7xULN | 6.7xULN | 1.3xULN | Y | Y | LSC | Acute Hepatitis A |
| **Summary of CAB+RPV Subjects with Maximum Post-Baseline Emergent increases in ALT ≥20 x ULN in Phase III Studies (Maintenance Phase)** | | | | | | | | | |
| Subject 12 | CAB+RPV | MP – oral Week 4 | 20.8xULN | 12.5xULN | WNL | Y | Y | LSC | Acute hepatitis C |
| Subject 13 | CAB+RPV | MP – LA Week 24 | 21.6xULN | 8.4xULN | 2.1xULN | N | Y | LSC | Acute hepatitis C |
| Subject 14 | CAB+RPV | MP – LA Week 20 | 30.2xULN | 17.9xULN | 1.7xULN | N | Y | LSC | Acute hepatitis B |
| Subject 15 | CAB+RPV | MP – LA Week 12 | 42.9xULN | 29.2xULN | 1.2xULN | Y | Y | LSC | Acute hepatitis B |
| Subject 16 | CAB+RPV | MP – oral Baseline | 43.7xULN | 36.5xULN | 1.3xULN | Y | Y | LSC | Illicit IV drug use, inorganic solvent abuse, chronic hepatitis C (HCV reactive at screen) |
| Subject 17 | CAB+RPV | MP – LA Week 32 | 98.1xULN | 89.3xULN | 6.9xULN | Y | N, Restarted Treatment | LSC | Acute Hepatitis A |
| Subject 18 | CAB+RPV | MP – LA Week 8 | 155xULN | 176.5xULN | 7xULN | Y | Y | LSC | Local labs. Acute hepatitis A |

Data Source: Mod5.3.5.3/209522 Output Tables & Figures/Table 3.135, Mod5.3.5.1/201584 W48 CSR/Sec7.3.3.1.2, Listing 61 and 64, and Mod5.3.5.1/201585 W48 CSR/Sec7.7.1.1 and Listing 56.

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

Liver chemistry parameters represent peak values for primary values, other parameters must occur on same day.

Each line represents an individual subject. Liver stopping criteria LSC = Liver Stopping Criteria; LMC = Liver monitoring criteria

* denotes hepatocellular injury defined as [(ALT/ALT ULN) / (ALP/ALP ULN)] >=5 and ALT >=3xULN. ALT and ALP values must occur on the same day.

Besides the liver chemistry changes discussed above, isolated, asymptomatic, non-progressive *total bilirubin* elevations have been observed during Phase III studies, without other liver chemistry abnormalities. Total bilirubin elevations were mostly Grade 1 or 2 (57/59 CAB + RPV; 28/31 CAR). No Grade 3 bilirubin elevations occurred. Five Grade 4 elevations occurred (2 CAB + RPV; 3 CAR). There was a positive correlation between CAB concentrations and change in bilirubin. The applicant remarks that bilirubin elevations could represent competition between CAB and unconjugated bilirubin for a common clearance pathway (UGT1A1).

*Phase II; LATTE-2*

During the maintenance phase, 46 (20%) subjects in the overall IM population had Grade 1-4 ALT elevations. The incidence in liver chemistry elevations is higher than in the pooled phase III studies.

*Phase IIIb data; study ATLAS-2M*

Maintenance emergent ALT abnormalities occurred in 37 (7%) subjects in the Q8W group and 46 (9%) subjects in the Q4W group, mostly with Grade 1 severity. Maintenance emergent bilirubin abnormalities occurred in 29 (6%) subjects in the Q8W group and 24 (5%) subjects in the Q4W group, mostly with Grade 1 severity. Maintenance emergent alkaline phosphatase (ALP) abnormalities occurred in 1 (<1%) subject in the Q8W group and 2 (<1%) subjects in the Q4W group. Results for liver chemistries were comparable with those observed in the CAB + RPV group in the pooled Phase III studies.

***Kidney function***

During the maintenance phase of the pooled Phase III studies the median change from Baseline in CKD-EPI GFR from creatinine (mL/min/1.73 m2) showed no significant difference between the CAB + RPV group and CAR group and little change from Baseline in either treatment group (-3.5 µmol/L for CAB + RPV vs +0.9 µmol/L for CAB). No clinically significant changes from Baseline over 48 weeks in eGFR using cystatin C were observed based on median values in either treatment group. No new safety concern was raised regarding the potential impact on renal function.

***CK***

Transient, asymptomatic elevations of creatine kinase (CK) levels have been observed in subjects in the CAB + RPV group of the pooled Phase III studies. During the Maintenance Phase, 122 (21%) subjects in the CAB + RPV group and 94 (16%) subjects in the CAR group had post-Baseline-emergent elevated CK levels. According to the applicant, changes in creatine kinase could be attributed to physical exercise. The CK elevations did not increase during the course of the Phase III trials, which is reassuring.

**Table 36 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) |

| | 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 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) |

Data Source: Mod5.3.5.3/209522 Output/Tab3.123.

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

***Lipase***

In the pooled Phase III studies, lipase elevations were observed in both treatment groups. The majority of lipase elevations were Grade 1 or 2 in severity (16% in CAB + RPV vs. 15% in CAR). However, there is a trend towards more Grade 3 or 4 lipase elevations in the CAB + RPV group as these occurred in 6% of subjects in the CAB + RPV group and 3% of subjects in the CAR group. This is reflected in the frequency table in section 4.8 of the SmPC as said above.

***Lipid parameters***

In the pooled Phase III studies, most of the treatment-emergent cholesterol and triglycerides abnormalities were Grade 1 or Grade 2. More Grade 1 cholesterol abnormalities occurred in the CAB + RPV (12%) group than in the CAR (5%) group. Results for fasting lipid National Cholesterol Education Program (NCEP) parameters at Week 48 for triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were similar in the 2 treatment groups. Although a change in lipid parameters has been observed for EDURANT, shifts in lipid parameters in the pooled phase III studies were similar between treatment groups.

***Bone biomarkers***

Bone biomarkers (bone-specific alkaline phosphatase, procollagen type 1-Npropeptide [P1NP], type 1 collagen cross-linked C-telopeptide [CTX], osteocalcin, and 25 hydroxy-Vitamin D) in the CAB + RPV treatment group were more favourable indicating less bone turnover compared with CAR. The findings regarding bone biomarkers are as might be expected and do not raise additional concerns.

***Haematology***

Post-Baseline emergent haematology abnormalities were mostly Grade 1 or Grade 2 (10% in the CAB + RPV group vs 9% in the CAR group). Eight subjects had Grade 3 haematology abnormalities: haemoglobin (2 CAB + RPV; 3 CAR), neutrophils (1 CAB + RPV; 1 CAR), and platelets (0 CAB + RPV; 1 CAR) and 3 subjects had Grade 4 haematology abnormalities (1 CAB + RPV [reduction in neutrophils]; 2 CAR [reduction in platelets, reduction in neutrophils]). No occurrences have resulted in SAEs or required hospitalization for myeloid growth factors. As changes (i.e. reductions) in white blood cell count, haemoglobin and platelet count have been included in the frequency table of Edurant, the applicant was requested to also incorporate these changes in the frequency table of section 4.8 of the RPV LA SmPC.

*Phase II data*

Overall, observed laboratory abnormalities in the LATTE-2 study (200056), were in line with those observed in the Phase III studies although the overall incidence of haematology abnormalities Grade 1-4 was higher (with 44/230 subjects (19%) experiencing haematology toxicities).

## Safety in special populations

In general, the AE profile for CAB + RPV was comparable across *age* (>18 years of age), *sex*, and *race*. In the pooled analysis, there was no significant difference noted in the number and types of AEs reported between males (N=413 (96%) in the CAB + RPV group) and females (N=148 (91%) in the CAB + RPV group). Adverse events occurring in subjects <50 years (N=465 (95%) in the CAB + RPV group) and ≥ 50 years (N=96 (97%) in the CAB + RPV group) were similar. No clear trends in the occurrence of AEs could be identified according to increasing age. However, results should be interpreted with caution as only a limited number of patients aged older than 65 was included in the clinical trials. No clinically significant difference was observed in the number of AEs reported among races in the CAB + RPV group; however, the majority of subjects were White. An additional analysis for AEs by baseline ART for both the OLI phase and the full maintenance phase, did not identify a difference in the pattern of AEs depending on the type of previous ART.

**Table 37 AEs in patients under and above 65 years old.**

| | **Age <65** | | **Age 65-74** | |
|---|---|---|---|---|
| | **CAB+RPV (N=584)** | **CAR (N=580)** | **CAB+RPV (N=7)** | **CAR (N=10)** |
| Total AEs | 554 (95%) | 436 (75%) | 7 (100%) | 8 (80%) |
| Serious AEs – Total | 31 (5%) | 26 (4%) | 0 | 0 |
| - Fatal | 0 | 1 (<1%) | 0 | 0 |
| - Hospitalization/prolong existing hospitalization | 25 (4%) | 22 (4%) | 0 | 0 |
| - Life-threatening | 1 (<1%) | 0 | 0 | 0 |
| - Disability/incapacity | 0 | 0 | 0 | 0 |
| - Other (medically significant) | 6 (1%) | 3 (<1%) | 0 | 0 |
| AE leading to drop-out | 22 (4%) | 8 (1%) | 0 | 1 (10%) |
| Psychiatric disorders | 70 (12%) | 51 (9%) | 0 | 0 |
| Nervous system disorders | 126 (22%) | 67 (12%) | 2 (29%) | 1 (10%) |
| Accidents and injuries | 67 (11%) | 67 (12%) | 1 (14%) | 1 (10%) |
| Cardiac disorders | 7 (1%) | 1 (<1%) | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Vascular disorders | 23 (4%) | 11 (2%) | 0 | 0 |
| Cerebrovascular disorders | 0 | 1 (<1%) | 0 | 0 |
| Infections and infestations | 381 (65%) | 331 (57%) | 4 (57%) | 5 (50%) |
| Anticholinergic syndrome | 0 | 0 | 0 | 0 |
| Quality of life decreased † | 0 | 0 | 0 | 0 |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 46 (8%) | 22 (4%) | 2 (29%) | 0 |
| Musculoskeletal and connective tissue disorders | 130 (22%) | 85 (15%) | 3 (43%) | 2 (20%) |

†Note that there were no instances of diminished quality of life reported as AEs, see below for further information deriving from quality of life instruments in Studies 201584 and 201585.

A comparison in the CAB + RPV group between patients with (50 and <90 mL/min/1.73m2) and without (≥ 90 mL/min/1.73m2) renal impairment at baseline did not lead to additional safety concerns as no trends or clustering of AEs were observed in patients with mild renal impairment at baseline.

HIV-infected patients with evidence of *hepatitis B coinfection* were excluded from the CAB + RPV development program, hence conclusions cannot be drawn on the safety of CAB + RPV in hepatitis B co-infected patients.

In the pooled Phase III studies, subjects receiving CAB + RPV who met LSC and were subsequently identified as having acquired *hepatitis C coinfection* had further dosing withheld. None of the subjects with acute hepatitis C during the pooled Phase III studies who met LSC resumed study drug treatment. Asymptomatic subjects with stable HCV were allowed to enroll in the Phase III and II studies for CAB + RPV provided that certain criteria were met, including that these subjects did not have advanced liver disease and were assessed by the investigator that HCV treatment was not necessary during the first 48 weeks of study. During the pooled Phase III studies, 7% of subjects were co-infected with HCV (based on HCV serology alone at Baseline) and they had similar treatment outcomes as mono-infected HIV subjects. These subjects had stable HCV with no suggestion of advanced chronic HCV infection, advanced liver disease, liver fibrosis, or liver decompensation. The subjects in the CAB + RPV group did not develop symptoms of DILI during study participation. However, no firm conclusions can be drawn based on the small number of patients with HCV co-infection. Additionally, five subjects acquired acute HCV during the Phase IIb studies (Study 200056) and restarted the study drug after recovery. One subject in the Phase II study 200056, with HCV co-infection and evidence of liver damage (Grade 3 or 4 fibrosis) accompanied by ongoing HCV replication (chronic active hepatitis) was treated with oral CAB and subsequently met protocol-defined LSC and developed suspected moderate DILI.

The safety of CAB + RPV during human *pregnancy and breastfeeding* has not been established. No studies have been conducted with RPV LA in pregnant women, and pregnant women were excluded from the CAB + RPV development program. Subjects who became pregnant on study were required to discontinue study drugs. During the CAB + RPV development program, out of 9 pregnancies while being exposed to RPV (3 oral and 6 LA), there were 2 live births of a healthy infant and 1 ongoing pregnancy at the time of database lock. There were 1 spontaneous abortion and 1 medical termination for anembryonic pregnancy. The remaining 4 pregnancies were electively terminated for non-medical reasons. In the EDURANT SmPC section 4.6 it is described that lower exposures of rilpivirine were observed during pregnancy; therefore viral load should be monitored closely or alternatively, switching

to another ART regime could be considered. This sentence has also been incorporated in sections 4.4 and 4.6 of the SmPC of RPV LA. Note that the use of RPV LA in pregnant women is included as Missing information in the Safety specification (see section 6.1. and 6.2 of the Rekambys Clinical AR). Maternal and foetal outcomes following RPV LA use during pregnancy will be assessed in the Antiretroviral Pregnancy Registry (APR), which is an additional pharmacovigilance study per RMP of RPV LA.

Studies in animals have shown no evidence of relevant *embryonic or fetal toxicity* or an effect on reproductive function. There was no teratogenicity with oral RPV in rats and rabbits. The exposures at the embryo-fetal NOAEL in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended oral dose of 25 mg once daily.

The safety of exposure of RPV LA to infants through *breastfeeding* has not been established. Some treatment guidelines recommend against breastfeeding to avert the risk of HIV transmission to the infant and product labelling for RPV LA will include standard recommendations not to breastfeed. There are no data on the presence of RPV in human milk, the effects on a breastfed infant, or the effects on milk production. In rats, RPV is present in milk when the mother is exposed to RPV.

## *Safety related to drug-drug interactions and other interactions*

Overall, there are limited safety implications resulting from theoretical or actual drug-drug interactions (DDIs) with CAB + RPV, during active therapy and following treatment discontinuation. Due to the fact that the pathways of metabolism and elimination of RPV are independent of formulation and method of administration and the fact that RPV exposure with RPV LA is in the same range as for oral RPV, results from DDI studies with oral RPV can be used to inform the recommendations for the RPV LA regimen. Rilpivirine has few clinically relevant interactions with other drugs, mainly drugs involving CYP3A pathways. Some relevant drug interactions with oral RPV are not relevant for RPV LA regimen given the method of administration (gastric acid modifiers). For more information on concomitant medication see the section on PD.

## *Discontinuation due to adverse events*

Maintenance phase, pooled Phase III data

*Injection Site Reactions Leading to Withdrawal*

In the pooled Phase III studies, 6 subjects withdrew due to 10 ISRs, including injection site pain, injection site nodule, and injection site swelling (see table below). Two additional subjects withdrew from the FLAIR study citing intolerability of injections but did not name a specific ISR term that led to withdrawal.

**Table 38 Summary of ISR Adverse Events Leading to Withdrawal/Permanent Discontinuation of Study Drug During the Maintenance Phase in Study 201584 and 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)** |
| Injection site pain. n (%) | 2 (<1) | 0 | 4 (1) | 0 | 6 (1) | 0 |
| Injection site nodule, n (%) | 0 | 0 | 1 (<1) | 0 | 1 (<1) | 0 |
| Injection site swelling | 0 | 0 | 1 (<1) | 0 | 1 (<1) | 0 |

Data Source: Mod5.3.5.3/209522 Output/Tab3.36.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

*Non-ISR AEs Leading to Withdrawal*

In the pooled Phase III studies, 16 (3%) subjects in the CAB + RPV group and 9 (2%) subjects in the CAR group experienced non-ISR AEs leading to withdrawal (Table 39). Additionally, 1 subject in the CAB + RPV group (Study 201585) was discontinued due to meeting the protocol-defined LSC. Non-ISR AEs leading to withdrawal were most frequently reported in the infections and infestations SOC (CAB + RPV, n=9 (8 acute viral hepatitis; 1 acute hepatitis A with secondary syphilis); CAR, n=0) and nervous system disorders SOC (CAB + RPV, n=3 (headache (n=2); memory impairment); CAR, n=4 (amnesia, disturbance in attention, dizziness, dysarthria)). With the exception of acute viral hepatitis, all non-ISR AEs (PTs) leading to withdrawal had an incidence of <1%.

**Table 39 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 (%) | 7 (2) | 4 (1) | 9 (3) | 5 (2) | 16 (3) | 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** | | | | | | |
| 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** | | | | | | |

| | 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)** |
| 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 |

Data Source: Mod5.3.5.3/209522 Output/Tab3.36.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In the pivotal Phase III studies, the rate of discontinuation was low; 22 (4%) in the CAB + RPV group vs. 9 (2%) in the CAR group. 16 (3%) subjects in the CAB + RPV group and 9 (2%) subjects in the CAR group had non-ISR AEs leading to withdrawal. The most frequently reported reason for withdrawal was viral hepatitis. All other events occurred in individual subjects and did not exhibit any obvious trend.

Oral lead in

During the OLI period, 6 subjects had 7 AEs that led to the withdrawal of study drug. In the FLAIR study these AEs were acute hepatitis C, hepatitis A, and transaminases increased (related to chronic hepatitis C infection, illicit drug use and inorganic solvent abuse). None of these AEs was considered to be related to study drug. In the ATLAS study these AEs were asthenia, myalgia, headache, and depression suicidal. All 4 AEs were considered to be related to study drug.

Phase II data; study LATTE-2

Through 160 weeks of study treatment in the LATTE-2 study, 15 (7%) subjects experienced AEs leading to withdrawal/permanent discontinuation of study drug; of whom 12 (10%) subjects were in the Q4W arm and 3 (3%) subjects were in the Q8W arm. With the exception of injection site pain, all other individually reported AE preferred terms resulting in withdrawal had an incidence of one subject in any arm. The fact that apart from injection site pain no trends in the occurrence of specific AEs are observed is reassuring.

Phase IIIb data; study ATLAS 2M

A total of 18 (2%) subjects withdrew due to AEs during the ATLAS-2M study. In the Q4W group 6 subjects reported Grade 3 or 4 AEs leading to withdrawal/permanent discontinuation of study drug (Grade 3 injection site pain in 1 subject; Grade 3 injection site swelling in 1 subject; Grade 3 fatigue and depression in 1 subject; Grade 3 transaminases increased in 1 subject; Grade 3 hypersensitivity in 1 subject; and Grade 4 glioblastoma in 1 subject) which were all considered related to study drugs except for glioblastoma.

## *Post marketing experience*

There is no post-marketing data on RPV LA as this product is not marketed in any country. Oral RPV tablets of 25 mg (EDURANT) have been approved for the treatment of HIV-1 infection in ARV treatment-naïve patients in over 85 countries including the US, EU, and Canada. The estimated post-marketing exposure of EDURANT (from launch to 30 April 2019) is 84,403,274 person-days or 231,242 person-years. The latest PSUR of oral RPV, covering the 3-year reporting period from 20 May

to 19 May 2018, concluded that no new important identified or potential risks or safety concerns for the product had been identified during the reporting period.

## 2.6.1. Discussion on clinical safety

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI), developed for the treatment of HIV-1 infection. Oral RPV is a globally available product marketed as EDURANT. The RPV LA formulation was developed as extended-release suspension for intramuscular injection to be administered in combination with cabotegravir (CAB) LA.

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 the pooled phase III studies, the safety population consisted of 591 subjects randomized to CAB + RPV and 591 subjects randomized to CAR. At the time of reporting, a slightly higher proportion of subjects in the CAB + RPV vs. CAR group had withdrawn from the study (51 vs. 40 subjects), with a greater number of subjects in the CAB + RPV group who withdrew due to AEs (22 vs 9 subjects). The duration of exposure was similar in both treatment groups with most patients treated 52 to 64 weeks. Together with the available data on the known safety profile of EDURANT, the overall exposure can be considered sufficient to establish a safety profile for RPV LA.

In the pooled phase III studies, baseline and demographic characteristics were comparable between treatment groups. Most patients were white Caucasian males aged around 38 years.

Adverse events

The incidence of *AEs* was higher in the CAB + RPV group than in the CAR group (95% vs. 75%). Apart from injection site reactions (ISRs), this might partly be due to the open label study design, in which the switch to a novel intervention could have induced the anticipation of adverse events. Also, patients in the CAR arm have been on their regimen for a longer period of time and are less likely to report side effects. In the CAB + RPV group, injection site reactions (ISRs) were the most frequently reported AE (84% of subjects).

Other *commonly reported AEs* with a higher incidence in the CAB + RPV group were headache (12% vs. 6%), back pain (7% vs. 4%), pyrexia (7% vs. 2%), fatigue (5% vs. 2%), dizziness (4% vs. 1%), and haemorrhoids (3% vs. <1%).

In both treatment groups, the majority of AEs reported during the Phase III studies had a *severity* of Grade 1 or 2. 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%). With the exception of injection site reactions (ISRs), differences between the treatment groups in Grade 3 and 4 AEs were ≤1%. Grade 2 to 4 non-ISR AEs occurring in ≥3% of the subjects in either pooled treatment group 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).

Overall, more *drug-related AEs* (83% vs. 6%) were observed with CAB + RPV compared with CAR, mainly attributable to the occurrence of ISRs (non-ISR drug-related AEs in 28% vs. 6%). Drug-related non-ISR AEs occurring in ≥2% of the subjects were headache (4% vs. <1%), pyrexia (4% vs. 0%), nausea (3% vs. 1%), fatigue (3% vs. <1%), asthenia (2% vs. 0%), body temperature increased (2% vs. 0%), myalgia (2% vs. <1%), and dizziness (2% vs. <1%). In both groups, most drug-related AEs were Grade 1 or 2. No fatal drug-related AEs occurred in the Phase III studies. Although many of the drug-related AEs have also been observed with EDURANT, it seems that there is a trend towards more influenza-like events (myalgia and pyrexia).

Drug-related AEs were reported for 400 (77%) subjects in the Q8W group and 399 (76%) subjects in the Q4W group. Most of the drug-related AEs were ISRs and the most frequently reported drug-related AE was injection site pain in both treatment groups. The most frequently reported non-ISR, drug-related AE was pyrexia, with similar frequency between treatment groups (Q8W: 4%, Q4W: 5%).

Adverse events of special interest

During the pooled phase III studies, 84% of subjects experienced ISRs. Only 1% of subjects discontinued because of ISRs. ISRs were generally self-limiting and decreased over time.

In the pooled Phase III Studies Grade 1 and 2 rash AEs were reported in 23 subjects (4%) in the CAB + RPV group and 14 subjects (2%) in the CAR group; of which 10 subjects were reported with rash AEs considered to be drug-related (9 CAB + RPV, 1 CAR), and none led to withdrawal of study drug. The occurrence of rash has been adequately included in the frequency table in the SmPC. Drug-related hypersensitivity reactions occurred in 2 subjects (lip swelling and eosinophilia) in the CAB + RPV group). These AEs were Grade 1 or 2 in severity. Hypersensitivity reactions are considered an important potential risk for CAB + RPV, mainly because of prolonged drug retention following an IM injection and the inability to remove the drug from circulation via means such as dialysis. The applicant has committed to evaluate hypersensitivity reactions (including timing of these reactions since start of RPV treatment) in future PSURs.

It is known from EDURANT that *QT prolongation* may occur with supratherapeutic doses (75 and 300 mg), while QT prolongation was not observed at the recommended dose of 25 mg. As shown in the section on PK/PD (Secondary Pharmacology section 2.2.4), exposure for RPV LA is in line with exposure observed with oral RPV 25 mg once daily, thus QT prolongation might not be expected and it can be agreed that no new dedicated QT studies have been performed for RPV LA. However, in the pooled Phase III trials higher rates of QT prolongation were observed in the CAB + RPV group compared with the CAR group. QT-prolongation was observed in 4 subjects receiving CAB + RPV in the pooled Phase III trials (and 3 subjects in Phase II trials). No correlation with RPV or CAB plasma concentrations was observed in these cases. As plasma concentrations with the recommended RPV LA dosing schedule remain within the same range as plasma concentrations that are reached after oral dosing with Edurant, QT prolongation is not expected. However, the effect of a sudden increase of the plasma concentration -as might occur after accidental iv administration- is not entirely known. Accidental IV administration and subsequent AEs will be evaluated in future PSURs.

The incidence of *neuropsychiatric AEs* was low (up to 6% of subjects), which is in line with observations for RPV and DTG. No additive effect of combining CAB with RPV was anticipated. Overall AEs were balanced between the treatment arms, except for depression, anxiety and insomnia, with higher rates in the CAB + RPV group. Psychiatric disorders are a known adverse event associated with several antiretroviral agents, including RPV and DTG. Depression, anxiety, abnormal dreams and insomnia are included in the frequency table in section 4.8 as common ADRs to RPV LA. No new safety concerns were raised.

During the phase III studies, there were no cases of DILI in subjects receiving CAB LA + RPV LA. However, DILI was identified during Phase II, in 4 subjects receiving oral CAB (incidence was <1%) and during the Phase IIIb study, in one subject receiving oral CAB + oral RPV. During the phase III studies, protocol-defined liver stopping criteria (LSC) were met by 11 (2%) subjects in the CAB + RPV group and 3 (1%) of subjects in the CAR group. Of 11 subjects in the CAB + RPV group meeting the LSC, 10 had acute viral hepatitis. The applicant describes that no mechanism has been identified that could explain the higher incidence of viral hepatitis which is acknowledged.

AEs related to hepatotoxicity occurred in 4 subjects in the CAB + RPV group (AEs in the CAB + RPV group were hepatic steatosis, hepatitis toxic, hepatocellular injury, and non-alcoholic steatohepatitis). None of these AEs were considered by the investigator to be related to study treatment.

A slight increase in body weight was observed for patients treated with CAB + RPV, which has been previously reported for INSTI treatment. No new safety concerns were raised.

Serious adverse events and deaths

The incidence of *SAEs* reported in the pivotal Phase III studies was 5% and 4% in the CAB + RPV and CAR group respectively; which is in line with expectations in this patient population. The most frequently reported SAE with CAB + RPV was acute hepatitis A (n=4). No drug related *deaths* were reported during the pivotal Phase III studies.

During the LATTE-2 study, 38 (17%) subjects reported a SAE, mostly unrelated to study drug. For an SAE of myocardial infarction (occurring in a patient with cardiovascular risk factors) resulting in death, a causal relation with study drug could not be excluded by the investigator. However, considering the absence of a clear mechanism and the presence of confounding factors, relatedness is considered unlikely. Through Week 24 of the ATLAS-2M study few SAEs were reported (3% in both study arms). Overall, the SAE with the greatest frequency was pneumonia (<1% in both study arms). Three drug-related SAEs were reported through Week 24 (gluteal abscess, hypersensitivity reaction after partial IV administration of RPV and pancreatitis resulting in death).

Review of *safety data of ongoing studies* yielded no additional *deaths or drug-related SAEs* for the ATLAS and the FLAIR study. In the LATTE-2 study one subject died of cocaine abuse and atherosclerotic heart disease; this case was not considered study drug-related. Additionally, one SAE of depression, possibly related to the study drugs, occurred. In the LATTE study, 2 deaths were reported, one from gastrointestinal haemorrhage and one from cardiac arrest. Neither were considered related to the study drugs. Three SAEs considered at least possibly related to the study drugs were reported (depression/suicidal ideation, major depression/suicide attempt and seizure to which the subject's use of crystal meth may have been contributed). In the Atlas-2M study, there was one additional SAE reported after the data lock point. This involved a subject who experienced a severe vasovagal reaction related to partial IV administration of RPV.

Laboratory findings

Results of the clinical laboratory findings in the pooled Phase III studies demonstrate that the majority of subjects (74.7% in the CAB + RPV group and 80.2% in the CAR group) had post-Baseline emergent clinical chemistry abnormalities of Grade 1 or Grade 2. However, a trend towards more Grade 3 or Grade 4 chemistry abnormalities in the CAB + RPV group vs. the CAR group was observed (with an incidence of 22% vs 17%). This trend is mainly attributable to elevations alanine aminotransferase; aspartate aminotransferase; creatine kinase and lipase. Liver enzyme abnormalities have been included in the SmPC. Regarding the CPK elevations, occurring in 8% vs. 4% in the CAB + RPV vs. CAR group, the applicant remarks that these were exercise-related. CK elevations did not increase over time during the Phase III trials. During the Phase III studies, lipase elevations were observed in both treatment groups. While Grade 1-2 lipase elevations occurred with similar frequency in both study groups, more Grade 3-4 lipase elevation occurred in the CAB + RPV group vs. the CAR group (6% vs. 3%). In the ATLAS-2M study, one subject died of pancreatitis that could be drug-related. As pancreatitis has been observed in other studies with other INSTIs or NNRTIs, the risk of pancreatitis and lipase elevations were added to section 4.8.

Notably 90 (15%) subjects in the CAB + RPV group vs. 62 (10%) in the CAR group had liver chemistry changes. Review of 18 subjects with relevant liver chemistry elevations (ALT ≥ 3 x ULN) in the pooled Phase 3 Studies identified transient liver chemistry changes, known Gilbert's and alcohol abuse and viral

hepatitis as causes of liver chemistry changes. No cases of DILI were observed in the pooled phase III studies.

Isolated, asymptomatic, non-progressive *total bilirubin* elevations have been observed during Phase III studies. There was a positive correlation between CAB concentrations and change in bilirubin. The applicant remarks that bilirubin elevations could represent competition between CAB and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Haematology

Haematology toxicities were observed in 10% of subjects receiving CAB + RPV in pooled phase III studies and 19% of subjects in the LATTE-2 study. No clear trends could be observed for the changes from Baseline in haematology values in the CAB + RPV and CAR groups, for the pooled Phase III studies. Eight subjects had Grade 3 haematology abnormalities (3 CAB + RPV; 5 CAR), and 3 subjects had Grade 4 haematology abnormalities (1 CAB + RPV; 2 CAR). As reductions in platelet count, haemoglobin and white blood cell count are incorporated in the frequency table in the SmPC of Edurant, the applicant was requested to also add these ADRs to the frequency table in 4.8 of the Rekambys SmPC.

Safety in special populations

In general, the AE profile for CAB + RPV was comparable across age (>18 years of age), sex, and race. As the majority of subjects were Caucasian males aged below 65 years, results should be interpreted with caution. A subgroup analysis of AEs according to the type of previous ART, did not reveal a difference in AE pattern according to previous ART.

In the pooled phase III studies, 41/591 subjects randomized to CAB + RPV were co-infected with HCV at Baseline. The subjects included in the study were not at increased risk of developing hepatotoxicity or increased transaminases compared with subjects infected with HIV only. Because of the small number of subjects, no firm conclusions on the safety of RPV LA in HCV co-infected patients can be drawn. HIV-infected patients with evidence of HBV co-infection were excluded from the clinical program.

A comparison in the CAB + RPV group between patients with (50 and <90 mL/min/1.73m2) and without (≥ 90 mL/min/1.73m2) renal impairment at baseline did not lead to additional safety concerns as no trends or clustering of AEs were observed in patients with mild renal impairment at baseline.

The safety of CAB + RPV during human pregnancy and breastfeeding has not been established. In the EDURANT SmPC it is described that lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely or alternatively, switching to another ART regime could be considered. This recommendation has been incorporated in the RPV LA SmPC. For the exact wording see separate SmPC assessment.

AEs Leading to Withdrawal

In the pivotal Phase III studies, the rate of discontinuation was low; 22 (4%) in the CAB + RPV group vs. 9 (2%) in the CAR group. The most common AEs leading to withdrawal with CAB + RPV were acute viral hepatitis (n=9 [2%]) and ISRs (n=6 [1%]). All other individual AEs (PTs) leading to withdrawal had an incidence of <1%.

Medication errors

In Study 201584 and Study 201585, medication errors and device malfunctions were reported infrequently. However, in the Phase IIb Study 200056 (LATTE-2) and Phase IIIb Study 207966 (ATLAS-2M), there were 3 subjects in total for whom post-dose RPV PK was consistent with partial IV administration. One of these subjects (Study 200056) experienced confirmed virologic failure (CVF) without treatment-emergent resistance and the other 2 subjects (Study 207966) were reported with SAEs (allergic reaction and vasovagal reaction). The applicant describes that this issue is further explored

at the moment. Accidental IV administration is an important risk of the LA formulation for which follow up is required, which has been incorporated in section 4.4 of the SmPC. The applicant has committed to carefully monitor and discuss medication errors in future PSURs**.**

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 in clinical efficacy minutes related to the SAG meeting

## 2.6.2. Conclusions on the clinical safety

Results from the CAB + RPV development program, support the use of CAB LA in virologically suppressed HIV-1 infected patients.

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

| |
|---|
| 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 anti-retroviral 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. |
| 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. |

## *2.7. Risk Management Plan*

The applicant submitted an updated EU Risk Management Plan for Rekambys (rilpivirine prolonged-release suspension), version number 1.5, data lock point for current RMP 6 June 2019, dated 12 October 2020.

## Safety concerns

| | |
|---|---|
| **Important Identified Risks** | None |
| **Important Potential Risks** | Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration) |
| **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 authorization | | | | |
| Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration With EuroSIDA<br><br>Planned | To better understand the patient population receiving RPV LA and/or CAB LA containing injection regimens in routine clinical practice, usage patterns, adherence, postmarketing clinical effectiveness of this regimen, discontinuations, and monitor for resistance among virologic failures for whom data on resistance testing are available. The DUS will also evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of RPV LA and/or CAB LA containing injection regimens according to the SmPC recommendations. | Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration) | Protocol Submission<br><br>Regular updates<br><br>Final Study Report | 31 December 2020<br><br>Yearly interim reports presenting the progress and status of the DUS will be prepared and discussed in the PBRER/PSUR.<br><br>30 September 2026 |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| Not Applicable | | | | |
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| Antiretroviral Pregnancy Registry (APR)<br><br>Planned | Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. | Use in pregnancy | Protocol submission<br><br>Regular updates | 31 December 2020<br><br>A registry interim report will be prepared semi-annually summarizing the aggregate data. Data from the APR will be presented in the PBRER/PSUR. |

## Risk minimisation measures

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important potential risks** | | |
| Medication errors (ie, non-adherence to the dosing schedule, incorrect route of administration) | **Routine risk minimization measures:**<br>• SmPC Sections 4.2 and 4.4<br>• PL Sections 2 and 3<br>• IFU<br>• SmPC Sections 4.2 and 4.4 provide detailed instructions on the correct administration of the regimen, importance of adherence to the injection schedule, and how to handle treatment discontinuation.<br>• PL Sections 2 and 3 include instructions on what to do when stopping treatment.<br>• IFU are provided in the PL and include detailed information on the preparation and administration of an IM injection.<br>• Administered by HCPs.<br>• Different packaging designs to differentiate between dose and medication. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients Initiating ARV Regimen of RPV LA+CAB LA, in Collaboration with EuroSIDA<br>Final study report: 30 September 2026 |
| | **Additional risk minimization measures:**<br>• None | |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| **Missing information** | | |
| Use in pregnancy | **Routine risk minimization measures:**<br>• SmPC Sections 4.4 and 4.6<br>• PL Section 2<br>• Recommendation regarding the use of Rekambys during pregnancy is provided in SmPC Sections 4.4 and 4.6, and PL Section 2.<br>• This is a prescription only medicine.<br>• Prescribed by HCPs.<br>**Additional risk minimization measures:**<br>• None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>• None<br>**Additional pharmacovigilance activities:**<br>• Review of Antiretroviral Pregnancy Registry (APR). A registry interim report will be prepared semi-annually summarizing the aggregate data. Data from the APR will be presented in the PBRER/PSUR. |

## Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 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 18/03/2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. Product information*

### 2.9.1. 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.*

### 2.9.2. Quick Response (QR) code

A request to include a QR code in the labelling has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code: A 2D barcode carrying the unique identifier has been included.

### 2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rekambys (rilpivirine) is included in the additional monitoring list as:

- *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

The following indication is claimed for Rekambys:
*Rekambys is indicated, in combination with 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) and have no known or suspected resistance to either rilpivirine or cabotegravir (see section 5.1).*

*Rekambys should always be co-administered with cabotegravir injection. Therefore, the cabotegravir injection Summary of Product Characteristics should be consulted.*

HIV-1 infection, and if not appropriately treated the subsequent development of a state of acquired immunodeficiency (AIDS), remains an incurable disease. The goal of antiretroviral (ARV) therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication.

### 3.1.2. Available therapies and unmet medical need

Standard treatment for HIV-1 infection consists of a combination of 3 antiretroviral agents (ARV), from at least 2 different classes, and typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI class. Several options are available for construction of a suppressive antiretroviral regimen. The most recent guideline of the European AIDS Clinical Society (EACS, version 9.1 issued October 2018) recommend the use of an INSTI as preferred third agent in ART-naïve adult HIV-positive persons; with the added note that tailoring antiretroviral regimens for each individual is essential as other classes of third agents (e.g boosted PI) might be indicated in the presence of resistance or risk of poor adherence.

Apart from triple therapy regimens, also dual-therapy regimens are available, e.g. Juluca (DTG+RPV) and Dovato (DTG+3TC). While Juluca is specifically indicated for use in virologically suppressed patients, Dovato may also be used in treatment-naïve patients.

Multiple therapeutic options have become available over time notably in first-line therapy. Other single-tablet regimens (STRs) are already available on the market for first-line therapy, combining 2 NRTI s + 1 NNRTI (Atripla, Eviplera, Odefsey), 1 INSTI (Stribild, Genvoya, Triumeq) or 1 boosted-PI (Symtuza).

Rekambys is not aimed at responding to an unmet medical need. This formulation has rather been developed to provide patients with an option of reduced dosing frequency compared with daily oral antiretrovirals.

### 3.1.3. Main clinical studies

The main clinical studies for the evaluation of Rekambys are the 3 Phase III studies FLAIR (Study 201584, n=566), ATLAS (Study 201585, n=616), and ATLAS-2M (Study 207966, n=1049). Both FLAIR and ATLAS are randomized (1:1), multicenter, parallel-group, open-label studies evaluating the efficacy, safety, and tolerability of long-acting intramuscular Cabotegravir and Rilpivirine for maintenance of virologic suppression following switch from an Integrase inhibitor single-tablet regimen (FLAIR) or current INI-,

NNRTI-, or PI-based antiretroviral regimen (ATLAS) in HIV-1 infected antiretroviral therapy-naive (FLAIR) or experienced (ATLAS) adult participants.

In ATLAS-2M, the 4W regimen is compared with the alternative 8W dose regimen. Week 48 results from this study became available as part of the response to the D120 LoQ.

## *3.2. Favourable effects*

The estimated **virologic failure rate**, i.e. the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 in the ITT-E Population, was 6/283 (2.1%) in the CAB + RPV arm and 7/283 (2.5%) in the CAR arm of Study FLAIR. The adjusted difference in proportion was -0.4% (95% CI -2.8, 2.1). In ATLAS, the estimated virologic failure rate was 5/308 (1.6%) in the CAB + RPV arm and 3/308 (1.0%) in the CAR arm, with an adjusted difference in proportion of 0.7% (95% CI -1.2, 2.5). Comparable estimates were obtained when considering the PP population.

For both studies, this remains within the by the applicant pre-defined non-inferiority margin of 6%.

Confirmed virologic failure (CVF), defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL, was met by 4/283 (1.4%) in the CAB + RPV arm and 3/283 (1.0%) in the CAR arm of Study FLAIR, and by 3/308 (1.0%) in the CAB + RPV arm and 4/308 (1.3%) in the CAR arm of Study ATLAS. Six of the 7 subjects with CVF in the pooled CAB + RPV arms had RPV **resistance associated mutations** (RAMs) at the time of failure. Five of the 7 subjects had phenotypic resistance against RPV at the virologic failure time point. Three subjects developed dual resistance to CAB and RPV.

**Virologic success rates**, i.e. the proportion of subjects with plasma HIV-1 RNA <50 copies/mL using the snapshot algorithm in the ITT-E at Week 48 were 265/283 (94%) and 264/283 (93%) for CAB + RPV vs. CAR, respectively, in FLAIR, and 285/308 (93%) and 294/308 (96%) for CAB + RPV vs. CAR in ATLAS. Adjusted differences in proportion and 95% confidence intervals were 0.4 (-3.7, 4.5) in FLAIR, and -3.0 (-6.7, 0.7) in ATLAS. The results from the PP population were comparable with those from the ITT-E population.

For both studies, this exceeds the by the applicant pre-defined non-inferiority margin of -10%.

In addition, the applicant has newly provided the 48 weeks efficacy data of 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), which is below the pre-defined 4% non-inferiority margin. Consistency was observed between the ITT and PP analyses.

## *3.3. Uncertainties and limitations about favourable effects*

**Dose selection.** The dose and dosing frequency of RPV LA are based on maintaining plasma trough concentration at the end of the dosing interval at or above exposures known to be induced by oral RPV 25 mg once daily. The maximal exposure of CAB and RPV (steady-state) will only be reached after 44-72 weeks and 2.2 years of treatment, respectively. Of relevance is that, except for one subject with CVF at the Week 48 time point in FLAIR, all virologic failures occurred in the first 28 weeks of treatment. Exposure-response analyses revealed that the 11 subjects with Snapshot virologic failure (11/591 (1.9%)) had exposures that are generally below the median.

**Patient population.** It is not self-evident what the appropriate target population would be. It is of importance that this is clarified given that there is an increased risk of selection (and potential

transmission) of dual class resistant virus, in patients who do not correctly use this long-acting regimen, or who do not switch to an alternative oral regimen after treatment discontinuation (see also below).

**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. Based on multivariable post hoc 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.

**Virologic failure and resistance development.** Virologic failure rates were low in the clinical studies, and adherence to the visit schedule was high. It is questionable whether this high adherence will also be reached in clinical practice (see also above, under Patient population). The applicant agreed to conduct a drug utilization study (DUS), as was already proposed for Cabotegravir. 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 duration 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. Further, an additional 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.

**Management of treatment discontinuation.** 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 RPV and CAB, and subsequent resistance development. This will be closely followed in the DUS. The HIV SAG was asked whether the currently proposed text in the SmPC suffices to allow proper patient selection, or whether additional measures such as an electronic or mobile app reminder system for patients to manage properly discontinuation of treatment may be useful for the safe and effective use of this first novel injectable regimen. The experts remarked that adherence is an extremely complex and heterogeneous topic that can change between patients, centers, 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, 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.

**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, 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. In addition, a 20 to 40% decrease of CAB/RPV predose concentrations are observed in the Q8W regimen in comparison to the Q4W regimen. 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 optimized 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 (VL). For patients who could have higher risk of VL it was remarked that starting with the Q4W regimen should be considered to minimize 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.

**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 post-approval.

## *3.4. Unfavourable effects*

**Adverse Events** were reported in 95% of subjects receiving CAB + RPV and 75% of subjects receiving CAR in the pooled phase III studies. Excluding injection site reactions (ISRs), that occurred in 84% of subjects, AEs were reported in 86% of subjects receiving CAB + RPV.

**Commonly reported AEs** occurring significantly more often in the CAB + RPV group were ISRs (84% vs. 0%), pyrexia (7% vs. 2%), headache (12% vs. 6%), fatigue (5% vs. 2%) and back pain (7% vs.4%).

**Drug-related AEs**, occurred in 83% of subjects in the CAB + RPV group vs 6% of subjects in the CAR group. This difference is mainly driven by ISRs. Excluding ISRs, drug-related AEs occurred in 28% of the subjects in the CAB + RPV group and 6% of the subjects in the CAR group. Most frequently reported, Grade 2 to 4, drug-related non-ISR AEs were headache, diarrhoea, pyrexia, and fatigue (each occurring in <1% of subjects). The ATLAS-2M study demonstrated a similar rate of drug-related AEs for the Q4 and Q8 Week regimens (76% vs. 77%).

**Serious adverse events** were reported in 5% of subjects receiving CAB + RPV and 4% of subjects receiving CAR.

**AEs leading to withdrawal.** During the oral lead in the pivotal phase III studies, 6 subjects had 7 AEs that led to withdrawal of study drug, of which 4 were considered study drug-related (asthenia, myalgia, headache, and depression suicidal). In the pooled Phase III studies, 8 (1%) subjects withdrew due to ISRs, including injection site pain, injection site nodule, and injection site swelling. 16 (3%) subjects withdrew due to non-ISR AEs. Most commonly reported non-ISR AEs leading to withdrawal were acute viral hepatitis, headache and memory impairment.

## *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 randomized 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.

**Missing information**. No specific clinical study was performed with CAB + RPV in paediatric subjects, elderly subjects, subjects with renal insufficiency or hepatic impairment and pregnant women. For RPV knowledge may be based on what is known from the established safety profile of EDURANT as exposure remains within the same range at the recommended dose.

## *3.6. Effects Table*

**Table 40. Effects Table for Rekambys, Week 48 analysis time point.**

| Effect | Short Description | Unit | CAB+RPV LA Q4W regimen | CAB+RPV LA Q8W regimen | CAR | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | | |
| Virologic failure rate | Percentage of patients with HIV-1 RNA ≥50 c/mL at week 48, (ITT-E population) | n/N (%) | 6/283 (2.1) | | 7/283 (2.5%) | **SoE:** Adjusted difference (95%CI): -0.4% (-2.8, 2.1) | FLAIR |
| | Percentage of patients with HIV-1 RNA ≥50 c/mL at week 48, (ITT-E population) | n/N (%) | 5/308 (1.6) | | 3/308 (1.0%) | **SoE:** Adjusted difference (95%CI): 0.7% (-1.2, 2.5) | ATLAS |
| | Percentage of patients with HIV-1 RNA ≥50 c/mL at Week 48 | n/N (%) | 5/523 (1.0) | 9/522 (1.7) | | **SeO:** Adjusted difference (95%CI): 0.8 (-0.6, 2.2) | ATLAS-2M |
| **Unfavourable Effects** | | | | | | | |
| Injection Site reactions | Local effects<br>• pain<br>• nodule<br>• induration<br>• swelling<br>• pruritus | % | Pooled ATLAS and FLAIR data<br><br>84<br>77<br>14<br>12<br>8<br>4 | ATLAS-2M data<br><br>71<br>10<br>8<br>6<br>5 | N/a | | Summary of clinical Safety |

| Effect | Short Description | Unit | CAB+RPV LA Q4W regimen | CAB+RPV LA Q8W regimen | CAR | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| | Systemic effects<br>• Pyrexia<br>• Headache<br>• Fatigue | % | <br>7<br>12<br>5 | <br>8<br>7<br>2 | N/a | | |

Abbreviations: CAB: Cabotegravir; RPV: Rilpivirine; LA: long-acting; CAR:continued/current antiretroviral regimen; CI: confidence interval; CVF: confirmed virologic failure; RAM: resistance associated mutation; RT: reverse transcriptase; IN: integrase; CSR: clinical study report; PP: per protocol, N/a: not applicable

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

While Rekambys, in combination with Vocabria 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.

Overall, it has been shown that the long-acting intramuscular injection regimen CAB + RPV LA is non-inferior to standard triple oral antiretroviral therapy. Virologic failure rates were low across studies (<2.2%), and HIV-1 viral load remained suppressed in the majority of subjects (>93%). The safety profile of Rekambys is, based on currently available information, favourable and in line with the known safety profile of the oral 25 mg tablet Edurant.

Due to the long-acting features of this regimen, it is important to evaluate tolerability to the regimen by using the oral components, before the injections are started. During the oral lead-in phase of the studies, only few subjects discontinued, which is reassuring.

The efficacy of the LA regimen should be seen in the light of the patient population that has been enrolled in the clinical studies, which was a population of HIV-infected, treatment naïve (FLAIR) or successfully treated (ATLAS) adult subjects with asymptomatic disease. This population showed a high level of adherence to the monthly visits, as reflected in a low proportion of out-of-window visits and discontinuations. It is, however, questionable if this population is representative for the patients that may be treated in clinical practice. It is considered important to ensure that only those patients are selected for treatment who understand the need of strict adherence to the monthly injections, especially during the initial period before steady-state exposures are reached, and who 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-time 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. 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. Fortunately, CAB and RPV both do not seem to interact with other ARVs and hence there are no restrictions for oral antiviral regimens after LA treatment discontinuation.

Although non-inferiority has been shown against standard triple oral antiretroviral therapy, it is noted that subjects with virologic failure had exposures of CAB and RPV that were on the low side, and all virologic failures occurred in the first weeks of treatment before steady-state exposures were reached. This makes it uncertain whether the regimen, as currently proposed, is the most optimal to keep the virus suppressed during the initial months after initiation of CAB + RPV long-acting, or whether there is some room for further improvement. In this respect, the results generated with the Q8W regimen are of interest. Based on currently available information, it seems that the Q8W regimen resulted in a numerically higher number of subjects with virologic failure in the Q8W arms (n=10) vs. the Q4W arms (n=3) of LATTE-2 and ATLAS-2M combined, as well as a higher proportion of subjects with predicted below target levels in the Q8W vs the Q4W regimen in the LATTE-2 study. As patients in real life may not be as strictly adherent to the visit schedule as the subjects enrolled in the clinical studies, there is

some uncertainty regarding the performance of this regimen in clinical practice. Also, it should be awaited to what extent certain practical issues with the LA regimen for which recommendations are currently based on modelling and simulation data, such as the period that can be bridged using the oral components and when another initiation dose should be given rather than a continuation dose, can be confirmed to be effective in real life.

The input of a HIV SAG was received to notably ensure that adequate safeguards have been put in place to minimize 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 to what 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 centers, 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.

### 3.7.2. Balance of benefits and risks

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%). As the safety profile of Rekambys is acceptable, it can be concluded that from a *clinical perspective*, the balance of benefits and risks for Rekambys is positive, provided adequate post-authorisation follow-up.

### 3.7.3. Additional considerations on the benefit-risk balance

It is considered important to note that the outcome of this application also depends on that of Vocabria, and harmonisation of the approach in the SmPC and RMP has been done whenever relevant.

## *3.8. Conclusions*

The overall B/R of Rekambys is positive

# 4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rekambys is favourable in the following indication:

Rekambys is indicated, in combination with 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 (see sections 4.4 ,4.2 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:

| |
|---|
| 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 anti-retroviral 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. |
| 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. |

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States*

Not applicable.

# Appendices

1.-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*<br><br>To gather further information about the clinical effectiveness and the development of resistance associated with this new injectable HIV treatment regimen (CAB/RPV LA).<br><br>*Background information on measure*<br><br>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.<br><br>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.<br><br>*Due dates*<br><br>Final protocol submission:<br><br>31 December 2020<br><br>Estimated Study start:<br><br>EMA approval of protocol and CAB+RPV LA commercially available<br><br>Estimated Study completion:<br><br>December 2025<br><br>Final report:<br><br>September 2026 (with prior annual reports to |

| Post-authorisation measure (s) | Motivation |
|---|---|
| | be submitted plus yearly updates) |
| **Proposed post-authorisation measure 2 with proposed classification:** | **Motivation/Background information on measure, including due date:** |
| 2. Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating ARV regimen of CAB+RPV (**Category 1 PASS**) | *Motivation*<br><br>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).<br><br>*Background information on measure*<br><br>Describe CAB LA and/or RPV LA containing regimens usage patterns.<br><br>Assess adherence, durability and discontinuation of CAB+ RPV regimen and the ARV regimen after switching from CAB+RPV.<br><br>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.<br><br>Monitor for resistance and next treatment response among individuals who switched off CAB LA and/or RPV LA (where data is available).<br><br>*Due dates*<br><br>Final protocol submission:<br><br>31 December 2020<br><br>Estimated Study start:<br><br>EMA approval of protocol and CAB+RPV LA commercially available<br><br>Estimated Study completion:<br><br>December 2025<br><br>Estimated Final report:<br><br>September 2026 (with prior annual reports to be submitted plus yearly updates) |

1. * 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)