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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Rekambys

International non-proprietary name: rilpivirine

Procedure No. EMEA/H/C/005060/II/0022

Marketing authorisation holder (MAH) Janssen-Cilag International N.V.

Note

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



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List of abbreviations

AE	Adverse event
AESI	Adverse event(s) of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AR	Adverse reaction
ARV	Antiretroviral
AUC	Area under the concentration-time curve
c/mL	Copies per milliliter
C _{0h}	Predose (trough) concentration
CAB	Cabotegravir
cART	Combination antiretroviral therapy
C _{max}	Maximum plasma concentration
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CSR	Clinical study report
CVF	Confirmed virological failure
DAIDS	Division of AIDS
ECG	Electrocardiogram
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HIV-1	Human immunodeficiency virus type 1
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
ISR	Injection site reaction
LA	Long-acting injectable, extended-release suspension for injection, or prolonged release suspension for injection
LSFU	Long-term safety and washout pharmacokinetic follow-up
mg	milligram
MOCHA	More Options for Children and Adolescents
NIAID	National Institute of Allergy and Infectious Diseases
NICHHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
OLI	Oral lead-in
pcVPC	Prediction-corrected visual predictive check
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PT	Preferred term
Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
QC	Quality control
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 4 June 2024 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include, in combination with cabotegravir injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Rekambys, based on interim results from study 208580. This is an ongoing Phase 1/Phase 2 multicentre, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and pharmacokinetic of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable combination antiretroviral therapy consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0397/2022 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 MAH 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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt

Co-Rapporteur:

Fátima Ventura

Timetable	Actual dates
Submission date	4 June 2024
Start of procedure:	22 June 2024
CHMP Rapporteur Assessment Report	19 August 2024
PRAC Rapporteur Assessment Report	19 August 2024
PRAC members comments	18 August 2024
CHMP Co-Rapporteur Assessment	29 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	09 September 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 September 2024
Request for supplementary information (RSI)	19 September 2024
PRAC Rapporteur Assessment Report	21 November 2024
PRAC members comments	20 November 2024
Updated PRAC Rapporteur Assessment Report	26 November 2024
CHMP Rapporteur Assessment Report	26 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	02 December 2024
Updated CHMP Rapporteur Assessment Report	05 December 2024
Opinion	12 December 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Rekambys is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated, in combination with cabotegravir (an integrase inhibitor (INI)) for the treatment of 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, and no prior virological failure with agents of the NNRTI and INI class.

This application provides new clinical data derived from the ongoing Phase 1/2 study 208580 to support the use of Rekambys for the treatment of HIV-1 in a new target population: adolescents at least 12 years of age and weighing at least 35 kg. The proposed dose and dosing regimen are identical for adults and adolescents.

Disease or condition

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.

State the claimed therapeutic indication

Rekambys is indicated, in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) 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 non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class (see sections 4.2, 4.4 and 5.1).

2.1.2. About the product

The current application concerns Rekambys, an extended-release (also called prolonged release) suspension for intramuscular (IM) injection of rilpivirine (RPV). RPV, a diarylpyrimidine derivate, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT).

Rilpivirine is also available as Edurant, (25 mg oral tablet formulation, 2.5 mg dispersible tablet), which in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and paediatric patients at least 2 years of age and weighing at least 14 kg without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, and with a viral load \leq 100,000 HIV 1 RNA copies/mL.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Development programme

The clinical development programme for Rekambys to support authorisation in adolescents at least 12 years of age and weighing at least 35 kg, consists of:

- Week 24 data (primary endpoint) from the ongoing Phase 1/2 Study 208580 (IMPAACT 2017 or MOCHA)
- Additional analyses to evaluate the PK of rilpivirine long-acting in adolescent patients. An initial rilpivirine long-acting population PK model was generated from Phase 3/3b adult data, and this was then updated with the adolescent data from Study 208580.

PIP

A Partial PIP Compliance Check has been performed on all paediatric studies to be completed to date. A copy of the PDCO Opinion on PIP Compliance (EMA-C1-000317-PIP02-18-M01) was provided with the submission.

According to EMA procedure EMA-C1-000317-PIP02-18-M01, study 1, which is the pivotal PK and safety study in adolescents (IMPAACT 2017; MOCHA study) for the use of long acting rilpivirine in combination

with long acting cabotegravir for the treatment of HIV infection, was conducted in compliance with the agreed paediatric investigation plan as set out the EMA's decision P/0397/2022 of 9 September 2022.

2.1.4. General comments on compliance with GCP

The MAH included a statement indicating that all clinical studies carried out in countries outside the European Union (EU) met the ethical requirements of Directive 2001/20/EC. All clinical studies in these countries were undertaken in accordance with standard operating procedures, which comply with the principles of Good Clinical Practice. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where regulatory approval was required, this was obtained from the relevant health authority. The countries outside the European Union that participated in the clinical development programme for Rekambys (rilpivirine) 600mg/2ml and 900mg/3ml prolonged release suspension for injection are Botswana, Thailand, US, South Africa and Uganda.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The extension of the indication of rilpivirine to adolescents was not considered to change the use pattern of the medicinal product, the maximum daily of 30 mg remains the same. Therefore, no increased environmental exposure is expected, and a revised Environmental Risk Assessment (ERA) was not deemed necessary. The disposal advice "Any unused medicinal product or waste material should be disposed of in accordance with local requirements" recommended by the CHMP is maintained.

2.2.2. Conclusion on the non-clinical aspects

The extended indication is not considered to lead to a significant increase in environmental exposure further to the use of rilpivirine. Rilpivirine is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

PK, efficacy and safety data from study 208580 (IMPAACT 2017; MOCHA) Cohort 1R (full analysis) and Cohort 2 (Week 24 primary analysis), and the updated RPV LA population pharmacokinetics (PopPK) model were submitted in order to support the clinical pharmacology of rilpivirine long-acting (RPV LA) as part of the cabotegravir + rilpivirine (CAB + RPV) dosing regimens in adolescents (12 to <18 years of age and weighing at least 35 kg) with HIV 1.

GCP

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

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

- Tabular overview of clinical studies

Table 1 Tabular overview of clinical studies

Study	Study Design	Population	Treatment Details	Primary Objectives
<p>208580 (IMPAACT 2017 or MOCHA)</p> <p>Status: Ongoing</p> <p>Full Cohort 1 and Cohort 2 Week 24 CSR completed</p>	<p>Open-label, noncomparative, Phase I/II study to confirm doses and evaluate safety, tolerability, acceptability, and PK of oral CAB, CAB LA, and RPV LA</p>	<p>HIV-1 infected cART experienced adolescents (12 to <18 years of age) weighing at least 35 kg who are virologically suppressed on a stable ARV regimen</p>	<p><u>Cohort 1:</u> Participants were assigned to Cohort 1C or Cohort 1R based on their background cART regimen. Cohort 1C: CAB 30 mg once daily orally for 4 to 6 weeks in addition to cART, followed by 3 IM injections of CAB LA each separated by 4 weeks (600 mg for first injection and 400 mg for second and third injections) in addition to cART; injections occurred at Weeks 4, 8, and 12. After the protocol was amended, additional participants in Cohort 1C received CAB 30 mg once daily orally for 4 to 6 weeks in addition to cART, followed by 2 IM injections of CAB LA 4 weeks apart (both 600 mg) at Weeks 4 and 8 in addition to cART. Week 16 was considered end of injection phase. Cohort 1R: RPV 25 mg once daily orally for 4 to 6 weeks in addition to cART, followed by 3 IM injections of RPV LA each separated by 4 weeks (900 mg for first injection and 600 mg for second and third injections) in addition to cART; injections occurred at Weeks 4, 8, and 12. After the protocol was amended, additional participants in Cohort 1R received RPV 25 mg once daily orally for 4 to 6 weeks in addition to cART, followed by 2 IM injections of RPV LA 4 weeks apart (both 900 mg) at Weeks 4 and 8 in addition to cART. Week 16 was considered end of injection phase. <u>Cohort 2:</u> No background cART. CAB 30 mg + RPV 25 mg once daily orally for 4 to 6 weeks followed by IM injections of CAB LA (600 mg) + RPV LA (900 mg) Q8W. Injections occur at Week 4 and Week 8, followed by injections Q8W through Week 96.</p>	<p><u>Cohort 1:</u></p> <ol style="list-style-type: none"> 1. To confirm doses for injectable RPV LA in adolescents living with HIV who are virologically suppressed by evaluating safety and multiple-dose PK of RPV LA through Week 16. 2. To confirm the doses for oral CAB followed by injectable CAB LA in adolescents living with HIV who are virologically suppressed by evaluating: 3. Safety and multiple-dose PK of oral CAB through Week 4; 4. Safety and multiple-dose PK of CAB LA through Week 16. <p><u>Cohort 2:</u> To assess the safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 24.</p>

2.3.2. Pharmacokinetics in HIV-infected adolescent participants

2.3.2.1. Study 208580 (MOCHA) – full Cohort 1 Analysis and Cohort 2 Week 24 Analysis

Study 208580 is an ongoing Phase 1/2, multicenter, open label, noncomparative study of the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable cART consisting of 2 or more drugs from 2 or more classes of antiretroviral (ARV) drugs.

Adolescent, HIV-1 infected participants have been enrolled in Cohort 1 and assigned to Cohort 1C (CAB in addition to continued background cART) or Cohort 1R (RPV in addition to continued background cART) based on their background cART regimen. Following enrollment, participants received at least 4 weeks of oral lead-in (OLI) of CAB or RPV while continuing their background cART (Cohort 1 Step 1) for assessing tolerability before starting the LA injections of the assigned drug. For participants enrolled under Protocol Version 2.0, LA injections were administered every 4 weeks (Q4W) for a total of 3 injections while continuing the background cART (Cohort 1 Step 2). For participants enrolled under Protocol Version 3.0, LA injections were administered every 8 weeks (Q8W) for a total of 2 injections while continuing the background cART (Cohort 1 Step 2).

In addition to the participants enrolling directly into Cohort 2, adolescents who participated in Cohort 1 Step 2 could continue study participation in Cohort 2, if eligible. Cohort 2 participants discontinued their pre-study cART regimen and received both CAB and RPV at the doses established in Cohort 1. Cohort 1 data indicated that the adult Q8W dosing regimen was appropriate for adolescents. Therefore, based on enrollment under Protocol Version 3.0, all Cohort 2 participants were scheduled to receive oral CAB + oral RPV for 4 to 6 weeks (Step 3) followed by CAB LA + RPV LA injections administered Q8W through Week 96 (Step 4).

Details of the CAB or RPV dosing for Cohort 1 are as follows (the remainder of this report only focusses on Cohort 1R and Cohort 2):

- CAB (Cohort 1C) – CAB 30 mg once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 IM injections of CAB LA for Q4W regimen, each separated by 4 weeks (600 mg for the first injection and 400 mg for the second and third injections) or followed by 2 IM injections of CAB LA for Q8W regimen, each separated by 4 weeks (both 600 mg), in addition to cART (Step 2).
- RPV (Cohort 1R) – RPV 25 mg once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 intramuscular (IM) injections of RPV LA for Q4W regimen, each separated by 4 weeks (900 mg for the first injection and 600 mg for the second and third injections) or followed by 2 IM injections of RPV LA for Q8W regimen, each separated by 4 weeks (both 900 mg), in addition to cART (Step 2).

Details of the CAB+RPV dosing for Cohort 2 are as follows:

- Oral CAB 30 mg + oral RPV 25 mg once daily for 4 to 6 weeks (Step 3)
- CAB LA (600 mg) + RPV LA (900 mg) Q8W through Week 96 (Step 4), with the first 2 injections separated by 4 weeks.

Bioanalysis

Rilpivirine was quantitated via LC-MS/MS using positive electrospray ionization and multiple reaction monitoring. For Study 208580, the human EDTA plasma assay for RPV (not previously submitted) was independently validated over the concentration range of 1 to 5000 ng/mL. by the Clinical Pharmacology

Analytical Laboratory at The Johns Hopkins University School of Medicine, Baltimore, Maryland. A summary of the validation data that supported application of the RPV bioanalytical method to Study 208580 was included in this submission including a cross validation.

A validated bioanalytical method was used for Study 208580 to measure concentrations of RPV in human plasma and QC samples for the study samples met the acceptance criteria for accuracy and precision.

A cross validation between PRA Health Sciences, The Netherlands (used in previous submissions) and the Clinical Pharmacology Analytical Laboratory was conducted, and the result was acceptable.

Participants included in PK Analysis

The RPV PK analysis includes all participants in the All Treated Population for both Cohort 1R and Cohort 2 who received at least 1 dose of RPV:

Cohort 1R: n = 25 participants (including 15 Cohort 1R Q4W and 10 Cohort 1R Q8W participants).

Cohort 2: n = 144 participants in Cohort 2 (including 44 participants who had previously participated in Cohort 1).

The analysis included available RPV PK sample data from the full Cohort 1R and Cohort 2 Week 24 analysis. In addition, plasma concentrations from some participants in Long-term safety and washout PK follow-up (LSFU) were available and were included in plasma concentration listings.

The demographics are presented under Baseline data in

Table 9. In general, the age and weight distribution cover the age range of 12-17 years. The median (range) weight in adolescent participants was 48 kg (35.2-98.5 kg).

Results Cohort 1R

For Cohort 1R, a sparse sampling scheme was employed during the OLI period, as RPV 25 mg tablet once daily is already approved for adolescents 12 to <18 years of age. Figure 1 displays the observed average RPV concentration-time profile with once daily oral dosing at Week 2.

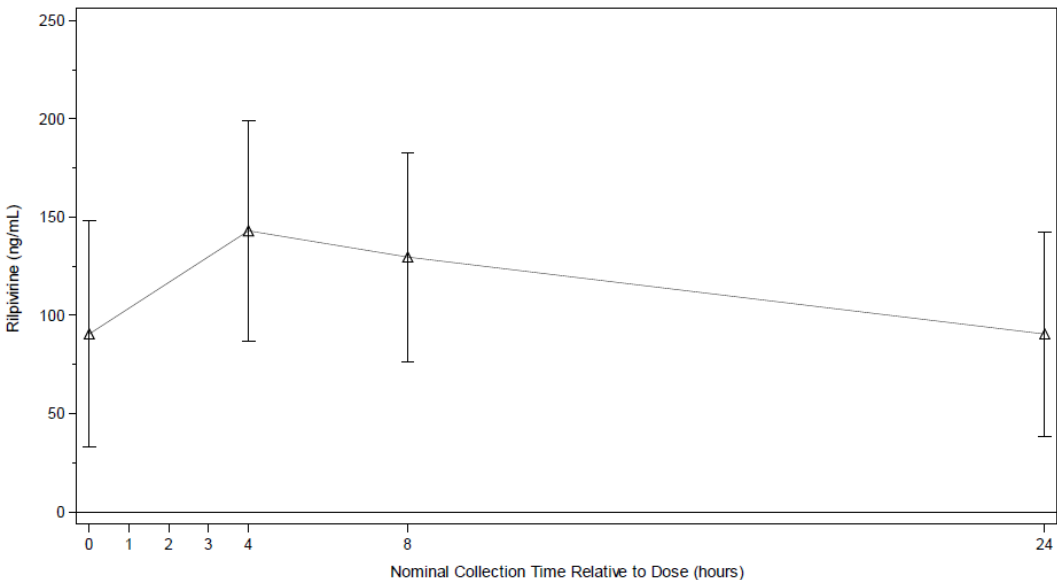


Figure 1 Arithmetic Mean (SD) Week 2 Plasma RPV Concentration-Time Profile Following Oral Administration of 25 mg RPV Once Daily – Linear Scale (Cohort 1R All Treated Population): Study 208580

Table 2 presents RPV PK parameters after IM administration (injections at Weeks 4b, 8, and 12 for the

Q4W regimen; injections at Weeks 4b and 8 for the Q8W regimen), including Injection 1 C_{max} and T_{max} for RPV and pre-dose concentrations. The observed average RPV concentration-time profiles during the injection phase (based on sparse PK sampling) are displayed in Figure 2 (Q4W dosing) and Figure 3 (Q8W dosing). The C_{max} for RPV after the first injection was also reflective of oral dosing because the initial injection was administered together with the last oral dose of study drug in OLI.

The median Week 16 C_{0h} (28 days after the third injection for the Q4W regimen or 56 days after the second injection for the Q8W regimen) for RPV following IM administration (52.9 ng/mL for the Q4W regimen and 39.1 ng/mL for the Q8W regimen; see Table 2) was within the target range for this study (between 25 and 100 ng/mL). The 5th percentile Week 16 C_{τ} for RPV following IM administration (31.9 ng/mL for the Q4W regimen and 27.2 ng/mL for the Q8W regimen) also met the target threshold for the study (>17.3 ng/mL).

Table 2 Summary of RPV PK Parameters Following IM Administration (Cohort 1R All Treated Population): Study 208580

PK parameter^a	Cohort 1R Q4W (N = 15)	Cohort 1R Q8W (N = 10)
Week 4b C_0 (ng/mL) (following 4 weeks OLI)	70.4 [32.3, 153] ^c 89.0 (1.00, 250) 1.00, 250 n = 14	70.3 [59.0, 83.7] 70.3 (46.4, 105) 46.4, 105 n = 10
Week 4b Injection 1 C_{max}^b (ng/mL)	132 [107, 163] 137 (80.5, 295) 80.5, 295 n = 13	129 [98.2, 169] 138 (60.7, 200) 60.7, 200 n = 10
Week 4b Injection 1 T_{max} (h)	N/C 2.40 (1.52, 597) 1.52, 597 n = 13	N/C 2.02 (0.0333, 171) 0.0333, 171 n = 10
Week 8 C_0 (ng/mL)	44.1 [29.4, 66.3] 37.4 (18.0, 197) 18.0, 197 n = 13	32.7 [26.7, 40.0] 31.0 (20.8, 60.2) 20.8, 60.2 n = 10
Week 12 C_0 (ng/mL)	55.5 [39.7, 77.7] 49.0 (26.0, 145) 26.0, 145 n = 12	44.5 [37.1, 53.4] 45.1 (32.3, 60.2) 32.3, 60.2 n = 9
Week 16 C_0^d (ng/mL)	64.4 [45.3, 91.5] 52.9 (31.9, 148) 31.9, 148 n = 12	44.9 [34.5, 58.5] 39.1 (27.2, 81.3) 27.2, 81.3 n = 10

Note: Data presented are geometric mean [95% CI]; median (min, max); P5, P95; n.

a. All C_{0h} concentrations were taken pre-dose, aside from the Week 12 Q8W C_{0h} concentration, which is mid-dose. C_{max} after the first injection was more reflective of oral dosing, because the initial injection was administered together with the last oral dose of study drug in OLI.

At Week 4b, 1 participant (3.4%) had RPV concentrations below the LLOQ (set to lower limit of 1 ng/mL for calculations) at the end of OLI; the concentration was imputed as the LLOQ.

C_{0h} at Week 16 is equivalent to C_{τ}

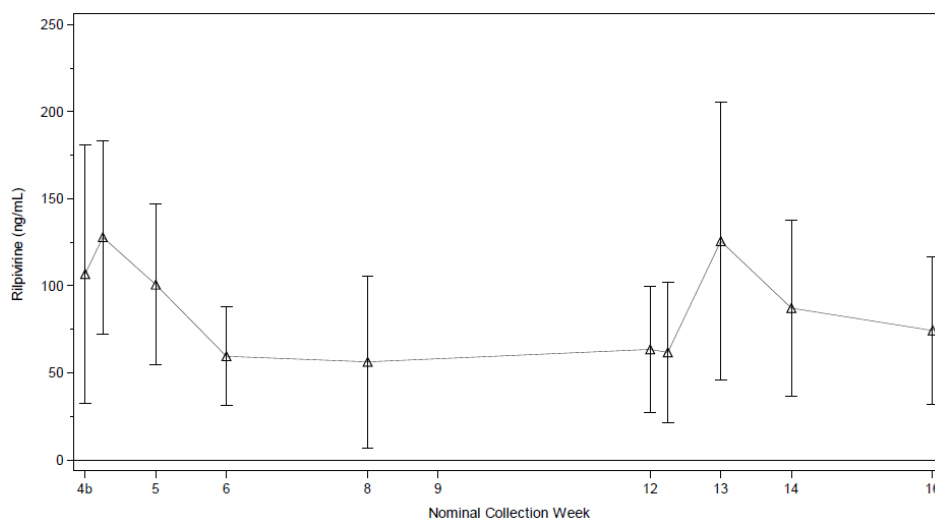


Figure 2 Arithmetic Mean (SD) Plasma RPV Concentration-Time Profile Following RPV LA Q4W Administration of 900 mg RPV LA at Week 4b, and of 600 mg RPV LA at Week 8, and Week 12 – Linear Scale (Cohort 1R All Treated Population With Q4W Dosing): Study 208580

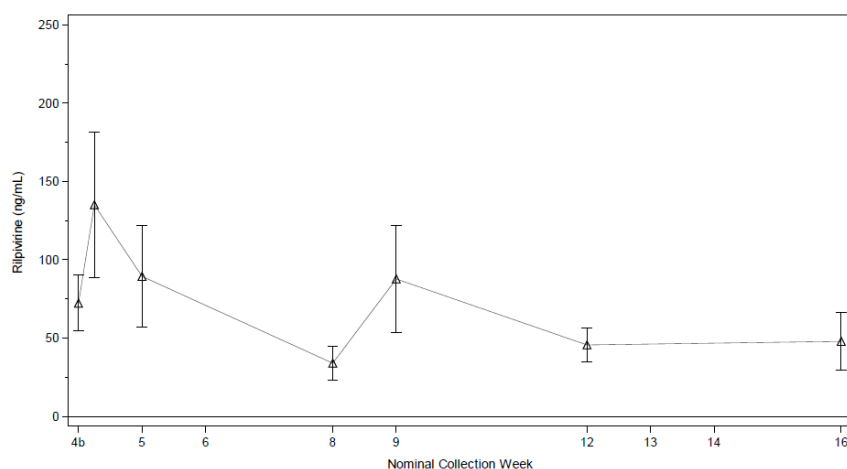


Figure 3 Arithmetic Mean (SD) Plasma RPV Concentration-Time Profile Following RPV LA Q8W Administration of 900 mg RPV LA at Week 4b and Week 8 – Linear Scale (Cohort 1R All Treated Population with Q8W Dosing): Study 208580

Results Cohort 2

The observed RPV PK parameters for Cohort 2 Week 24 following oral administration of 25 mg RPV once daily through Week 4a followed by IM Q8W administration are summarized in Table 3. Figure 4 displays the observed average RPV concentration-time- profile for Cohort 2 participants during the injection phase. The RPV C_{0h} increased from Week 8 through Week 24 and was generally consistent between participants who had previously participated in Cohort 1R and participants who were new to the study (Table 3).

Table 3 Summary of RPV PK parameters following RPV LA Q8W administration (Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 analysis

PK parameter ^a	Cohort 2 total (N = 144)
Ratio of Week 24 C _{0h} : Week 8 C _{0h}	1.35 [1.25, 1.45] 1.29 (0.384, 7.19) 0.617, 2.75 n = 139
Ratio of Week 24 C _{0h} : Week 16 C _{0h}	1.22 [1.16, 1.29] 1.22 (0.534, 3.56) 0.690, 2.14 n = 139
Week 8 C _{0h} (ng/mL)	35.4 [33.0, 38.0] 35.4 (12.3, 177) 16.2, 70.5 n = 142
Week 16 C _{0h} (ng/mL)	39.0 [36.7, 41.5] 39.1 (12.4, 124) 21.7, 76.9 n = 142
Week 24 C _{0h} (ng/mL)	47.7 [45.0, 50.6] 49.5 (14.2, 205) 25.9, 78.1 n = 139

Note: Data presented are geometric mean [95% CI]; median (min, max); P5, P95; n.

a. All C_{0h} concentrations were taken pre-dose.

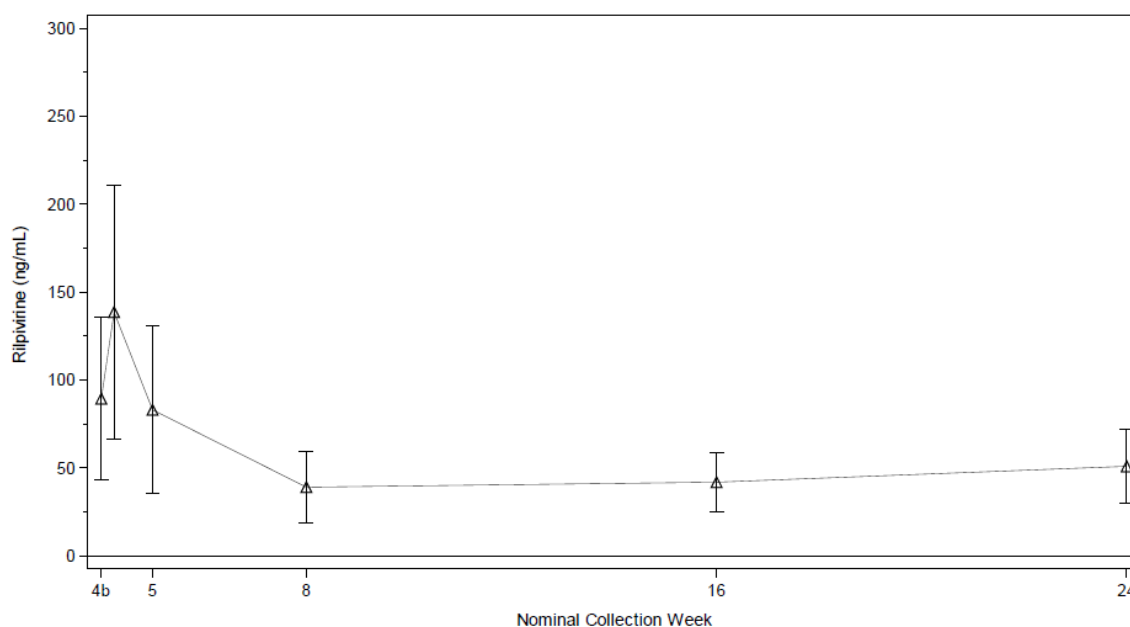


Figure 4 Arithmetic Mean (SD) plasma RPV Concentration-Time Profile Following RPV LA Q8W Administration of 900 mg RPV LA – Linear Scale (Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 Analysis

The observed PK profiles met the key exposure targets, i.e. median C_{0h} between 25 and 100 ng/mL and 5th percentile > 17.3 ng/mL, which are based on adult data for RPV (IM administration), confirming that the dosing regimen established for the adult population is also appropriate for the adolescent population (12 to <18 years of age and weighing at least 35 kg). Only the 5th percentile for Week 8 C_{0h} is just below

this threshold, but this is not considered clinically relevant and thus not further pursued. All individual C_{0h} values were above (the $PAIC_{90}$ of) 12.0 ng/mL. The cut-offs have been accepted previously.

2.3.2.2. Rilpivirine PopPK model update

The objectives of the PopPK analysis were:

- To characterize the PK of RPV LA following IM administration in adolescents aged 12 to <18 years weighing ≥ 35 kg in Study 208580 receiving either RPV LA 600 mg Q4W (after a first injection of RPV LA 900 mg) or RPV LA 900 mg Q8W (after 2 injections of RPV LA 900 mg 1 month apart), and to assess the effect of covariates on the PK of RPV LA
- To determine the individual RPV exposure parameters AUC_{τ} , C_{τ} , C_{max} after first injection (RPV LA 900 mg) and at Week 24 and 48 for participants receiving Q4W (RPV LA 600 mg) and for participants receiving Q8W (RPV LA 900 mg) IM maintenance dosing in Study 208580
- To assess whether RPV exposure parameters (after first injection and at Week 48) following RPV LA dosing are similar between the adolescent participants from Study 208580 and the adult participants from Phase 3 studies
- To perform simulations to evaluate the impact of adherence to the RPV LA dosing regimen and/or to support various dosing modification scenarios.

Methodology

A RPV LA PopPK model was previously built based on data in adults to support the CAB + RPV dosing regimens. The RPV LA PopPK model was built based on a total of 26,634 RPV plasma concentrations collected from 131 healthy (28%) and 1881 HIV-infected (72%) adult participants (age 19 to 83 years). Participants received RPV LA via IM administration at doses ranging from 300 to 1200 mg, either as a single dose or multiple dose regimen (Q4W or Q8W). The RPV LA PopPK structural model was independent of the LA dosing regimen (Q4W or Q8W).

The PK of RPV after IM dosing in adolescents was initially assumed to be comparable to adults, as was also observed for oral RPV. As a first step, the model parameters of the previously developed PopPK model, with covariates removed were kept fixed and only maximum-a-posteriori estimates of individual PopPK parameters were generated based on the combined dataset. Subsequently, an update of the model parameter estimates was performed. Post-hoc estimates of the RPV exposure (AUC , C_{max} , and C_{τ}) in adolescents in Study 208580 were estimated and compared with those in adults from the adult RPV oral and LA clinical development studies. Also, RPV PK profiles and exposure following long-term dosing of RPV LA Q4W and Q8W regimens were simulated for a virtual adolescent population, and simulations were conducted to assess the impact of the OLI, and of Q4W/ Q8W +1 week (i.e. Q5W/Q9W). RPV trough concentrations were compared with the protein-adjusted 90% inhibitory concentration ($PAIC_{90}$) (12 ng/mL) and the 5th percentile of observed RPV trough concentrations after the first injection in adults in Phase 3 studies 201584 and 201585 (17.3 ng/mL).

A total of 1527 RPV plasma concentrations from 148 HIV-infected adolescent participants (12 to <18 years old) weighing at least 35 kg from Study 208580 Cohort 1R and Cohort 2 were used in the PopPK analysis. The weight range in adolescent participants was 35.2-98.5 kg (median 48 kg) and the BMI range was 16.0-33.9 kg/m² (median 19.5 kg/m²). The original RPV LA PopPK model adequately characterized RPV exposures in adolescents and only minor refinement of the model was performed (see next section under Results).

Simulations were based on 1000 subjects with age and body weight characteristics sampled from an adolescent dataset previously created using Sim-Pediatric Version 18.0.0 in Simcyp Simulator Version

18.0.104.0. The virtual adolescent population was aged 12 to <18 years and weighing ≥ 35 kg. These ranges of age and body weight were the same as the inclusion criteria for these covariates in Study 280580.

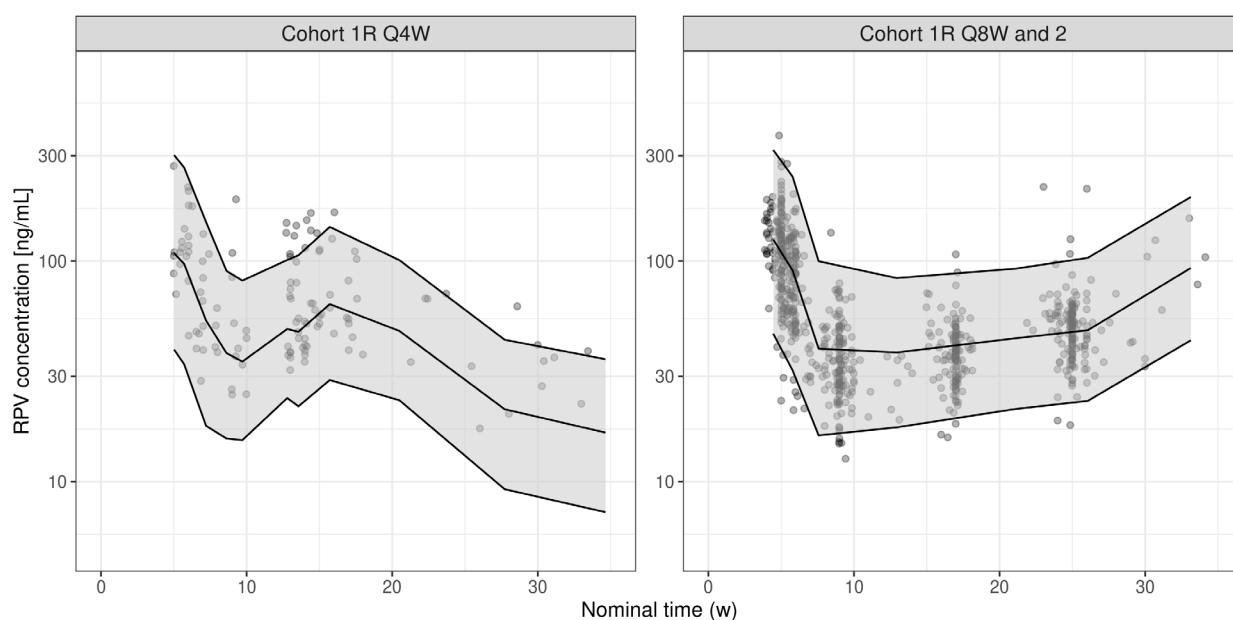
Results PopPK

The model parameters of the previously developed PopPK model, with covariates removed (i.e. age on KA2), were kept fixed and only maximum-a-posteriori estimates of individual PopPK model were generated based on the final dataset, which included both adolescents and adult data. GOF plots showed no visible trends at the population level nor at the individual level.

The final PopPK model describing the totality of the data (from both adolescents and adults) converged successfully.

The relative bioavailability with respect to Phase 1 studies as reference (REL_F) was separately estimated for the 208580 study and was slightly lower than that for the Phase 3/3b studies (corresponding to a REL_F of 97.0% compared to adult Phase 3 studies ATLAS/FLAIR, of 88.0% compared to adult Phase 3b study ATLAS-2M 600 mg Q4W or of 76.6% compared to ATLAS-2M 900 mg Q8W).

Results of the pcVPC for the adolescent data, presented in Figure 5, show that the updated model adequately captures the central tendency and variability of the PK profiles in adolescents from Study 208580 following RPV LA treatment, as demonstrated by the agreement between the observed data and the 90% prediction interval obtained from the simulations.



Note: Gray dots represent observed RPV plasma concentrations versus time since first IM injection from Study 208580, overlaid on the 90% prediction interval (light gray band, with black lines denoting the 5th, 50th, and 95th percentiles of the 500 simulations of the analysis dataset). Left panel represents adolescents in Study 208580 1R receiving RPV LA 600 mg IM Q4W; right panel represents adolescents in Study 208580 Cohort 2 receiving RPV LA 900 mg IM Q8W.

Figure 5 Visual Predictive Check of the Adolescent Data

Population- and individual-level GOF and residual plots indicated that the data from Study 208580 for both oral RPV and RPV LA were well-described both at a population level and at an individual level, with no apparent trends in the residuals.

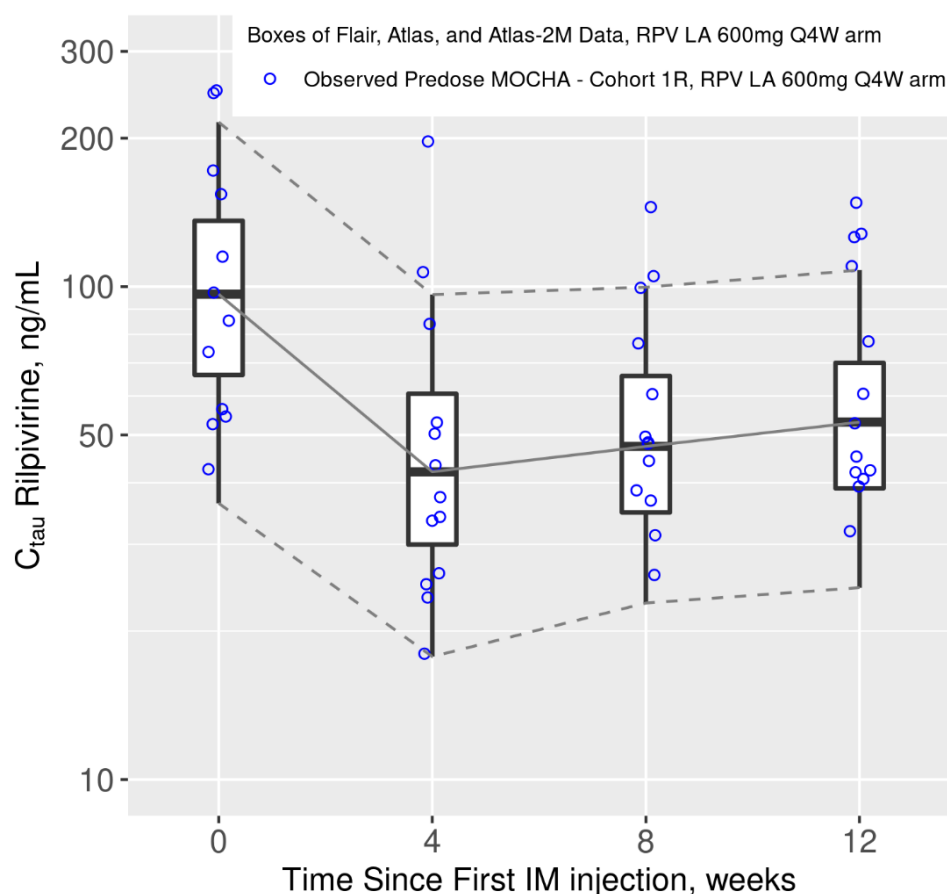
Goodness-of-fit plots for the final model relative to PK samples occurring within either the RPV LA 600 mg IM Q4W or the 900 mg IM Q8W regimens did not show major trends either at population or individual levels. Random effects were approximately centered around 0 and approximately have a normal distribution, however, the shrinkage was large (shrinkage >43.5% computed for Study 208580) for almost all parameters (not shown here).

The updated PopPK model is considered fit-for-purpose.

2.3.2.3. Comparison of RPV Exposure Between Adolescents and Adults

Overall, the RPV trough plasma concentrations were largely comparable between adolescents and adults for both the monthly and every 2 months dosing regimen.

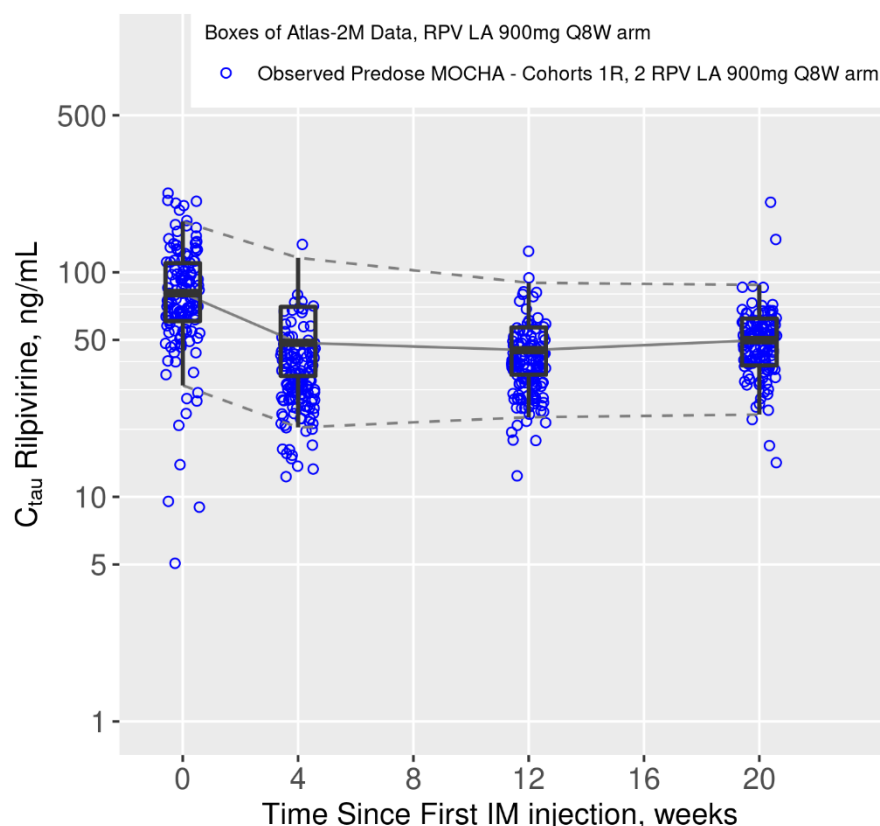
Figure 6 shows the observed individual RPV C_{τ} versus time since first IM injection in the time frame of 0 to 12 weeks (3 injections), with data in adolescents from Study 208580 (Cohort 1R Q4W) overlaid on boxplots of data in adults (combined Phase 3 studies 201584, 201585, and 207966), with the same RPV LA Q4W dosing interval.



Note: Blue dots represent the individual RPV pre-dose plasma concentrations in the RPV LA treatment phase of Study 208580 (Cohort 1R Q4W) overlaid on boxplots of RPV pre-dose plasma concentrations from the combined adult Phase 3 studies 201584 (FLAIR), 201585 (ATLAS), and 207966 (ATLAS-2M) (participants with no prior exposure). The boxplots are defined by the median (central line in the box), 25th and 75th percentiles (lower and upper limits of the box, respectively), with lower and higher whiskers 5th and the 95th percentile, respectively. Note: Time 0 corresponds to the Week 4b visit (end of OLI); Time 4, 8, and 12 correspond to Week 8, 12, and 16 visits, respectively.

Figure 6 Individual RPV Trough Plasma Concentrations in Adolescents (Cohort 1R Q4W) in Study 208580 and Adults – Q4W Dosing

Figure 7 shows the individual RPV C_{tr} versus time since first IM injection in the time frame of 0 to 20 weeks (3 injections), with data in adolescents from Study 208580 (Cohort 1R Q8W and Cohort 2) overlaid on boxplots of data in adults (Study 207966), with the same RPV LA Q8W dosing interval.



Note: Blue dots represent the individual RPV pre-dose plasma concentrations in the RPV LA treatment phase of Study 208580 (Cohort 1R Q8W and Cohort 2) overlaid on boxplots of RPV pre-dose plasma concentrations from the combined adult Phase 3 Study 207966 (ATLAS-2M) (participants with no prior exposure). The boxplots are defined by the median (central line in the box), 25th and 75th percentiles (lower and upper limits of the box, respectively), with lower and higher whiskers 5th and the 95th percentile, respectively. Note: Time 0 corresponds to Week 4b visit (end of OLI); Time 4, 12 and 20 correspond to Week 8, 16 and 24 visits, respectively.

Figure 7 Individual RPV Trough Plasma Concentrations in Adolescents (Cohort 1R Q8W and Cohort 2) in Study 208580 and Adults – Q8W Dosing

The individual exposure parameters were calculated for RPV Q4W and Q8W injections over 48 weeks: the first RPV LA injection, the fifth Q4W RPV LA injection (dosing interval Week 20-24), the third Q8W RPV LA injection (dosing interval Week 16 to 24), the eleventh Q4W RPV LA injection (dosing interval Week 44 to 48) and the sixth Q8W RPV LA injection (dosing interval Week 40 to 48). The individual exposure parameters were compared with the corresponding individual exposure parameters in adults (combined Phase 3 Studies 201585, 201584, and 207966 [participants with no prior exposure]) in Table 4.

The individual estimated exposure parameters were largely comparable in adults and adolescents, with the adolescent/adult GMR varying between 0.79 and 1.27. These minor differences in exposure between adolescents and adults after single and multiple doses are not considered clinically relevant.

Table 4 Summary of Simulated Individual Exposure Parameters for RPV LA in Adolescents (Study 208580) and Adults (pooled Studies 201584, 201585, and 207966)

Exposure parameter	Adolescents (Study 208580) (5th-95th %) (n)	Adults (Studies ATLAS, FLAIR, ATLAS-2M) (5th-95th %) (n)	GMR adolescents to adults (90% CI)
AUCtau initial injection (ng.h/mL) ^a	35259 (20301 - 63047) (n=148)	44842 (21712 - 87575) (n=1359)	0.79 (0.74-0.83)
Ctau initial injection (ng/mL) ^a	36.5 (22.4 - 59.4) (n=148)	41.9 (21.7 - 78.9) (n=1359)	0.87 (0.82-0.92)
Cmax initial injection (ng/mL) ^a	135 (85.8 - 211) (n=148)	144 (93.9 - 221) (n=1359)	0.94 (0.890-0.97)
AUCtau Q4W maintenance regimen Week 48 (ng.h/mL) ^b	84280 (49444 - 156987) (n=13)	68324 (39042 - 118111) (n=969)	1.23 (1.05-1.45)
Ctau Q4W maintenance regimen Week 48 (ng/mL) ^b	109 (64.8 - 202) (n=13)	85.8 (49.6 - 147) (n=969)	1.27 (1.08-1.48)
Cmax Q4W maintenance regimen Week 48 (ng/mL) ^b	146 (84.8 - 269) (n=13)	121 (68.1 - 210) (n=969)	1.21 (1.03-1.42)
AUCtau Q8W maintenance regimen Week 48 (ng.h/mL) ^c	110686 (78480 - 151744) (n=125)	132450 (76638 - 221783) (n=390)	0.84 (0.79-0.88)
Ctau Q8W maintenance regimen Week 48 (ng/mL) ^c	61.8 (44.5 - 88.0) (n=125)	68.9 (38.0 - 119) (n=390)	0.90 (0.85-0.95)
Cmax Q8W maintenance regimen Week 48 (ng/mL) ^c	108 (68.0 - 164) (n=125)	138 (80.6 - 228) (n=390)	0.79 (0.75-0.83)

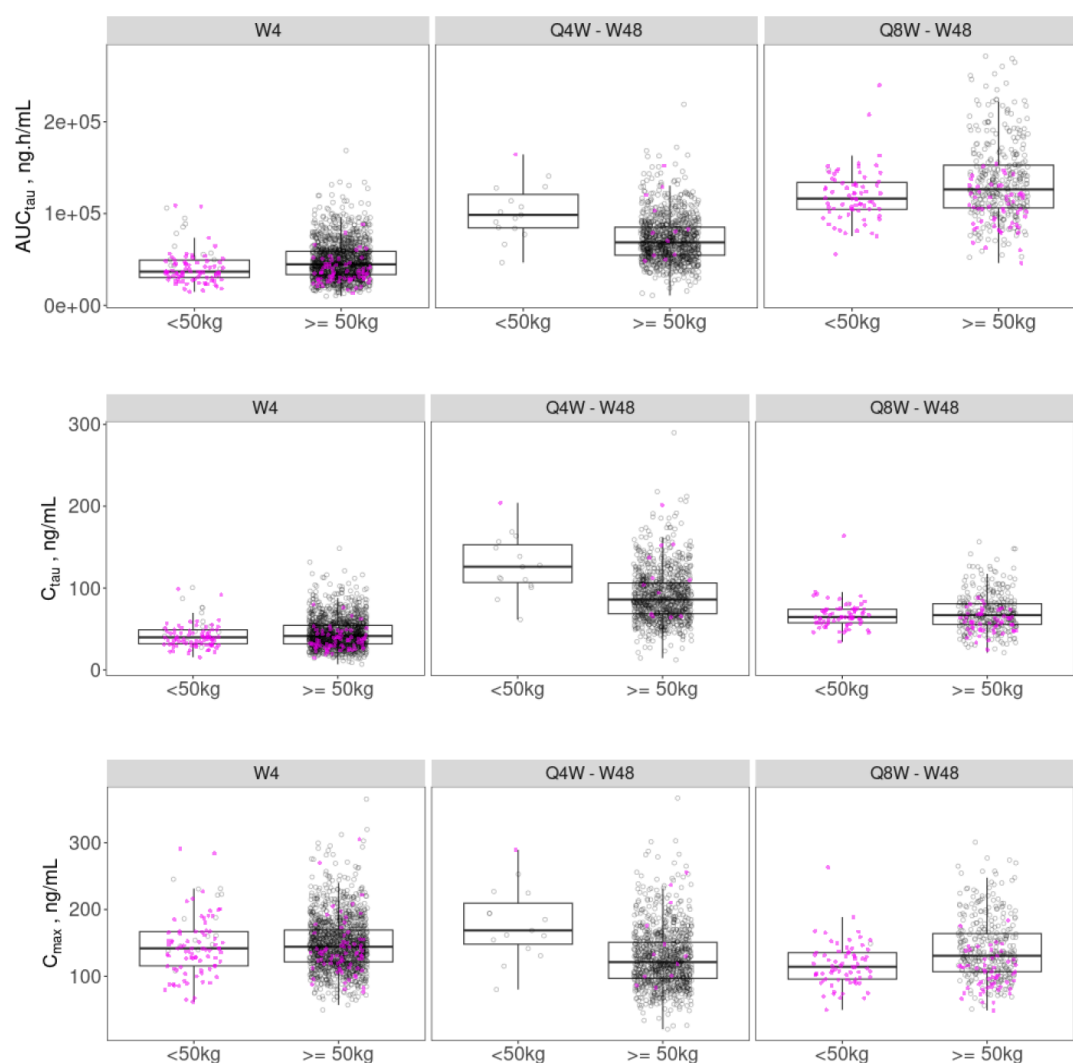
Note: Values are shown as geometric mean (5th and 95th percentiles) and sample size (n); the adults' individual parameters are computed from the previously developed adult PopPK model.^{19,21}

Overall, the RPV exposure parameters appear largely comparable between adolescents and adults. This is further supported by a subgroup analysis by weight category (<50 kg, ≥50 kg) for adults and adolescents combined, which shows comparable exposure parameters across weight categories (see Figure 8).

The results from an additional comparative analysis of the exposure between adolescents and adults across different weight cohorts (bands of 15 kg) confirm that the proposed flat RPV LA dosing regimen

provides comparable exposures between adolescent and adult populations including adolescents >50 kg, with no observable different impact of obesity (BMI ≥ 30 kg/m²).

Figure 8 Distribution of RPV LA Individual Exposure Parameters in Participants Weighing <50 kg vs Participants Weighing ≥ 50 kg Irrespective of Age (Studies 208580, ATLAS, FLAIR, ATLAS-2M)



Magenta and gray dots overlaid on the boxplots represent, respectively, the individual adolescent data from Study 208580 and the individual adult data from Studies ATLAS, FLAIR, and ATLAS-2M. For Study ATLAS-2M, only participants in the RPV LA 600 mg Q4W arm, and with no prior exposure, are shown in the central panels; while participants only in the RPV LA 900 mg IM Q8W arm, and with no prior exposure, are shown in the right panels. The adults' individual parameters are computed from the previously developed adult PopPK model^{12,13}.

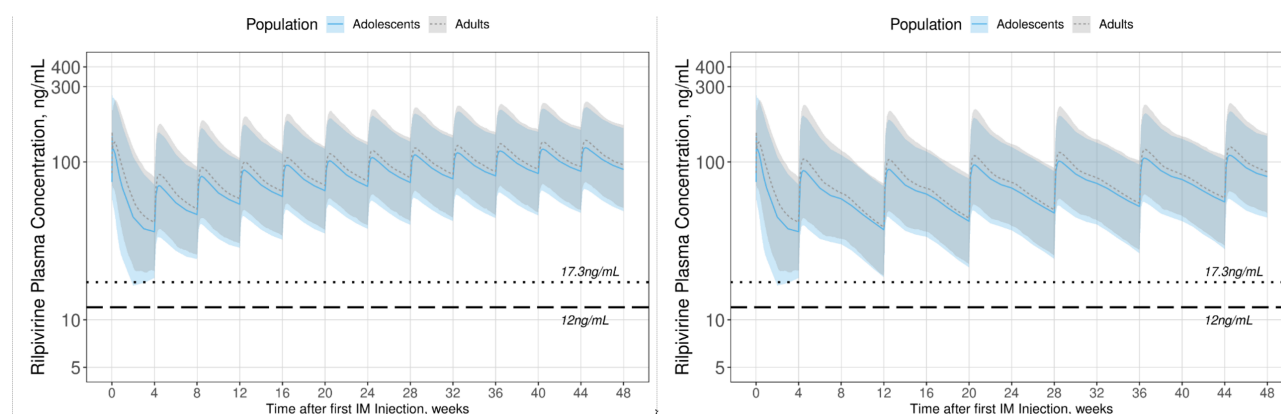
2.3.2.4. Simulated RPV Exposure Following RPV LA Q4W/Q8W Dosing Intervals in Adolescents

The final RPV LA PopPK model was deemed appropriate and able to reliably describe and simulate RPV PK in adolescents (Section 5.3.2.2), and therefore was used to simulate RPV systemic exposure following both Q4W and Q8W dosing intervals in adolescents.

PopPK simulations were conducted to assess the time course of RPV PK in the adolescent population following RPV LA treatment with Q4W and Q8W maintenance dosing intervals, as well as to assess the impact of the OLI, and the impact of increasing the dosing interval with 1 week (Q4W/Q8W + 1 week).

Simulated RPV concentration-versus-time profiles following RPV LA Q4W and Q8W dosing intervals in a virtual population of adolescents 12 to <18 years of age and weighing at least 35 kg are presented in Figure 9. The simulated 1000 adult profiles were generated by fixing the covariate effect on the relative bioavailability parameter (RELF) to the ATLAS/FLAIR value (-0.346) for 50% of the profiles and to the ATLAS-2M value for the treatment arm with 900 mg Q8W maintenance dosing (-0.11) for the other 50% of the profiles.

For both Q4W and Q8W dosing intervals, the simulations show that the time course of RPV PK was comparable between adolescents and adults, and RPV concentrations after RPV LA IM administration were in range with those observed with oral RPV 25 mg once daily. The 5th percentile of RPV trough concentration was above the target concentration of 17.3 ng/mL throughout the profiles. Median simulated RPV C_{max} after IM was below the mean observed C_{max} in a thorough QT (TQT) study with RPV 25 mg once daily (247 ng/mL), which was not associated with a prolongation of the QT interval.

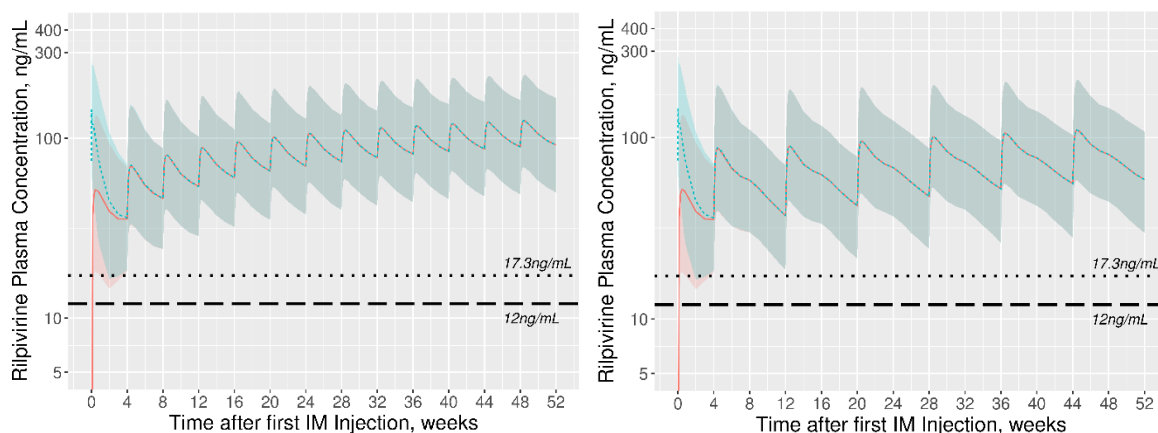


Source: [Mod5.3.3.5/Study 208580-Week 24-RPV-PopPK-report/Figure 5](#).

Note: Lines (blue and dashed grey) and shaded areas represent (respectively) the median and 90% prediction interval (based on 1000 PopPK simulations) for simulations of a RPV LA 600 mg Q4W dosing regimen starting 4 weeks after the first 900 mg injection (left panel) and for RPV LA 900 mg Q8W injections starting 4 weeks after the first 900 mg injection (right panel). In both scenarios, treatment with oral RPV 25 mg QD from Day -28 up to and including Day 1 was simulated. The $PAIC_{90}$ value of 12 ng/mL and the 5th percentile of the observed RPV concentrations 4 weeks after the initial IM administration of 900 mg RPV LA in the combined adult studies 201584 and 201585 (17.3 ng/mL) are overlaid for reference (black long-dashed and short-dashed lines, respectively).

Figure 9 Simulated RPV PK Profiles for Q4W (RPV LA 600 mg) and Q8W (RPV LA 900 mg) Dosing Intervals

Simulations show that similar results were obtained when comparing participants who switched to LA after the OLI phase (oral RPV 25 mg QD) with those directly receiving RPV LA IM without prior oral RPV (Figure 7). Slightly lower concentrations were observed at 2 weeks for the 5th percentile after the first 900 mg IM injection for participants without the OLI phase, but this reversed by 4 weeks after injection, and is not considered clinically relevant.



Note: Lines (dashed red and dashed blue) and shaded areas represent (respectively) the median and 90% prediction interval (based on 1000 PopPK simulations) for simulations of a RPV LA 600 mg Q4W dosing regimen starting 4 weeks after the first 900 mg injection (left panel) and for RPV LA 900 mg Q8W injections starting 4 weeks after the first 900 mg injection (right panel). In both scenarios, treatment including oral RPV 25 mg QD from Day -28 up to and including Day 1 are shown in blue and treatment without the OLI phase are shown in red. The PAIC₉₀ value of 12 ng/mL and the 5th percentile of the observed RPV concentrations 4 weeks after the initial IM administration of 900 mg RPV LA in the combined adult studies ATLAS and FLAIR (17.3 ng/mL) are overlaid for reference (black long-dashed and short-dashed lines, respectively).

Figure 10 Simulated RPV LA PK Profiles for Q4W (RPV LA 600 mg Q4W Starting 4 Weeks After the Initial 900 mg injection) and Q8W (RPV LA 900 mg Q8W Starting 4 weeks after the initial 900 mg injection) in Adolescents, Comparing Scenarios with and Without OLI

The PK profiles of RPV in adolescent participants were compared following treatment with CAB + RPV Q4W or Q8W +1 week up to steady-state (i.e. Q5W and Q9W). Despite the Q4W/ Q8W +1 week injections, in all scenarios, the 90% prediction interval from the simulations was higher than (i) the 90% inhibitory concentration for wild-type HIV-1 virus adjusted for plasma protein binding PAIC₉₀ of 12 ng/mL, and (ii) the target concentration value of 17.3 ng/mL. Specifically, the percentage of subjects with C_τ above the PAIC₉₀ value and the percentage of subjects with C_τ above 17.3 ng/mL, as derived from the PopPK simulations, were 95% or greater for both reference values and for both the first and the second RPV LA injections (subsequent injections not considered since C_τ will keep increasing following the first 2 injections), with the exception of the Q9W scenario which had a percentage of 93.4% after the first 9 weeks from the injection, but >95% for later injections. Also, the median simulated RPV concentrations remained below the mean C_{max} observed in the TQT study with RPV 25 mg once daily.

The simulations support the same posology in adolescents as compared to adults.

2.3.2.5. Drug interactions

CAB and RPV have been co-dosed across several adult studies without any clinically relevant interaction observed. Results from Study 208580 Cohort 2 Week 24 showed no major difference in exposure in adolescents between full Cohort 1, when CAB and RPV were dosed separately with background cART, and Cohort 2 Week 24, when CAB and RPV were co-administered.

The results were considered in line with those previously reported in adults.

2.3.3. Pharmacodynamics

No new pharmacodynamic data were submitted.

2.3.4. PK/PD modelling

No new PK/PD modelling was submitted, among other because through the full Cohort 1 analysis and the Cohort 2 Week 24 analysis no participant met confirmed virologic failure (CVF) while receiving RPV and CAB+RPV treatment.

2.3.5. Discussion on clinical pharmacology

The observed RPV PK Cohort 1R and Cohort 2 Week 24 data in adolescents in Study 208580 provided data to update the existing RPV PopPK model. The model was refined to describe adult and adolescent data with a minimal impact on the primary PK parameters estimates.

The use of oral RPV 25 mg tablets in ARV treatment-naïve HIV-1 infected adolescents aged 12 to <18 years was investigated before in a Phase 2, open-label, single arm study to evaluate the PK, safety and tolerability, and efficacy of RPV in combination with an investigator-selected background regimen containing 2 nucleoside reverse transcriptase inhibitors (NRTI) (Study TMC278-C213-W48-CSR Cohort 1). The study showed that the RPV 25 mg once daily dose in adolescents aged 12 to <18 years resulted in similar RPV exposure as that observed in adults. There was no clinically significant impact of body weight on RPV PK in adolescent participants in study C213 (33 to 93 kg). These data formed the basis for the approval of oral RPV 25 mg once daily, in combination with other ARVs, for the treatment of HIV-1 infection in adolescents aged 12 to <18 years.

Data from the OLI period in Study 208580 confirmed that the RPV 25 mg once daily dose in adolescents results in similar exposure compared with adults (Table 5).

Table 5 PK Parameters of RPV After Multiple Dose Administration of RPV 25 mg Once Daily in Adolescents and Adults

Pharmacokinetics of RPV Median (Min, Max)	Adolescents		Adults
	TMC278-C213	208580	TMC278-C209, TMC278-C215
N	34	128	679
C _{0h} , ng/mL	79 (7, 202)	71 (7, 215)	73 (2, 288)
C _{max} , ng/mL	100 (49, 182) ^a	135 (62, 312) ^b	112 (41, 329) ^c

a. n = 23 (intensive PK substudy)

n = 24 (Cohort 1R); C_{4h} as surrogate for C_{max} OLI PK parameter values represent steady state.

n = 44 (intensive PK substudy)

The existing RPV LA PopPK model was further developed with PK data in healthy adults and HIV-1 infected adults and adolescents, across several dosing regimens. This model was employed to recommend appropriate dosing regimens and to simulate exposures in the adolescent population. Results from Cohort 1 and Cohort 2 of Study 208580 showed that the observed RPV exposures after IM administration of the adult RPV LA dosing regimen in adolescents are comparable to those observed in adults. This was also confirmed through the RPV LA PopPK modeling for adolescents. The updated RPV LA PopPK model sufficiently described the data in adolescents. The RPV LA PopPK model is the same for Q4W and Q8W dosing, and as such, results can be extrapolated regardless of RPV LA dosing regimen.

The simulated systemic exposures with the same dosing regimens for adolescents as for adults are comparable to those in adults (Table 6). These results have also been updated in Section 5.2 of the SmPC, which was agreed by the CHMP.

Table 6 Summary of Simulated RPV PK Parameters In Adolescents Compared With Adults Following Administration of CAB + RPV Dosing Regimens

Population	Dosing Phase	Dosage Regimen	Plasma RPV PK Parameter Geometric Mean (5 th , 95 th percentile)		
			AUC _T (ng•h/mL)	C _{max} (ng/mL)	C _T (ng/mL)
Adolescents	OLI ^a	25 mg PO once daily	2389 (1259, 4414)	144 (80.8, 234)	76.1 (27.9, 184)
	Initial Injection ^b	900 mg IM Initial Dose	35259 (20301, 63047)	135 (85.8, 211)	36.5 (22.4, 59.4)
	Every month injection ^c	600 mg IM Every month	84280 (49444, 156987)	146 (84.8, 269)	109 (64.8, 202)
	Every 2 months Injection ^d	900 mg IM Every 2 months	110686 (78480, 151744)	108 (68.0, 164)	61.8 (44.5, 88.0)
Adults	OLI ^a	25 mg PO once daily	2083 (1125, 3748)	116 (48.6, 244)	79.4 (31.8, 177)
	Initial Injection ^b	900 mg IM Initial Dose	44,842 (21712, 87575)	144 (93.9, 221)	41.9 (21.7, 78.9)
	Every month injection ^c	600 mg IM Every month	68324 (39042, 118111)	121 (68.1, 210)	85.8 (49.6, 147)
	Every 2 months Injection ^d	900 mg IM Every 2 months	132450 (76638, 221783)	138 (80.6, 228)	68.9 (38.0, 119)

OLI PK parameter values represent steady state.

Initial Injection C_{max} values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose; however, the AUC_T and the C_T value at Week 4 reflect the initial injection.

Every month injection: 11th RPV LA IM Injection (40-44 weeks after initiation injection).

Every 2 months injection: 6th RPV LA IM Injection (36-44 weeks after initiation injection).

Overall, the CHMP considered the following points:

- Oral RPV 25 mg once daily, in combination with other ARVs, for the treatment of HIV-1 infection in adolescents aged 12 to <18 years and weighing ≥35 kg has already been approved. The current study 208580 confirmed that the RPV 25 mg once daily dose in adolescents aged 12 to <18 years resulted in similar RPV exposure as that observed in adults.
- The proposed CAB + RPV dosing regimens in adolescents, as investigated in Study 208580, consist of the same doses and dosing intervals used for adults.
- The observed RPV PK Cohort 1R and Cohort 2 Week 24 data in adolescents in Study 208580 provided data to update the existing RPV LA PopPK model. The model was refined to describe adult and adolescent data with a minimal impact on the primary PK parameters estimates. These population PK analyses demonstrated that the proposed dosing regimens for RPV, when administered with CAB, resulted in systemic exposures in adolescents similar to those in adults (within the range of adult data and within established safety and efficacy thresholds for adults).
- This is further supported by a subgroup analysis by weight category (<50 kg, ≥50 kg) for adults and adolescents combined, which shows comparable exposure parameters across weight categories (see Figure 8). However, adolescents >50kg show exposures in the lower range of the adult exposure range for the same body weight cohort. This may be related to an impact of obesity on exposure. Therefore, a comparative analysis of the exposure between adolescents and adults across different weight cohorts was requested to be performed in order to verify that the proposed flat regimen provides comparable exposures between both populations. The results from this additional comparative analysis confirm that the proposed flat RPV LA dosing regimen provides comparable

exposures between adolescent and adult populations including adolescents >50 kg, with no observable different impact of obesity. However, the available obese data were very limited.

- Variations on dosing recommendations (e.g., optional OLI, Q4W/ Q8W + 1 week dosing regimens) are the same for adolescents and adults weighing at least 35 kg.

2.3.6. Conclusions on clinical pharmacology

The CHMP considered that the data from the Study 208580 full Cohort 1R and Cohort 2 Week 24 analysis support the use of rilpivirine, when used with cabotegravir, in adolescents 12 to <18 years of age and weighing at least 35 kg, at the same doses and dosing intervals as in adults. Since the exposure of rilpivirine in adolescents and adults is similar, safety and efficacy are expected to be similar in adolescents at the same doses used in adults.

2.4. Clinical efficacy

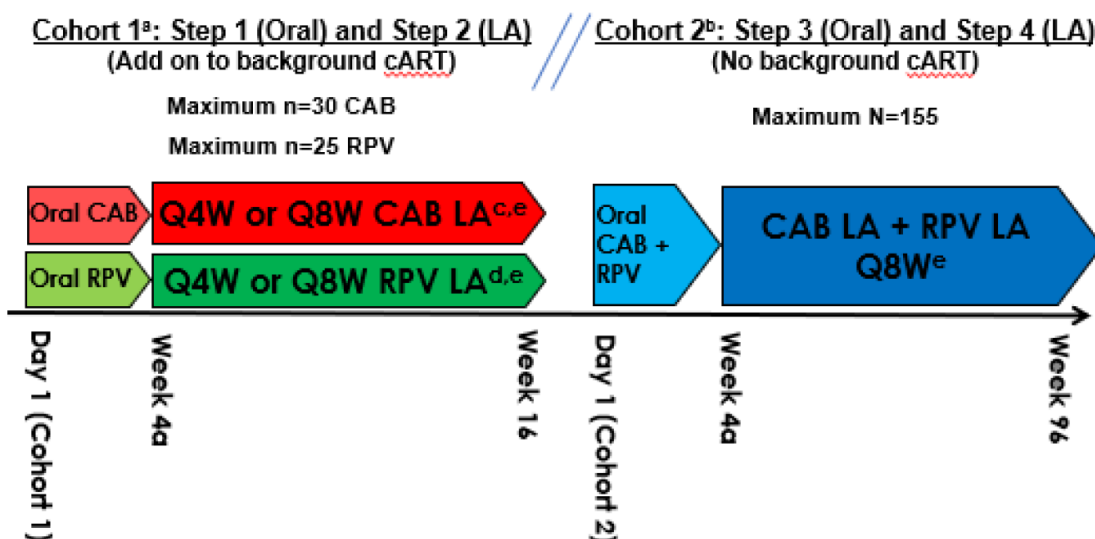
2.4.1. Main study

Study 208580; IMPAACT2017; MOCHA: 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

Methods

This is an ongoing Phase I/II, multi-center, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and PK of oral and long-acting (LA) injectable cabotegravir (CAB) and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable cART consisting of 2 or more drugs from 2 or more classes of ARV drugs.

A schematic of the study design for Study 208580 is presented in [Figure 11](#).



- Cohort 1 participants were assigned to Cohort 1C (participants received CAB + cART) or Cohort 1R (participants received RPV + cART) based on their pre-study cART regimen.
- Cohort 2 was open to eligible participants who had completed Cohort 1 as well as eligible participants who had not been previously enrolled in the study.
- PI/NNRTI-based cART
- INSTI-based cART
- Participants enrolled to Cohort 1 under Protocol Version 2.0 received every 4 weeks (Q4W) LA injections during the injection phase. Participants enrolled in both Cohort 1 and Cohort 2 under Protocol Version 3.0 received every 8 weeks (Q8W) LA injections during the injection phase.

Figure 11 Overview of study design for treatment period

The CHMP considered that the design of the study is fit for purpose. The main focus is on PK and safety, which is agreed, as this study will be used to extrapolate the exposure to the adolescent population.

Cohort 1 aims to confirm that PK in adolescents is matched to adult PK for oral and injectable CAB (Cohort 1C) as well as injectable RPV following lead-in with oral RPV (Cohort 1R) and to obtain safety information. During Cohort 2 virologically suppressed adolescents living with HIV-1 will stop their oral cART and switch to CAB plus RPV. Again PK will be the main focus, although it will be established whether virologically suppressed adolescents living with HIV remain suppressed upon switching to a 2-drug IM regimen of CAB LA + RPV LA.

The current report will focus on the assessment regarding RPV or the combination regimen, i.e. Cohort 1R and Cohort 2.

Study participants

Key inclusion criteria for participants to be eligible for enrolment in Step 1 of Cohort 1 or in Step 3 of Cohort 2 included:

- Aged 12 to <18 years at enrolment
- Body weight ≥ 35 kg (77 pounds) at enrolment
- For Cohort 1, BMI ≤ 31.5 kg/m² at enrolment
- Confirmed HIV-1-infection based on documented testing of 2 samples collected at different time points

- Must have been on stable unchanged cART consisting of 2 or more drugs from 2 or more classes of ARV drugs (for at least 6 consecutive months per Protocol Version 2.0; for at least 3 consecutive months per Protocol Version 3.0)
- Plasma HIV-1 RNA <50 c/mL at Screening
- Plasma HIV-1 RNA levels prior to Screening:
 - Participants enrolled under Protocol Version 2.0: Documented evidence of plasma HIV-1 RNA results <50 c/mL in the 6 months prior to Screening and from 6 to 12 months prior to Screening.
 - Participants enrolled under Protocol Version 3.0:
 - Documented evidence of plasma HIV-1 RNA measurements less than the lower limit of detection from 6 to 12 months prior to Screening; OR
 - Documented evidence of plasma HIV-1 RNA measurements less than the lower limit of detection in the 6 months prior to Screening and from 12 to 18 months prior to Screening.

Key exclusion criteria included:

- For Cohort 1 participants enrolling to Cohort 2 Step 3, occurrence of any Grade 3 or higher adverse event assessed as related to study product or permanent discontinuation of study product due to an adverse event of any grade assessed as related to study product, during participation in Cohort 1 (including any long-term safety and washout PK follow-up visits).
- As determined by the IoR or designee, and based on available medical records, known or suspected resistance to RPV or INSTIs.
- History of congestive heart failure, symptomatic arrhythmia, or any clinically significant cardiac disease, as determined by the IoR or designee based on available medical records
- At entry, known active tuberculosis infection, hepatitis B or hepatitis C infection, as determined by the Investigator of Record (IoR) or designee based on available medical records
- Clinically significant hepatic disease, as determined by the IoR or designee based on available medical records
- History of known or suspected bleeding disorder including history of prolonged bleeding, as determined by the IoR or designee, based on available medical records
- Known or suspected allergy to study product components. Note: For Cohort 1 participants enrolling to Cohort 2, participants who experienced mild allergic reactions which resolved whilst on continued study drug or when rechallenged with study drug during Cohort 1 may be exempted from this criterion at the discretion of the IoR.

The in- and exclusion criteria reflect a population of HIV-infected, successfully treated adolescent subjects with asymptomatic disease, which is considered appropriate by the CHMP. Of note, there are two NNRTI resistance mutations that are allowed in the current study as they do not have an impact on RPV susceptibility, K103 and V106. The inclusion of patients with these mutations, although not included in the approved adult indication, is not expected to have any clinical impact as viruses harbouring these mutations are still susceptible to RPV.

Treatments

Participants in Cohort 1 will be assigned to Cohort 1C (oral CAB followed by intramuscular CAB LA) or Cohort 1R (oral RPV followed by intramuscular RPV LA) based on their pre-study cART regimen:

- Participants on a PI-based and/or NNRTI-based cART regimen will be assigned to Cohort 1C
- Participants on a non-boosted INSTI-based cART regimen will be assigned to Cohort 1R

All participants in Cohort 1 were to continue their pre-study cART regimen and receive either CAB (Cohort 1C) or RPV (Cohort 1R) as shown in Table 7. Study participants were to receive the first dose of CAB LA (Cohort 1C) or RPV LA (Cohort 1R) on the same day as the last dose of oral CAB or oral RPV, respectively (i.e., at the Week 4b Step 2 entry visit).

Table 7 Cohort 1: Study drug regimen and administration

Cohort	Step	Study drug regimen and administration (with non-study-provided cART regimen)
1C	1	CAB administered orally as one 30 mg tablet once daily, beginning at the entry visit, for 4 to 6 weeks, with or without food.
	2	Participants enrolled under Protocol Version 2.0 (Q4W LA injections): <ul style="list-style-type: none"> • CAB LA administered as 1 IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (600 mg), at Week 8 (400 mg), and at Week 12 (400 mg). Participants enrolled under Protocol Version 3.0 (Q8W LA injections): <ul style="list-style-type: none"> • CAB LA administered as 1 IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (600 mg), and at Week 8 (600 mg).
1R	1	RPV administered orally as one 25 mg tablet once daily, beginning at the entry visit, for 4 to 6 weeks, with a meal.
	2	Participants enrolled under Protocol Version 2.0 (Q4W LA injections): <ul style="list-style-type: none"> • RPV LA administered as 1 IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (900 mg), at Week 8 (600 mg), and at Week 12 (600 mg). Participants enrolled under Protocol Version 3.0 (Q8W LA injections): <ul style="list-style-type: none"> • RPV LA administered as 1 IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (900 mg), and at Week 8 (900 mg).

All participants in Cohort 2 were to discontinue their pre-study cART regimen and receive both CAB and RPV as shown in Table 8. Study participants were to receive the first doses of CAB LA and RPV LA on the same day as the last doses of oral CAB and oral RPV (i.e., at the Week 4b Step 4 entry visit).

Table 8 Cohort 2: Study drug regimen and administration

Cohort	Step	Study drug regimen and administration (without cART regimen)
2	3	CAB administered orally as one 30 mg tablet AND RPV administered orally as one 25 mg tablet once daily, taken together and with a meal, beginning at the entry visit, for 4 to 6 weeks.
	4	First and second set of injections: <ul style="list-style-type: none"> • CAB LA administered as 1 IM injection (600 mg) in the gluteus medius AND RPV LA administered as 1 IM injection (900 mg) in the gluteus medius at Week 4b (Step 4 Entry) and at Week 8. Subsequent injections: <ul style="list-style-type: none"> • Starting at the Week 16 visit, CAB LA administered as 1 IM injection (600 mg) in the gluteus medius AND RPV LA administered as 1 IM injection (900 mg) in the gluteus medius every 8 weeks through Week 96.

The CHMP considered that treatments are in general comparable to the posology of Rekambys included for adults, except that none of the participants directly switched to LA injectables, while this is an option in the SmPC for Rekambys in adults. However, in case equal exposure is observed, a direct switch could also be included for adolescents as there is no reason to assume a different exposure between adults and adolescents with a direct switch.

Objectives

Primary objectives for Cohort 1 (continuing a background combination antiretroviral therapy [cART] regimen):

- To confirm the doses for oral cabotegravir (CAB) followed by injectable CAB long-acting (LA) in adolescents living with human immunodeficiency virus (HIV) who are virologically suppressed by evaluating:
 - Safety and multiple dose pharmacokinetics (PK) of oral CAB through Week 4;
 - Safety and multiple dose PK of CAB LA through Week 16.
- To confirm doses for injectable rilpivirine (RPV) LA in adolescents living with HIV who are virologically suppressed by evaluating safety and multiple-dose PK of RPV LA through Week 16.

Primary objectives for Cohort 2 (discontinuing a background cART regimen):

- To assess the safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 24.

Secondary objectives for Cohort 1:

- To monitor maintenance of viral suppression through Week 16 in adolescents living with HIV who are virologically suppressed.
- To evaluate the tolerability and acceptability of CAB LA through Week 16 in adolescents living with HIV who are virologically suppressed.
- To evaluate the tolerability and acceptability of RPV LA through Week 16 in adolescents living with HIV who are virologically suppressed.

Secondary objectives for Cohort 2:

- To assess safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 48.
- To evaluate repeat dose pharmacokinetics of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 24 and through Week 48.
- To assess antiviral activity of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 24 and through Week 48.

As this study will be used to extrapolate efficacy and safety in adults to the adolescent population based on the exposure of LA RPV, the CHMP considered that the objectives are appropriately chosen.

The primary objectives are related to PK and safety. Efficacy is a secondary objective. This is agreed by the CHMP, as efficacy will only be used to support PK and safety data in the approval of the adolescent population.

Outcomes/endpoints

The primary study endpoints were related to safety and PK; there were no primary efficacy endpoints. The secondary efficacy endpoints summarized in this document include:

Cohort 1:

- Participants with plasma HIV-1 RNA <50 c/mL through Week 16.
- Participants with protocol-defined confirmed virologic failure.

Cohort 2:

- Participants with plasma HIV-1 RNA <50 c/mL through Week 24.
- Participants with plasma HIV-1 RNA <50 c/mL at Week 24 per Snapshot algorithm.
- Participants with plasma HIV-1 RNA <200 c/mL through Week 24.
- Participants with plasma HIV-1 RNA <200 c/mL at Week 24 per Snapshot algorithm.
- Participants with protocol-defined confirmed virologic failure.

The CHMP considered that the endpoints are aligned with the information collected for adults.

Sample size

No formal sample size calculation has been performed, as this is an open label, single arm trial.

The sample size is the minimum number of participants, driven primarily by safety considerations, which is likely to be needed to determine the dosage across the possible weight, age and sex at birth distributions. Monte Carlo simulations based on existing PK models in adults with extrapolation to the study population characteristics were performed to estimate the variability for selected primary and secondary parameters and confidence intervals.

The sample size is mainly driven by safety considerations, which was considered acceptable by the CHMP.

Randomisation

There will be no randomization for Cohorts 1 and 2. Participants for Cohort 1 will be placed into CAB or RPV arms based on suppressive oral cART at entry: participants on PI-based or NNRTI-based cART will be assigned to Cohort 1C, while participants on INSTI-based cART will be assigned to Cohort 1R. In Cohort 2, participants will either receive oral CAB+RPV for 4 weeks followed by CAB LA +RPV LA Q8W (Cohort.

This is an open-label study; therefore, no blinding was required.

The CHMP considered that the study is designed as a single-arm open-label study. This can be accepted as the primary endpoint is an objective measurement (PK measurement of exposure), therefore it is not expected that this endpoint will be influenced by the open-label design. In addition, also the efficacy endpoint is based on an objective measurement of plasma HIV-1 RNA. The results of the subjective parameters, including safety parameters, should be interpreted with care.

Statistical methods

No formal hypothesis is tested.

The intent-to-treat (ITT) population will be used as primary and only population for all analyses. This ITT population is defined as the set of all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

Results

Participant flow

Study 208580 is an ongoing, multicentre study. Cohort 1 was conducted in a total of 15 sites in 4 countries (Botswana, Thailand, US, and South Africa); Cohort 2 was conducted in a total of 18 sites in 5 countries (Botswana, Thailand, US, South Africa, and Uganda).

Cohort 1

A total of 59 participants were screened in Cohort 1 and 55 participants were enrolled. The 55 enrolled participants were assigned to either Cohort 1C (n=30, receiving CAB + cART) or Cohort 1R (n=25, receiving RPV + cART) based on their pre-study cART. In total 3 participants discontinued study treatment prematurely and 5 discontinued the study prematurely (see [Figure 12](#)).

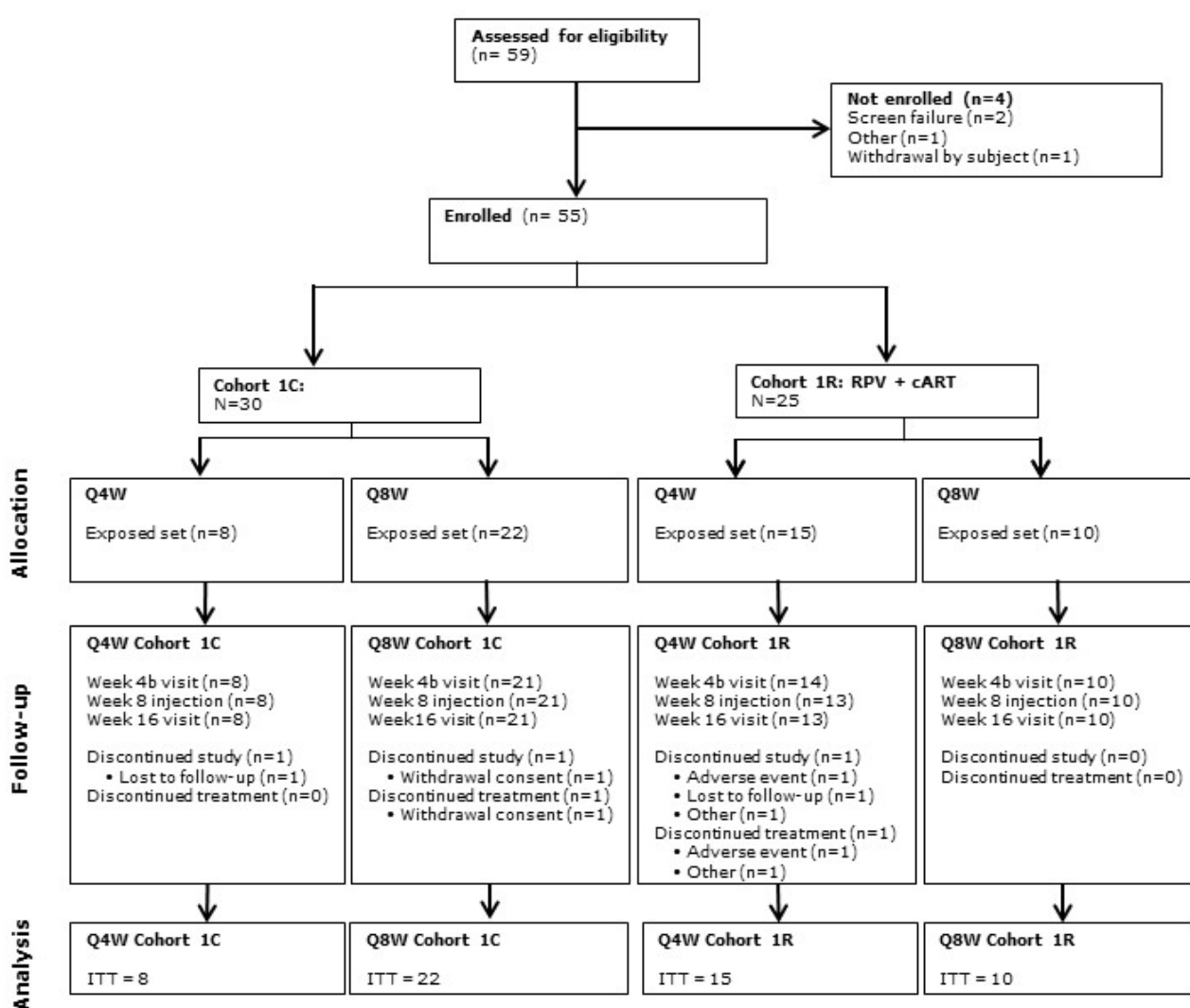


Figure 12 Participant flow Cohort 1 Study 208580

Cohort 2

A total of 159 participants were screened in Cohort 2 and 144 participants were enrolled. Of the 144 participants enrolled in Cohort 2, 44 participants had previously participated in Cohort 1 and 100 participants were newly recruited into the study.

In Cohort 2, all participants were to discontinue their pre-study cART regimen and receive both CAB and RPV. At the time of data cut-off for this report, 142 of the 144 Cohort 2 participants were on study and 2 participants were off study. 141 participants had completed the Cohort 2 Week 24 assessments and 116 participants had completed the Cohort 2 Week 48 assessments.

Of the 3 participants in Cohort 2 that discontinued study treatment prematurely, 2 participants discontinued prior to receiving any injections and one participant (Participant 1274594) became pregnant and entered LSFU prior to the Week 24 visit (see *Figure 13*).

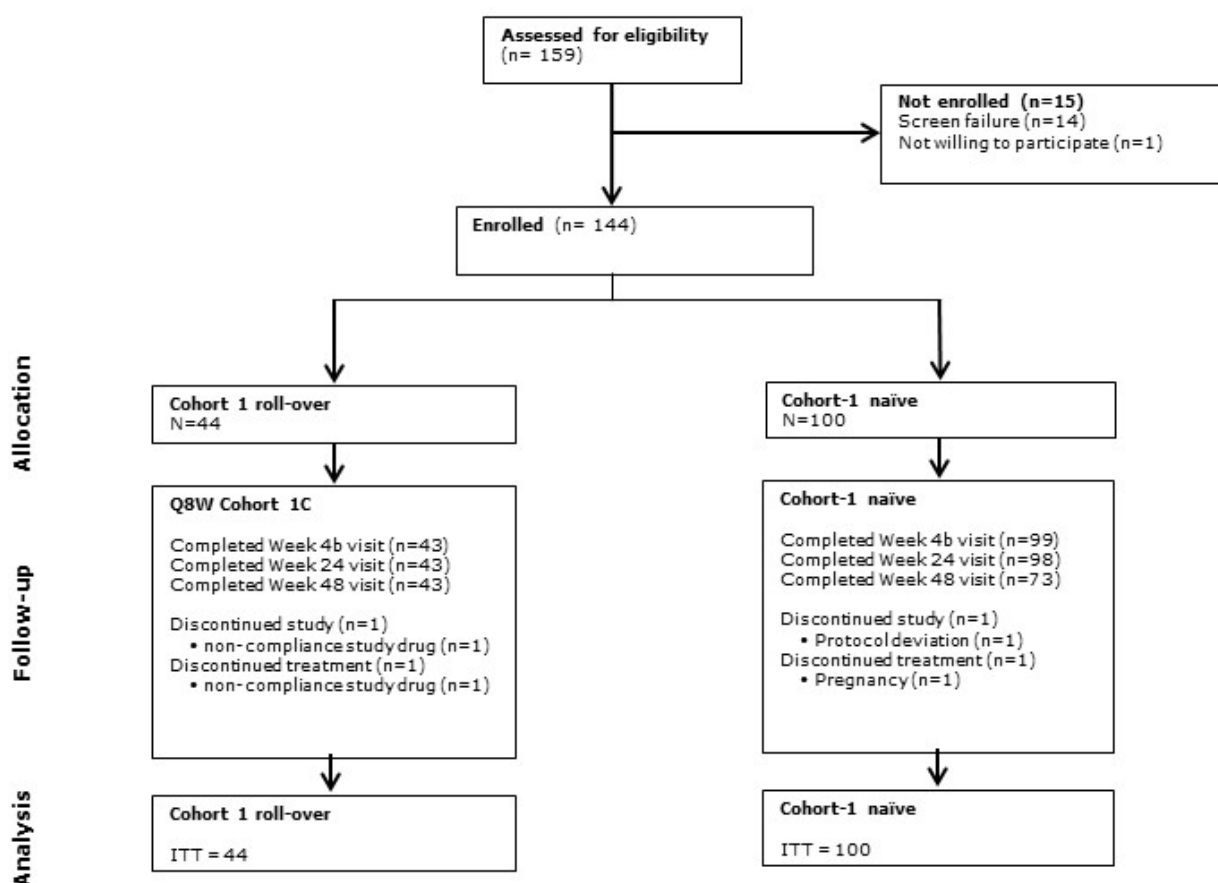


Figure 13 Participant flow Cohort 2 Study 208580

Recruitment

The first participant was enrolled on 03 April 2019. The Cohort 2 Week 24 last participant visit was 18 February 2023; available data were included up to 07 June 2023, which is the database lock for this analysis. This study is ongoing.

Conduct of the study

The original protocol was amended 3 times. Based on the information provided, Amendment 2 (Protocol 3.0) was used to implement Q8W dosing in the injection phases of Cohort 1 and Cohort 2 and is considered by the CHMP to be the most impactful. Both Q4W and Q8W dosing in the injection phase were approved during MAA of Rekambys (approved 2020). Therefore, this change is considered acceptable as it would ensure that the PK of both Q4W and Q8W could be assessed.

In Amendment 3 (Protocol 4.0) an additional Cohort was added to potentially eliminate the oral lead in phase. This direct to injection posology was approved for adults in 2021, and it is therefore in line with the posology in adults. However, none of the participants included in Cohort 2 utilized DTI and were enrolled in Cohort 2B.

Important protocol deviations were observed in 3 participants in Cohort 1R: 2 participants had deviations relating to inclusion/exclusion criteria and 1 participant had a study product dispensing error (received too much study drug 900 mg instead of 600 mg). The 900 mg dose is used for Q8W dosing regimen. No clear impact is expected.

In Cohort 2 important protocol deviations were observed in 5 participants: 1 participant had a deviation relating to inclusion/exclusion criteria, 2 participants continued their pre-study ARV medications and 2 participants had study product management deviation. The 2 participants received incorrect doses: CAB LA 400 mg and RPV LA 600 mg instead of CAB LA 600 mg and RPV LA 900 mg at Week 16 (Participant 382319) or at Week 16 and Week 24 (Participant 382315; participant received additional injections of CAB LA 200 mg and RPV LA 300 mg 10 days after Week 24). In these participants the reduced dose or doses did not result in loss of efficacy.

In both Cohort 1R and Cohort 2 deviations with regard to informed assent/consent process were observed for 8 (32%) and 25 (30.9%) participants respectively. Based on the listings reporting on these issues, no indication of GCP issues were observed.

Baseline data

Cohort 1R

Cohort 1R participants were enrolled at sites in the US (68.0%), Botswana (20.0%), and South Africa (12.0%) (Table 9). The majority of participants were Black or African American and had a Baseline CD4 cell count of at least 500 cells/mm³; no participants had a Baseline CD4 cell count less than 350 cells/mm³. In Cohort 1R, 52.0% of the participants were male, 48.0% of the participants were female.

Cohort 2

The majority of participants in Cohort 2 were enrolled at sites in South Africa (29.9%) or Thailand (25.0%), were Black or African American, and had a Baseline CD4 cell count of at least 500 cells/mm³; 4 (2.8%) participants had a Baseline CD4 cell count less than 350 cells/mm³. Approximately half the participants were female and approximately half were male.

Table 9 Baseline Characteristics (Cohort 1R All Treated Population): Study 208580 Full Cohort 1 Analysis

		Cohort 1R (N=25) n (%)	Cohort 2 total (N=144) n (%)
Age (years)	n	25	144
	Mean (SD)	15.6 (1.71)	14.9 (1.57)
	Median (Q1,Q3)	16.0 (15.0, 17.0)	15.0 (14.0, 16.0)
	Min, Max	12, 17	12, 17
Age (years) (n [%])	12	3 (12.0)	11 (7.6)
	13	0	23(16.0)
	14	3 (12.0)	19 (13.2)
	15	4 (16.0)	35 (24.3)
	16	4 (16.0)	27 (18.8)
	17	11 (44.0)	29 (20.1)
Sex at Birth (n [%])	Female	12 (48.0)	74 (51.4)
	Male	13 (52.0)	70 (48.6)
Race (n [%])	Asian	0	36 (25.0)
	Black or African American	21 (84.0)	106 (73.6)

		Cohort 1R (N=25) n (%)	Cohort 2 total (N=144) n (%)
Ethnicity (n [%])	White	4 (16.0)	2 (1.4)
	Not Hispanic or Latino	22 (88.0)	141 (97.9)
	Hispanic or Latino	3 (12.0)	3 (2.1)
Weight (kg)	n	25	144
	Mean (SD)	57.668 (16.1346)	51.355 (12.4208)
	Median (Q1,Q3)	54.000 (44.300, 71.000)	48.450 (43.450, 55.440)
	Min, Max	37.40, 98.50	35.20, 100.90
BMI (kg/m ²)	n	25	144
	Mean (SD)	22.311 (4.6534)	20.466 (3.6132)
	Median (Q1,Q3)	20.680 (18.000, 24.670)	19.535 (17.845, 21.955)
	Min, Max	16.98, 31.32	15.98, 34.31
Country (n [%])	Botswana	5 (20.0)	25 (17.4)
	Thailand	0	36 (25.0)
	Uganda	0	20 (13.9)
	US	17 (68.0)	20 (13.9)
	South Africa	3 (12.0)	43 (29.9)
Baseline CD4 cell counts ^a (cells/mm ³)	n	24	142
	Mean (SD)	859.3 (350.97)	796.8 (306.23)
	Median (Q1,Q3)	788.0 (610.0, 1041.0)	739.5 (594.0, 964.0)
	Min, Max	412, 1808	81, 1925
Baseline CD4 cell counts categories ^a (cells/mm ³) (n [%])	Missing	1 (4.0)	2 (1.4)
	<350	0	4 (2.8)
	350 to <500	3 (12.0)	12 (8.3)
	500 to <750	7 (28.0)	60 (41.7)
	≥750	14 (56.0)	66 (45.8)

Concomitant antiretroviral drugs

Cohort 1R

In Cohort 1R, all participants (25/25 [100%]) were receiving an INSTI and 2 NRTIs. The most common cART regimens were Bictegravir, Emtricitabine, Tenofovir Alafenamide (28.0% of participants) and Dolutegravir, Abacavir, Lamivudine (28.0% of participants).

Cohort 2

Per protocol, all participants enrolled in Cohort 2 were to discontinue their pre-study cART regimen and receive both CAB and RPV during the study. However, 2 participants did not discontinue their ARVs (Participant 8505872: Lopinavir, Ritonavir, Lamivudine, Zidovudine; Participant 8509031: Nevirapine, Lamivudine, Zidovudine) as expected upon enrolling to Cohort 2 and starting study treatment. When the error was recognized at Week 2, both participants discontinued their pre-study cART and continued on study.

The CHMP considered that the study population consists of mostly perinatally infected adolescents who have a stable suppressed HIV-1 viral load and are otherwise in relative good health. Adolescents of 12 years (n=3 in Cohort 1R and 11 in Cohort 2) and/or weight of 35 kg have been included in the study, in line with the extension of indication sought by the MAH.

Outcomes and estimation

Cohort 1R

At Week 16, all Cohort 1R participants with a viral load assessment (n=23) remained virologically suppressed (plasma HIV-1 RNA value <50 c/mL).

Through Week 16, 1 participant in Cohort 1R had a single quantifiable HIV-1 RNA value of ≥50 c/mL at Week 2; the participant resuppressed at subsequent visits.

Through the full Cohort 1 analysis, no participant met confirmed virologic failure (CVF; defined as two consecutive plasma HIV-1 RNA test results ≥ 200 copies/mL from two separate specimens) while receiving CAB or RPV treatment.

Cohort 2

Based on the HIV-1 RNA < 50 c/mL Snapshot analysis at Week 24, 139 of 144 Cohort 2 participants (96.5%) had outcomes of 'virologic success' (*Table 10*). 3 participants in Cohort 2 had outcomes of 'virologic failure' at Week 24, including 2 participants with HIV-1 RNA ≥ 50 c/mL at Week 24 (Participant 6096600 and Participant 6096640) (HIV-1 RNA values returned to < 50 c/mL at Week 32 or Week 40; see Section 6.1) and 1 participant who discontinued study drug for other reason while HIV-1 RNA was ≥ 50 c/mL (Participant 801912 had an elevated viral load at Cohort 2 study entry related to a protocol deviation of eligibility failure). 2 participants had no virologic data.

Through the Cohort 2 Week 24 analysis, no Cohort 2 participant met CVF.

Table 10 Virologic Outcome for Week 24 treatment period (Snapshot algorithm) (Cohort 2 All Treated Population)

Outcome at Week 24	Cohort 2 total (N=144) n (%)
Snapshot outcome < 50 copies/mL	
Virologic success	139 (96.5)
HIV-1 RNA < 50 c/mL	139 (96.5)
Virologic failure	3 (2.1)
HIV-1 RNA ≥ 50 c/mL	2 (1.4)
Discontinued study drug due to virologic failure	0
Discontinued study drug for other reason while HIV-1 RNA was ≥ 50 c/mL	1 (0.7)
No virologic data	2 (1.4)
Discontinued study drug due to AE or death	0
Discontinued study drug for other reason while HIV-1 RNA was missing or < 50 c/mL	2 (1.4)
On study but missing data in window	0
Snapshot outcome < 200 copies/mL	
Virologic success	141 (97.9)
HIV-1 RNA < 200 c/mL	141 (97.9)
Virologic failure	1 (0.7)
HIV-1 RNA ≥ 200 c/mL	0
Discontinued study drug due to virologic failure	0
Discontinued study drug for other reason while HIV-1 RNA was ≥ 200 c/mL	1 (0.7)
No virologic data	2 (1.4)
Discontinued study drug due to AE or death	0
Discontinued study drug for other reason while HIV-1 RNA was missing or < 200 c/mL	2 (1.4)
On study but missing data in window	0

Virological testing

Participant 8500063 (Cohort 1C) met CVF 46 weeks past their last CAB injection (LSFU Week 48) with an HIV-1 RNA of 8750 c/mL. This suspected virologic failure event was confirmed 4 weeks later with an HIV-1 RNA of 339 c/mL. Entry genotypic and phenotypic testing failed to yield results; therefore, it was not possible to assess potential pre-existing resistance to CAB or RPV. Samples collected at the CVF visit showed no evidence of resistance to CAB or RPV. 9 months after the Cohort 1 LSFU Week 48 visit, the participant successfully screened for Cohort 2 and remains on study as of the data cut-off for this report.

After an elevated HIV-1 RNA at Cohort 2 entry (643 copies/mL), the participant is suppressed (HIV-1 RNA <200 c/mL) on study treatment through Week 64.

Participant 801912 enrolled in Cohort 2 with an elevated viral load at entry. The participant stopped suppressive oral therapy between the screening and entry visit. As a result, HIV-1 RNA at study entry was 168 053 c/mL (168 053 c/mL). The participant had two on treatment HIV-1 RNA measurements \geq 200 c/mL (354 and 296 c/mL), but they were conducted 8 days apart. Based on a post-hoc assessment by the CMC, the participant was not considered a CVF due to pre-existing viremia at study entry. Resistance testing was performed for this participant at study entry (HIV-1 RNA 168 053 c/mL) and 2 weeks later at the Week 2 unscheduled visit (HIV-1 RNA 296 c/mL). The results from both samples showed no INSTI, NNRTI, NRTI, or PI resistance associated mutations present. The participant was withdrawn at Week 2 due to a protocol deviation related to enrolment inclusion/exclusion criteria violation that was discovered after study entry. The participant was withdrawn from study prior to receiving any injections in Cohort 2.

Participant experience

Overall, IM injections of study medication appeared to be generally acceptable and tolerable in the adolescents enrolled in Cohort 1 and Cohort 2. Nearly all participants in Cohort 2 (139 of 141 participants) reported a preference for injections of long-acting treatment over daily oral treatment at Week 24. In addition, participants in Cohort 2 reported a high level of medication satisfaction (assessed only in English or Spanish speaking participants located in the US; n=19 participants total) at Week 24. Due to the small sample size, these results should be interpreted with caution.

Summary of main study(ies)

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).

Summary of Efficacy for trial 208580 (MOCHA)

Title: 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 – Full Cohort 1 and Cohort 2 Week 24 Report		
Study identifier	Study 208580 (IMPAACT2017 or MOCHA)	
Design	Phase 1/Phase 2 multicenter, open-label, non-comparative study	
	Duration of main phase: Duration of follow-up: Duration of Extension phase:	Cohort 1R 16 weeks 48 weeks Optional roll-over in Cohort 2 Cohort 2 96 weeks 48 weeks Not applicable
Hypothesis	No hypothesis tested	
Treatments groups	Cohort 1R	In addition to cART: RPV 25 mg once daily orally for 4 to 6 weeks followed by 2 (Q8W; 900 mg for both injections) or 3 (Q4W; 900 mg for first injection and 600 mg for the 2 following injections)) RPV LA IM injections N= 25

	Cohort 2		No cART: CAB 30 mg + RPV 25 mg once daily orally for 4 to 6 weeks followed by IM injections of CAB LA (600 mg) + RPV LA (900 mg) Q8W. Injections occur at Week 4 and Week 8, followed by injections Q8W through Week 96 N= 144
Endpoints and definitions	Co-Primary endpoint	PK	PK of RPV LA through Week 16
Cohort 1R	Co-Primary endpoint	Safety and tolerability	Safety of RPV LA through Week 16
	Secondary endpoint	Efficacy	Monitor maintenance of viral suppression through Week 16
	Secondary endpoint	Other	Tolerability and acceptability of RPV LA through Week 16
Endpoints and definitions	Primary endpoint	Safety	Safety of CAB LA + RPV LA through Week 24
Cohort 2	Secondary endpoint	Safety	Safety of CAB LA + RPV LA through Week 48
	Secondary endpoint	PK	Evaluate repeat-dose pharmacokinetics of CAB LA + RPV through Week 24 and 48
	Secondary endpoint	Efficacy	Assess antiviral activity of CAB LA + RPV LA through Week 24 and 48
Database lock	07 June 2023 (Cohort 2 Week 24 database lock)		
Results and Analysis			
Analysis description	Main efficacy analyses		
Analysis population and time point description	Intent to treat (all subjects who have taken at least 1 dose of RPV)		
Descriptive statistics and estimate variability	Treatment group	Cohort 1R Week 16	Cohort 2 week 24
	Number of subject	25 with 23 having viral load assessment	144
	Virologic response (<50 copies/ml) n(%)	23 (100%)	139 (96.5%)
	Confirmed virologic failure	0	0
Notes	As no participants met the definition of CVF, no standard genotypic resistance data were generated		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was not powered for a precise estimate of efficacy and no control arm is available for comparison. Instead, given that exposure is comparable to exposure observed in adults, efficacy was estimated through a PK/PD-bridge which is in line with EMA guidance.

The study contained 2 cohorts. Cohort 1 was used to confirm that PK in adolescents is matched to adult PK for injectable RPV following lead-in with oral RPV (Cohort 1R) and to obtain safety information. In Cohort 2, PK is the main focus and it will be established whether virologically suppressed adolescents living with HIV remain suppressed upon switching to a 2-drug IM regimen of CAB LA + RPV LA.

The in- and exclusion criteria reflect a population of HIV-infected, successfully treated adolescent subjects with asymptomatic disease, which is appropriate. Treatments are in general comparable to the currently approved adult posology of Rekambys, except that none of the participants directly switched to long-acting injectables, while this is an option in the SmPC for Rekambys in adults. However, in case equal exposure is observed, a direct switch could also be included for adolescents as there is no reason to assume a different exposure between adults and adolescents with a direct switch.

The open-label design is considered acceptable as the primary endpoint is an objective measurement (PK measurement of exposure) and also the efficacy endpoint is based on an objective measurement of plasma HIV-1 RNA. Therefore, it is not expected that these endpoints would be influenced by the open-label design.

All participants in Cohort 1R remained virologically suppressed (plasma HIV-1 RNA VL <50 copies/mL) up to week 16, and none had virologic failure. In Cohort 2 the vast majority of participants (139 out of 144, 96.5%) remained virologically suppressed (plasma HIV-1 RNA VL <50 copies/mL) up to week 24 after switching to treatment with CAB and RPV. Of the remaining 5 participants, 2 participants had detectable viral load but subsequently resuppressed while remaining on treatment. The other 3 participants discontinued the study drug and no virologic data was available at Week 24. Of these 3, only 1 participant stopped while their HIV-1 RNA was ≥ 200 c/mL. This participant had elevated viral load at entry due to erroneously stopping suppressive cART between the screening and entry visit) and stopped study drug at Week 2 prior to receiving CAB and RPV injections. As the participant had viraemia at study entry, this is not seen as virologic failure. The efficacy results presented are reassuring and suggest similar efficacy of the combination CAB+RPV as for adults in the treatment of adolescents with HIV-1 infection.

No participant met CVF while receiving CAB or RPV. One participant in Cohort 1C (receiving CAB), met CVF 46 weeks after study drug discontinuation. No resistance to either CAB or RPV was observed in samples collected at the CVF visit. The participant did enrol in Cohort 2 and after an elevated HIV-1 RNA at Cohort 2 entry (643 copies/mL), the participant was suppressed (HIV-1 RNA <200 c/mL) on study treatment through Week 64.

Although it is a small sample size, and follow-up time is limited, preference for injectable treatment appears high throughout the study, with 138/142 participants preferring long-acting treatment compared with daily oral treatment at Week 8 and 139/141 at Week 24.

These results were generally in line with what has been observed in adults.

The CHMP considered that compliance to the monthly or every 2 months injections visits is the key element to maintain virological suppression with the cabotegravir + rilpivirine combination treatment, even more so than for the usual oral antiretroviral therapy. A lack of adherence to the administration visits could lead to the emergence of mutations and resistance to the NNRTI and INSTIs, which would dramatically impact the long-term treatment and life expectancy of the HIV-infected adolescents. Although compliance data in this study were reassuring, the context of a clinical trial, which could be the best way to get HIV treatment in some low-income countries, biases these compliance data. During the initial Marketing Authorisation Application in adults, the risk of adherence issue was raised and consequently, a PAES (COMBINE-2 study) was imposed to assess adherence, durability and discontinuation for persons starting the regimen. However, considering that various publications (Moyo et al; Rakhmanina et al; Abrams et al) support the assumption that long-acting regimens are likely to result in better compliance than daily oral administration as well as the fact that interim results from the ongoing PAES in adults did not show adherence, efficacy or virologic concerns, an additional study to specifically assess adherence in real clinical setting in adolescents was not requested. The CHMP was of the view that adherence to the dosing regimen in this population can be evaluated via routine pharmacovigilance activities, also considering that the SmPC is very clear on the need of a careful patient selection to ensure compliance.

2.4.3. Conclusions on the clinical efficacy

Given that exposure is comparable to exposure observed in adults, long-acting rilpivirine can be considered effective in the treatment of HIV-1 in adolescents at least 12 years of age and weighing at least 35 kg who are virologically suppressed (HIV-1 RNA < 50 copies/mL).

2.5. Clinical safety

Introduction

The safety profile in the existing indication is mainly characterised by injection site reactions (ISRs): pain, nodule, induration, swelling, and pruritus. The most frequently reported adverse drug reactions from either the every 1 month (Q4W) or every 2 months (Q8W) dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia (up to 10%). ISRs were generally self-limiting and decreased over time.

Patient exposure

Overall, 25 participants were enrolled in Cohort 1R (RPV + cART) and 144 participants were enrolled in Cohort 2 (CAB + RPV). Of the 144 participants enrolled in Cohort 2, 44 participants had previously participated in Cohort 1 (ie, Cohorts 1R or 1C) and 100 participants were newly recruited into the study.

Cohort 1R

For the entire study, the median (range) exposure to study intervention for Cohort 1R was 134.0 (1-142) days. In total, 23 of the 25 participants in Cohort 1R received the protocol-specified injections (3 injections for Q4W and 2 injections for Q8W participants). Two participants in Cohort 1R did not receive any injections: 1 participant discontinued study intervention due to hypersensitivity following the first oral RPV dose and 1 participant had a needle injection at Week 4b, but no study drug was administered because of Grade 1 injection procedural pain.

Table 11 Exposure to study drugs Cohort 1R (All Treated Population)

	Cohort 1R Q4W (N=15) n (%)	Cohort 1R Q8W (N=10) n (%)	Cohort 1R total (N=25) n (%)
Days of exposure to oral study drugs^a			
Mean (SD)	36.3 (10.47)	34.8 (4.57)	35.7 (8.51)
Median (Q1, Q3)	39.0 (36.0, 43.0)	36.0 (29.0, 37.0)	36.0 (36.0, 41.0)
Min, Max	1, 43	29, 43	1, 43
Number of injections			
0 Injection	2 (13.3)	0	2 (8.0)
1 Injection	0	0	0
2 Injections	0	10 (100.0)	10 (40.0)
3 Injections	13 (86.7)	N/A	13 (52.0)
Days of exposure to study drugs^b			
Mean (SD)	120.4 (40.90)	130.5 (6.75)	124.4 (31.92)
Median (Q1, Q3)	134.0 (132.0, 138.0)	131.0 (128.0, 135.0)	134.0 (129.0, 136.0)
Min, Max	1, 142	120, 141	1, 142

a. Oral treatment duration was calculated as oral treatment end date - oral treatment start date +1 day.

b. Treatment duration for participants who discontinued treatment during OLI was calculated as oral treatment end date - oral treatment start date +1 day. Otherwise, treatment duration was calculated as last injection date +42 days - oral treatment start date +1 day for Protocol Version 2.0 participants and last injection date +70 days - oral treatment start date +1 day for Protocol Version 3.0 participants

Cohort 2

In Cohort 2, the median exposure to oral study drugs was 36.0 days; the median exposure to study drug for the entirety of Cohort 2 was 371.5 days. As shown in [Table 12](#), 141 of the 144 participants in Cohort 2 had the protocol-specified injection visits through Week 24 (4 injection visits). Two participants discontinued prior to receiving any injections in Cohort 2: Participant 8507381 withdrew due to the primary reason of noncompliance with study drug and Participant 801912 withdrew for a protocol deviation of eligibility failure discovered after study entry. One participant (Participant 1274594) had 2 injection visits; the participant became pregnant and entered LSFU prior to the Week 24 visit.

Table 12 Exposure to study drugs Cohort 2 (All Treated Population)

	Cohort 2 total (N=144) n (%)
Days of exposure to oral study drugs^a	
Mean (SD)	36.2 (4.53)
Median (Q1, Q3)	36.0 (36.0, 37.0)
Min, Max	15, 62
Number of injection visits	
0 Injection visits	2 (1.4)
1 Injection visits	0
2 Injections visits	1 (0.7)
3 Injections visits	0
4 Injections visits	0
5 Injections visits	1 (0.7)
6 Injections visits	24 (16.7)
7 Injections visits	74 (51.4)
8 Injections visits	14 (9.7)
9 Injections visits	14 (9.7)
10 Injections visits	3 (2.1)
11 Injections visits	4 (2.8) ^c
12 Injections visits	7 (4.9)
13 Injections visits	0
Days of exposure to study drugs^b	
Mean (SD)	394.5 (95.69)
Median (Q1, Q3)	371.5 (351.0, 433.5)
Min, Max	15, 682

a. Oral treatment duration was calculated as oral treatment end date - oral treatment start date +1 day.

b. Treatment duration for participants who discontinued treatment during OLI was calculated as oral treatment end date - oral treatment start date +1 day. Otherwise, treatment duration was calculated as last injection date +70 days - oral treatment start date +1 day.

c. 1 participant (Participant 370392) captured in the 11 injection visits category actually had 12 full sets of injections. Starting with the Week 72 injection, the participant's injection visits drifted into the previous analysis visit window; therefore, the Week 64 analysis window consolidated the Week 64 and Week 72 injections into a single set of injections.

Adverse events

Cohort 1

The majority (>90%) of participants in Cohort 1R reported ≥ 1 AE, and 36% reported ≥ 1 ISR ([Table 13](#)). No SAEs were reported in Cohort 1R.

One participant in Cohort 1R (Q4W) discontinued study intervention due to a related AE. One participant in Cohort 1R reported an AE assessed as related to study intervention that was Grade 3 or 4.

Table 13 Overview Summary of Adverse Events Cohort 1R All Treated Population - Week 16

AE parameter	Cohort 1R Q4W (N=15) n (%)	Cohort 1R Q8W (N=10) n (%)	Cohort 1R total (N=25) n (%)
Any AE	15 (100.0)	8 (80.0)	23 (92.0)
Any AE excluding ISRs	14 (93.3)	8 (80.0)	22 (88.0)
Any ISR AE	8 (53.3)	1 (10.0)	9 (36.0)
Any AE ≥Grade 3 ^a	3 (20.0)	2 (20.0)	5 (20.0)
Any drug-related AE ^b	9 (60.0)	3 (30.0)	12 (48.0)
Any drug-related AE ^b excluding ISRs	4 (26.7)	3 (30.0)	7 (28.0)
Any drug-related AE ^b ≥Grade 3 ^a	1 (6.7)	0	1 (4.0)
Any drug-related AE ^b causing permanent treatment discontinuation	1 (6.7)	0	1 (4.0)
Any SAE	0	0	0
Any drug-related SAE ^b	0	0	0
Any fatal SAE	0	0	0

a. Grade 3 = Severe, 4 = Potentially Life-Threatening; no Grade 5 AEs were reported.

b. Relatedness of AEs was determined by the investigators

The most common (reported in ≥3 participants in Cohort 1R) AEs through Week 16 in Cohort 1R were injection site pain (n=9), headache (n=5), cough (n=4), oropharyngeal pain (n=4), nasal congestion (n=4), rhinorrhoea (n=3), vomiting (n=3), nasal mucosal disorder (n=3), and nausea (n=3).

Cohort 2

The majority (~85%) of participants in Cohort 2 reported ≥1 AE, and 34% reported ≥1 ISR (*Table 14*). Approximately 15% of participants reported ≥1 AE that was Grade 3 or 4; these AEs were assessed as related to the study intervention for 2 participants in Cohort 2.

No participants in this cohort discontinued study intervention due to a related AE. At least 1 SAE was reported for 2 participants, but neither of these 2 participants had an SAE assessed as related to the study intervention.

Table 14 Overview Summary of Adverse Events Cohort 2 (All Treated Population) – Week 24

AE parameter	Cohort 2 total (N=144) n (%)
Any AE	122 (84.7)
Any AE excluding ISRs	119 (82.6)
Any ISR AE	49 (34.0)
Any AE ≥Grade 3 ^a	22 (15.3)
Any drug-related AE ^b	51 (35.4)
Any drug-related AE ^b excluding ISRs	15 (10.4)
Any drug-related AE ^b ≥Grade 3 ^a	2 (1.4)
Any drug-related AE ^b causing permanent treatment discontinuation	0
Any SAE	2 (1.4)
Any drug-related SAE ^b	0
Any fatal SAE	0

a. Grade 3 = Severe, 4 = Potentially Life-Threatening; no Grade 5 AEs were reported.

b. Relatedness of AEs was determined by the investigators

The most common AE in Cohort 2 was injection site pain (*Table 15*). Other AEs reported by ≥10% of participants were cough, blood pressure increased, headache, nasal congestion, and upper respiratory tract infection.

Table 15 Adverse events reported by at least 5% of participants for Cohort 2 (All Treated Population)

PT	Cohort 2 total (N=144) n (%)
Injection site pain	48 (33.3)
Cough	28 (19.4)
Blood pressure increased	17 (11.8)
Headache	16 (11.1)
Nasal congestion	16 (11.1)
Upper respiratory tract infection	16 (11.1)
Pyrexia	14 (9.7)
Blood pressure systolic increased	13 (9.0)
Oropharyngeal pain	12 (8.3)
Rhinorrhoea	11 (7.6)
Blood creatine phosphokinase increased	9 (6.3)
COVID-19	9 (6.3)

In both Cohorts, the vast majority of participants experienced at least 1 AE, with the majority also experiencing an injection site reaction. Drug related AEs were experienced by 48% in Cohort 1R and 35.4% in Cohort 2, with the majority being ISRs.

The percentage of participants experiencing SAEs was low in both Cohorts and none of the SAEs were considered drug-related.

Injection site pain was the most commonly reported AE overall. This is in line with the data from adults.

Adverse Events Related to Study Intervention

Cohort 1R

In Cohort 1R, 48.0% of participants reported ≥ 1 AE assessed as related to study intervention through Week 16. Other than ISRs, most AEs assessed as related to study intervention were reported by single participants within either subcohort (Table 16). AEs assessed as related to study intervention and reported by >1 participant were nausea and hypersensitivity.

Table 16 Drug-related adverse events through Week 16 Cohort 1 (All Treated Population)

PT	Cohort 1R Q4W (N=15) n (%)	Cohort 1R Q8W (N=10) n (%)	Cohort 1R total (N=25) n (%)
Injections site reactions	8 (53.3)	1 (10.0)	9 (36.0)
Injection site hypoaesthesia	1 (6.7)	0	1 (4.0)
Injection site nodule	1 (6.7)	0	1 (4.0)
Injection site pain	8 (53.3)	1 (10.0)	9 (36.0)
Injection site swelling	1 (6.7)	0	1 (4.0)
Diarrhoea	0	0	0
Nausea	1 (6.7)	1 (10.0)	2 (8.0)
Hypersensitivity	1 (6.7)	1 (10.0)	2 (8.0)
Dizziness	1 (6.7)	0	1 (4.0)
Headache	1 (6.7)	0	1 (4.0)
Somnolence	0	1 (10.0)	1 (4.0)
Insomnia	1 (6.7)	0	1 (4.0)
Pruritus	0	1 (10.0)	1 (4.0)
Rash	0	1 (10.0)	1 (4.0)

Rash maculo-papular	0	1 (10.0)	1 (4.0)
Rash papular	1 (6.7)	0	1 (4.0)

All of these AEs assessed as related to study intervention were \leq Grade 2 except for 1 participant (Cohort 1R) with hypersensitivity, which was Grade 3.

Cohort 2

In total, 35.4% of participants in Cohort 2 reported ≥ 1 AE assessed as related to study intervention (Table 14).

Most participants with AEs assessed as related to study intervention reported ISRs. Otherwise, most AEs assessed as related to study intervention were reported by single participants (Table 17). AEs assessed as related to study intervention and reported by >1 participant were headache, nausea, rash, and rash pruritic. Other than the SOC of General disorders and administration site conditions (under which ISRs are categorized), the SOCs with the highest number of participants with ≥ 1 AE assessed as related to study intervention were Nervous system disorders (6 participants) and Skin and subcutaneous tissue disorders (5 participants).

Table 17 Drug-related adverse Week 24 analysis (All Available Data for Cohort 2 All Treated Population)

PT	Cohort 2 total (N=144) n (%)
Injection site reactions	
Injection site pain	44 (30.6)
Injection site nodule	6 (4.2)
Injection site swelling	4 (2.8)
Injection site abcess	2 (1.4)
Injection site pruritus	2 (1.4)
Injection site bruising	1 (0.7)
Injection site erythema	1 (0.7)
Injection site induration	1 (0.7)
Injection site joint pain	1 (0.7)
Abdominal pain upper	1 (0.7)
Flatulence	1 (0.7)
Nausea	2 (1.4)
Vomiting	1 (0.7)
Asthenia	1 (0.7)
Chest pain	1 (0.7)
Chills	1 (0.7)
Product administration error	1 (0.7)
Alanine aminotransferase increased	1 (0.7)
Myalgia	1 (0.7)
Dizziness	1 (0.7)
Headache	3 (2.1)
Presyncope	1 (0.7)
Somnolence	1 (0.7)
Cough	1 (0.7)
Dyspnoea	1 (0.7)
Hyperhidrosis	1 (0.7)
Papule	1 (0.7)
Rash	2 (1.4)
Rash maculo-papular	1 (0.7)

Rash pruritic	2 (1.4)
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All non-ISR AEs assessed as related to study intervention were \leq Grade 2. Grade 3 ISRs were reported: injection site pain (1 participant) and injection site abscess (2 participants).

Drug-related AEs were reported by 12 participants (48.0%) in Cohort 1R and 51 participants (35.4%) in Cohort 2. Most of the drug-related AEs were ISRs and the most frequently reported drug-related AE was injection site pain in both Cohorts. The most frequently reported non-ISR, drug-related AE were nausea and hypersensitivity in Cohort 1 and headache, nausea, rash and rash pruritic in Cohort 2. The majority of all drug-related AEs reported by >1 participant are already included in the SmPC of Rekambys.

The majority of drug-related AEs were grade ≤ 2 , except 1 case of hypersensitivity in Cohort 1 and 3 cases of ISRs in Cohort 2.

Serious adverse event/deaths/other significant events

At the time of the full Cohort 1 analysis and the Week 24 analysis for Cohort 2, there have been no deaths and no SAEs assessed as related to study intervention.

In total, 2 participants had a total of 4 nonfatal SAEs in Cohort 2. These were a Grade 3 SAE of malaria in one participant (onset: Day 234; duration: 15 days), and 3 SAEs in another participant all with onset on Day 522/Week 74 (Grade 4 blood creatine phosphokinase increased (reported CPK value: 16 605 U/L [RR: 55-170 U/L], and Grade 3 aspartate aminotransferase increased (not a protocol-required laboratory assessment), which led to hospital admission for monitoring and rehydration for suspected rhabdomyolysis (reported as Grade 4 SAE). All 4 SAEs were assessed as not related to study intervention, and no action was taken with the study intervention.

Overall, no new safety serious/deaths/significant adverse event data emerged from Study 208580.

Adverse Events of Special interest

Injection site reactions

Cohort 1

In total 9 participants (36.0%) reported ≥ 1 ISR through Week 16 ([Table 18](#)). In Cohort 1R, all ISR AEs were \leq Grade 2. The most commonly reported ISR was injection site pain. In Cohort 1R, 100% of injection site pain AEs resolved within 7 day, and none had a duration >14 days. No participants withdrew from the study due to ISRs, and no ISRs met the criteria for an SAE.

Table 18 Injection site reactions by grade through Week 16 (Cohort 1R)

PT	Cohort 1R Q4W (N=15) n (%)		Cohort 1R Q8W (N=10) n (%)		Cohort 1R total (N=25) n (%)	
	1	2	1	2	1	2
Any ISR	5 (33.3)	3 (20)	0	1 (10)	5 (20)	4 (16)
Injection site hypoaesthesia	1 (6.7)	0	0	0	1 (4)	0
Injection site nodule	1 (6.7)	0	0	0	1 (4)	0
Injection site pain	5 (33.3)	3 (20)	0	1 (10)	5 (20)	4 (16)
Injection site swelling	1 (6.7)	0	0	0	1 (4)	0

Note: The results in the table are calculated with the denominators as shown; it should be noted, however, that the number of participants who received an injection is different (23 of 25 in Cohort 1R; Source: Table 3.85).

Note: Grade: 1 = Mild, 2 = Moderate; a participant may have reported an AE more than once; however, for each PT, a participant was only counted for the worst grade.

Among the 23 participants in Cohort 1R with an injection, there were 22 ISRs reported for 59 total injections. Overall, 95.5% of ISRs resolved within 7 days for Cohort 1R, and no ISRs had a duration >14 days.

Cohort 2

Approximately one-third of participants in Cohort 2 reported ≥ 1 ISR through the data cutoff date. No participants withdrew from the study due to ISRs, and no ISRs met the criteria for an SAE.

With the exception of injection site pain, all other types of ISRs were reported in <5% of participants, and most participants had ISRs that were Grade 1 or 2 at worst (*Table 19*); there were 2 participants who had Grade 3 ISRs, 2 with injection site abscess and 1 of these 2 also with Grade 3 injection site pain. Both participants were enrolled at the same site and remained on study following resolution of the signs/symptoms.

Overall, 89.6% of injection site pain ISRs resolved within 7 days, and 3.8% of injection site pain ISRs resolved within 8 to 14 days. 1.6% of injection site pain ISRs had a duration of >14 days, and 4.9% of injection site pain ISRs were ongoing at the data cutoff date.

Table 19 Injection site reactions by grade Week 24 analysis Cohort 2

PT	Cohort 2 total (N=144) n (%)			
	1	2	3	Total
Injection site pain	38 (26.4)	9 (6.3)	1 (0.7)	48 (33.3)
Injection site nodule	5 (3.5)	1 (0.7)	0	6 (4.2)
Injection site swelling	5 (3.5)	0	0	5 (3.5)
Injection site abscess	0	0	2 (1.4)	2 (1.4)
Injection site pruritus	2 (1.4)	0	0	2 (1.4)
Injection site bruising	1 (0.7)	0	0	1 (0.7)
Injection site erythema	1 (0.7)	0	0	1 (0.7)
Injection site induration	1 (0.7)	0	0	1 (0.7)
Injection site joint pain	1 (0.7)	0	0	1 (0.7)

Note: The results in the table are calculated with the denominators as shown; it should be noted, however, that the number of participants who received an injection is different (142 of 144).

Note: Grade: 1 = Mild, 2 = Moderate, 3 = Severe; a participant may have reported an AE more than once; however, for each PT, a participant was only counted for the worst grade.

In Cohort 2, 142 participants received at least 1 injection, and there were 209 ISRs occurring for 2 130 total injections. Overall, 86.1% of ISRs resolved within 7 days, and 5.3% of ISRs resolved within 8 to 14 days. 4.3% of ISRs had a duration of >14 days, and also 4.3% of ISRs were ongoing at the data cutoff date. The numbers of participants with any ISR decreased over time.

The CHMP considered that the profile of injection site reactions in adolescents is similar to the profile in adults. The most frequently reported ISR was injection site pain and the majority of ISR are Grade ≤ 2 . The

percentage of subjects reporting ISRs decreased over time. None of the participants discontinued due to ISR.

Rash and hypersensitivity

All events associated with rash were \leq Grade 2, none were serious, and none led to discontinuation of study intervention.

There were no events consistent with suspected hypersensitivity reactions in Cohort 2. In Cohort 1R, 2 events of hypersensitivity were reported of which 1 event led to discontinuation, but no serious events were reported.

- On the first day of OLI, a participant in Cohort 1R (Q4W) had a nonserious, RPV-related, Grade 3 AE of hypersensitivity (verbatim term: acute allergic reaction). Approximately 2 hours after taking study intervention, the participant contacted the site to inform them of rash and itchiness; after approximately an hour, the participant reported symptoms resolving, with the rash fading and the itching improved; the symptoms completely resolved after 6 days. No medications were taken, and no interventions were implemented. Per protocol, RPV was permanently discontinued due to the AE.
- A second participant in Cohort 1R (Q8W) developed 3 rashes (all Grade 2) on Day 11 (OLI), followed by Grade 2 hypersensitivity (verbatim term: allergic reaction) on Day 15 (OLI), all considered related to study intervention. One of the rashes resolved in 1 day; the other 2 rashes resolved after 9 days. The resolution of the AE of hypersensitivity (duration: 5 days) was the same day as the resolution of the 2 rashes. No action was taken with the study intervention, and the participant remained on study.

Neuropsychiatric disorders

Most AESIs associated with neuropsychiatric disorders were sleep disorders and were \leq Grade 2. None were serious, and none led to discontinuation of study intervention.

There have been no confirmed reports of seizure in the study to date.

Weight gain

All events associated with weight gain were Grade 1, none were serious, and none led to discontinuation of study intervention.

Rhabdomyolysis

The participants reporting myalgia, which could be an indicator of rhabdomyolysis, did not have any other indications of rhabdomyolysis. In Cohort 2, one participant did report an SAE of Grade 4 rhabdomyolysis, but this was linked to exercise. No cases of rhabdomyolysis related to study drug and no new safety signals were observed.

Laboratory findings

No safety signals with regards to laboratory findings were observed.

Safety in special populations

One pregnancy occurred in Cohort 2 while on CAB + RPV. This participant entered the long-term safety follow-up after Week 16. The pregnancy resulted in a live birth (assisted vaginal delivery).

No conclusions can be drawn on this single case of pregnancy. No change has been made by the MAH to the recommendations for use in pregnancy following review of the data in this submission, which was agreed by the CHMP.

Safety related to drug-drug interactions and other interactions

No additional data are available. No differences are expected with regard to the drug-drug interaction profile in adolescents compared to adults.

Discontinuation due to adverse events

In total, only one participant discontinued the study intervention in Cohort 1R due to an AE of Grade 3 hypersensitivity during the oral lead in phase when the participant received Edurant.

Post marketing experience

As of 17 March 2023, the total number of vials of rilpivirine 300 mg/mL (Rekambys) for IM injection sold from launch to December 2022 is 22,216, which is equivalent to approximately 1,851 patient-years.

The total number of vials of CAB 200 mg/mL + RPV 300 mg/mL (CABENUVA) for IM injection sold between July 2020 and December 2022 is 100,058 which is equivalent to approximately 8,338 patient-years.

The post-marketing exposure predominantly reflects use in adults. There are no reliable estimates for post-marketing exposure specifically in adolescents.

2.5.1. Discussion on clinical safety

To support the use of Rekambys for the treatment of HIV-1 in adolescents at least 12 years of age and weighing at least 35 kg, the MAH provided new clinical data derived from the ongoing Phase 1/2 study 208580. The CHMP considered that the safety database was limited, with only 25 participants in Cohort 1R and 144 in Cohort 2. As the extension of indication is mainly supported by PK data, this is acceptable, but it limits the chance of detecting adverse events.

The safety profile of Rekambys in adolescents was in line with the safety profile in adults. The vast majority of participants experienced at least 1 adverse event, with the majority also experiencing an injection site reaction. Drug-related adverse events were reported by 12 participants (48.0%) in Cohort 1R and 51 participants (35.4%) in Cohort 2. Most of the drug-related AEs were injection site reactions and the most frequently reported drug-related AE was injection site pain in both Cohorts. The most frequently reported non-ISR drug-related AEs were nausea and hypersensitivity in Cohort 1 and headache, nausea, rash and rash pruritic in Cohort 2. The majority of all drug-related AEs reported by >1 participant are already included in the SmPC of Rekambys.

In total, two participants experienced events of hypersensitivity considered related to study intervention during the oral-lead in phase of Cohort 1, when participants received Edurant. In one participant, the event of non-serious rilpivirine-related, Grade 3 AE of hypersensitivity (verbatim term: acute allergic reaction), led to permanent discontinuation of study intervention. The symptoms of hypersensitivity (rash and itchiness) were self-limiting and were already resolving 3 hours after administration, prior to reaching peak exposure, which is generally achieved within 4-5 hours after administration. Currently, this

information does not constitute a new safety signal for Rekambys. The CHMP re-iterated that hypersensitivity should be closely followed in the future PSURs.

The profile of injection site reactions in adolescents is similar to the profile in adults. The most frequently reported ISR was injection site pain and the majority of ISR are Grade ≤ 2 . The percentage of subjects reporting ISRs decreased over time.

During the study, only two participants (both in Cohort 2) reported four serious adverse events (in total). The CHMP agreed that these events were not related to study intervention. No deaths were reported.

Overall, no new safety signals were observed with the use of Rekambys in adolescents. The available safety data from study 208580 did not reveal safety concerns that would preclude its use in adolescents. No new safety signals were identified.

2.5.2. Conclusions on clinical safety

The CHMP concluded that safety data from study 208580 support the use of Rekambys in virologically suppressed HIV-1 infected adolescents.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5.2 with the following content:

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 Ongoing	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 Submitted	31 December 2020
			Regular updates	Interim data presenting the progress and status of the DUS will be discussed in the PBRER/PSUR and will be submitted as annual standalone reports.
			Final study report	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				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Antiretroviral Pregnancy Registry (APR) Ongoing	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 submitted Regular updates	16 December 2021 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)	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • SmPC Sections 4.2 and 4.4 • PL Sections 2 and 3 • IFU • 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. • PL Sections 2 and 3 include instructions on what to do when stopping treatment. • IFU are provided in the PL and include detailed information on the preparation and administration of an IM injection. • Administered by HCPs. • Different packaging designs to differentiate between dose and medication. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • None 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • Cumulative review of medication error cases in adolescents (ie, non-adherence to the dosing schedule, incorrect route of administration) in the PBRER/PSUR. <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • 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 Final study report: September 2026

Missing information		
Use in pregnancy	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> SmPC Sections 4.4 and 4.6 PL Section 2 Recommendation regarding the use of REKAMBYS during pregnancy is provided in SmPC Sections 4.4 and 4.6, and PL Section 2. This is a prescription only medicine. Prescribed by HCPs. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> None 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> 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.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the latest QRD template version 10.4 which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The updates of the Package Leaflet in section 1 (*at least 12 years of age and weighing at least 35 kg*) and in section 2 (*not for use in children less than 12 years of age or adolescents weighing less than 35 kg*) are considered minimal and do not otherwise change the content or the lay-out.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

In 2023, 630 000 (500 000–820 000) people died because of HIV-related causes globally. There were approximately 39.9 million (36.1–44.6 million) people living with HIV at the end of 2023, including 1.4 million (1.1 million–1.7 million) children (0–14 years).

3.1.2. Available therapies and unmet medical need

The aim of antiretroviral therapy in children is to achieve undetectable HIV RNA levels, to provide a high barrier to resistance development, to maintain viral suppression and thus to allow normal immune function, whilst minimizing drug toxicities.

The combination of cabotegravir + rilpivirine is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL). This regimen is expected to provide another treatment option for adolescents, with a reduced dosing frequency compared to daily oral antiretrovirals, to reduce pill burden and to be more convenient and tolerable than the previously available HIV therapeutics.

3.1.3. Main clinical studies

For an extension of indication to include treatment in adolescents, similar exposure in adolescents vs adults forms the basis of approval. As it is assumed that the pharmacokinetic/pharmacodynamic relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred.

The MAH submitted the ongoing Phase 1/2 open-label, non-comparative study 208580 to support the use of Rekambys for the treatment of HIV-1 in adolescents at least 12 years of age and weighing at least 35 kg. Cohort 1 of Study 208580 was undertaken to assess the safety and pharmacokinetics of sequentially dispensed oral rilpivirine followed by long-acting injectable rilpivirine (Cohort 1R; n=25), as well as oral cabotegravir followed by long-acting injectable cabotegravir (Cohort 1C; not described in this report) in virologically suppressed adolescents living with HIV who continued their oral combination antiretroviral treatment regimen. Cohort 2 (n=144) further assessed the safety, pharmacokinetics and virological suppression in adolescents living with HIV upon switching to the two-drug intramuscular regimen of long-acting cabotegravir + rilpivirine.

The proposed cabotegravir + rilpivirine dosing regimens in adolescents, as investigated in Study 208580, consisted of the same doses and dosing intervals as used for adults.

In addition, PK modelling and simulation were performed.

3.2. Favourable effects

The observed pharmacokinetic Cohort 1R and Cohort 2 Week 24 data in adolescents in Study 208580 supported the update of the existing population pharmacokinetic model of long-acting rilpivirine. The population pharmacokinetic analyses demonstrated that the proposed dosing regimens for rilpivirine, when administered with cabotegravir, resulted in systemic exposures in adolescents similar to those in adults (within the range of adult data and within the established safety and efficacy thresholds for adults). The adolescent/adult geometric mean ratios for exposure parameters ranged from 0.79 to 1.27. These minor differences in exposure between adolescents and adults are not considered clinically relevant.

All participants in Cohort 1R remained virologically suppressed (plasma HIV-1 RNA VL <50 copies/mL) up to week 16. In Cohort 2 the vast majority of participants (139 out of 144, 96.5%) remained virologically

suppressed (plasma HIV-1 RNA VL <50 copies/mL) up to week 24 after switching to treatment with cabotegravir and rilpivirine. None of the subjects experienced protocol-defined virologic failure.

3.3. Uncertainties and limitations about favourable effects

The MAH supported their pharmacokinetic comparison by a subgroup analysis by weight category (<50 kg, ≥50 kg) for adults and adolescents combined, which showed comparable exposure parameters across weight categories. In this respect, there are no uncertainties.

Although compliance data in study 208580 were reassuring, the context of a clinical trial was considered to introduce a bias. Given the importance of adherence to the injection visits, the CHMP discussed the appropriate measures to monitor this aspect. Overall, the CHMP concluded that adherence to the dosing regimen in the adolescents will be adequately evaluated via routine pharmacovigilance activities and that cumulative reviews of medication error cases will be presented in the future PSURs.

3.4. Unfavourable effects

The safety profile in adolescents was in line with the safety profile in adults, which is mainly characterised by injection site reactions. The vast majority of participants experienced at least 1 adverse event, with the majority also experiencing an injection site reaction. Drug-related adverse events were reported by 12 participants (48.0%) in Cohort 1R and 51 participants (35.4%) in Cohort 2. Most of the drug-related adverse events were injection site reactions and the most frequently reported drug-related adverse event was injection site pain in both cohorts.

Serious adverse events reported in two patients were not considered related to the study intervention. No cases of death were reported.

3.5. Uncertainties and limitations about unfavourable effects

The limited safety database is considered to limit the detection of adverse events.

Hypersensitivity remains an important potential issue with long-acting rilpivirine. This will continue to be followed up in future PSURs.

3.6. Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
PK similarity	AUC _{0-τ} , C _{max} and C _τ comparison based on PopPK modelling		Adolescents	Adults	Adolescent/adult geometric mean ratio (GMR) ranged from 0.79 to 1.27
Virological success	Percentage of patients with HIV-1 RNA <50 c/mL at Week 24 in Cohort 2	n/N (%)	139/144 (96.5%)		None of the participants had confirmed virologic failure
Unfavourable Effects					
ISR	Injection site reactions Pain Nodule Swelling	%	30.6-36.0 4.0-4.2 2.8-4.0		SoE: similar occurrence in both Cohort 1R (RPV+background ART) and Cohort 2

Abbreviations: ISR = injection site reactions

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The population PK analyses showed that the proposed dosing regimens for rilpivirine administered with cabotegravir resulted in systemic exposures in adolescents similar to those in adults. Since the exposure of rilpivirine in adolescents and adults is similar, safety and efficacy are expected to be similar in adolescents at the same doses used in adults.

When switching to long-acting cabotegravir + rilpivirine, the vast majority of participants remained virologically suppressed up to week 24. There was no case of confirmed virological failure in any participant. No new safety signals were observed with adolescents.

The safety profile in adolescents was comparable to the safety profile in adults, which is acceptable, and mainly characterised by injection site reactions.

3.7.2. Balance of benefits and risks

Based on the pharmacokinetic analyses showing comparable drug exposure in adolescents and adults, further supported by the submitted efficacy and safety data, the long-acting rilpivirine + cabotegravir can be administered in adolescents aged ≥ 12 years and weighing at least 35 kg, following the same posology as approved in adults.

3.8. Conclusions

The overall benefit-risk balance of Rekambys remains positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include, in combination with cabotegravir injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Rekambys, based on interim results from study 208580. This is an ongoing Phase 1/Phase 2 multicentre, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and pharmacokinetic of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable combination antiretroviral therapy consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in

accordance. Version 5.2 of the RMP has also been adopted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Rekambys-H-C-005060-II-0022'