12 December 2024
EMA/1951/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Vocabria

International non-proprietary name: cabotegravir

Procedure No. EMEA/H/C/004976/II/0022

Marketing authorisation holder (MAH) ViiV Healthcare B.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
ChAESI	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
Cmax	Maximum plasma concentration
C0	Predose (trough) concentration
CAB	Cabotegravir
cART	Combination antiretroviral therapy
c/mL	Copies per milliliter
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CSR	Clinical study report
CVF	Confirmed virological failure
DAIDS	Division of AIDS
ECG	Electrocardiogram
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
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
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health

AE	Adverse event
OLI	Oral lead-in
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
pcVPC	Prediction-corrected visual predictive check
Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
QC	Quality control
RMP	Risk Management Plan
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
tNDA	Treatment New Drug Application

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, ViiV Healthcare B.V. submitted to the European Medicines Agency on 24 May 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 and IIIB

Extension of indication to include, in combination with rilpivirine injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Vocabria, 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 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes and 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 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/0396/2022 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: Jean-Michel Race Co-Rapporteur: Patrick Vrijlandt

Timetable	Actual dates
Submission date	24 May 2024
Start of procedure:	22 June 2024
CHMP Rapporteur Assessment Report	20 August 2024
PRAC Rapporteur Assessment Report	20 August 2024
PRAC members comments	28 August 2024
Updated PRAC Rapporteur Assessment Report	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	18 November 2024
PRAC members comments	20 November 2024
Updated PRAC Rapporteur Assessment Report	21 November 2024
CHMP Rapporteur Assessment Report	27 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

Cabotegravir is an HIV integrase inhibitor indicated, in combination with rilpivirine (a non-nucleoside reverse transcriptase inhibitor), 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 to support the use of cabotegravir as part of the two-drug regimen (cabotegravir + rilpivirine) for the treatment of HIV-1 infection in adolescents 12 to <18 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 the therapeutic indication

The full indication for Vocabria prolonged-release suspension for injection will be as follows:

> Vocabria injection is indicated, in combination with rilpivirine 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).

The full indication for Vocabria film-coated tablets will be as follows:

> Vocabria tablets are indicated, in combination with rilpivirine tablets, for the short-term 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) for:
>
> - Oral lead-in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting cabotegravir injection plus long acting rilpivirine injection.
> - Oral therapy for adults **and adolescents** who will miss planned dosing with cabotegravir injection plus rilpivirine injection.

2.1.2. About the product

Cabotegravir is an HIV integrase inhibitor acting by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

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

The paediatric study 208580 submitted within this application is in compliance with the agreed paediatric investigation plan as set out the EMA's decision P/0396/2022 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 of the GlaxoSmithKline group of companies, 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 Vocabria (cabotegravir) 400mg/2ml and 600mg/3ml prolonged-release suspension for injection and Vocabria (cabotegravir) film coated tablets, 30 mg are Botswana, Thailand, US, South Africa and Uganda.

2.2. Non-clinical aspects

No specific non-clinical data have been generated and submitted to support the administration of cabotegravir in adolescents aged 12 to <18 years of age.

2.2.1. Ecotoxicity/environmental risk assessment

The CHMP considered that the ERA previously provided and accepted as part of the initial Marketing Authorization adequately addresses the environmental risks associated with the product and is deemed sufficient to support the current extension application.

2.2.2. Discussion on non-clinical aspects

The CHMP considered the MAH´s justification for not conducting additional juvenile toxicity studies acceptable. The principal toxicological findings associated with the gastrointestinal (GI) and cardiovascular (CV) systems, identified in repeat-dose studies, did not appear to be linked to functional immaturity of these organs. Furthermore, the proposed paediatric population (12–18 years of age) has structurally and functionally mature GI and CV systems, as noted in ICH S11 (2020), with any remaining cardiovascular changes limited to adaptive growth rather than critical developmental processes. Regarding other long-maturing systems, such as the central nervous system (CNS), endocrine and reproductive systems, no specific toxicities were identified in nonclinical studies conducted in peripubertal animals (rats and monkeys). Given that the pharmacological target of

cabotegravir is a viral protein with no mammalian orthologs, the risk of unexpected off-target toxicities in these systems is minimal. Thus, the existing data sufficiently support the safety profile of cabotegravir in the adolescent population, and additional juvenile toxicity studies are unlikely to provide significant new information.

2.2.3. Conclusion on the non-clinical aspects

The CHMP concluded that no additional non-clinical data are necessary to support the treatment with cabotegravir in adolescent patients.

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

2.3. Clinical aspects

2.3.1. Introduction

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

The key clinical study supporting the CAB + RPV regimen for use in adolescents for the treatment of HIV-1 is Study 208580 (MOCHA):

Study	**Study Design**	**Population**	**Treatment Details**
208580 (IMPAACT 2017 or MOCHA) Study Report No. TMF-16153855 Status: Ongoing; Cohort 1 and Cohort 2 Week 24 CSR completed	Open-label, non-comparative, Phase 1/2 study to confirm doses and evaluate safety, tolerability, acceptability, and PK of oral CAB, CAB LA, and RPV LA	HIV-1-infected cART-experienced children and adolescents (12 to <18 years of age) weighing at least 35 kg who are virologically suppressed on a stable ARV regimen	**Cohort 1:** Participants were assigned to Cohort 1C **or** Cohort 1R based on their background cART regimen. <u>Cohort 1C:</u> 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

Study	Study Design	Population	Treatment Details
			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. **Cohort 2:** 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 every 8 weeks through Week 96.

Additional analyses were conducted to evaluate the PK of CAB in adolescent populations. An initial CAB population PK model was generated from Phase 3 adult data. The CAB population PK model was updated with additional data, including the full data set from Study 208580 Cohort 1 and Cohort 2 Week 24.

2.3.2. Pharmacokinetics

Study 208580 (MOCHA)

Study design

Study 208580 is an ongoing Phase 1/2, multicentre, open-label, non-comparative 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 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 enrolment, participants received at least 4 weeks of 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 IM 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 IM 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. These participants could screen and enroll into Cohort 2 either prior to completing all scheduled LSFU study visits or resuming study participation after having already exited the study (see Protocol Version 4.0, Section 6.2).

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 dosing regimens for Cohort 1 are as follows:

- 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).

Details of the CAB and RPV dosing regimens 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.

Objectives were:

- Primary Objectives

Primary objectives for Cohort 1 (continuing a background cART regimen):

- To confirm the doses for oral CAB followed by injectable CAB LA in adolescents living with HIV who are virologically suppressed by evaluating:

1. Safety and multiple dose PK of oral CAB through Week 4;
2. Safety and multiple dose PK of CAB LA through Week 16.

- 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.

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

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.

Analytical method

The bioanalytical method for the measurement of CAB concentrations in human EDTA plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labelled internal standard ([13C, 15N, 2H2]-GSK1265744 in 50/50, acetonitrile/water) followed by HPLC-MS/MS using multiple reaction monitoring.

For Study 208580, the human plasma assay for CAB was independently validated over the concentration range of 25 to 25 000 ng/mL by the Clinical Pharmacology Analytical Laboratory at The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Table 1: Bioanalytical method summary

Validation report	Clinical studies supported	Method description and performance	
Quantification of Cabotegravir (GSK1265744) in Human K_2EDTA Plasma via Combined Liquid Chromatography-Tandem Mass Spectrometric (LC-MS/MS) Analysis Version 9 - Document Number: 2023N538234_00 The Johns Hopkins University School of Medicine Clinical Pharmacology Analytical Laboratory Mason Frank Lord Center Tower Suite 6000, Bayview Medical Center 5200 Eastern Avenue Baltimore, MD 21224, USA	208580	GSK1265744 is extracted from 25 µL of human plasma by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([^{13}C, ^{15}N, $^{2}H_2$]-GSK1265744, in 50/50, acetonitrile/water). Extracts are analyzed by HPLC-MS/MS using multiple reaction monitoring.	
		LLOQ	25 ng/mL
		Validated range	25 to 25 000 ng/mL
		Within-run precision (%CV)	≤12.9%
		Between-run precision (%CV)	≤11.7%
		Accuracy (%Bias)	-14.3% ≤ bias ≤ -1.29%
		Stability in human blood	8 hours at 42°C 96 hours at ambient conditions
		Stability in human plasma	2 days stored at ambient conditions 7 days stored at 4°C 2962 days at -80°C 5 freeze-thaw cycles at -80°C
		Processed extract stability	3 days of extract matrix stability at 4°C to 8°C 3 days of extract matrix re-injection reproducibility at 4°C to 8°C

Validation report	Clinical studies supported	Method description and performance					
Cross Validation between Covance Madison and Johns Hopkins University of a Method for the Determination of GSK1265744 in Human Plasma by HPLC with MS/MS Detection Document Number: 2020N448203_00	Not applicable	GSK1265744 is extracted from 25 µL of human plasma by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([^{13}C, ^{15}N, $^{2}H_2$]-GSK1265744, in 50/50, acetonitrile/water). Extracts are analyzed by HPLC-MS/MS using multiple reaction monitoring.					
		LLQ	25.0 ng/mL				
		Validated Range	25.0 to 25 000 ng/mL				
		Cross Validation Result	Cross validation test results passed				
	Sample	Sample 1 Johns Hopkins	Sample 2 Johns Hopkins	Sample 3 Johns Hopkins	Sample 4 Johns Hopkins	Sample 5 Johns Hopkins	Sample 6 Johns Hopkins
	Overall Mean (ng/mL)	694	2510	7330	10800	1470	84.4
	SD	55.1	82	191	477	24	8.32
	Precision (%CV)	7.9	3.3	2.6	4.4	1.6	9.9
	n=	3	2	3	3	3	3
	Sample	Sample 1 Covance	Sample 2 Covance	Sample 3 Covance	Sample 4 Covance	Sample 5 Covance	Sample 6 Covance
	Overall Mean (ng/mL)	715	2230	7300	10700	1430	83.6
	SD	22.4	125	68.5	117	38.7	3.33
	Precision (%CV)	3.1	5.6	0.9	1.1	2.7	4.0
	n=	6	6	6	6	6	6
	Relative % Difference	3.0	-11.8	-0.4	-0.9	-2.8	-1.0
	Relative % Difference = ((B-A) / ((A+B)/2)))*100, A = Johns Hopkins, B = Covance - Madison Mean values were used in Relative % Difference.						

A cross-validation of the 25 to 25 000 ng/mL method for CAB was conducted between the Covance, Madison, Wisconsin laboratory and the Clinical Pharmacology Analytical Laboratory and the result was acceptable.

All methods were validated to perform to the same, predefined acceptance criteria for precision and accuracy.

Quality control (QC) samples were analysed with each batch of study samples. Performance results of the bioanalytical methods used for each study were generated from bioanalytical runs meeting the same run acceptance criteria based upon the predefined requirements for QC performance that no more than one-third of the QC results and 50% from each QC concentration were to deviate from the nominal concentration by more than 15%.

Table 2: Bioanalysis QCs

Study (Document Number)		CAB Nominal Concentration (ng/mL)					
		75.0 (outliers excluded)	75.0 (outliers included)	1200 (outliers excluded)	1200 (outliers included)	18800 (outliers excluded)	18800 (outliers included)
208580 (2021N468354_00)	Overall Mean (ng/mL)	74.3	76.0	1225	1253	18586	18586
	SD (within-run means)	4.92	7.17	68	99	1065	1065
	Precision (%CV)	6.6	9.4	5.55	7.91	5.73	5.73
	Average Bias (%)	-0.89	1.36	2.03	4.30	-1.14	-1.14
	n	29	32	28	32	32	32
208580 (2021N468354_01)	Overall Mean (ng/mL)	78.3	79.8	1273	1293	19073	19375
	SD (within-run means)	5.27	6.96	65.9	90.2	1279	1755
	Precision (%CV)	6.73	8.72	5.18	6.98	6.71	9.06
	Average Bias (%)	4.27	6.22	5.89	7.44	1.44	3.01
	n	71	80	72	80	74	80

Study population

The PK analysis includes all participants in the All Treated Population who received at least 1 dose of treatment:

- Cohort 1: n = 30 participants in Cohort 1C (including 8 Cohort 1C Q4W and 22 Cohort 1C Q8W participants)
- Cohort 2: n = 144 participants in Cohort 2 (including 44 participants who had previously participated in Cohort 1).

The analysis included available CAB PK sample data from the full Cohort 1 and Cohort 2 Week 24 analysis. In addition, plasma concentrations from some participants in LSFU were available and were included in plasma concentration listings.

Study population demographics is presented in *Table 3* below.

Table 3: PK study, population demographics

		Cohort 1C (N=30) n (%)	Cohort 1R (N=25) n (%)	Cohort 1 total (N=55) n (%)
Age (years)	n	30	25	55
	Mean (SD)	14.9 (1.53)	15.6 (1.71)	15.2 (1.63)
	Median (Q1, Q3)	15.0 (14.0, 16.0)	16.0 (15.0, 17.0)	15.0 (14.0, 17.0)
	Min, Max	12, 17	12, 17	12, 17
Age (years) (n [%])	12	1 (3.3)	3 (12.0)	4 (7.3)
	13	5 (16.7)	0	5 (9.1)
	14	7 (23.3)	3 (12.0)	10 (18.2)
	15	6 (20.0)	4 (16.0)	10 (18.2)
	16	4 (13.3)	4 (16.0)	8 (14.5)
	17	7 (23.3)	11 (44.0)	18 (32.7)
Sex at Birth (n [%])	Female	14 (46.7)	12 (48.0)	26 (47.3)
	Male	16 (53.3)	13 (52.0)	29 (52.7)
Race (n [%])	Asian	9 (30.0)	0	9 (16.4)
	Black or African American	21 (70.0)	21 (84.0)	42 (76.4)
	White	0	4 (16.0)	4 (7.3)
Ethnicity (n [%])	Not Hispanic or Latino	30 (100.0)	22 (88.0)	52 (94.5)
	Hispanic or Latino	0	3 (12.0)	3 (5.5)
Height (cm)	n	30	25	55
	Mean (SD)	159.41 (10.844)	159.96 (11.862)	159.66 (11.215)
	Median (Q1, Q3)	159.75 (150.50, 166.00)	157.50 (152.50, 164.40)	159.50 (151.50, 166.00)
	Min, Max	137.0, 185.3	140.0, 191.8	137.0, 191.8
Weight (kg)	n	30	25	55
	Mean (SD)	52.663 (11.6940)	57.668 (16.1346)	54.938 (13.9808)
	Median (Q1,Q3)	47.850 (43.600, 60.000)	54.000 (44.300, 71.000)	50.000 (44.100, 64.000)
	Min, Max	39.40, 84.00	37.40, 98.50	37.40, 98.50
BMI (kg/m²)	n	30	25	55
	Mean (SD)	20.648 (3.6622)	22.311 (4.6534)	21.404 (4.1863)
	Median (Q1, Q3)	19.640 (18.110, 21.480)	20.680 (18.000, 24.670)	19.880 (18.000, 24.140)
	Min, Max	16.41, 30.48	16.98, 31.32	16.41, 31.32
Country (n [%])	Botswana	0	5 (20.0)	5 (9.1)
	Thailand	8 (26.7)	0	8 (14.5)
	US	8 (26.7)	17 (68.0)	25 (45.5)
	South Africa	14 (46.7)	3 (12.0)	17 (30.9)
Baseline CD4 cell counts[a] (cells/mm³)	n	30	24	54
	Mean (SD)	743.9 (226.20)	859.3 (350.97)	795.2 (291.20)
	Median (Q1, Q3)	701.0 (586.0, 924.0)	788.0 (610.0, 1041.0)	725.0 (586.0, 985.0)
	Min, Max	397, 1206	412, 1808	397, 1808
Baseline CD4 cell counts categories[a] (cells/mm³) (n [%])	Missing	0	1 (4.0)	1 (1.8)
	<350	0	0	0
	350 to <500	4 (13.3)	3 (12.0)	7 (12.7)
	500 to <750	15 (50.0)	7 (28.0)	22 (40.0)
	≥750	11 (36.7)	14 (56.0)	25 (45.5)

Source: Table 1.6

a. For 1 participant in Cohort 1R (Participant [redacted]), the first CD4 evaluation was 4 days following the first administration of study drug; therefore, the Baseline CD4 count is missing.

Cabotegravir PK

Cohort 1C

CAB is rapidly absorbed following oral dosing, with peak concentrations observed between 0 and 4 hours.

Table 4: PK study, Summary of CAB PK parameters following oral administration of CAB 30 mg once daily (Step 1) (Cohort 1C All Treated Population): Study 208580 full Cohort 1 analysis

PK parameter	**Cohort 1C Q4W (N = 8)**	**Cohort 1C Q8W (N = 22)**	**Cohort 1C total (N = 30)**
Number of participants with results	8	21	29
Cmax (μg/mL)	10.5 [8.28, 13.3] 10.1 (7.66, 17.3)	8.36 [6.84, 10.2] 8.94 (3.54, 21.0)	8.90 [7.61, 10.4] 9.28 (3.54, 21.0)
AUC(0-τ[a]) (mg·h/mL)	171 [126, 232] 160 (94.3, 325)	128 [98.1, 168] 122 (37.2, 433)	139 [113, 171] 148 (37.2, 433)
Tmax (h)	N/A 2.46 (1.05, 4.10)	N/A 3.00 (0.00, 4.10)	N/A 2.93 (0.00, 4.10)
Cτ[a] (μg/mL)	4.76 [2.99, 7.56] 5.25 (1.97, 10.6)	3.61 [2.43, 5.37] 3.75 (0.320, 21.0)	3.89 [2.87, 5.28] 4.04 (0.320, 21.0)

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

τ is dosing interval (24 hours for oral CAB).

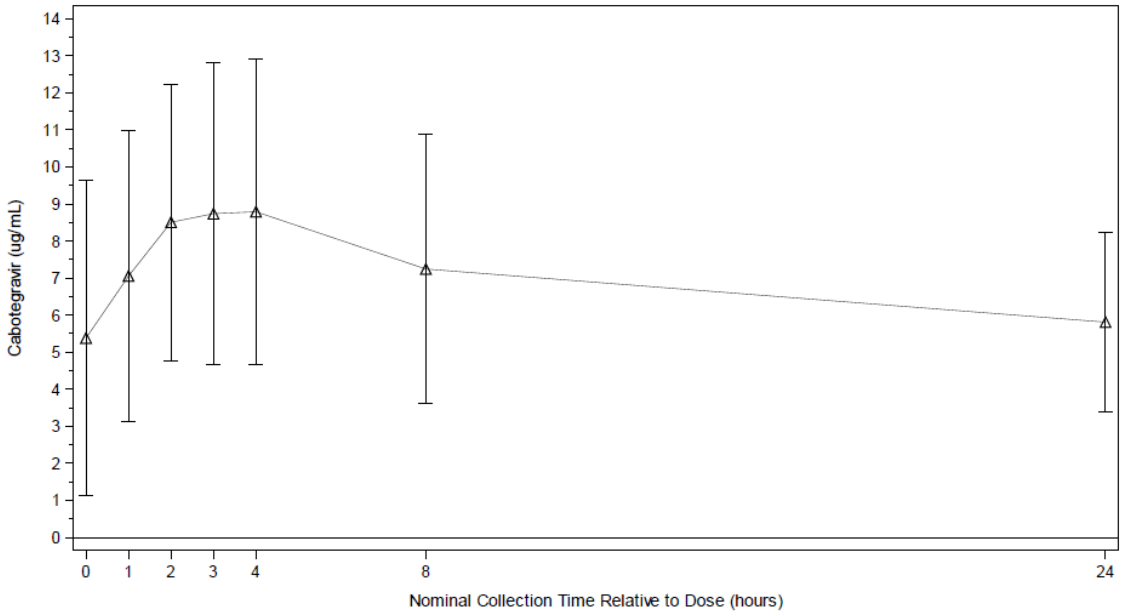


Figure 1: PK study, Arithmetic mean (SD) Week 2 plasma CAB concentration-time profile following oral administration of 30 mg CAB once daily – Linear scale (Cohort 1C All Treated Population): Study 208580 full Cohort 1 analysis

A sparse PK sampling scheme was employed during the injection phase (Cohort 1C Step 2; Week 4 through Week 16). Cabotegravir PK parameters after IM administration (injections at Weeks 4b, 8, and 12 for the Q4W regimen) are summarised in *Figure 2*. injections at Weeks 4b and 8 for the Q8W regimen) including Injection 1 Cmax and Tmax for CAB and pre-dose concentrations are summarized

in *Figure 3*. The Cmax for CAB after the first injection was reflective of oral dosing, because the initial injection was administered together with the last oral dose of study drug in OLI.

Table 5: PK study, Summary of CAB PK parameters following IM administration (Cohort 1C All Treated Population): Study 208580 full Cohort 1 analysis

PK parameter[a]	Cohort 1C Q4W (N = 8)	Cohort 1C Q8W (N = 22)
Number of participants with results at each timepoint	8	21
Injection 1 Cmax[b] (µg/mL)	9.56 [7.36, 12.4] 9.73 (6.50, 17.9) 6.50, 17.9	6.42 [5.34, 7.72] 6.75 (2.48, 15.4) 2.60, 14.9
Injection 1 Tmax (h)	N/A 1.59 (0.200, 1.97) 0.200, 1.97	N/A 2.00 (-1.77[c], 2.15) -1.39, 2.15
Week 4b C0 (µg/mL)	5.46 [3.97, 7.51] 5.63 (2.50, 9.44) 2.50, 9.44	2.89 [1.64, 5.11][d] 3.47 (0.0250, 11.9) 0.156, 11.7
Week 8 C0 (µg/mL)	2.10 [1.55, 2.83] 2.24 (1.01, 3.43) 1.01, 3.43	1.33 [0.903, 1.97] 1.64 (0.227, 6.02) 0.244, 5.82
Week 12 C0 (µg/mL)	2.73 [1.54, 4.81] 3.08 (0.616, 5.34) 0.616, 5.34	2.28 [1.60, 3.27] 2.93 (0.391, 9.88) 0.413, 9.56
Week 16 C0[e] (µg/mL)	2.91 [1.84, 4.59] 3.11 (1.22, 6.19) 1.22, 6.19	1.01 [0.538, 1.88][d] 1.15 (0.0250, 5.29) 0.0257, 5.17

Source: Study Report TMF-16153855 Table 4.1 and Table 4.4.

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

a. All C0 concentrations were taken pre-dose, aside from the Week 12 Q8W C0 concentration, which is mid-dose.
b. Cmax 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.
c. A negative Tmax value for 1 participant resulted from the PK sample being recorded as taken 1.77 hours before the reference time (first CAB injection), which impacted both the minimum and the 5th percentile values.
d. 1 (4.8%) participant at Week 4b and 1 (4.8%) participant at Week 16 had a concentration below the LLOQ; the concentrations were imputed as the LLOQ.
e. C0 at Week 16 is equivalent to Cτ.

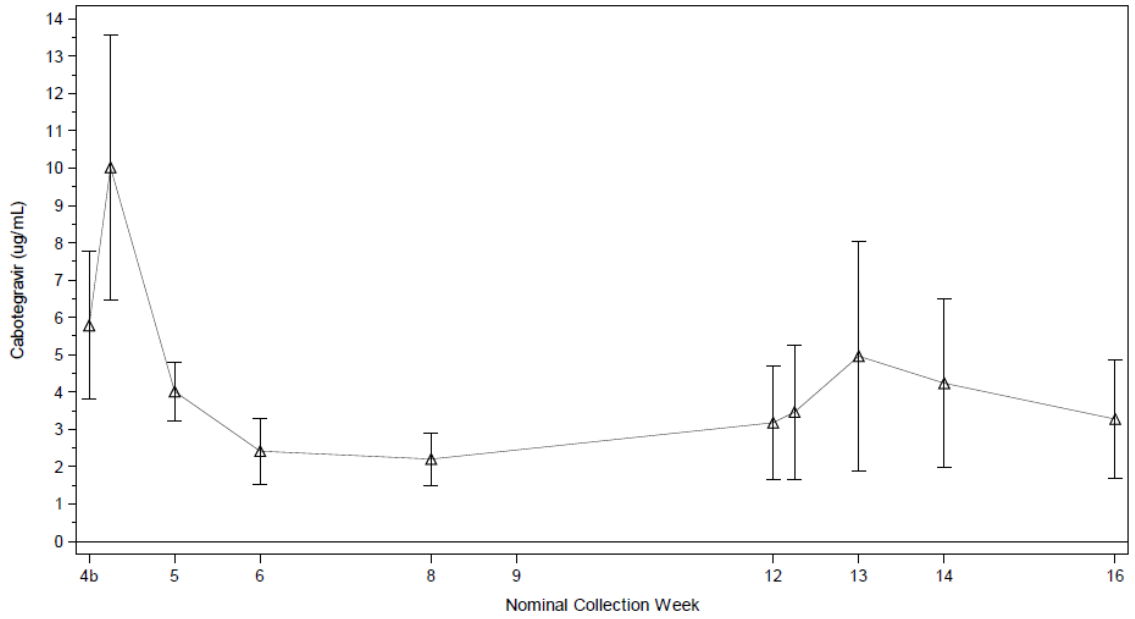


Figure 2: PK study, Arithmetic mean (SD) plasma CAB concentration-time profile following CAB LA Q4W administration at Week 4b, Week 8, and Week 12 – Linear scale (Cohort 1C All Treated Population with Q4W dosing): Study 208580 full Cohort 1 analysis

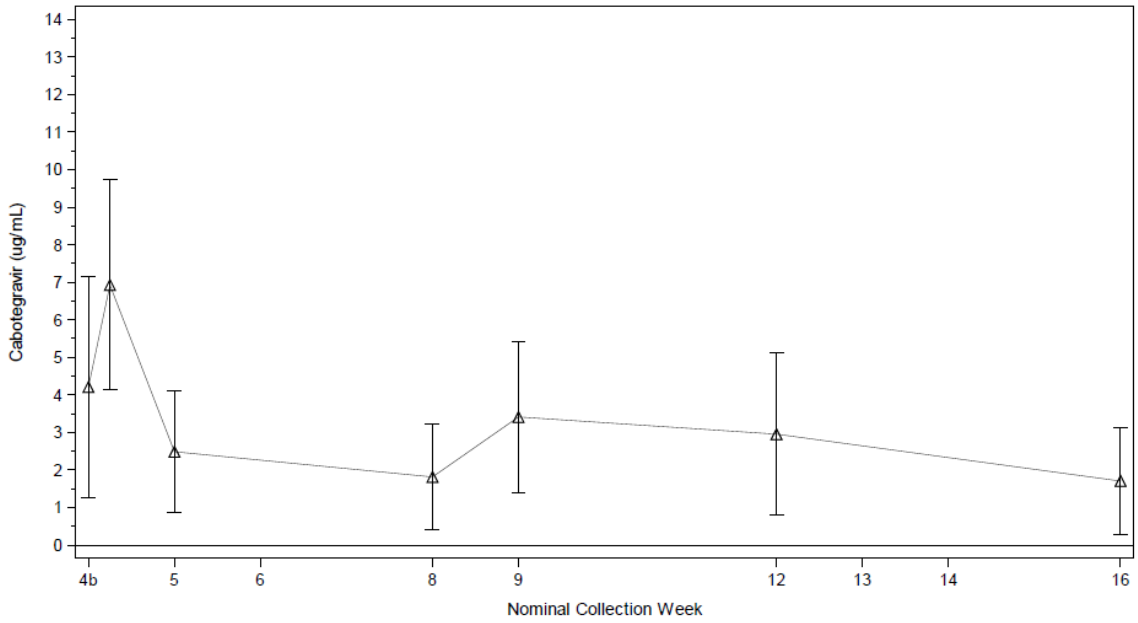


Figure 3: PK study, Arithmetic mean (SD) plasma CAB concentration-time profile following CAB LA Q8W administration at Week 4b and Week 8 – Linear scale (Cohort 1C All Treated Population with Q8W dosing): Study 208580 full Cohort 1 analysis

PK acceptance criteria for this study were based on available data from adults at the time of protocol writing and are detailed in Protocol Version 4.0 Section 10.5. Per protocol, the PK results from Cohort 1 were assessed to determine if any changes to the proposed dosing regimen were required.

The observed exposures for oral CAB (Cohort 1C, Step 1) met the target ranges for the study. The median Week 2 AUC(0-τ) for CAB following daily oral dosing (160 mg·h/mL for the Q4W group and 122 mg·h/mL for the Q8W regimen) was within the study target range of 46 to 277 mg·h/mL. The

observed median trough for CAB following oral dosing (C_T of 5.25 mg/mL for the Q4W regimen and 3.75 mg/mL for the Q8W regimen) met the study target of ≥0.45 mg/mL. The observed median Cmax for CAB following oral dosing (10.1 mg/mL for the Q4W regimen and 8.94 mg/mL for the Q8W regimen) met the study target of ≤22.5 mg/mL.

For the Q4W and Q8W regimens, the observed exposures for CAB LA (Cohort 1C, Step 2) met the key target range for median Week 16 C_T. Though the Q8W regimen did not meet the target threshold for 5th percentile Week 16 C_T, the study team determined that no changes were needed to the proposed dosing regimens based on the totality of the PK data.

The median Week 16 C_T (28 days after the third injection for Q4W regimen and 56 days after the second injection for the Q8W regimen) for CAB following IM administration (3.11 mg/mL for Q4W regimen and 1.15 mg/mL for Q8W regimen) was within the study target range of 0.71 to 6.7 mg/mL. Of note, the median Week 16 C_T was the single CAB LA PK acceptance criteria in place for participants receiving Q4W dosing under Protocol Version 2.0 at the time of the Interim Analysis 1. Subsequently, the protocol was updated to also assess the calculated 5th percentile Week 16 concentration, as detailed below.

The target study threshold for 5th percentile Week 16 C_T following IM administration was 0.45 mg/mL; for CAB following IM administration, this target was met for the Q4W regimen (1.22 mg/mL) but not for the Q8W regimen (0.0257 mg/mL). Based on the totality of the PK data, the study team determined that no changes were needed to the proposed dosing regimen. Of note, 2 participants receiving Q8W dosing had very low CAB concentrations at Week 16 (<0.025 and 0.032 µg/mL, respectively); these extreme outlier concentrations were less than 10% of all other observed participant concentrations. Investigations for these participants did not reveal any administration or bioanalytical issues, nor were there any distinctive demographics. The 2 participants subsequently progressed to Cohort 2, where their Week 16 CAB concentrations were 1.607 and 0.964 µg/mL, respectively, which were aligned with expected values based on data from adults. Aside from the 2 outliers, the observed Week 16 concentrations for all other Cohort 1 participants were above the target study threshold of 0.45 mg/mL, and Cohort 2 was initiated without any change to the regimen.

Cohort 2

The observed CAB PK parameters for Cohort 2 Week 24 following oral administration of 30 mg CAB once daily through Week 4a followed by IM Q8W administration are summarized below. The C0 for CAB was generally consistent across Cohort 2 visits and between participants who had previously participated in Cohort 1 and participants who were new to the study.

Table 6: PK study, Summary of CAB PK parameters following CAB 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 C0: Week 8 C0	1.14 [0.983, 1.32] 1.27 (0.00729, 8.46) 0.347, 4.19 n = 139
Ratio of Week 24 C0: Week 16 C0	0.974 [0.904, 1.05] 0.999 (0.114, 7.07)

PK parameter[a]	Cohort 2 total (N = 144)
	0.538, 1.88 n = 139
Week 8 C0 (μg/mL)	1.99 [1.80, 2.19] 2.09 (0.371, 8.35) 0.703, 5.19 n = 142
Week 16 C0 (μg/mL)	2.33 [2.14, 2.52] 2.43 (0.236, 6.34) 0.986, 4.92 n = 142
Week 24 C0 (μg/mL)	2.27 [2.06, 2.49] 2.34 (0.0268, 6.79) 1.11, 4.15 n = 139

Source: Study Report TMF-16153855 Table 4.8.

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

a. All C0 concentrations were taken pre-dose.

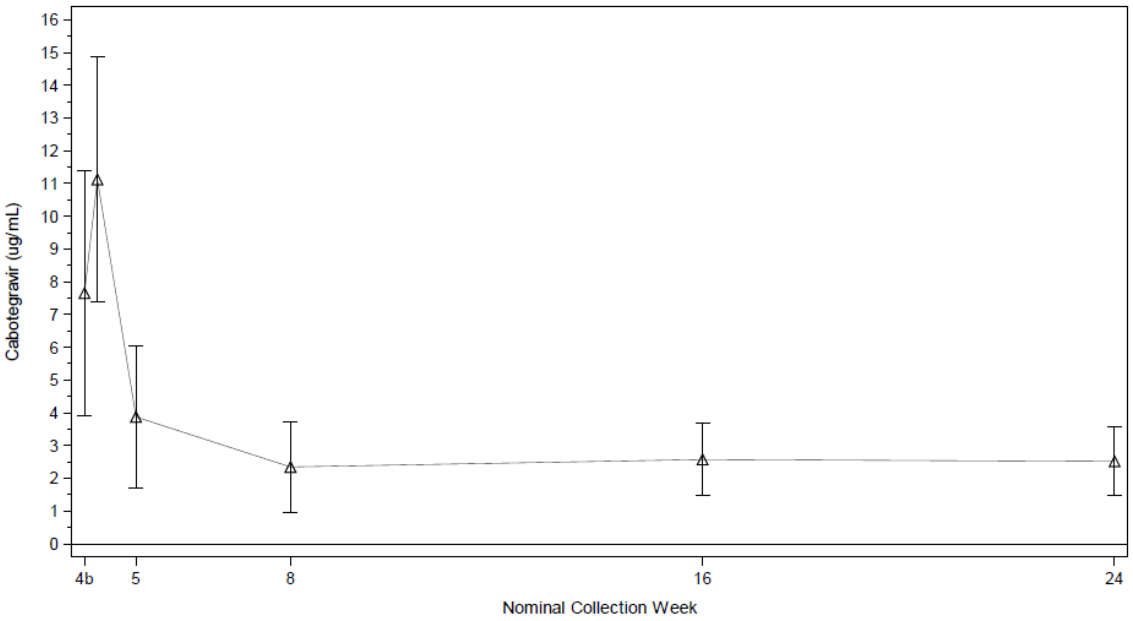


Figure 4: Arithmetic mean (SD) plasma CAB concentration-time profile following CAB LA Q8W administration – Linear scale (Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 analysis

Population PK modelling

Objectives:

- To assess the adequacy and predictive performance of the previously developed adult CAB tNDA PopPK model for describing and predicting CAB PK in adolescent participants in Studies 208580, 213002, and 213003
- To update the existing CAB PopPK model as needed if Objective 1 is not satisfactory with the PK data from Studies 208580, 213002, and 213003
- To derive individual model-based steady state exposure parameters (i.e., AUC0-τ,ss, Cmax,ss, and Cτ,ss) for adolescents enrolled in Studies 208580, 213002, and 213003 using post hoc PK parameters and to compare exposures between adolescents and adult participants in historical adult CAB studies
- To perform simulations to provide options for guiding dose modification under various scenarios

Endpoints:

- Population estimates of PK parameters of CAB and associated IIV and residual error
- Individual CAB steady state PK parameters and exposure metrics

Previous models

The PK of CAB following oral and LA IM administration has been previously characterized in healthy adult participants and HIV-1-infected, treatment-experienced adult participants (n = 1647) by a linear 2-compartment model with first-order oral and LA IM absorption and first-order elimination as the structural PK. IIV was included on the KA1, KA2, CL/F, V2/F, and F1. The final covariate model in the same analysis revealed that weight was a significant determinant of CL/F, Q/F, V2/F, and V3/F, while

smoking status was a significant determinant of CL/F only. Furthermore, needle length, female sex (at birth), splitting of the injection, and time-varying BMI were significant determinants of KA2. The existing adult CAB tNDA PopPK model was used for this analysis.

Methodology:

External model validation was used to evaluate the adequacy of the previously developed adult CAB tNDA PopPK model to explain PK central tendency and variability in adolescents. The tNDA PopPK model parameters were re-estimated based on a new dataset including intensive and sparse concentration, dosing, demographic, and covariate data from adolescent participants in Studies 208580, 213002, and 213003. The external predictive performance of the tNDA PopPK model was evaluated using prediction- and simulation-based diagnostics. The final CAB PopPK model was then used to simulate plasma concentration-versus-time profiles of CAB in adolescent and adult participants, and subsequently used to derive individual secondary exposure parameters, in particular at steady state ($AUC_{0-\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$). The PopPK analysis employed NONMEM software Version 7.3, with run management using Pirana Version 2.0.0. Data summaries were created using R (Version 4.0.0 or higher).

Adolescent data included in the PK analysis

The PopPK analysis dataset included 209 adolescent participants from Studies 208580, 213002, and 213003 who met the following requirements:

- Had taken at least 1 CAB dose, either oral CAB or CAB LA IM injection.
- Had at least 1 quantifiable CAB plasma concentration measurement available.
- Had information on drug administration (i.e., dosing time and dose), PK sampling (i.e., sampling time and plasma concentration), demographic information, and selected clinical and laboratory covariates. For Studies 213002 and 213003, missing OLI dosing time was imputed as steady state dosing (SS function in NONMEM) 24 hours prior to the first LA injection.
- Had no protocol violation (such as improper sample collection or handling) considered to have a negative impact on the modeling.

For Study 208580, the CAB PopPK analysis included all available PK data from participants included in Cohort 1C and Cohort 2 (n = 174 total). All 144 participants from Cohort 2 are included, including those who also participated in Cohort 1C. In addition, there are 3 participants with PK data in Cohort 1C that did not participate in Cohort 2.

Table 7: Population PK modelling, continuous variables for baseline demographics

	Adult studies (N=1647)	HPTN 083-01 (N=9)	HPTN 084-01 (N=53)	MOCHA (N=147)	Overall adolescents (N=209)	Overall population (N=1856)
Baseline age (year)						
Mean (SD)	37.9 (11.5)	16.4 (0.726)	16.0 (1.13)	14.9 (1.58)	15.2 (1.54)	35.3 (13.0)
Median [min, max]	36.0 [18.0, 74.0]	17.0 [15.0, 17.0]	16.0 [12.0, 17.0]	15.0 [12.0, 17.0]	15.0 [12.0, 17.0]	34.0 [12.0, 74.0]
Baseline weight (kg)						
Mean (SD)	78.5 (16.1)	83.9 (32.8)	55.9 (8.55)	51.0 (12.1)	53.6 (14.4)	75.7 (17.8)
Median [min, max]	76.6 [41.2, 168]	70.6 [63.0, 167]	55.5 [39.9, 80.8]	47.7 [35.2, 98.5]	50.8 [35.2, 167]	74.8 [35.2, 168]
Baseline body mass index (kg/m²)						
Mean (SD)	26.2 (5.01)	26.4 (10.2)	22.4 (3.26)	20.4 (3.60)	21.2 (4.21)	25.6 (5.17)
Median [min, max]	25.4 [15.3, 69.5]	21.6 [20.0, 51.6]	22.2 [15.8, 34.1]	19.4 [16.0, 33.9]	20.4 [15.8, 51.6]	24.7 [15.3, 69.5]
Baseline albumin (g/L)						
Mean (SD)	43.8 (3.40)	Not collected	Not collected	45.1 (2.90)	45.1 (2.90)	43.8 (3.39)
Median [min, max]	44.0 [28.0, 56.0]	Not collected	Not collected	45.0 [36.0, 50.0]	45.0 [36.0, 50.0]	44.0 [28.0, 56.0]
Missing	134 (8.10%)	9 (100%)[a]	53 (100%)[a]	126 (85.7%)	188 (90.0%)	322 (17.3%)
Baseline total bilirubin (µmol/L)						
Mean (SD)	9.64 (4.90)	9.49 (5.69)	9.40 (4.93)	7.94 (8.18)	8.38 (7.40)	9.50 (5.25)
Median [min, max]	8.00 [1.71, 42.8]	6.80 [5.10, 22.2]	7.20 [3.90, 23.1]	6.10 [1.20, 82.1]	6.80 [1.20, 82.1]	8.00 [1.20, 82.1]

Source: gsk-cabotegrair-mocha-eda-v10.Rmd → gsk-cabotegrair-mocha-eda-v10.html

a Not collected.

Notes: Numeric columns are formatted as mean (SD) and median [min, max].

Adolescent participants are included in Studies 208580 (MOCHA), 213002 (HPTN 083-01), and 213003 (HPTN 084-01) only.

Abbreviations: max=maximum; min=minimum; N=number of participants with available information; SD=standard deviation

Table 8: Population PK modelling, categorical variables for baseline demographics

	Adult studies (N=1647)	HPTN 083-01 (N=9)	HPTN 084-01 (N=53)	MOCHA (N=147)	Overall adolescents (N=209)	Overall population (N=1856)
Gender						
Male	1223 (74.3%)	9 (100%)	0 (0%)	72 (49.0%)	81 (38.8%)	1304 (70.3%)
Female	424 (25.7%)	0 (0%)	53 (100%)	75 (51.0%)	128 (61.2%)	552 (29.7%)
Race						
American Indian/ Alaskan Native	27 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27 (1.5%)
Asian	56 (3.4%)	0 (0%)	0 (0%)	37 (25.2%)	37 (17.7%)	93 (5.0%)
Black/African American	394 (23.9%)	3 (33.3%)	53 (100%)	108 (73.5%)	164 (78.5%)	558 (30.1%)
Latino or Hispanic	36 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	36 (1.9%)
Missing	2 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)
Mixed	6 (0.4%)	1 (11.1%)	0 (0%)	0 (0%)	1 (0.5%)	7 (0.4%)
Native Hawaiian/ Other Pacific Islander	2 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.1%)
Other	22 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	22 (1.2%)
White	1102 (66.9%)	5 (55.6%)	0 (0%)	2 (1.4%)	7 (3.3%)	1109 (59.8%)
Race category						
Non-White	545 (33.1%)	4 (44.4%)	53 (100%)	145 (98.6%)	202 (96.7%)	747 (40.2%)
White	1102 (66.9%)	5 (55.6%)	0 (0%)	2 (1.4%)	7 (3.3%)	1109 (59.8%)
HIV						
Healthy participants	458 (27.8%)	9 (100%)	53 (100%)	0 (0%)	62 (29.7%)	520 (28.0%)
HIV patients at baseline	1189 (72.2%)	0 (0%)	0 (0%)	147 (100%)	147 (70.3%)	1336 (72.0%)
Smoking status						
Never	590 (35.8%)	0 (0%)	0 (0%)	147 (100%)	147 (70.3%)	737 (39.7%)
Former	210 (12.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	210 (11.3%)
Current	447 (27.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	447 (24.1%)
Not current	120 (7.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	120 (6.5%)
Missing	280 (17.0%)	9 (100%)	53 (100%)	0 (0%)	62 (29.7%)	342 (18.4%)
Age group						
Adolescents	0 (0%)	9 (100%)	53 (100%)	147 (100%)	209 (100%)	209 (11.3%)
Adults	1647 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1647 (88.7%)

CAB PopPK model

The previous PopPK model was updated and refined with adolescent data from Studies 208580, 213002, and 213003. The final PopPK model was used to derive individual CAB exposure parameters for respective participants included in the PopPK analysis, and to simulate plasma concentration-versus-time profiles and secondary exposure parameters of CAB in adults and adolescent participants over an observation period of approximately 1 year.

Post hoc validation

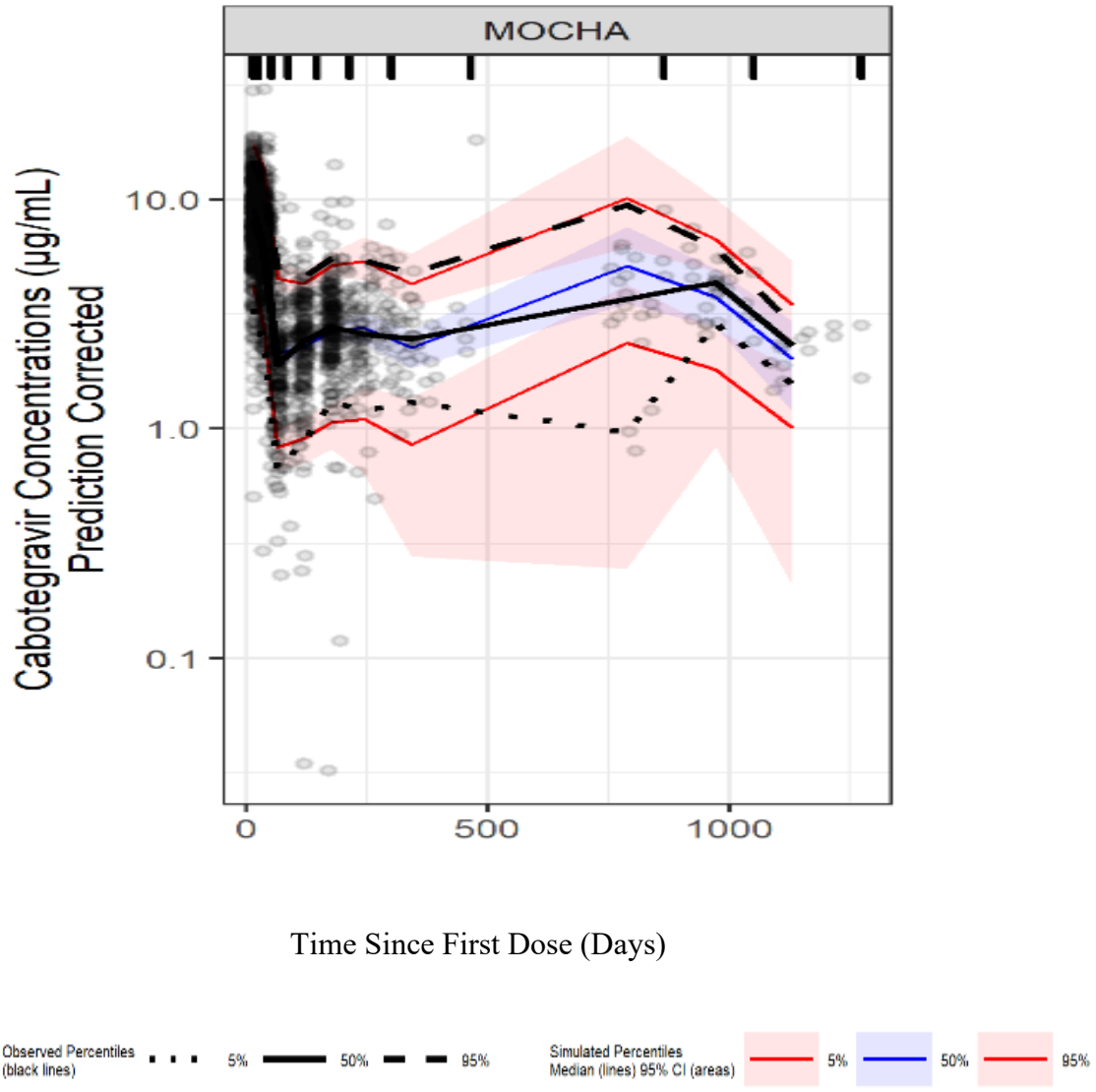
CAB post hoc PK parameters were used to compare exposures in adult participants from historical CAB adult studies with those from adolescent studies. The virtual population was used to assess the performance of the dosing regimens to maintain exposures within the desired window.

The virtual adolescent population was aged 12 to <18 years with body weight of ≥35 kg. These ranges of age and body weight were the same as the inclusion criteria for age and body weight in Study 208580. The male-to-female ratio was approximately 1 in each age group (year). The number of virtual participants was chosen to ensure >500 virtual participants in each of the 5-kg weight band increments (e.g., 35 to <40 kg and 40 to <45 kg) for each age group (year).

The final PopPK model was able to predict the observed median and the 5th and 95th percentiles of observed CAB concentrations. The median concentration was fully captured throughout the profile for CAB concentrations. The observed median was slightly outside the predicted bands for short segments of the time course but generally predicted well for adolescent participants.

In the current analysis, weight and smoking status were significant determinants of CL/F, and only weight was a determinant of V2/F, V3/F, and Q/F. Needle length, female sex, splitting of the injection, and time-varying BMI were significant determinants of KA2. No additional covariates were identified as compared to the tNDA PopPK model. The findings were consistent with the conclusion of the previous analyses in healthy and HIV infected adult participants [Document No. 2018N384611; Document No. 2019N421460].

The pcVPC results suggest that the model adequately described the data between the observations and model predictions across all percentiles (Figure 5 pcVPC of the final CAB PopPK model).



Notes: The open circles represent the observed data from Study 208580. The solid black lines represent the median of the observed data, and the dashed lines represent the 5th and 95th percentiles of the observed data. The blue solid lines represent the median of the simulated data, and the pink solid lines represent the 5th and 95th percentiles of the simulated data. The blue and pink shaded areas represent the 95% CI of the median and the 5th and 95th percentiles of the simulated data, respectively.

Figure 5 pcVPC of the final CAB PopPK model

Parameters estimates for final model are shown in *Table 9* below.

Table 9: Population PK modeling, parameters for final model

Parameter	[redacted]	%RSE[a]	95% CI (SIR)	IIV (variance)	95% CI (SIR)	IIV (%CV)[b]	%RSE of IIV[a,c]	Shrinkage (%)	[redacted]
CL/F (L/h)	[redacted]	0.829	[0.143, 0.147]	0.0549	[0.0509, 0.0603]	23.8	2.43	10.8	[redacted]
V2/F (L)	[redacted]	2.01	[4.85, 5.43]	0.0354	[0.0225, 0.0501]	19.0	10.9	30.6	[redacted]
KA1 (1/h)	[redacted]	4.54	[1.21, 1.54]	0.768	[0.550, 0.993]	108	5.38	69.4	
Q/F (L/h)	[redacted]	6.91	[0.375, 0.603]						[redacted]
V3/F (L)	[redacted]	5.09	[2.06, 2.63]						[redacted]
KA2 (1/h)	[redacted]	2.24	[0.000700, 0.000762]	0.327	[0.302, 0.357]	62.2	2.29	16.6	[redacted]
F1	[redacted]	0.912	[0.734, 0.755]	0.0355	[0.0298, 0.0412]	19.0	4.89	36.8	
Additive error (µg/mL)	[redacted]	19.4	[0.0277, 0.0357]					6.80	
Proportional error	[redacted]	1.06	[0.274, 0.280]						
BWT on CL/F and Q/F	[redacted]	4.03	[0.629, 0.726]						
BWT on V2/F and V3/F	[redacted]	5.73	[0.672, 0.831]						
Current smoking status on CL/F	[redacted]	8.44	[0.162, 0.225]						
BMI on KA2	[redacted]	10.8	[-0.941, -0.698]						
NDL on KA2	[redacted]	30.4	[0.371, 0.718]						
Gender (if female) on KA2	[redacted]	3.72	[-0.541, -0.471]						
Split injection on KA2	[redacted]	13.5	[0.432, 0.561]						
Covariance									
Parameter	[redacted]	**%RSE**	**95% CI (SIR)**						
Covariance (KA2, CL/F)	[redacted]	71.1	[-0.00172, 0.0163]						
Covariance (KA2, V2/F)	[redacted]	29.4	[0.0160, 0.0507]						
Covariance (CL/F, V2/F)	[redacted]	13.1	[0.0251, 0.0406]						

Source: GOF_Run11.Rmd → GOF_Run11.html.

a Obtained from the $COV step.

b IIV in %CV calculated using $\sqrt{e^{\omega^2} - 1} \times 100$.

c %RSE of IIV expressed on approximate standard deviation scale calculated using (SE/ω²)/2 ×100.

Notes: Parameters are expressed as median (95% CI). The reference population for CL/F is a 74.8 kg non-smoker participant. The reference population for V2/F, V3/F, and Q/F is a 74.8 kg participant. The reference population for KA2 is a male participant (BMI=24.8 kg/m²) using an NDL of 1.5 inches with unsplit injection.

MOCHA=Study 208580; HPTN 083-01=Study 213002; HPTN 084-01=Study 213003.

Comparison of CAB exposure between adolescents and adults

CAB post hoc exposure estimates were compared between the adolescent participants in the adolescent studies and the adult participants from historical CAB studies (Table 10 and Figure 6). Based on the simulated values from individual post hoc estimates, CAB exposure in adolescent participants was similar to that in adult participants. The exposures in the adolescent participants were generally within or slightly higher than the exposure range observed in the adult participants across all dosing phases.

Table 10 Summary of CAB post hoc exposure metrics by population

Dosing phase		Adult participants			Adolescent participants from Study 208580 (MOCHA) only		
		AUC0-τ,ss (µg·h/mL)	**Cmax,ss (µg/mL)**	**Cτ,ss (µg/mL)**	**AUC0-τ,ss (µg·h/mL)**	**Cmax,ss (µg/mL)**	**Cτ,ss (µg/mL)**
OLI	N	1647	1647	1647	147	147	147
	Geomean [95% CI]	142 [140, 144]	7.59 [7.49, 7.69]	4.43 [4.37, 4.50]	195 [187, 204]	10.3 [9.92, 10.8]	6.14 [5.87, 6.43]
	%CV	87.1	83.7	93.5	83.0	81.8	87.0
	Median [min, max]	142 [49.5, 452]	7.59 [2.96, 22.6]	4.46 [1.16, 15.9]	189 [85.8, 523]	9.98 [4.15, 26.7]	5.92 [2.69, 17.7]
	Percentiles						
	5th	89.2	4.92	2.61	135	7.11	4.01
	25th	118	6.37	3.61	168	8.87	5.18
	50th	142	7.59	4.46	189	9.98	5.92
	75th	172	9.05	5.50	222	11.7	7.00
	95th	222	11.6	7.23	306	15.7	10.0
Initial injection	Geomean [95% CI]	1577 [1545, 1609]	7.60 [7.50, 7.70]	1.45 [1.42, 1.48]	2138 [2004, 2281]	10.4 [10.0, 10.8]	1.95 [1.82, 2.08]
	%CV	116	83.5	120	111	80.6	116
	Median [min, max]	1609 [223, 5739]	7.59 [2.97, 22.6]	1.54 [0.164, 5.25]	2155 [792, 4981]	10.1 [4.64, 26.7]	2.04 [0.598, 4.58]
	Percentiles						
	5th	773	4.93	0.654	1104	7.42	0.951
	25th	1204	6.37	1.11	1620	8.98	1.46
	50th	1609	7.59	1.54	2155	10.1	2.04
	75th	2109	9.10	1.97	2782	11.9	2.61
	95th	3158	11.6	2.72	4342	15.7	3.62
Q4W maintenance regimen	Geomean [95% CI]	2395 [2365, 2426]	4.09 [4.04, 4.15]	2.89 [2.85, 2.93]	3376 [3255, 3501]	5.74 [5.52, 5.97]	4.09 [3.92, 4.28]
	%CV	83.3	86.4	86.3	75.5	78.6	85.0

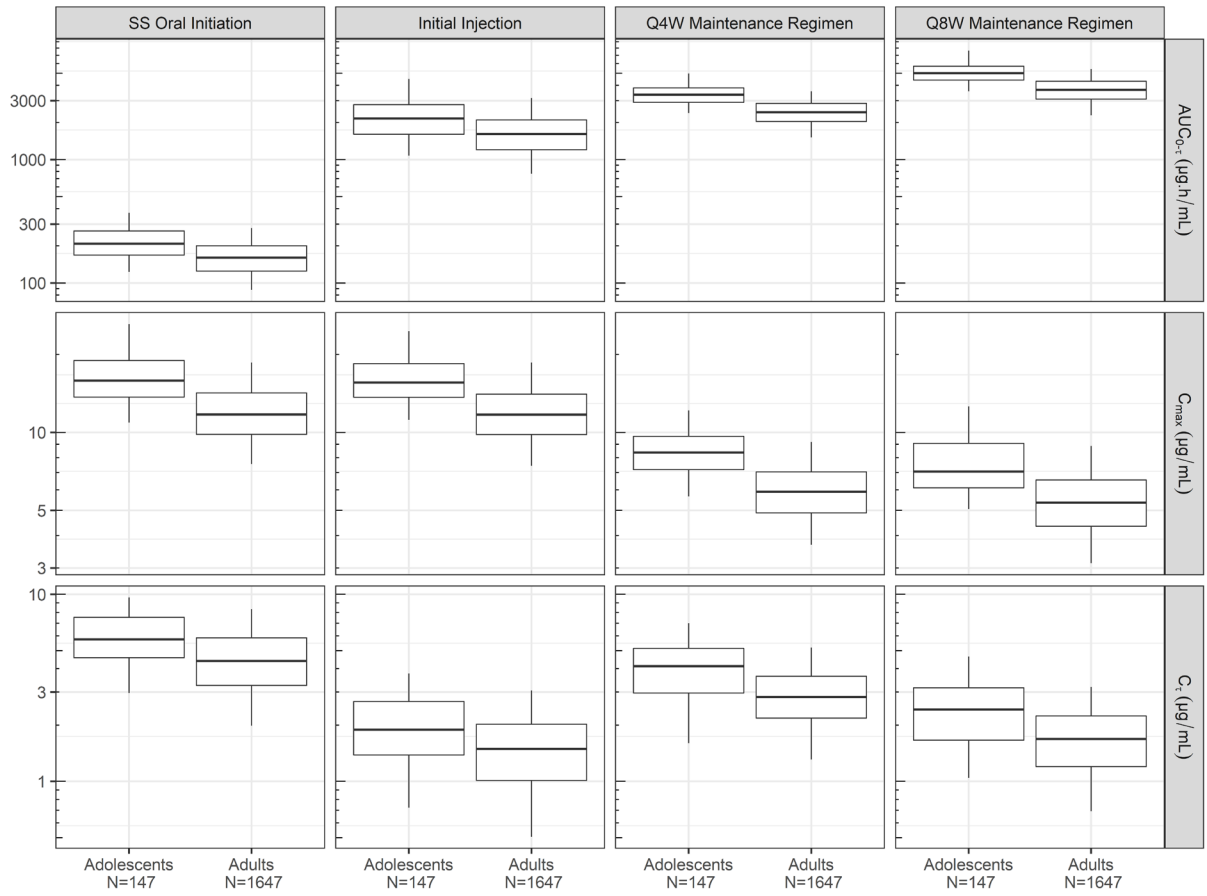
Dosing phase		Adult participants			Adolescent participants from Study 208580 (MOCHA) only		
		AUC0-τ,ss (µg·h/mL)	**Cmax,ss (µg/mL)**	**Cτ,ss (µg/mL)**	**AUC0-τ,ss (µg·h/mL)**	**Cmax,ss (µg/mL)**	**Cτ,ss (µg/mL)**
(11th LA IM injection)	Median [min, max]	2427 [619, 7390]	4.15 [0.947, 12.3]	2.93 [0.895, 9.10]	3336 [1932, 7331]	5.69 [2.98, 11.9]	4.09 [1.34, 9.41]
	Percentiles						
	5th	1510	2.54	1.80	2333	3.90	2.69
	25th	2053	3.48	2.42	2937	4.91	3.56
	50th	2427	4.15	2.93	3336	5.69	4.09
	75th	2846	4.91	3.47	3752	6.68	4.75
	95th	3562	6.22	4.44	5001	8.89	6.42
Q8W maintenance regimen (6th LA IM injection)	Geomean [95% CI]	3625 [3580, 3672]	3.72 [3.66, 3.78]	1.67 [1.64, 1.70]	5116 [4935, 5305]	5.18 [4.95, 5.43]	2.38 [2.22, 2.55]
	%CV	82.9	94.4	105	75.1	87.9	117
	Median [min, max]	3673 [961, 11 131]	3.77 [0.759, 11.1]	1.72 [0.203, 5.23]	5084 [2986, 11 078]	5.12 [2.42, 12.0]	2.52 [0.160, 5.75]
	Percentiles						
	5th	2282	2.20	0.858	3594	3.26	1.17
	25th	3106	3.09	1.34	4441	4.28	1.95
	50th	3673	3.77	1.72	5084	5.12	2.52
	75th	4300	4.54	2.15	5724	6.08	3.15
	95th	5384	6.23	2.87	7576	8.78	4.07

Notes: Adolescent participants consist of participants from Study 208580 only. AUC0-τ and Cτ, τ is different for different regimens. For time-varying BMI (designated as PBMI in the dataset), BMI at time = 0 was used for simulations. Post hoc simulations were performed without residual variability. Numeric values are presented as 3 significant figures.

[redacted].

The standard Q4W and Q8W dosing regimens were simulated with OLI: OLI of CAB QD for 4 weeks, followed by 600 mg CAB LA IM 2 hour after the last oral dose, followed by CAB LA IM 400 mg Q4W or 600 mg Q8W thereafter.

a. The Cmax following the first CAB LA injection is likely determined by the last oral dose instead of the initiation LA dose.



Notes: For box plots, the horizontal center solid line in each box represents the median value, the box represents the 25th to 75th percentiles, and the whiskers represent the 5th and 95th percentiles. Only adolescent participants from Study 208580 are included in the figure. For AUC0-τ and Cτ, τ is different for different regimens.

Figure 6 Comparison of CAB post hoc exposure in adult and adolescent participants

Predicted CAB exposure following CAB LA Q4W and Q8W dosing in adolescents

Both CAB Q4W and Q8W dosing regimens were predicted to result in adequate CAB plasma concentrations in adolescents (i.e., predicted CAB trough concentrations exceeded the efficacy threshold of 0.45 µg/mL in ≥95% of the virtual adolescent population) and the median predicted CAB concentrations were below the safety threshold of 22.5 µg/mL (geometric mean Cmax observed in the TQT study at the supratherapeutic dose of oral CAB at 150 mg) throughout the CAB LA Q4W and Q8W dosing course.

The scope of simulations was as follows:

- Q4W versus Q8W dosing regimen:

Scenario 1 compared the PK profiles of CAB in adult and adolescent participants following treatment with the standard Q4W (scenario 1a) and Q8W (scenario 1b) dosing regimens.

Scenario 2: Simulation of the Q4W dosing regimen +1 week (i.e., Q5W) up to steady state and simulation of the Q8W dosing regimen +1 week (i.e., Q9W) up to steady state without OLI (scenario 2a and 2b, respectively).

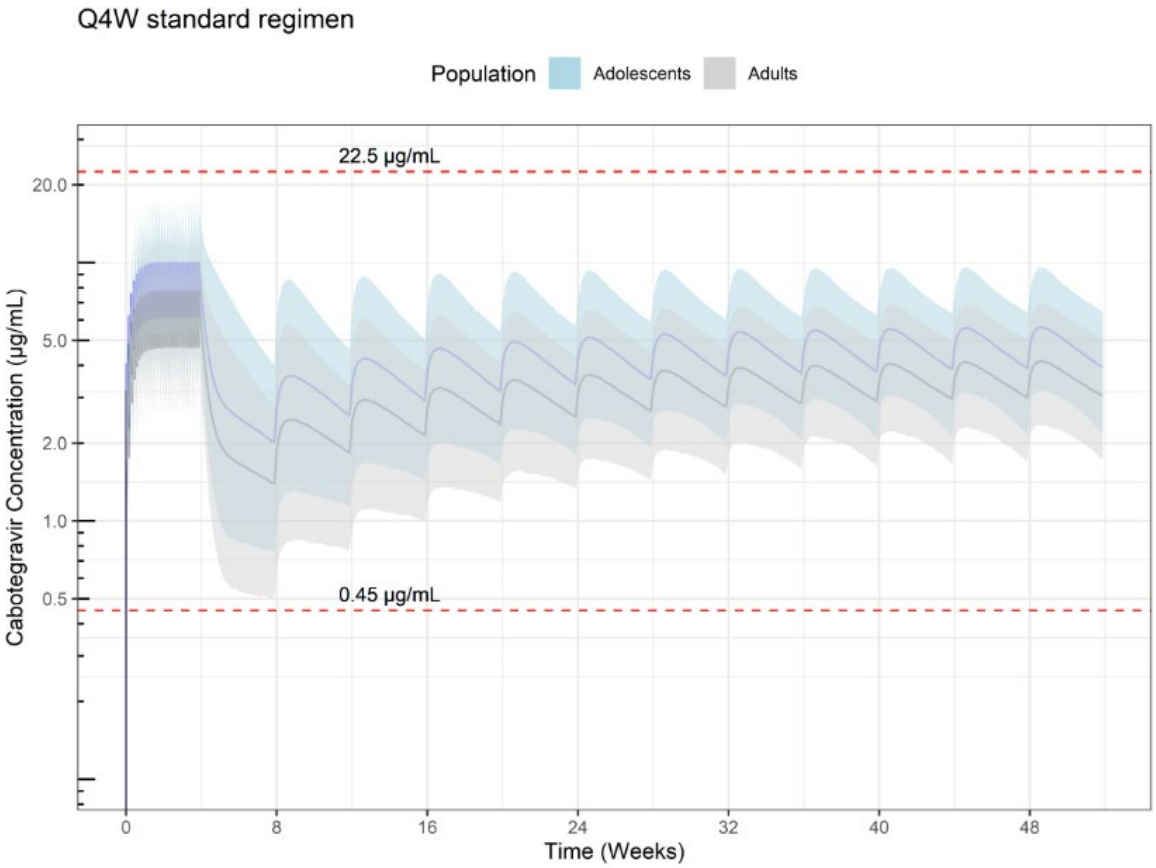
- Q4W or Q8W regimen without OLI:

Scenario 3 compared the PK profiles of CAB in adult and adolescent participants following treatment with Q4W (scenario 3a) and Q8W (scenario 3b) dosing regimens without 28-day OLI.

Q4W versus Q8W dosing regimen

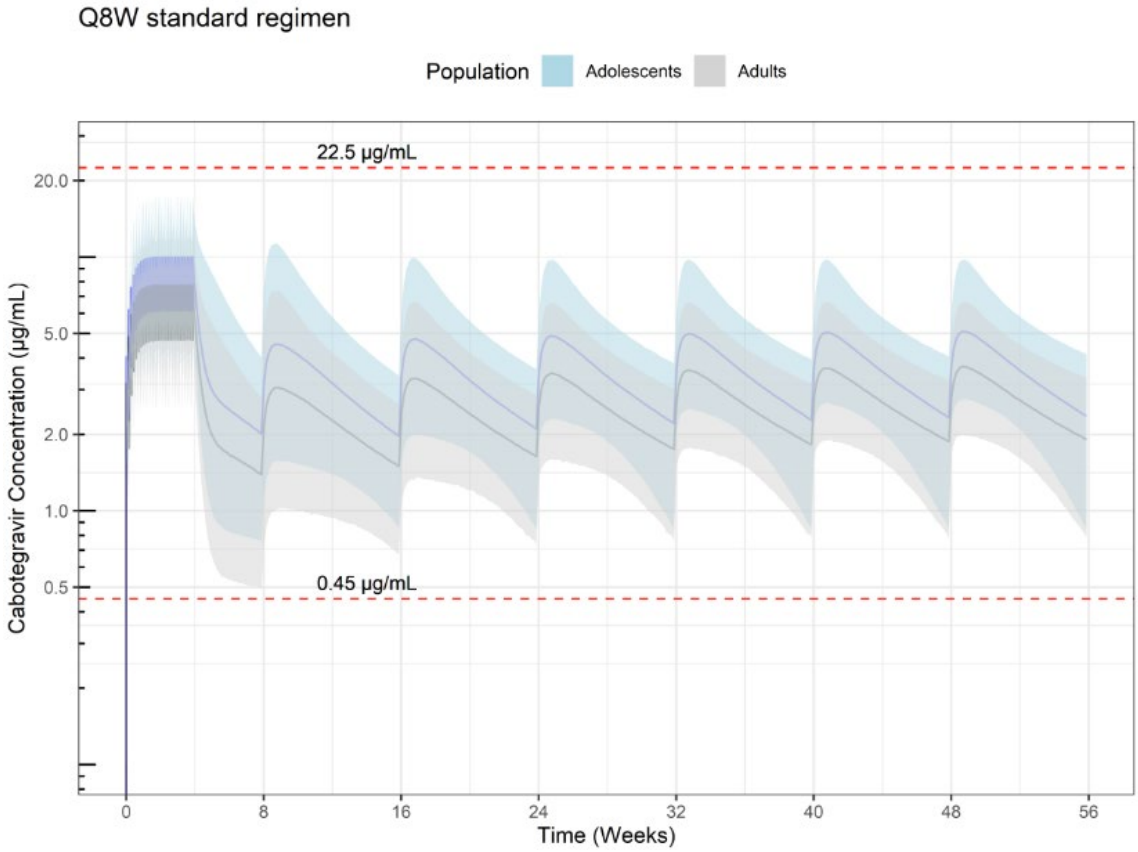
In Scenario 1a and Scenario 1b, the PK profiles of CAB in adult and adolescent participants were compared following treatment with the proposed standard Q4W and Q8W dosing regimens, respectively. The CAB PK profiles across the entire treatment period for the Q4W dosing regimen and the Q8W dosing regimen by population are shown in Figure 7 and Figure 8, respectively. CAB concentrations were predicted to remain above the Phase 3 efficacy threshold of 0.45 µg/mL and below the safety threshold of 22.5 µg/mL in ≥95% of the virtual adolescent population throughout the CAB LA IM Q4W and Q8W dosing course.

Although CAB exposure was predicted to be slightly higher in adolescent participants than adult participants following both CAB Q4W and Q8W regimens, median (90% PI) predicted CAB concentrations for Cmax were below the safety threshold of 22.5 µg/mL for both adolescent and adult participants. For Cmax,ss during the IM dosing phase, the median (90% PI) predicted CAB concentrations for adolescent participants were 5.82 (3.33, 9.86) µg/mL for the CAB Q4W regimen and 5.27 (2.88, 10.1) µg/mL for the CAB Q8W regimen. The median (90% PI) predicted CAB concentrations for adult participants for Cmax were 4.31 (2.47, 7.17) µg/mL for the CAB Q4W regimen and 3.83 (2.10, 6.88 µg/mL) for the CAB Q8W regimen for adult participants.



Notes: The red dashed lines represent the efficacy (0.45 µg/mL) and safety thresholds (22.5 µg/mL). The shaded areas represent the 90% PI. The solid lines represent the simulated median CAB concentrations.

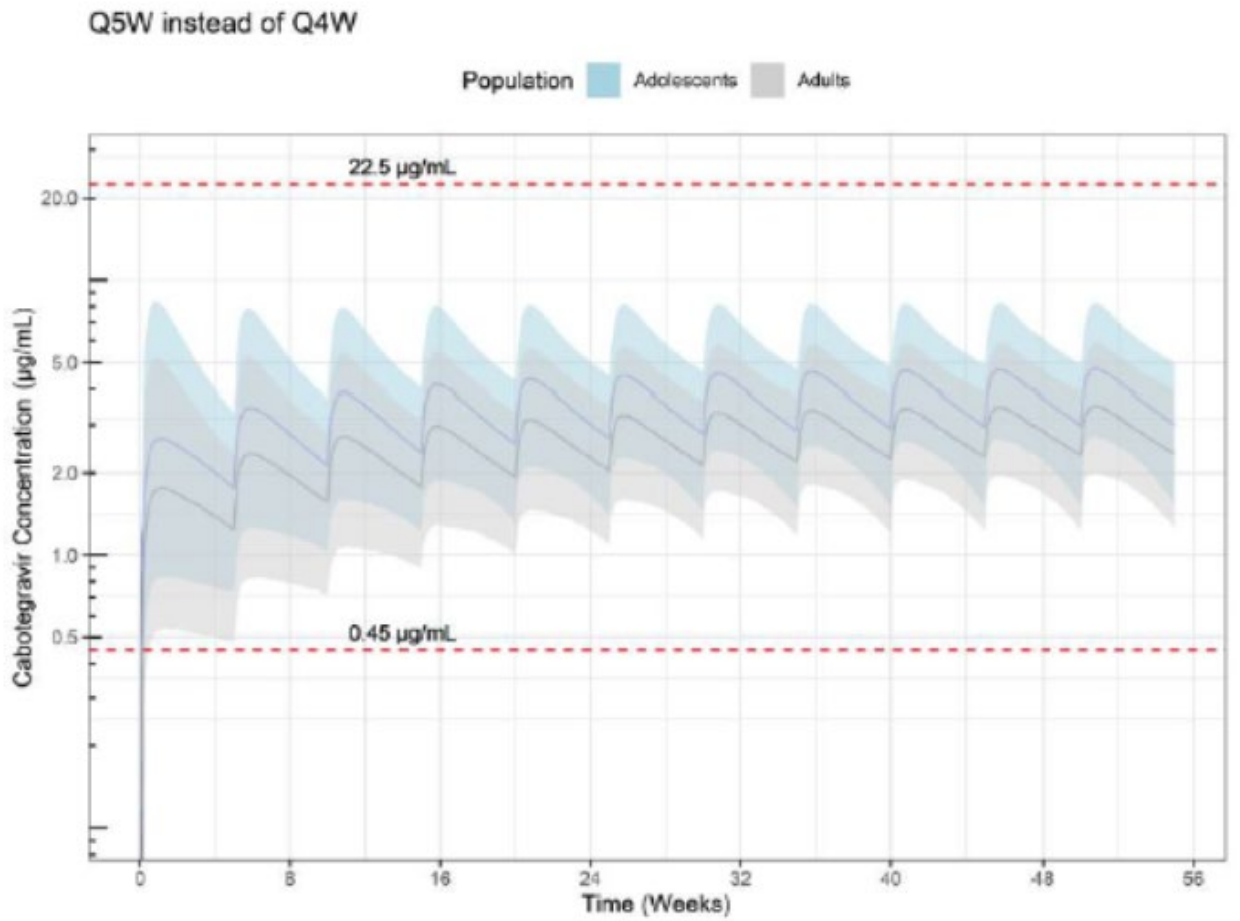
Figure 7 CAB concentration-versus-time following Q4W dosing by population (Scenario 1a)



Notes: The red dashed lines represent the efficacy (0.45 µg/mL) and safety thresholds (22.5 µg/mL). The shaded areas represent the 90% PI. The solid lines represent the simulated median CAB concentrations.

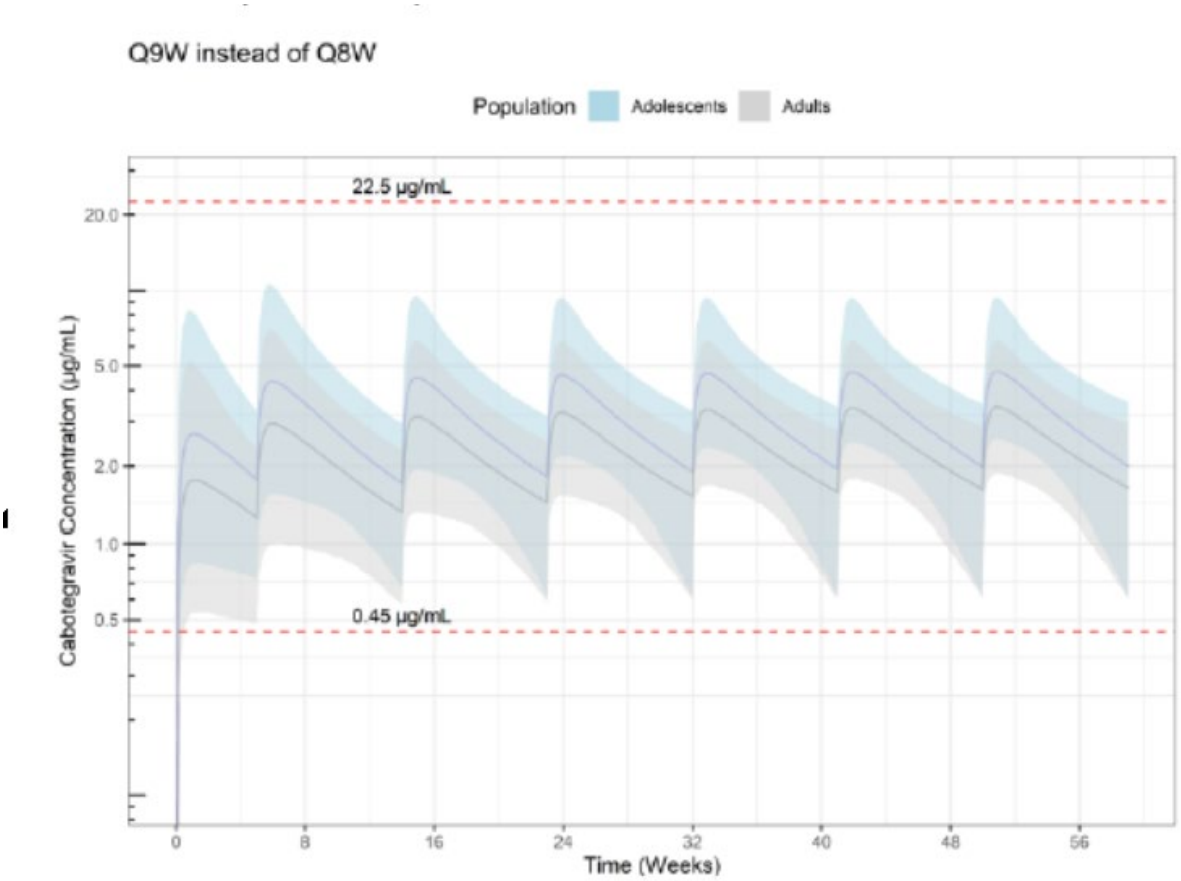
Figure 8 CAB concentration-versus-time following Q8W dosing regimen by population (Scenario 1b)

In Scenario 2a and Scenario 2b (Figure 9 and Figure 10 below), the PK profiles of CAB in adult and adolescent participants were compared following treatment with CAB + RPV Q4W/ Q8W +1 week up to steady state (i.e., Q5W and Q9W) without OLI, respectively. The CAB PK profiles across the entire treatment period for the Q5W dosing regimen and the Q9W dosing regimen by population are shown in the CAB PopPK report. Simulated exposures are presented in the CAB PopPK Report. Despite an injection interval of Q4W/ Q8W +1 week, even without OLI, CAB concentrations were predicted to stay above the efficacy threshold of 0.45 µg/mL in ≥95% of the virtual adolescent population throughout the dosing course following CAB Q5W and Q9W dosing regimens, and the median predicted CAB concentrations were below the safety threshold of 22.5 µg/mL.



Source: cab-ped-simulations-run11-ver2.Rmd → cab-ped-simulations-run11-ver1-scen-1-6.html
Notes: The red dashed lines represent the efficacy (0.45 µg/mL) and safety (22.5 µg/mL) thresholds. The shaded areas represent the 90% PI. The solid lines represent the simulated median CAB concentrations.
Abbreviations: CAB=cabotegravir; PI=prediction interval; Q4W=every 4 weeks; Q5W=every 5 weeks

Figure 9 CAB concentration versus time following Q5W dosing by population (Scenario 2a)



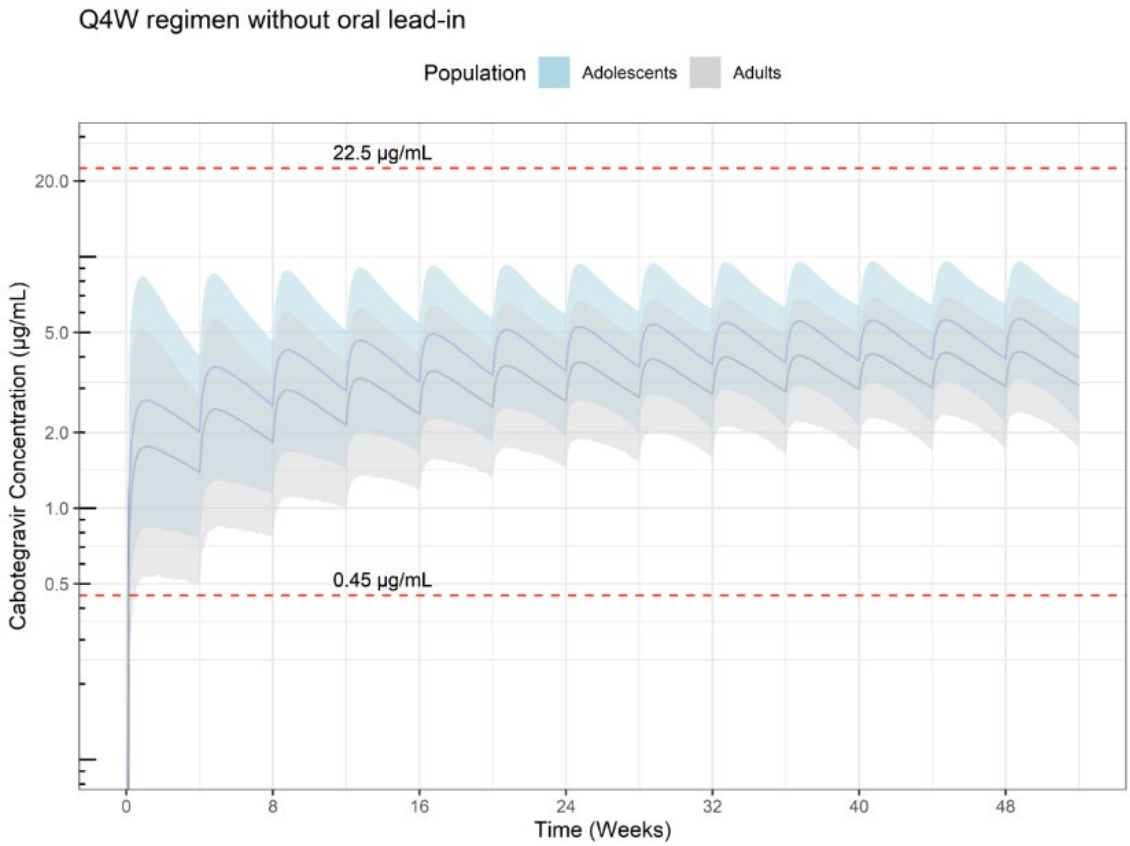
Source: cab-ped-simulations-run11-ver2.Rmd → cab-ped-simulations-run11-ver1-scen-1-6.html
Notes: The red dashed lines represent the efficacy (0.45 µg/mL) and safety (22.5 µg/mL) thresholds. The shaded areas represent the 90% PI. The solid lines represent the simulated median CAB concentrations.
Abbreviations: CAB=cabotegravir; PI=prediction interval; Q8W=every 8 weeks; Q9W=every 9 weeks

Figure 10 CAB concentration versus time following Q9W dosing by population (Scenario 2b)

Q4W or Q8W dosing regimen without OLI

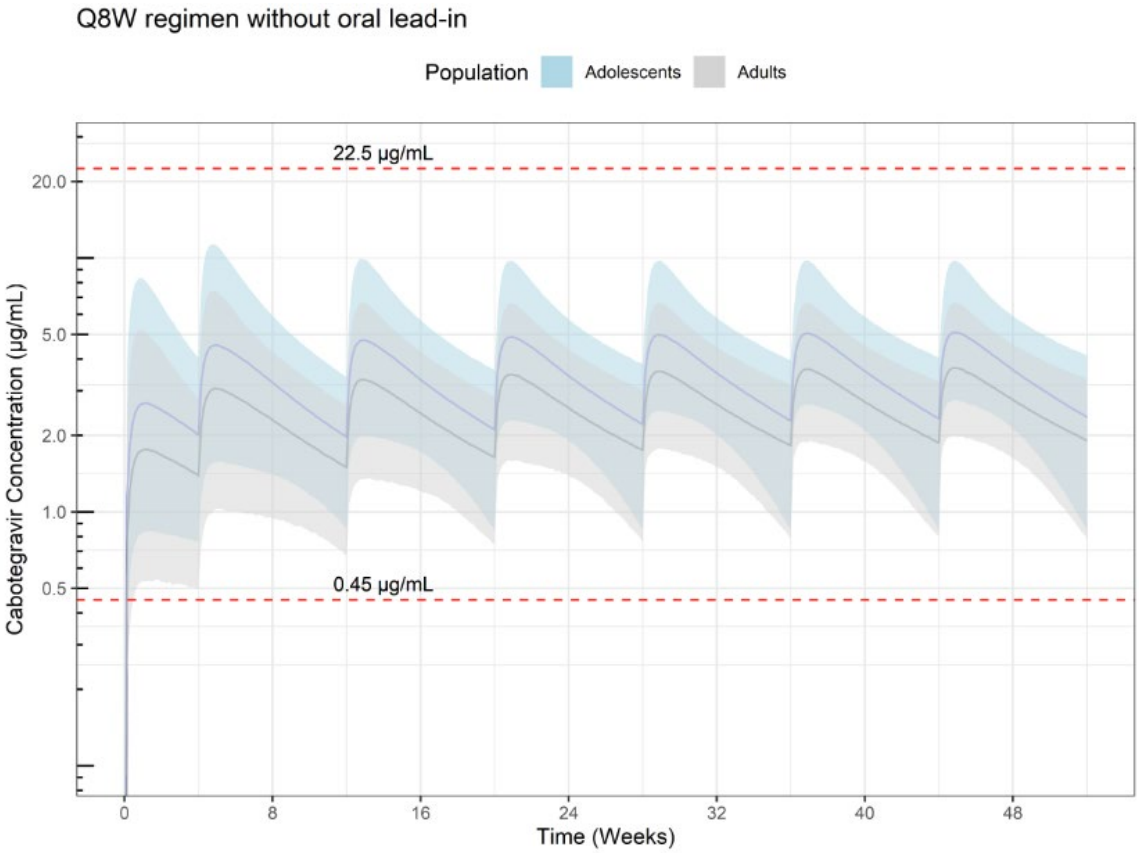
In Scenarios 3a and 3b, the PK profiles of CAB in adult and adolescent participants were compared following treatment with the standard Q4W (Scenario 1a; Figure 7) and Q8W (Scenario 1b; Figure 8) dosing regimens without a 28-day OLI, respectively. The CAB PK profiles across the entire treatment period for the Q4W dosing regimen and the Q8W dosing regimen by population are shown in

and Figure 12, respectively. Simulated exposures are summarized in the CAB PopPK Report. PK profiles without OLI showed that the OLI had a limited impact on the exposure throughout the dosing period. In both scenarios, CAB concentrations were predicted to stay above the efficacy threshold of 0.45 µg/mL in ≥95% of the virtual adolescent population throughout the dosing course following CAB Q4W and Q8W dosing regimens, and the median predicted CAB concentrations were below the safety threshold of 22.5 µg/mL.



Source: Document No. TMF-16443596 Figure 27.
Notes: The red dashed lines represent the efficacy (0.45 µg/mL) and safety (22.5 µg/mL) thresholds. The shaded areas represent the 90% PI. The solid lines represent the simulated median CAB concentrations.

Figure 11 CAB concentration-versus-time following Q4W dosing without OLI by population (Scenario 3a)



Source: Document No. TMF-16443596 Figure 28.
Notes: The red dashed lines represent the efficacy (0.45 µg/mL) and safety (22.5 µg/mL) thresholds. The shaded areas represent the 90% PI. The solid lines represent the simulated median CAB concentrations.

Figure 12 CAB concentration-versus-time following Q8W dosing without OLI by population (Scenario 3b)

The MAH made the overall conclusions:

• The re-estimated model described the adolescent PK data adequately.

• The addition of adolescent data to the adult model-building dataset had a minimal impact on the primary PK parameter estimates and the covariate relationship (%change <20%).

• No new covariates were identified or added to the updated PopPK model (with allometric exponents estimated).

• CAB exposure was similar between the adolescents from Studies 208580 (MOCHA), 213002 (HPTN 083-01), and 213003 (HPTN 084-01) and adult participants from historical CAB studies.

• No dose adjustment was recommended for adolescent participants (12 to <18 years of age) weighing at least 35 kg in accordance with the current label for CAB.

2.3.3. Pharmacodynamics

Exposure-efficacy observation

The evaluated CAB dosing regimens in adolescents achieve exposures that are similar to those in adults and are expected to result in similar efficacy as observed across multiple adult clinical studies. This expectation was supported by the data from full Cohort 1 and Cohort 2 Week 24 of Study 208580 in adolescents. In Cohort 1, all participants with a viral load assessment at Week 16 remained virologically suppressed (plasma HIV-1 RNA value <50 c/mL); in Cohort 2, 98.6% of participants with a viral load assessment at Week 24 remained virologically suppressed. Through the full Cohort 1 analysis and the Cohort 2 Week 24 analysis, no participant met CVF while receiving CAB.

2.3.4. PK/PD modelling

Exploratory PK/PD analyses performed on data from the adult CAB + RPV Phase 3 studies (201584, 201585, and 207966) did not identify a relationship between CAB plasma concentrations and safety parameters of interest, including QTc changes, ALT changes from Baseline, or changes in total bilirubin.

2.3.5. Discussion on clinical pharmacology

The study 208580 provided additional pharmacokinetic datapoints for adolescents above 12 years old and above 35 kg. The bioanalytical method was provided and is sufficiently documented, and the study plan for PK is considered adequate.

The MAH provided additional information and justification regarding the negative Tmax in cohort 1C Q8W. The negative Tmax comes from the delay between the IM LA injection and the oral administration, the Tmax happening between these administration. It is reasonable to consider that the Tmax is relative to the oral dose and the Cmax observed is consistent with that. The additional information was considered sufficient and no further consequences on PK are expected.

The CHMP considered that the MAH added categories of weight in each cohort and presented the relevant exposure data by weight category, which was reassuring. It was concluded that exposure will be sufficiently similar between weight groups, in particular with Ctau being well within the efficacy range.

The population PK modelling incorporated the results of this study with additional data from the adolescent population. Data included were able to provide a good representativity of age and weight. pcVPCs plots showed good fit between observed and predicted values for median and upper CI bound, less good for the lower CI bound, but overall acceptable. There was a large shrinkage value for absorption parameter ka1.

Adolescent cabotegravir exposure data appeared to be higher than adult exposure data. To substantiate the quantification of the difference between adults and adolescents the MAH presented the adolescent/adult ratios for the PK parameters. When categorised by both adolescent/adult status and weight group, the difference in PK parameters between adolescents and adults becomes negligible; thus this was not a difference of age, but of weight groups.

Simulation was performed for adults and adolescents. Both Q4W and Q8W simulations yielded after a few injections the 0.42 to 22.3 microg/mL concentration ranges that are considered relevant for efficacy and safety, showing these regimens are appropriate for adolescents 12-17 years old above 35 kg.

In the paediatric simulation, all weights were initially pooled together. In response to the request from the CHMP, the MAH performed simulations by weight range, starting with the 35-40 kg range. Simulations by

weight group confirmed that by weight group, PK in adolescents is characterised and similar to exposure in adults.

Results showed similar exposure ranges between adolescents and adults after the initial injection and Q8W regimens at week 48, but higher exposures were predicted with the 4QW at week 48. On the other hand, the figures depicted that adolescents >50kg show exposures in the lower range of the adult exposure range for the same body weight cohort. The CHMP was of the view that this may be related to an impact of obesity on exposure. In order to investigate this issue, the MAH performed a comparative analysis of the exposure between adolescents and adults across different weight cohorts. This confirmed that weight was the main factor and that the proposed flat regimen provides comparable exposures between both populations.

2.3.6. Conclusions on clinical pharmacology

The CHMP concluded that data from the study 208580 together with modelling and simulation on adolescent and adult data indicated that the proposed regimen can result in exposure appropriate for the new adolescent population over 35 kg and over 12 years old. The CHMP noted that while PK parameters from the parenteral administration have been substantiated in adolescents, the same did not apply for the oral tablet. Nevertheless, it was acknowledged that it is intended for a short duration, it corresponds to the adult oral dose and is already approved for PrEP.

2.4. Clinical efficacy

2.4.1. Main study(ies)

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

Study participants

Participants were HIV-1 infected adolescents 12 to <18 years of age weighing ≥ 35 kg, virologically-suppressed (HIV-1 RNA below the lower limit of detection for at least 6 months) on a stable unchanged cART (for at least 3 months). Based on medical records, participants must not have known or suspected resistance to RPV or INSTIs.

Design

This is an ongoing Phase 1/Phase 2 multicentre, open-label, non-comparative study, including two cohorts:

- Cohort 1: participants, in addition to continuing their pre-study cART regimen, will receive either oral CAB or oral RPV (Step 1) followed by either CAB LA or RPV LA (Step 2). Cohort 1 participants will be assigned either CAB (Cohort 1C) or RPV (Cohort 1R) based on their pre-study cART regimen: 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.

- Cohort 2: participants will discontinue their pre-study cART regimen and receive both study products — CAB and RPV — at the doses established in Cohort 1. Cohort 2 participants may enrol per participant's preference to either:

- Cohort 2A to receive both oral CAB + oral RPV (Step 3) followed by both CAB LA + RPV LA (Step 4), or
- Cohort 2B to directly receive both CAB LA + RPV LA (Step 5)

Treatments

- Cohort 1C: participants received 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: participants received 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.

- Cohort 2: participants switched from their current ART to 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 every 8 weeks through Week 96.

Objectives and outcomes/endpoints

Cohort 1: the primary objectives are:

- To confirm the doses for oral CAB followed by injectable CAB LA in adolescents living with HIV who are virologically suppressed by evaluating:

- Safety and multiple-dose PK of oral CAB through Week 4;
- Safety and multiple-dose PK of CAB LA through Week 16.

- 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.

Cohort 2: the primary objective is to assess the safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 24.

Sample size

- Cohort 1: initially, up to 55 participants were to be enrolled to achieve approximately 35 evaluable participants (20 evaluable in Cohort 1C and 15 evaluable in Cohort 1R). The Evaluable Population in each Cohort 1 group was to include at least 4 female adolescents, at least 4 male adolescents, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry. Protocol Version 3.0 amended the sample size such that Cohort 1C was to enroll

approximately 15 to 20 evaluable participants and Cohort 1R was to enroll approximately 15 evaluable participants.

- Cohort 2: Most (or all) of the participants of Cohort 1 were expected to proceed to Cohort 2, where they were to take the full regimen (CAB + RPV), consisting of both products. There was not a restriction (minimum or maximum) on the number of eligible Cohort 1 participants allowed to proceed to Cohort 2, to provide the most flexibility in study design. It was expected that 100 additional participants would need to be enrolled directly into Cohort 2 to achieve an approximate additional 70 evaluable participants receiving the final recommended dose of CAB and RPV.

Statistical methods

- Cohort 1: initially, up to 55 participants were to be enrolled to achieve approximately 35 evaluable participants (20 evaluable in Cohort 1C and 15 evaluable in Cohort 1R). The Evaluable Population in each Cohort 1 group was to include at least 4 female adolescents, at least 4 male adolescents, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry. Protocol Version 3.0 amended the sample size such that Cohort 1C was to enroll approximately 15 to 20 evaluable participants and Cohort 1R was to enroll approximately 15 evaluable participants.

- Cohort 2: Most (or all) of the participants of Cohort 1 were expected to proceed to Cohort 2, where they were to take the full regimen (CAB + RPV), consisting of both products. There was not a restriction (minimum or maximum) on the number of eligible Cohort 1 participants allowed to proceed to Cohort 2, to provide the most flexibility in study design. It was expected that 100 additional participants would need to be enrolled directly into Cohort 2 to achieve an approximate additional 70 evaluable participants receiving the final recommended dose of CAB and RPV.

Results

Participant flow

Cohort 1 : A total of 59 participants were screened in Cohort 1 and 55 participants were enrolled (4 screen failures: 2 subjects for protocol-defined inclusion/exclusion criteria, 1 subject for withdrew consent and 1 subject for other reason).

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.

Table 11 Study and treatment status (Cohort 1 All Treated Population): Study 208580 full Cohort 1 analysis

	Cohort 1C Q4W (N=8) n (%)	Cohort 1C Q8W (N=22) n (%)	Cohort 1C total (N=30) n (%)	Cohort 1R Q4W (N=15) n (%)	Cohort 1R Q8W (N=10) n (%)	Cohort 1R total (N=25) n (%)
Completed Week 4b visit	8 (100.0)	21 (95.5)	29 (96.7)	14 (93.3)	10 (100.0)	24 (96.0)
Received Week 8 injection	8 (100.0)	21 (95.5)	29 (96.7)	13 (86.7)	10 (100.0)	23 (92.0)
Completed Week 16 visit	8 (100.0)	21 (95.5)	29 (96.7)	13 (86.7)	10 (100.0)	23 (92.0)
Cohort 1 study status						
Off study[a]	8 (100.0)	22 (100.0)	30 (100.0)	15 (100.0)	10 (100.0)	25 (100.0)
On study	0	0	0	0	0	0
Prematurely discontinued study						
Adverse event	0	0	0	1 (6.7)	0	1 (4.0)
Lost to follow-up	1 (12.5)	0	1 (3.3)	1 (6.7)	0	1 (4.0)
Other	0	0	0	1 (6.7)	0	1 (4.0)
Withdrawal of consent	0	1 (4.5)	1 (3.3)	0	0	0
Cohort 1 treatment status						
Off treatment	8 (100.0)	22 (100.0)	30 (100.0)	15 (100.0)	10 (100.0)	25 (100.0)
On treatment	0	0	0	0	0	0
Prematurely discontinued study treatment						
Adverse event	0	0	0	1 (6.7)	0	1 (4.0)
Other	0	0	0	1 (6.7)	0	1 (4.0)
Withdrawal of consent	0	1 (4.5)	1 (3.3)	0	0	0

Source: Table 1.5

a. 'Off study' refers to Cohort 1 study status; 44 participants considered 'off study' in Cohort 1 subsequently enrolled in Cohort 2.

Cohort 2 : A total of 159 participants were screened in Cohort 2 and 144 participants were enrolled (15 screen failures: 14 participants for protocol-defined inclusion/exclusion criteria and 1 participant for withdrew consent). 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.

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.

Table 12 Study and treatment status (Cohort 2 All Treated Population):

Study 208580 Cohort 2 Week 24 analysis

	Cohort 2 total (N=144) n (%)
Completed Week 4b visit	142 (98.6)
Completed Week 24 visit	141 (97.9)
Completed Week 48 visit	116 (80.6)
Cohort 2 study status	
Off study	2 (1.4)
On study	142 (98.6)
Prematurely discontinued study	
Noncompliance with study drug	1 (0.7)
Protocol deviation	1 (0.7)
Cohort 2 treatment status	
Off treatment	3 (2.1)
On treatment	141 (97.9)
Prematurely discontinued study treatment	
Noncompliance with study drug	1 (0.7)
Pregnancy	1 (0.7)
Protocol deviation	1 (0.7)

Recruitment

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).

Conduct of the study

Amendments:

The original protocol has been amended 3 times. The main clinically relevant protocol amendment was to implement Q8W dosing in the injection phases of Cohort 1 and Cohort 2 (Protocol Version 3.0). Therefore, Cohort 1 participants enrolled under Protocol Version 2.0 received Q4W LA injections (Protocol Version 1.0 was never implemented). Cohort 1 and Cohort 2 participants enrolled under Protocol Version 3.0 and treated under Protocol Version 3.0 or Protocol Version 4.0 received Q8W LA injections. No participants were enrolled under Protocol Version 4.0.

Protocol deviations:

- Cohort 1: 42 participants had protocol deviations. The most common deviation types were other, informed assent/consent process, and assessment deviations, reported for 30 (71.4%), 15 (35.7%), and 15 (35.7%) of the 42 participants with protocol deviations, respectively. 1 participant (Cohort 1R) had a protocol deviation of study product dispensing error; the participant received 900 mg of study drug instead of 600 mg at Week 8. 2 participants had deviations relating to inclusion/exclusion criteria; both were due to participants failing to meet the requirements relating to the current cART regimen.

- Cohort 2: 81 participants had protocol deviations. The most common deviation types were other, specimen handling, and informed assent/consent process, reported for 69 (85.2%), 33 (40.7%), and 25 (30.9%) of the 81 participants with protocol deviations, respectively. 2 participants had a study product management deviation; the 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, or at Week 16 and Week 24 (of note, this participant received additional injections of CAB LA 200 mg and RPV LA 300 mg 10 days after the initial Week 24 dosing). 1 participant had a deviation relating to inclusion/exclusion criteria; the participant failed to meet the requirements relating to the current cART regimen. 2 participants had deviations relating to use of disallowed medications; the participants continued their pre-study ARV medications, resulting in exposure to additional medications.

No other GCP noncompliance issues were identified by monitoring or audit.

Interim analyses:

The first interim analysis was conducted under Protocol Version 2.0 Letter of Amendment 1 dated 20 May 2020. After 7 evaluable participants in Cohort 1C and 7 evaluable participants in Cohort 1R completed the Week 16 visit, a planned interim analysis of safety and PK data was performed. The results of this analysis supported the selection of the doses to be used in Cohort 2.

The second interim analysis was conducted to support regulatory submission under Protocol Version 2.0, when all currently enrolled participants in Cohort 1 (n=8 for Cohort 1C and n=15 for Cohort 1R) completed the Week 16 visit. Data available as of 10 September 2020 were included in the interim analysis. The observed PK and safety data from the interim analysis supported the use of the adult CAB + RPV dosing regimens in adolescents.

A third interim analysis was planned once approximately 15 to 20 Cohort 1C participants and approximately 15 Cohort 1R participants who could contribute to the dose-finding algorithm had enrolled,

and 80% of these participants had completed the Step 2 Week 8 visit. The analysis was conducted on data collected from 55 participants enrolled in Cohort 1 (n=30 for Cohort 1C and n=25 for Cohort 1R). Data available as of 17 February 2022 were included in Protocol Version 3.0 Interim Analysis 2 (analysis for SMC). The observed PK and safety data from the interim analysis supported the opening of Cohort 2 accrual to study-naive participants.

Baseline data

Table 13 Cohort 1C:

		Cohort 1C (N=30) n (%)
Age (years)	n	30
	Mean (SD)	14.9 (1.53)
	Median (Q1,Q3)	15.0 (14.0, 16.0)
	Min, Max	12, 17
Age (years) (n [%])	12	1 (3.3)
	13	5 (16.7)
	14	7 (23.3)
	15	6 (20.0)
	16	4 (13.3)
	17	7 (23.3)
Sex at Birth (n [%])	Female	14 (46.7)
	Male	16 (53.3)
Race (n [%])	Asian	9 (30.0)
	Black or African American	21 (70.0)
	White	0
Ethnicity (n [%])	Not Hispanic or Latino	30 (100.0)
	Hispanic or Latino	0
Height (cm)	n	30
	Mean (SD)	159.41 (10.844)
	Median (Q1,Q3)	159.75 (150.50, 166.00)
	Min, Max	137.0, 185.3
Weight (kg)	n	30
	Mean (SD)	52.663 (11.6940)
	Median (Q1,Q3)	47.850 (43.600, 60.000)
	Min, Max	39.40, 84.00
BMI (kg/m^2)	n	30
	Mean (SD)	20.648 (3.6622)
	Median (Q1,Q3)	19.640 (18.110, 21.480)
	Min, Max	16.41, 30.48
Country (n [%])	Botswana	0
	Thailand	8 (26.7)
	US	8 (26.7)
	South Africa	14 (46.7)
Baseline CD4 cell counts (cells/mm^3)	n	30
	Mean (SD)	743.9 (226.20)
	Median (Q1,Q3)	701.0 (586.0, 924.0)
	Min, Max	397, 1206
Baseline CD4 cell counts categories (cells/mm^3) (n [%])	Missing	0
	<350	0
	350 to <500	4 (13.3)
	500 to <750	15 (50.0)
	≥750	11 (36.7)

83.3% of participants reported at least 1 current or past medical condition.

The most commonly reported classes of prior ARV therapy were NRTIs (83.3% of participants), NNRTIs (50.0% of participants), and PIs (33.3% of participants).

In combination to CAB, all participants were receiving 2 NRTIs, 13 (43.3%) participants were receiving an NNRTI, and 17 (56.7%) were receiving at least 1 PI (1 of whom [3.3%] was also receiving cobicistat). The most common cART regimens were Lopinavir, Ritonavir, Abacavir, Lamivudine (40.0% of participants) and Efavirenz, Emtricitabine, Tenofovir Disoproxil (20.0% of participants).

63.3% of enrolled participants took at least 1 concomitant non-ARV medication while receiving study drug. The most commonly used non-ARV concomitant medications were ibuprofen (20.0%), paracetamol (13.3%), and tozinameran (26.7%).

Table 14 Cohort 2:

		Cohort 2 total (N=144) n (%)
Age (years)	n	144
	Mean (SD)	14.9 (1.57)
	Median (Q1,Q3)	15.0 (14.0, 16.0)
	Min, Max	12, 17
Age (years) (n [%])	12	11 (7.6)
	13	23 (16.0)
	14	19 (13.2)
	15	35 (24.3)
	16	27 (18.8)
	17	29 (20.1)
Sex at Birth (n [%])	Female	74 (51.4)
	Male	70 (48.6)
Race (n [%])	Asian	36 (25.0)
	Black or African American	106 (73.6)
	White	2 (1.4)
Ethnicity (n [%])	Not Hispanic or Latino	141 (97.9)
	Hispanic or Latino	3 (2.1)
Height (cm)	n	144
	Mean (SD)	157.83 (9.861)
	Median (Q1,Q3)	156.55 (151.25, 165.00)
	Min, Max	136.0, 191.5
Weight (kg)	n	144
	Mean (SD)	51.355 (12.4208)
	Median (Q1,Q3)	48.450 (43.450, 55.440)
	Min, Max	35.20, 100.90
BMI (kg/m^2)	n	144
	Mean (SD)	20.466 (3.6132)
	Median (Q1,Q3)	19.535 (17.845, 21.955)
	Min, Max	15.98, 34.31
Country (n [%])	Botswana	25 (17.4)
	Thailand	36 (25.0)
	Uganda	20 (13.9)
	US	20 (13.9)
	South Africa	43 (29.9)
Baseline CD4 cell counts	n	142

(cells/mm^3)	Mean (SD)	796.8 (306.23)
	Median (Q1,Q3)	739.5 (594.0, 964.0)
	Min, Max	81, 1925
Baseline CD4 cell counts categories (cells/mm^3) (n [%])	Missing	2 (1.4)
	<350	4 (2.8)
	350 to <500	12 (8.3)
	500 to <750	60 (41.7)
	≥750	66 (45.8)

74.3% of participants reported at least 1 current or past medical condition. The most commonly reported conditions were creatinine renal clearance decreased (n=14), lipase increased (n=11), alanine aminotransferase increased (n=10), childhood asthma (n=8), and blood bilirubin increased (n=8).

The most commonly reported classes of prior ARV therapy were NRTIs (98.6% of participants), NNRTIs (60.4% of participants), and INSTIs (58.3% of participants).

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. 2 participants did not discontinue their ARVs (Participant one: Lopinavir, Ritonavir, Lamivudine, Zidovudine; Participant two: 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.

117 of 144 (81.3%) of enrolled participants took at least 1 concomitant non-ARV medication while receiving study drug. The most commonly used non-ARV concomitant medications were paracetamol (37.5%), tozinameran (11.8%), and chlorphenamine maleate (10.4%).

Exposure and compliance

Table 15 Exposure to study drugs (Cohort 1 All Treated Population): Study 208580 full Cohort 1 analysis

Cohort 1:

	Cohort 1C Q4W (N=8) n (%)	Cohort 1C Q8W (N=22) n (%)	Cohort 1C total (N=30) n (%)	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)	38.3 (2.60)	35.7 (2.66)	36.4 (2.84)	36.3 (10.47)	34.8 (4.57)	35.7 (8.51)
Median (Q1, Q3)	37.5 (36.0, 40.0)	36.0 (36.0, 36.0)	36.0 (36.0, 37.0)	39.0 (36.0, 43.0)	36.0 (29.0, 37.0)	36.0 (36.0, 41.0)
Min, Max	36, 43	29, 42	29, 43	1, 43	29, 43	1, 43
Number of injections						
0 Injection	0	1 (4.5)	1 (3.3)	2 (13.3)	0	2 (8.0)
1 Injection	0	0	0	0	0	0
2 Injections	0	21 (95.5)	21 (70.0)	0	10 (100.0)	10 (40.0)
3 Injections	8 (100.0)	N/A	8 (26.7)	13 (86.7)	N/A	13 (52.0)
Days of exposure to study drugs[b]						
Mean (SD)	137.6 (4.24)	128.3 (22.50)	130.8 (19.71)	120.4 (40.90)	130.5 (6.75)	124.4 (31.92)
Median (Q1, Q3)	136.5 (134.5, 141.0)	134.0 (131.0, 134.0)	134.0 (133.0, 136.0)	134.0 (132.0, 138.0)	131.0 (128.0, 135.0)	134.0 (129.0, 136.0)
Min, Max	133, 144	29, 140	29, 144	1, 142	120, 141	1, 142

Source: Table 1.8, Table 1.9, Table 1.11

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.

Of the 53 Cohort 1 participants who completed oral treatment without premature treatment discontinuation, the majority had 100% oral treatment compliance (26 [49.1%] participants) or 90 to <100% oral treatment compliance (22 [41.5%] participants).

29 of 30 participants in Cohort 1C and 23 of the 25 participants in Cohort 1R received the protocol-specified injections (3 injections for Q4W and 2 injections for Q8W participants). 1 participant (in Cohort

1C) got 2 injections for the first IM administration of study drug (300 mg in each buttock); the injections were separated by approximately 3 minutes and were considered as 1 injection for all analyses.

In Cohort 1C, injection visits were conducted within the allowable −7/+3 day window for 28 of 29 participants at Week 8 and 5 of 8 participants at Week 12 injection visits. In Cohort 1C, the 4 out-of-window injections were all in Cohort 1C Q4W: the Week 8 out-of-window injection was ≥8 days after target; of the 3 injections at Week 12 that were administered outside the allowed window, 1 was administered 4 to 7 days after target and 2 were administered ≥8 days after target. All injection visits for Cohort 1R participants were conducted within the allowable −7/+3 day window (n=23 at Week 8 and n=13 at Week 12).

Cohort 2:

Table 16 Exposure to study drugs (Cohort 2 All Treated Population):

Study 208580 Cohort 2 Week 24 analysis

	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

Source: Table 1.23, Table 1.24, Table 1.26

Note: If a participant completed an injection week visit, the participant was expected to have an injection for that visit.

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 [redacted]) 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.

All participants in Cohort 2 had received CAB+RPV with the Q8W regimen.

Of the 142 Cohort 2 participants who completed oral treatment without premature treatment discontinuation, the majority had 100% oral treatment compliance (CAB: 70 [49.3%] participants; RPV:

80 [56.34%] participants) or 90 to <100% oral treatment compliance (CAB: 54 [38.03%] participants; RPV: 46 [32.39%] participants).

141 of the 144 participants in Cohort 2 had the protocol-specified injection visits through Week 24 (4 injection visits). 2 participants received no injection, and 1 participant had only 2 injection visits. 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, or at Week 16 and Week 24 (of note, this participant received additional injections of CAB LA 200 mg and RPV LA 300 mg 10 days after the initial Week 24 dosing).

All Week 8 and Week 16 injection visits for Cohort 2 participants were conducted within the allowable -7/+3 day window (n=142 at Week 8 and Week 16). In addition, all Week 24 injection visits for Cohort 2 participants were conducted within the allowable -7/+7 day window (n=141).

Outcomes and estimation

Only efficacy data from Cohort 2 could be considered relevant.

Plasma HIV-1 RNA <50 c/ml at Week 24 per Snapshot algorithm

At Week 24, 139 of 144 Cohort 2 participants (96.5%) had outcomes of 'virologic success'.

3 participants in Cohort 2 had outcomes of 'virologic failure' at Week 24. 2 of the 3 participant had HIV-1 RNA ≥50 c/mL at Week 24; their HIV-1 RNA values returned to <50 c/mL at Week 32 or Week 40. The remaining participant discontinued study drug for other reason while HIV-1 RNA was ≥50 c/mL (the participant had an elevated viral load at Cohort 2 study entry).

2 participants had no virologic data.

Table 17 Summary of study outcomes (Plasma HIV-1 RNA<50 c/mL Threshold) at Week 24 per Snapshot algorithm (Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 analysis

Outcome at Week 24	Cohort 2 total (N=144) n (%)
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

Plasma HIV-1 RNA <200 c/mL at Week 24 per Snapshot algorithm

At Week 24, 141 of 144 Cohort 2 participants (97.9%) had outcomes of 'virologic success'.

1 participant had outcomes of 'virologic failure' at Week 24 (discontinuation of study drug for other reason while HIV-1 RNA was ≥200 c/mL; this participant had an elevated viral load at Cohort 2 study entry).

2 participants had no virologic data.

Table 18 Summary of study outcomes (Plasma HIV-1 RNA <200 c/mL Threshold) at Week 24 per Snapshot algorithm (Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 analysis

Outcome at Week 24	Cohort 2 total (N=144) n (%)
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

Confirmed virologic failure

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

Ancillary analyses

Participant experience outcomes

Based on the participant experience outcomes overall, IM injections of study medication appeared to be generally acceptable and tolerable in the adolescents enrolled in Cohort 1C 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.

2.4.2. Discussion on clinical efficacy

The pivotal study for this application is a Phase 1/Phase 2 multicentre, open-label, non-comparative study including 2 cohorts: a first cohort assessing cabotegravir or rilpivirine in addition to the current ART regimen, and a second cohort where participants switched from their current ART regimen to cabotegravir + rilpivirine regimen. Such study design is endorsed for paediatric extensions and was in accordance with the PIP.

Overall, the included population (mainly in cohort 2) was varied in terms of age, weight, sex, ethnicity and concomitant medications. Except for a few subjects in cohort 1, almost all subjects were treated with the Q8W regimen. There was a low rate of dosing errors and delays reported, which is reassuring given adolescent subjects are a population at significant risk of compliance problems.

Of note, the proportion of subjects with low CD4 level was very limited, but this was not expected to have a significant impact on the study objectives.

All subjects were virologically suppressed adolescents without known resistance or failure to INSTIs and RPV. Of note, the current approval for cabotegravir and rilpivirine in adults is a little more restrictive, i.e. including subjects without resistance to the whole of non-nucleoside reverse transcriptase inhibitor

instead of only to rilpivirine in this study. However, this could be considered not significant for this paediatric extension.

As expected for this paediatric study, assessment of antiviral activity was a secondary endpoint given the low number of subjects and the non-comparative design. This was agreed. This paediatric extension is based on PK and safety endpoints, which is commonly endorsed for such applications. Efficacy data are thus only supportive. Furthermore, since the adult dosing regimen was used for adolescents, no efficacy concern was expected.

The CHMP considered that the rates of virological control at Week 24 were over 95% and in accordance to those observed in clinical studies performed in adults. Overall, there is no clinical efficacy concern with regards to the use of cabotegravir + rilpivirine in adolescent subjects with the currently approved adult dosing regimen. The CHMP noted that the Week 48 data are expected and will be provided when available.

Subgroup analyses according to BMI-for-age z-score did not highlight efficacy concern in overweight adolescents.

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 request. 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 cabotegravir 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

Patient exposure

In Study 208580, 30 participants were enrolled in Cohort 1C (CAB + 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 and 100 participants were newly recruited into the study.

For the entire study, the median exposure to study intervention for Cohort 1C was 134.0 days (m2.7.4 Section 1.2.2). During participation in Cohort 2, the median (range) exposure to study intervention thus far was 371.5 (15, 682) days.

For Cohort 2, at the time of the Week 24 analysis, the largest percentage of participants (51.4%) had 7 injection visits, and the next largest percentage (16.7%) had 6 injection visits (m2.7.4 Section 1.2.2). There were 7 (4.9%) participants with 12 injection visits. Most participants (78.5%) had been on treatment for 48 to 71 weeks.

Adverse events

AE data were consistent with those in the current product labelling for CAB when used in combination with RPV. An overview of adverse events for Cohort 1C and Cohort 2 Week 24 is provided inTable 19 and Table 20, respectively.

Table 19 Overview summary of adverse events (Cohort 1C All Treated Population – Week 16): Study 208580 full Cohort 1C analysis

AE parameter	Cohort 1C Q4W (N = 8) n (%)	Cohort 1C Q8W (N = 22) n (%)	Cohort 1C total (N = 30) n (%)
Any AE	7 (87.5)	19 (86.4)	26 (86.7)
Any AE excluding ISRs	7 (87.5)	19 (86.4)	26 (86.7)
Any ISR AE	5 (62.5)	4 (18.2)	9 (30.0)
Any AE ≥Grade 3[a]	3 (37.5)	4 (18.2)	7 (23.3)
Any drug-related AE[b]	5 (62.5)	4 (18.2)	9 (30.0)
Any drug-related AE[b] excluding ISRs	2 (25.0)	1 (4.5)	3 (10.0)
Any drug-related AE[b] ≥Grade 3[a]	1 (12.5)	0	1 (3.3)
Any drug-related AE[b] causing permanent treatment discontinuation	0	0	0
Any SAE	0	1 (4.5)	1 (3.3)
Any drug-related SAE[b]	0	0	0
Any fatal SAE	0	0	0

Source: m2.7.4 Table 1.
Grade 3 = Severe, 4 = Potentially Life-Threatening; no Grade 5 AEs were reported.
Relatedness of AEs was determined by the sites.

The majority (≈85%) of participants in Cohort 2 reported ≥1 AE, and 34% reported ≥1 injection site reaction (ISR). 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 20 Overview summary of adverse events (All Available Data for Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 analysis

AE parameter	Cohort 2 total (N = 144) n (%)
Any AE	122 (84.7)
Any AE excluding ISRs	119 (82.6)

AE parameter	Cohort 2 total (N = 144) n (%)
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

Source: m2.7.4 Table 2.
Grade 3 = Severe, 4 = Potentially Life-Threatening; no Grade 5 AEs were reported.
b. Relatedness of AEs was determined by the sites.

The most frequently reported AE in study 208580 was injection site pain. Other than injection site pain in Cohort 1C, frequently reported (in ≥3 participants) AEs were cough, blood pressure increased, hypertension, oropharyngeal pain and nasal congestion. In Cohort 2, the most commonly reported (by ≥10% of participants) AEs after injection site pain were cough, blood pressure increased, headache, nasal congestion, and upper respiratory tract infection. Across the cohorts, most AEs had a maximum intensity of Grade 1 or 2.

In both cohorts, most AEs assessed as related to the study intervention were ISRs. Other than ISRs, AEs assessed as related to study intervention generally were reported by single participants within a cohort. In Cohort 1C, all non-ISR AEs assessed as related to study intervention were ≤Grade 2 except for 1 participant with insomnia, which was Grade 3 in intensity. In Cohort 2, all non-ISR AEs assessed as related to study intervention were ≤Grade 2. These drug related AEs are presented in Table 21 and Table 22 below:

Table 21 Drug-related adverse events excluding ISRs through Week 16 (Cohort 1 All Treated Population – Week 16): Study 208580 full Cohort 1 analysis

PT	Cohort 1C Q4W (N=8) n (%)	Cohort 1C Q8W (N=22) n (%)	Cohort 1C total (N=30) n (%)	Cohort 1R Q4W (N=15) n (%)	Cohort 1R Q8W (N=10) n (%)	Cohort 1R total (N=25) n (%)
Diarrhoea	1 (12.5)	0	1 (3.3)	0	0	0
Nausea	0	0	0	1 (6.7)	1 (10.0)	2 (8.0)
Swelling	0	1 (4.5)	1 (3.3)	0	0	0
Hypersensitivity	0	0	0	1 (6.7)	1 (10.0)	2 (8.0)
Scar	0	1 (4.5)	1 (3.3)	0	0	0
Decreased appetite	1 (12.5)	0	1 (3.3)	0	0	0
Dizziness	0	0	0	1 (6.7)	0	1 (4.0)
Headache	1 (12.5)	0	1 (3.3)	1 (6.7)	0	1 (4.0)
Somnolence	0	0	0	0	1 (10.0)	1 (4.0)
Insomnia	1 (12.5)	0	1 (3.3)	1 (6.7)	0	1 (4.0)
Pruritus	0	0	0	0	1 (10.0)	1 (4.0)
Rash	0	0	0	0	1 (10.0)	1 (4.0)
Rash maculopapular	0	0	0	0	1 (10.0)	1 (4.0)

PT	Cohort 1C Q4W (N=8) n (%)	Cohort 1C Q8W (N=22) n (%)	Cohort 1C total (N=30) n (%)	Cohort 1R Q4W (N=15) n (%)	Cohort 1R Q8W (N=10) n (%)	Cohort 1R total (N=25) n (%)
Rash papular	0	0	0	1 (6.7)	0	1 (4.0)

All of these AEs (Table 21 above) assessed as related to study intervention were ≤ Grade 2 except for 1 participant (Cohort 1R) with hypersensitivity and 1 participant (Cohort 1C) with insomnia, both of which were Grade 3.

Table 22 Drug-related adverse events excluding ISRs (All Available Data for Cohort 2 All Treated Population): Study 208580 Cohort 2 Week 24 analysis

PT	Cohort 2 total (N=144) n (%)
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)

Serious adverse event/deaths/other significant events

No deaths were reported in Study 208580 Cohort 1 or Cohort 2 Week 24.

3 participants total (1 in Cohort 1C and 2 in Cohort 2) in Study 208580 reported non-fatal SAEs. All of the reported SAEs (gastritis alcoholic haemorrhagic, Cohort 1C Q8W; malaria, Cohort 2; aspartate aminotransferase increased, blood creatine phosphokinase increased, and rhabdomyolysis, Cohort 2) were assessed as not related to the study intervention.

Based on analyses of adolescent safety data to date, no new or additional safety concerns related to adverse events of special interest (AESI) categories specified in this section were identified.

In Cohort 1C, there were no AESIs relevant to hypersensitivity reactions; neuropsychiatric events of suicidal ideation/behaviour, bipolar disorder, psychosis, or mood disorders; hepatotoxicity; pancreatitis; or impact on creatinine, and no AESIs were serious.

The only AESI in Cohort 1C (Q4W) that was >Grade 2 in intensity was Grade 3 insomnia. All other AESIs were ≤Grade 2 in intensity, and none led to withdrawal of study intervention.

In Cohort 2, there were no AESIs relevant to hypersensitivity reactions; neuropsychiatric events of suicidal ideation/behaviour, depression, bipolar disorder, psychosis, or mood disorders; hepatotoxicity, or pancreatitis.

All ISRs in Cohort 1C were ≤Grade 2 in intensity, non-serious, and not treatment limiting. Injection site pain was the most frequently reported ISR. All ISRs resolved in ≤13 days.

In Cohort 2, of the 34% of participants who had an ISR, most had an ISR that was Grade 1 or 2. 2 participants had Grade 3 ISRs. There were no Grade 4 or 5 ISRs. Injection site pain was the most frequently reported ISR. The majority of ISRs resolved within 1 week. No ISRs were serious or led to discontinuation of study intervention.

Adolescents reported injection of study medication to be generally acceptable and tolerable. These perceptions of injection pain were relatively consistent (83.0% of participants) at Week 24.

In Cohort 2, four participants had ≥1 AE associated with rash. In 3 participants, the events occurred early on in Cohort 2 participation (during or shortly after OLI) and were considered related to study intervention. A fourth participant had an event of rash during the injection phase, which was considered unrelated to study intervention. All events were Grade 1 in intensity and non-serious. None led to discontinuation of study intervention.

1 participant in Cohort 1C (Q4W) had a Grade 3 insomnia with onset the same day as the start of the injection phase. Diphenhydramine was administered, and the participant continued in the study. Insomnia resolved in 5 days.

AESIs associated with anxiety and sleep disorders were reported in Cohort 2. All events were ≤Grade 2 in intensity and were non-serious. None led to discontinuation of study intervention.

There have been no confirmed reports of seizure in the study to date. In Cohort 2, a participant reported Grade 1 syncope after approximately 41 weeks on study, concurrent with Grade 1 injection site pain Syncope was non-serious, considered unrelated to study intervention, and resolved the same day it occurred.

In Cohort 2, 2 participants had AEs associated with weight increased; the AEs were Grade 1 in intensity and considered to be not related to study intervention.

Other than myalgia, no participants in Cohort 1C had AESIs relevant to rhabdomyolysis.

In Cohort 2, rhabdomyolysis associated with exercise was reported for 1 participant. The event (as well as a Grade 4 CPK elevation) was serious and assessed as not related to study intervention. No action was taken with the study intervention and the event resolved within a few days.

In Cohort 2, 1 participant with a medical history of creatinine renal clearance decreased had Grade 2 chronic kidney disease (onset Day 283), assessed as not related to study intervention, that was reported as resolved after 67 days. This participant had a Grade 1 AE of autoimmune thyroiditis and multiple Grade 3 AEs of creatinine renal clearance decreased.

During long-term safety follow-up (LSFU) in Cohort 1C, there were no deaths or other SAEs. Otherwise, 1 participant in Cohort 1C had AEs during LSFU that were Grade 3 in intensity; none were considered related to study intervention.

Laboratory findings

Results from Study 208580 full Cohort 1 and Cohort 2 Week 24 analysis in adolescents related to clinical laboratory data are consistent with current product labelling for CAB + RPV dosing regimens for adults. Clinically important changes in laboratory assessments for participants receiving CAB + RPV in Study 208580 Week 24 primary analysis were assessed as not related to the study intervention.

Across the cohorts, the majority of participants had no changes in grade for all graded chemistry laboratory parameters.

No participants in either Cohort 1C or Cohort 2 met Hy's law criteria or other protocol-defined liver monitoring criteria. In Cohort 2, increases in ALT or bilirubin were all ≤Grade 2.

In Cohort 1C, most participants did not have any grade shift from Baseline in renal parameters. 2 participants in Cohort 1C had shifts to Grade 3 for serum creatinine and/or CrCl, reported as AEs. None of the AEs associated with these shifts in laboratory values were assessed as related to study intervention.

In Cohort 2, most participants did not have any grade shift from Baseline in renal parameters. Shifts in serum creatinine to Grade 1 or 2 were observed in 3 participants in Cohort 2. 3 participants had shifts to Grade 3 in CrCl, reported as AEs. None of the AEs of creatinine renal clearance decreased were assessed as related to study intervention.

In Cohort 1C, most participants did not have any grade increase from Baseline in CPK. 1 participant in Cohort 1C had a grade increase to Grade 4 in CPK through Week 16. The Grade 4 CPK result was associated with a relevant exercise history.

In Cohort 2, most participants in did not have any grade increase from Baseline in CPK. Of the 9 participants with changes to Grade 3 or 4 CPK, 8 of 9 had a relevant exercise history, and the 1 participant without a relevant exercise history had concurrent thyroid disease. These Grade 3 and 4 CPK results were reported as AEs of blood CPK increased, all of which were assessed as not related to the study intervention. Furthermore, none led to discontinuation of study intervention. One Grade 4 blood CPK increased AE was serious.

All Cohort 1C and Cohort 2 grade increases from Baseline in lipase were ≤Grade 2.

Across the cohorts, there was a small number of participants with clinically relevant changes in neutrophils (reported as AEs), but all of the changes were assessed as not related to the study intervention. Otherwise, no patterns of clinically important changes in haematology parameters have been observed.

No clinically important findings have been noted in the study with respect to median observed data for vital signs. AEs relevant to increased blood pressure have been observed in Cohort 1C and in Cohort 2, but all were assessed as not related to study intervention.

Potential alternative causes reported for the increased blood pressure included anxiety regarding injections or blood draws, white coat hypertension, and measurements being taken before the minimum optimal resting time.

In Cohort 2, there were no indications of adverse effects on growth at Week 24, with both median weight and median height representing increases from Baseline.

In Cohort 2 at Week 24, both median weight and median height increased from Baseline per expected growth trends for this age group.

There were no ECG data indicative of a prolonged QT interval in participants in Study 208580. All maximum observed QTc intervals were <500 msec across the cohorts. In addition, all maximum increases in QTc interval were <60 msec across the cohorts.

Safety in special populations

No participants became pregnant in Cohort 1C, and 1 participant became pregnant in Cohort 2. The pregnancy outcome was a live birth (assisted vaginal delivery).

Discontinuation due to adverse events

No participants in Cohort 1C or in Cohort 2 discontinued study intervention due to an AE as of the Week 24 data cutoff date.

Post marketing experience

The post-marketing exposure predominantly reflects use in adults. There are no reliable estimates for post-marketing exposure specifically in adolescents. Review of all available post-marketing data has not identified any significant new safety findings with respect to cabotegravir + rilpivirine use for HIV treatment specific to the adolescent population.

2.5.1. Discussion on clinical safety

To support the use of Vocabria 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 30 participants in Cohort 1C and 144 in Cohort 2. As the extension of indication is mainly supported by PK data, this was considered acceptable, but it limits the chance of detecting adverse events (AEs).

The majority of AEs were related to injection site reactions and the most common AEs reported were injection site pain, cough, blood pressure increased, hypertension, oropharyngeal pain, nasal congestion and upper respiratory tract infection. Most AEs were Grade 1 and 2 intensity.

Oropharyngeal pain, cough, nasal congestion and upper respiratory tract infection are more likely due to concomitant infection and do not raise a new safety issue.

The cases of increased blood pressure and hypertension were not considered related to the study intervention.

Reactions other than injection site reactions assessed as related to study intervention were generally reported by single participants within a cohort. They were ≤ Grade 2, except for one participant with insomnia, which was Grade 3 in intensity. The CHMP considered that insomnia is already listed in the Product Information.

No safety concern was identified with regards to the tolerability and acceptability of the cabotegravir injection.

Overall, the CHMP considered that the AEs assessed as related to cabotegravir are already listed in the Product Information and no new safety issues were identified.

2.5.2. Conclusions on clinical safety

Based on data from study 208580, no new safety concerns were identified in adolescents (aged at least 12 years and weighing 35 kg or more) when compared with the safety profile established in adults.

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 4.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.3 with the following content:

Safety concerns

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

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA Ongoing	Describe CAB LA and/or RPV LA containing regimens usage patterns Assess adherence, durability and discontinuation for persons starting CAB+ RPV LA regimen Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who are on CAB+RPV regimen Monitor for resistance and next treatment response among individuals who discontinued CAB + RPV LA regimen Evaluate the effectiveness of routine risk minimisation measures for regimen adherence, discontinuation due to incorrect route of administration and off-label use of CAB+RPV LA regimen	Medication errors including treatment non-compliance	Estimated Study completion	30 June 2026 or 5 years following commercial availability of CAB
			Estimated Final report	30 September 2026
			Regular updates	Yearly interim reports presenting the progress and status of the study will be submitted to the EMA.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3- Required additional pharmacovigilance activities				
A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating CAB containing antiretroviral regimen Ongoing	Monitor for hepatotoxicity, Estimate the number of patients discontinuing CAB based ARV regimen due to adverse events, and adverse events related to hepatic events	Hepatotoxicity	1st Interim Report	March 2023
			2nd Interim Report	March 2024
			3rd Interim Report	Estimated – March 2025
			4th Interim Report	Estimated – March, 2026
			Estimated study completion	30 June 2026 or 5 years following commercial availability of CAB
			Estimated Final report	30 June 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
EPPICC: Ongoing	To assess maternal and foetal outcomes following CAB use during pregnancy	Use in pregnancy	Updated Interim Report 1 (25 pregnancies)	Estimated 31 December 2026
			Interim Report2 (100 Pregnancies)	Estimated 31 December 2028
			Interim Report 3 (200 Pregnancies)	Estimated 31 December 2030
			Final report	12 months after third analysis Estimated 31 December 2031
APR Ongoing	Assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy.	Use in pregnancy	Updated Interim Report 1 (25 Pregnancies)	Estimated 31 December 2024
			Interim Report 2 (100 Pregnancies)	Estimated 31 December 2026
			Interim Report 3 (200 Pregnancies)	Estimated 31 December 2028
			Final report	12 months after third analysis Estimated 31 December 2029

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8. • PL section 2 & 4 • Recommendation for liver chemistry monitoring are included in SmPC section 4.4 • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional Pharmacovigilance activities:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen

Medication errors including treatment non-compliance	**Routine risk minimisation measures:** • SmPC section 4.2, 4.4 • PL section 2 & 3 • Administered by Healthcare Professional. • Different packaging colours and logo for each phase of treatment. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Other pharmacovigilance activities: Cumulative review of adolescent cases of medication errors including treatment non-compliance to be included in PBRER/PSUR. **Additional pharmacovigilance activities:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA
Use in Pregnancy	**Routine risk minimisation measures:** • SmPC section 4.6. • PL section 2 • This is a prescription only medicine. • Prescribed by physicians experienced in the treatment of HIV **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Antiretroviral Pregnancy Registry (APR) European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

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 and minor editorial changes introduced throughout the Product Information.

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 minimal and do not otherwise introduce major changes 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 oral cabotegravir followed by long-acting injectable cabotegravir (Cohort 1C; n=30), as well as oral rilpivirine followed by long-acting injectable rilpivirine (Cohort 1R; 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

Data from the study 208580 as well as modelling and simulation on adolescent and adult data showed that the proposed regiment can result in exposure appropriate for the new adolescent population over 35 kg and over 12 years old.

There was no clinical efficacy concern as regards the use of cabotegravir + rilpivirine in adolescent subjects with the currently approved adult dosing regimen.

Given that exposure is comparable to exposure observed in adults, long-acting cabotegravir 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).

3.3. Uncertainties and limitations about favourable effects

This paediatric extension is based on PK bridging and the number of adolescents in this study is limited to assess the long-term clinical efficacy.

Although compliance data in study 208580 were reassuring, the context of a clinical trial was considered to introduces 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 majority of AEs were related to injection site reactions and the most common AEs reported were injection site pain, cough, blood pressure increased, hypertension, oropharyngeal pain, nasal congestion and upper respiratory tract infection. Most AEs were Grade 1 and 2 intensity.

No new safety signals in adolescents were identified and the safety profile in the adolescents is consistent with the known safety profile in adults.

3.5. Uncertainties and limitations about unfavourable effects

The number of adolescents in this study is considered limited to assess the long-term clinical safety.

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

3.6. Benefit-risk assessment and discussion

Efficacy and safety of cabotegravir in the adolescents is expected to be the same as in the adults.

3.7. Conclusions

The overall benefit-risk balance of Vocabria 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 and IIIB

Extension of indication to include, in combination with rilpivirine injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Vocabria, 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 4.3 of the RMP has also been adopted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes and 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 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 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 'Vocabria-H-C-004976-II-0022'