Clinical Review, Cross-Discipline Team Leader (CDTL) Review, and Division Director Summary Review

Date	September 12, 2024
From	Timothy Jancel, PharmD, MHS, BCPS, BCIDP (Clinical Reviewer) Stephanie Troy, MD (CDTL) Yodit Belew, MD (Associate Director for Therapeutic Review)
Subject	Combined Clinical Review, CDTL Review, and Division Director Summary Memo
NDA/BLA #, Supplement#	212887/S-009 212888/S-015
Applicant	ViiV Healthcare
Date of Submission	March 21, 2024
PDUFA Goal Date	September 21, 2024
Proprietary Name / Established (USAN) names	NDA 212887 Vocabria (cabotegravir [CAB]) NDA 212888 Cabenuva (CAB + rilpivirine [RPV] injectable co-pack)
Dosage forms / Strength	Vocabria • single-dose, film-coated tablet (30 mg CAB) Cabenuva 400-mg/600-mg Kit: • single-dose vial of 400 mg/2 mL (200 mg/mL) CAB • single-dose vial of 600 mg/2 mL (300 mg/mL) RPV Cabenuva 600-mg/900-mg Kit: • single-dose vial of 600 mg/3 mL (200 mg/mL) CAB • single-dose vial of 900 mg/3 mL (300 mg/mL) RPV
Indications/ Populations	Vocabria is indicated in combination with Edurant (RPV) for short-term treatment of HIV-1 infection in adults and adolescents aged 12 years and older and weighing at least 35 kg who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV, for use as: • oral lead-in to assess the tolerability of CAB prior to administration of Cabenuva for HIV-1 treatment • oral therapy for patients who will miss planned injection dosing with Cabenuva for HIV-1 treatment Cabenuva is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older and weighing at least 35 kg to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.
Dosing Regimen	Prior to initiating monthly or every-2-month dosing with Cabenuva, oral lead-in dosing with daily CAB and RPV may be used for

	approximately 1 month (at least 28 days) to assess the tolerability of CAB and RPV. Cabenuva intramuscular injections are initiated on the last day of current antiretroviral therapy or oral lead-in. Monthly Dosing Cabenuva, 600 mg of CAB and 900 mg of RPV, is given as the initiation doses. Cabenuva, 400 mg of CAB and 600 mg of RPV, is administered monthly for all subsequent doses. Every-2-Month Dosing Cabenuva, 600 mg of CAB and 900 mg of RPV, is given as the initiation doses 1 month apart for two consecutive months. Cabenuva, 600 mg of CAB and 900 mg of RPV, is administered every 2 months for all subsequent doses.
Recommendation on Regulatory Action:	*Approval*

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1. Introduction

The Applicant submitted NDA efficacy supplements (sNDAs) for Vocabria (cabotegravir [CAB] tablets) and Cabenuva (CAB extended-release injectable suspension and Rilpivirine [RPV] extended-release injectable suspension) to support the currently approved indication for Vocabria (with Edurant [RPV]) for the short-term treatment of HIV-1 infection and for Cabenuva (CAB+RPV) as a complete regimen for the treatment of HIV-1 infection in adolescents aged ≥12 years and weighing ≥35 kg who are virologically suppressed on a stable antiretroviral (ARV) regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

Vocabria and Cabenuva were approved in adolescents aged ≥12 years and weighing ≥35 kg on March 29, 2022. These approvals were based on the interim analysis of Cohort 1 from the Phase 1/2 Study 208580 (MOCHA, IMPAACT 2017, NCT03497676), *A Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents.* The current sNDAs for Vocabria and Cabenuva include information from the MOCHA full Cohort 1 analysis and the Cohort 2 Week 24 primary analysis.

2. Background

HIV is a significant public health concern, both globally and domestically. At the end of 2023, there were an estimated 40 million people living with HIV globally, and there were 630,000 deaths from HIV-related causes in 2023.[1] In 2022, it is estimated that 31,800 people received a new diagnosis of HIV infection in the United States. It is also estimated that 1.2 million people in the United States were living with diagnosed and undiagnosed HIV at the end of 2022.[2] Without effective treatment, HIV leads to progressive destruction of the immune system and premature death in almost all cases. However, effective treatment can suppress HIV replication, preserve and restore the immune system, reduce HIV-associated morbidity, and ultimately improve long term survival to approximate a normal lifespan.

The standard of care treatment of HIV infection is lifelong and generally involves the administration of two to three drugs from different mechanistic classes targeting different events in the HIV life cycle. Approved drugs belong to eight mechanistic classes: nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, integrase strand transfer inhibitors (INSTIs), CCR5 antagonists, post-attachment inhibitors, and capsid inhibitors. Recently, the development of long-acting (LA) drugs for the treatment and prevention of HIV-1 has increased, including the approval of injectable Cabenuva (CAB+RPV) for the treatment of HIV-1 infection in adults and adolescents, and Apretude (NDA 215499; CAB extended-release injectable suspension) for HIV-1 pre-exposure prophylaxis (PrEP) in adults and

[1] "HIV/AIDS." World Health Organization, https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Accessed August 2, 2024.
[2] "HV Surveillance Supplemental Report: Estimated HIV Incidence and Prevalence in the United States, 2018–2022." Centers for Disease Control and Prevention, https://stacks.cdc.gov/view/cdc/156513. Accessed August 2, 2024.

adolescents. Although these LA injectable drugs have the ability to improve treatment adherence, they also present unique logistical challenges (e.g., clinic workflow, procurement, reimbursement).[3]

2.1 Product Information

Cabenuva is a two-drug, co-packaged product of CAB, an HIV-1 INSTI, and RPV, an HIV-1 NNRTI, administered every 4 weeks (Q4W) or every 8 weeks (Q8W) as intragluteal intramuscular (IM) injections. Cabenuva is currently indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents aged ≥12 years and weighing ≥35 kg to replace the current antiretroviral (ARV) regimen in those who are virologically suppressed (HIV-1 RNA <50 copies per mL [c/mL]) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

Vocabria (CAB) is indicated in combination with Edurant (RPV) for the short-term oral treatment of HIV-1 infection in adults and adolescents aged ≥12 years and weighing ≥35 kg who are virologically suppressed (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. Vocabria may be used as oral lead-in (OLI) to assess the tolerability of CAB prior to administration of IM Cabenuva (CAB+RPV), and as oral therapy for patients who will miss planned injection dosing with Cabenuva (CAB+RPV).

Edurant (RPV) is indicated in combination with Vocabria (CAB) for short-term oral treatment of HIV-1 infection in adults and adolescents aged ≥12 years and weighing ≥35 kg who are virologically suppressed (HIV-1 RNA <50 c/mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. Edurant is also indicated in combination with other ARVs for the treatment of HIV-1 infection in adults and adolescents aged ≥12 years and weighing ≥35 kg who are virologically suppressed, and in combination with other ARVs for the treatment of HIV-1 infection in treatment-naïve patients aged ≥2 years and weighing ≥14 kg with HIV-1 RNA ≤100,000 c/mL.

2.2 Summary of Regulatory Activity Related to Submission

Vocabria and Cabenuva were initially approved in adults on January 21, 2021, supporting a dose regimen of an oral lead-in period with Vocabria (CAB) and Edurant (RPV) followed by Q4W injection of Cabenuva (CAB+RPV). Subsequently, Q8W dosing and direct-to-inject (DTI) with an optional oral lead-in were approved on January 31, 2022, and March 23, 2022, respectively.

In accordance with the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c), PREA postmarketing requirements (PMRs) were issued at the time of the original approval of Vocabria and Cabenuva. Studies in children <2 years of age were waived because a study would be impossible to conduct, considering the epidemiology and natural history of the

[3] Howe ZW, Norman S, Lueken AF, et al. Therapeutic review of cabotegravir/rilpivirine long-acting antiretroviral injectable and implementation considerations at an HIV specialty clinic. Pharmacotherapy. 2021;41:686-699.

disease in infants and young children. A Pediatric Written Request (PWR) was also issued to the Applicant.

Vocabria and Cabenuva were approved in adolescents aged ≥12 years and weighing ≥35 kg on March 29, 2022 (Vocabria 212887/S-005 and S-006; Cabenuva 212888/S-005 and S-006). These approvals were based on the interim analysis of Cohort 1 (Week 16) from MOCHA that assessed the safety and pharmacokinetics (PK) of sequential oral CAB followed by IM CAB (Cohort 1C), as well as oral RPV followed by IM RPV (Cohort 1R) in virologically suppressed adolescents living with HIV-1 who continued their oral combination antiretroviral therapy (cART) regimen.

The current sNDAs (Vocabria 212887/S-009; Cabenuva 212888/S-015) were submitted to support the approved indications for Vocabria and Cabenuva as treatment for adolescents aged ≥12 years and weighing ≥35 kg. This review summarizes safety, PK, and antiviral activity from MOCHA Cohort 1 and Cohort 2 through the Cohort 2 Week 24 primary analysis cut-off date of June 7, 2023.

MOCHA is an ongoing study that is being conducted to fulfill the following required PREA PMRs. Of note, each approved dosing regimen (e.g., Q4W, Q8W, DTI) may have an associated PMR, which explains the duplicate PREA PMRs listed below.

Vocabria NDA 212887 PMR 3997-1

- *Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral (ARV) regimen at the time of enrollment, to assess the pharmacokinetics, tolerability, and short-term safety of VOCABRIA after 4-week administration in combination with other ARVs.*

Vocabria NDA 212887 PMR 4223-5

- *Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, tolerability, and short-term safety of VOCABRIA after 4-week administration in combination with other antiretroviral drug(s).*

Cabenuva NDA 212888 PMR 3998-1

- *Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable ARV regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of CABENUVA. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.*

Cabenuva NDA 212888 PMR 4221-1

- *Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of CABENUVA.*

Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

Cabenuva NDA 212888 PMR 4232-1

- *Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of CABENUVA. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.*

3. Product Quality

The drug product used in MOCHA and submitted in these sNDA submissions is identical to the approved formulations of Vocabria and Cabenuva. These sNDA submissions contain no new chemistry manufacturing and controls information.

4. Nonclinical Pharmacology/Toxicology

Extensive nonclinical studies with CAB and RPV have previously been conducted and deemed acceptable. Additional nonclinical data were not needed for the approval of these sNDAs. Please refer to the original NDA reviews of Vocabria and Cabenuva for further details.

5. Clinical Pharmacology

Please refer to Clinical Pharmacology's review for additional details; a brief summary is provided below.

In MOCHA, geometric mean CAB exposures after OLI, Q4W, and Q8W injections in adolescents were 29 to 43% higher than the exposures in adults but largely within the range of exposures observed in adults. Geometric mean RPV exposures after OLI, Q4W, and Q8W injections in adolescents were 21% lower to 27% higher than the exposures in adults and within the range of exposures observed in adults. Based on the updated CAB and RPV PK parameters for adolescents, the Clinical Pharmacology review team continues to agree with the labeling statement that there are no clinically relevant differences in CAB or RPV exposure between adolescents and adults.

In addition, the Applicant's population PK (popPK) analysis was found to be acceptable for the purpose of deriving CAB and RPV and metabolite exposure metrics (C_{max}, AUC, C_{tau}) for labeling.

6. Clinical Virology

Please refer to Clinical Virology's review for additional details; a brief summary is provided below.

Through the full Cohort 1 analysis, no participant met the criteria for confirmed virologic failure (CVF; defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL) while receiving CAB or RPV treatment. Participant (b) (6) (Cohort 1C) met CVF criteria approximately 46 weeks after the last CAB injection while receiving oral ARVs (abacavir/lamivudine and atazanavir/cobicistat). Samples collected at the CVF visit showed no evidence of resistance to CAB or RPV and the CAB concentration was <0.025 mcg/mL.

Through the Cohort 2 Week 24 analysis, no Cohort 2 participant met CVF criteria. At Week 24, 139 of the 141 (98.6%) Cohort 2 participants with a HIV-1 RNA assessment were virologically suppressed (plasma HIV-1 RNA value <50 copies/mL). Two participants with HIV-1 RNA ≥50 copies/mL at Week 24 (Participants (b) (6)) returned to HIV-1 RNA values <50 copies/mL at Week 32 or Week 40 and remained suppressed at subsequent visits.

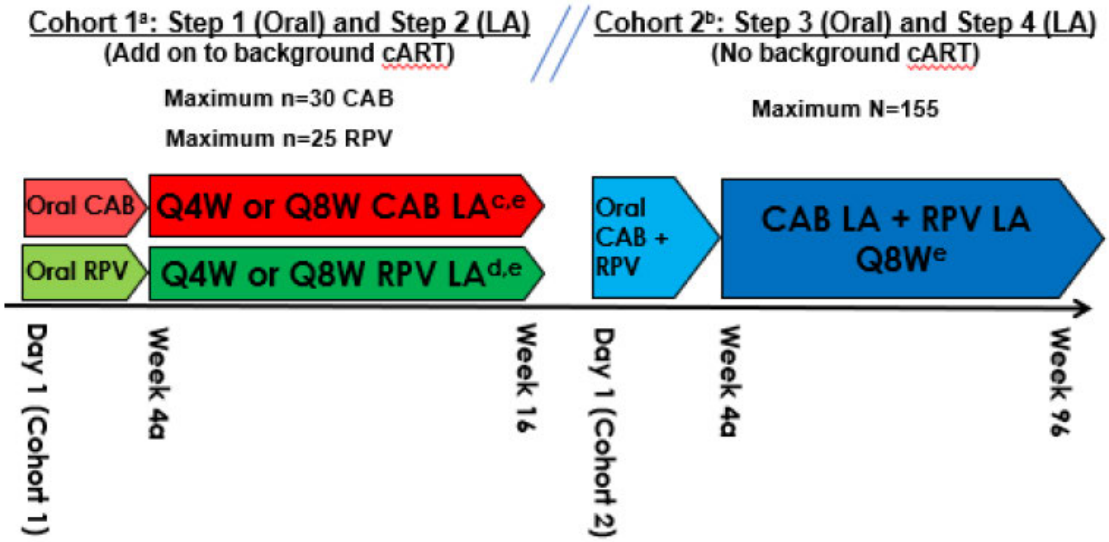
With no significant resistance information generated from MOCHA, the Applicant proposed no revisions to the *Microbiology* subsection of labeling for Vocabria or Cabenuva.

7. Clinical/Statistical – Efficacy (Antiviral Activity)

7.1 Overview of the Study Design

MOCHA is an ongoing Phase 1/2 multicenter, open-label, non-comparative study evaluating the safety, tolerability, and PK of oral and injectable CAB and injectable RPV in virologically suppressed adolescents aged ≥12 years and weighing ≥35 kg, who are receiving stable cART consisting of two or more drugs from two or more classes of ARV drugs. The MOCHA study design is presented in Figure 1.

Figure 1. Overview of Study Design for Study 208580 (MOCHA)



Source: Applicant's Clinical Study Report for MOCHA (Figure 1, page 26).
Abbreviations: CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.

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

The results presented in the Applicant's Clinical Study Report (CSR) represent the full Cohort 1 through Week 16 analysis and the Cohort 2 Week 24 primary analysis. Available data were included up to June 7, 2023, which is the database lock for this analysis.

Cohort 1

Adolescent participants living with HIV-1 were enrolled in Cohort 1 and assigned to Cohort 1C (CAB) or Cohort 1R (RPV) based on their background cART regimen; participants on a PI-based and/or NNRTI-based cART regimen were assigned to Cohort 1C, and participants on an INSTI-based cART regimen were assigned to Cohort 1R.

Following enrollment, participants received at least 4 weeks OLI of CAB or RPV while continuing their background cART (Cohort 1, Step 1) for assessing tolerability before starting the IM injections of the assigned drug. For participants enrolled under Protocol Version 2.0, IM injections were administered Q4W for a total of three injections while continuing the background cART (Cohort 1, Step 2). For participants enrolled under Protocol Version 3.0, IM injections were administered Q8W for a total of two injections while continuing the background cART (Cohort 1, Step 2). Details of the CAB or RPV dosing for Cohort 1 are included in Table 1.

Table 1. Study Drug Dosing and Administration, MOCHA Cohort 1

Cohort	Step	Study Drug Dosing*
1C	1	CAB administered orally as one 30 mg tablet once daily, beginning at the entry visit, for 4 to 6 weeks, with or without food
	2	Participants enrolled under Protocol Version 2.0 (Q4W injections): • CAB administered as one IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (600 mg), at Week 8 (400 mg), and at Week 12 (400 mg) Participants enrolled under Protocol Version 3.0 (Q8W injections): • CAB administered as one IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (600 mg), and at Week 8 (600 mg)
1R	1	RPV administered orally as one 25 mg tablet once daily, beginning at the entry visit, for 4 to 6 weeks, with a meal
	2	Participants enrolled under Protocol Version 2.0 (Q4W injections): • RPV administered as one IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (900 mg), at Week 8 (600 mg), and at Week 12 (600 mg) Participants enrolled under Protocol Version 3.0 (Q8W injections): • RPV administered as one IM injection in the gluteus medius at Week 4b (Step 2 entry) study visit (900 mg), and at Week 8 (900 mg)

Source: Adapted from the Applicant's Clinical Study Report for MOCHA (Table 2, page 32).
*Study drugs (CAB or RPV) were taken *with* non-study-provided oral combination antiretroviral regimen.
Abbreviations: CAB, cabotegravir; IM, intramuscular; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Only data from participants enrolled in Cohort 1 (Step 1, Step 2, and long-term safety and washout PK follow-up [LSFU]) are included in the Cohort 1 Week 16 analysis.

Cohort 2

Adolescent participants living with HIV-1 who were enrolled in Cohort 2 discontinued their pre-study oral cART regimen and received both CAB and RPV at the doses established in Cohort 1. Based on enrollment under Protocol Version 3.0, all Cohort 2 participants received both oral CAB + oral RPV (Step 3) followed by both IM CAB + IM RPV injections administered Q8W through Week 96 (Step 4). Study participants received the first doses of CAB and RPV injections on the same day as the last doses of oral CAB and oral RPV (i.e., at the Week 4b Step 4 entry visit). Details of the CAB or RPV dosing for Cohort 2 are included in Table 2.

Table 2. Study Drug Dosing and Administration, MOCHA Cohort 2

Cohort	Step	Study Drug Dosing*
2	3	CAB administered orally as one 30 mg tablet *and* RPV administered orally as one 25 mg tablet once daily; taken together and with a meal, beginning at the entry visit, for 4 to 6 weeks
	4	First and second set of injections: • CAB administered as one IM injection (600 mg) in the gluteus medius *and* RPV administered as one IM injection (900 mg) in the gluteus medius at Week 4b (Step 4 Entry) and at Week 8 Subsequent injections: • Starting at the Week 16 visit, CAB administered as one IM injection (600 mg) in the gluteus medius *and* RPV administered as one IM injection (900 mg) in the gluteus medius every 8 weeks through Week 96

Source: Adapted from the Applicant's Clinical Study Report for MOCHA (Table 2, page 33).
*Study drugs (CAB+RPV) were taken without oral combination antiretroviral regimen.
Abbreviations: CAB, cabotegravir; IM, intramuscular; Q4W, every 4 weeks; Q8W, every 9 weeks; RPV, rilpivirine.

Long-term Safety and Washout PK Follow-up

Participants entered into the LSFU (up to an additional 48 weeks) to assess long-term safety and washout PK of the study products for the following reasons:

- Premature permanent discontinuation of injectable study product
- Completion of the Cohort 1 Step 2 Week 16 visit but not enrolling to Cohort 2
- Completion of Cohort 2 Step 4 Week 96 study visit but do not wish to receive injectable CAB+RPV external to the protocol
- Participants assigned female at birth who discontinue study product use (either oral or injectable study product) because of pregnancy

7.2 Disposition and Baseline Demographics

The first participant was screened on April 3, 2019, and the Cohort 2 Week 24 last participant visit was February 18, 2023.

The All Treated Population is defined as below:

- Cohort 1 All Treated Population: All Cohort 1 participants who took at least one dose of any study product
    - Cohort 1 All Treated Population with Q4W Dosing: All Cohort 1 participants who took at least one dose of any study product who were enrolled under Version 2.0 of the protocol

- Cohort 1 All Treated Population with Q8W Dosing: All Cohort 1 participants who took at least one dose of any study product who were enrolled under Version 3.0 of the protocol
- Cohort 2 All Treated Population: All Cohort 2 participants who took at least one dose of any study product

Cohort 1

Cohort 1 was conducted in a total of 15 sites in 4 countries (Botswana, Thailand, United States, and South Africa). A total of 59 participants were screened in Cohort 1 and 55 participants were enrolled. The 55 enrolled participants were assigned to either Cohort 1C (n=30, receiving CAB + oral cART) or Cohort 1R (n=25, receiving RPV + oral cART) based on their pre-study cART. A total of 29 of the 30 Cohort 1C participants and 23 of the 25 Cohort 1R participants completed the Cohort 1 Week 16 assessments (Table 3). At the time of data cut-off for this report, all Cohort 1 participants were considered off study under Cohort 1.

One participant in Cohort 1C and two participants in Cohort 1R did not receive any injections, as detailed below:

- One participant (Participant (b) (6)) in Cohort 1C Q8W permanently discontinued study intervention before completing the oral phase (withdrew consent due to study visits taking too long and not wanting to take extra tablets) and did not receive any study drug injections
- One participant (Participant (b) (6)) in Cohort 1R Q4W proceeded directly to LSFU without completing Step 2 (injection phase); the needle was inserted, but no study drug was administered at Week 4b because of Grade 1 injection procedural pain
- One participant (Participant (b) (6)) in Cohort 1R Q4W permanently discontinued study intervention because of hypersensitivity following the first oral RPV dose and was discontinued from the study

Table 3. Study and Treatment Status (All Treated Population), MOCHA 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 (%)	Cohort 1 Total (N=55) n (%)
Completed Week 4b visit	8 (100)	21 (96)	29 (97)	14 (93)	10 (100)	24 (96)	53 (96)
Received Week 8 injection	8 (100)	21 (96)	29 (97)	13 (87)	10 (100)	23 (92)	52 (95)
Completed Week 16 visit	8 (100)	21 (96)	29 (97)	13 (87)	10 (100)	23 (92)	52 (95)
Cohort 1 Study Status							
Off study*	8 (100)	22 (100)	30 (100)	15 (100)	10 (100)	25 (100)	55 (100)
On study	0	0	0	0	0	0	0
Cohort 1 Treatment Status							
Off treatment	8 (100)	22 (100)	30 (100)	15 (100)	10 (100)	25 (100)	55 (100)
On treatment	0	0	0	0	0	0	0
Prematurely Discontinued Study Treatment							
Adverse event	0	0	0	1 (7)	0	1 (4)	1 (2)
Other	0	0	0	1 (7)	0	1 (4)	1 (2)
Withdrawal of consent	0	1 (5)	1 (3)	0	0	0	1 (2)

Source: Clinical Reviewer's analysis (JMP 16.2.0) of adsl.xpt dataset for MOCHA.
*Refers to Cohort 1 study status; 44 participants considered "off study" in Cohort 1 subsequently enrolled in Cohort 2.

Baseline characteristics of participants in Cohort 1 are summarized in Table 4. The majority of participants in Cohort 1 were enrolled at sites in the United States or South Africa, were Black or African American, and had a baseline CD4 cell count of ≥500 cells/mm^3.

Table 4. Baseline Characteristics (All Treated Population), MOCHA Cohort 1

	Cohort 1C N=30 n (%)	Cohort 1R N=25 n (%)	Cohort 1 Total N=55 n (%)
Age (years)			
Mean (SD)	14.9 (1.5)	15.6 (1.7)	15.2 (1.6)
Median (Min, Max)	15.0 (12, 17)	16.0 (12, 17)	15.0 (12, 17)
Sex at Birth			
Female	14 (46.7)	12 (48.0)	26 (47.3)
Male	16 (53.3)	13 (52.0)	29 (52.7)
Race			
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			
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)			
Mean (SD)	159.4 (10.84)	160.0 (11.86)	159.7 (11.21)
Median (Min, Max)	159.8 (137.0, 185.3)	157.5 (140.0, 191.8)	159.5 (137.0, 191.8)
Weight (kg)			
Mean (SD)	52.7 (11.69)	57.7 (16.13)	54.9 (13.98)
Median (Min, Max)	47.9 (39.4, 84)	54.0 (37.4, 98.5)	50.0 (37.4, 98.5)
BMI (kg/m^2)			
Mean (SD)	20.6 (3.66)	22.3 (4.65)	21.4 (4.19)
Median (Min, Max)	19.6 (16.4, 30.5)	20.7 (17.0, 31.3)	19.9 (16.41, 31.3)
Country			
Botswana	0	5 (20.0)	5 (9.1)
South Africa	14 (46.7)	3 (12.0)	17 (30.9)
Thailand	8 (26.7)	0	8 (14.5)
United States	8 (26.7)	17 (68.0)	25 (45.5)
Baseline CD4 Cell Counts (cells/mm^3)			
Mean (SD)	743.9 (226.2)	859.2 (351.0)	795.2 (291.2)
Median (Min, Max)	701.0 (397, 1206)	788.0 (412, 1808)	725.0 (397, 1808)
Baseline CD4 Cell Counts Categories (cells/mm^3)			
>=750	11 (36.7)	14 (56.0)	25 (45.5)
500 to <750	15 (50.0)	7 (28.0)	22 (40.0)
350 to <500	4 (13.3)	3 (12.0)	7 (12.7)
Missing	0	1 (4.0)	1 (1.8)

Source: Clinical Reviewer's Analysis (OCS Analysis Studio, Custom Table Tool) of adsl.xpt dataset for MOCHA.
Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; SD, Standard Deviation.

Details regarding the age and weight of the 55 participants from Cohort 1 are summarized in Table 5.

Table 5. Baseline Age, Weight, and Body Mass Index (All Treated Population), MOCHA Cohort 1

	Cohort 1C (n=30) n (%)	Cohort 1R (n=25) n (%)	Cohort 1 Total (N=55) n (%)
Age (years)			
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)
Weight (kg)			
35 to <50	17 (56.7)	10 (40.0)	27 (49.1)
≥50	13 (43.3)	15 (60.0)	28 (50.9)
BMI (kg/m^2)			
<30	28 (93.3)	22 (88.0)	50 (90.9)
≥30	2 (6.7)	3 (12.0)	5 (9.1)

Source: Clinical Reviewer's analysis (JMP 16.2.0) of adsl.xpt dataset for MOCHA.
Abbreviations: BMI, body mass index.

Concomitant Antiretroviral Drugs

All participants enrolled in Cohort 1 were receiving oral cART at enrollment, which was continued throughout Cohort 1.

In Cohort 1C, all participants (30 [100%] participants) were receiving two NRTIs, 13 (43%) participants were receiving an NNRTI, and 17 (57%) were receiving at least one PI. The most common cART regimens were lopinavir, ritonavir, abacavir, lamivudine (40% of participants) and efavirenz, emtricitabine, tenofovir disoproxil (20% of participants).

In Cohort 1R, all participants (25 [100%] participants) were receiving an INSTI and two NRTIs. The most common cART regimens were bictegravir, emtricitabine, tenofovir alafenamide (28% of participants) and dolutegravir, abacavir, lamivudine (28% of participants)

Cohort 2

Cohort 2 is being conducted in a total of 18 sites in 5 countries (Botswana, Thailand, United States, South Africa, and Uganda). A total of 159 participants were screened in Cohort 2 and 144 participants were enrolled. Of the 144 participants enrolled in Cohort 2, 44 participants had previously participated in Cohort 1 (rollover) and 100 participants were newly recruited into the MOCHA study.

In Cohort 2, all participants were to discontinue their pre-study cART regimen and receive both CAB and RPV. The first Cohort 2 participant enrolled in July 2021. At the time of data cut-off for this report, 142 of the 144 Cohort 2 participants were on study and two participants

were off study (Table 6). A total of 141 (98%) participants had completed the Cohort 2 Week 24 assessments and 116 (81%) participants had completed the Cohort 2 Week 48 assessments.

Of the three participants in Cohort 2 who discontinued study treatment prematurely, two participants discontinued prior to receiving any injections; one participant (Participant (b) (6)) withdrew due to the primary reason of noncompliance with study drug and one participant (Participant (b) (6)) withdrew for a protocol deviation of eligibility failure discovered after study entry. The additional participant (Participant (b) (6)) became pregnant and entered the LSFU prior to the Week 24 visit.

Table 6. Study and Treatment Status (All Treated Population), MOCHA Cohort 2

	Cohort 2 Total (N=144) n (%)
Completed Week 4b visit	142 (99)
Completed Week 24 visit	141 (98)
Completed Week 48 visit	116 (81)
Cohort 2 Study Status	
Off study	2 (1)
On study	142 (99)
Cohort 2 Treatment Status	
Off treatment	3 (2)
On treatment	141 (98)
Prematurely discontinued study treatment	
Noncompliance with study drug	1 (<1)
Pregnancy	1 (<1)
Protocol deviation	1 (<1)

Source: Clinical Reviewer's analysis (JMP 16.2.0) of adsl.xpt dataset for MOCHA.

Baseline characteristics of Cohort 2 participants are summarized in Table 7. The majority of participants in Cohort 2 were enrolled at sites in South Africa and Thailand, were Black or African American or Asian, and had a baseline CD4 cell count of ≥500 cells/mm^3.

Table 7. Baseline Characteristics (All Treated Population), MOCHA Cohort 2

	Cohort 2 Total (N=144) n (%)
Age (years)	
Mean (SD)	14.9 (1.6)
Median (Min, Max)	15.0 (12, 17)
Sex at Birth	
Female	74 (51)
Male	70 (49)
Race	
Asian	36 (25.0)
Black or African American	106 (73.6)
White	2 (1.4)
Ethnicity	
Hispanic or Latino	3 (2.1)
Not Hispanic or Latino	141 (97.9)
Country	
Botswana	25 (17.4)
Thailand	36 (25.0)
Uganda	20 (13.9)
United States	20 (13.9)
South Africa	43 (29.9)
Height (cm)	
Mean (SD)	157.8 (9.9)
Median (Min, Max)	156.6 (136.0, 191.5)
Weight (kg)	
Mean (SD)	51.4 (12.4)
Median (Min, Max)	48.5 (35.2, 100.9)
BMI (kg/m^2)	
Mean (SD)	20.5 (3.6)
Median (Min, Max)	19.5 (16.0, 34.3)
Baseline CD4 Cell Counts (cells/mm^3)	
Mean (SD)	796.8 (306.2)
Median (Min, Max)	739.5 (81, 1925)
Baseline CD4 Cell Counts Categories (cells/mm^3)	
No Data	2 (1.4)
<350	4 (2.8)
350 to <500	12 (8.3)
500 to <750	60 (41.7)
≥750	66 (45.8)

Source: Clinical Reviewer's Analysis (OCS Analysis Studio, Custom Table Tool) of adsl.xpt dataset for MOCHA.
Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; SD, Standard Deviation.

Details regarding the age and weight of the 144 participants from Cohort 2 are summarized in Table 8.

Table 8. Baseline Age, Weight, and Body Mass Index (All Treated Population), MOCHA Cohort 2

	Cohort 2 Total (N=144) n (%)
Age (years)*	
12	11 (7.6)
13	23 (16.0)
14	19 (13.2)
15	35 (24.3)
16	27 (18.8)
17	29 (20.1)
Weight (kg)	
35 to <50	76 (52.8)
≥50	68 (47.2)
BMI (kg/m^2)	
<30	139 (96.5)
≥30	5 (34.7)

Source: Clinical Reviewer's analysis (JMP 16.2.0) of adsl.xpt dataset for MOCHA.
*Baseline age that was used for the 44 rollover participants from Cohort 1 was their Cohort 1 baseline age.
Abbreviations: BMI, body mass index.

7.3 Intervention Compliance and Extent of Exposure

Cohort 1

The median number of days of exposure to oral CAB for Cohort 1C and oral RPV for Cohort 1R was 36 days. The median number of days of exposure to oral and injectable CAB or RPV for the entire study for Cohort 1C and Cohort 1R was 134 days (Table 9). Three participants did not receive any injections and are summarized in Section 7.2.

Table 9. Exposure to Study Drugs (All Treated Population), MOCHA Cohort 1

	Cohort 1C Total N=30 n (%)	Cohort 1R Total N=25 n (%)
Days of exposure to oral study drugs*		
Mean (SD)	36.4 (2.8)	35.7 (8.5)
Median (Q1, Q3)	36.0 (36.0, 37.0)	36.0 (35.5, 41.5)
Min, Max	29, 43	1, 43
Number of injections		
0 Injection	1 (3.3)	2 (8.0)
1 Injection	0	0
2 Injections	21 (70.0)	10 (40.0)
3 Injections	8 (26.7)	13 (52.0)
Days of exposure to study drugs†		
Mean (SD)	130.8 (19.7)	124.4 (31.9)
Median (Q1, Q3)	134.0 (132.5, 136.3)	134.0 (128.5, 136.5)

	Cohort 1C Total N=30 n (%)	Cohort 1R Total N=25 n (%)
Min, Max	29, 144	1, 142

Source: Source: Clinical Reviewer's Analysis of adsl.xpt dataset (MOCHA); JMP 16.2.0.
*Per the Applicant: Oral treatment duration was calculated as oral treatment end date - oral treatment start date +1 day.
†Per the Applicant: Treatment duration for those 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.
Abbreviations: SD, standard deviation; Q1, first quartile; Q3, third quartile.

Cohort 2

In Cohort 2, the median exposure to oral study drugs was 36 days, and the median exposure to study drug for the entirety of Cohort 2 was 372 days (Table 10). The two participants who discontinued prior to receiving any injections in Cohort 2 are summarized in Section 7.2.

Table 10. Exposure to Study Drugs (All Treated Population), MOCHA Cohort 2

	Cohort 2 Total N=144 n (%)
Days of exposure to oral study drugs*	
Mean (SD)	36.2 (4.5)
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)‡
12 Injections visits	7 (4.9)
Days of exposure to study drugs†	
Mean (SD)	394.5 (95.7)
Median (Q1, Q3)	371.5 (351.0, 433.8)
Min, Max	15, 682

Source: Source: Clinical Reviewer's Analysis of adsl.xpt dataset (MOCHA); JMP 16.2.0.
*Per the Applicant: Oral treatment duration was calculated as oral treatment end date - oral treatment start date +1 day.
†Per the Applicant: Treatment duration for those 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.
‡One participant (Participant (b) (6) 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.
Abbreviations: SD, standard deviation; Q1, first quartile; Q3, third quartile.

Needle Length

Needle length for the CAB and/or RPV injections in Cohort 1 and Cohort 2 was chosen by the investigator for each participant based on guidance in the manual of procedures. The majority of injections in Cohort 1 (74%) were administered using a 1.5-inch needle. An additional 16%, 7%, and 2% of injections overall were administered with a 1.3-inch, 2.0-inch, and 1.0-inch needle, respectively. The majority of injections in Cohort 2 (85%) were administered using a 1.5-inch needle. An additional 13%, <1%, <1%, <1%, and <1% of injections were administered with a 1.3-inch, 2.0-inch, 1.1-inch, 1.0-inch, and 0.5-inch needle, respectively.

Each Cabenuva dosing kit contains two needles for intramuscular injection (23-gauge, 1.5 inch) and the labeling (2.5 *Administration Instructions*) includes the following in regard to needle length:

> *Consider the body mass index (BMI) of the patient to ensure that the needle length is sufficient to reach the gluteus muscle. Longer needle lengths (not included in the dosing kit) may be required for patients with higher BMI (example: greater than 30 kg/m^2) to ensure that injections are administered intramuscularly as opposed to subcutaneously.*

The needle length is an important consideration to ensure the injections were administered into the gluteal muscle. In the original NDA review of Cabenuva, it was noted that the protocols for the ATLAS and FLAIR adult trials specified the injection needle, gauge, and anatomical site for administration. A 1.5-inch, 23-gauge needle for CAB and RPV were recommended for most participants, but various needle lengths or gauges were permitted to accommodate various body types such as those with body mass index (BMI) ≥30 kg/m^2.

In Cohort 1, all the participants with a baseline BMI ≥30 kg/m^2 had injections with ≥1.5-inch needles. In Cohort 2, all the participants with a baseline BMI ≥30 kg/m^2 had injections with ≥1.5-inch needles. In the original NDA review of Cabenuva, no statistically significant associations between the change in HIV-1 RNA from baseline and needle length used for the CAB or RPV injections were observed after controlling for age, baseline BMI, baseline disease stage, baseline HIV-1 RNA, stratification factors, and visit; however, these exploratory analyses have several limitations that were discussed in the original NDA review that also apply to MOCHA (e.g., trials were not designed to formally study the impact of the needle size on the outcome).

7.4 Summary of Efficacy

The assessment of efficacy of Vocabria and Cabenuva in adolescents for the proposed indications is primarily based on extrapolation from the adult studies by demonstrating similar pharmacokinetic profiles in the adolescent and adult populations.

Cohort 1
This section focuses on the Week 16 virologic and immunologic results for MOCHA Cohort 1, which provide supportive evidence of efficacy. CVF was defined as two consecutive plasma HIV-1 RNA test results ≥200 c/mL.

There were no primary efficacy endpoints included in the protocol for Cohort 1; however, virologic activity was measured as part of the secondary and tertiary endpoints.

At Week 16, all participants with an HIV-1 RNA assessment (n=28 in Cohort 1C; n=23 in Cohort 1R) had an HIV-1 RNA value <50 c/mL (Table 11). One participant in Cohort 1C had a missing HIV-1 RNA assessment at Week 16 because of the COVID-19 pandemic; therefore, that participant's HIV-1 RNA assessment was missing. The other three participants without an HIV-1 RNA assessment at Week 16 did not receive any CAB or RPV injections as described in Section 7.2. Through Week 16, only a small number of participants in Cohort 1 had quantifiable HIV-1 RNA values ≥50 c/mL at any visit. A summary of HIV-1 RNA assessments per visit through Week 16 is presented in Table 11.

Table 11. Summary of HIV-1 RNA Assessments per Visit (All Treated Population), MOCHA Cohort 1

Analysis Visit			Cohort	
			Cohort 1C (N=30)	Cohort 1R (N=25)
Cohort 1 Baseline	Results available	n	30	23
	<50 copies/mL	n (%)	30 (100.0)	22 (95.7)
	>=50 copies/mL	n (%)	0	1 (4.3)
		n (%) <LLOQ	0	1 (4.3)
Cohort 1 Week 2	Results available	n	30	24
	<50 copies/mL	n (%)	30 (100.0)	23 (95.8)
	>=50 copies/mL	n (%)	0	1 (4.2)
		n (%) <LLOQ	0	0
Cohort 1 Week 4b	Results available	n	29	21
	<50 copies/mL	n (%)	28 (96.6)	20 (95.2)
	>=50 copies/mL	n (%)	1 (3.4)	1 (4.8)
		n (%) <LLOQ	1 (3.4)	1 (4.8)
Cohort 1 Week 8	Results available	n	29	23
	<50 copies/mL	n (%)	26 (89.7)	23 (100.0)
	>=50 copies/mL	n (%)	3 (10.3)	0
		n (%) <LLOQ	2 (6.9)	0
Cohort 1 Week 12	Results available	n	8	13
	<50 copies/mL	n (%)	8 (100.0)	13 (100.0)
	>=50 copies/mL	n (%)	0	0
		n (%) <LLOQ	0	0
Cohort 1 Week 16	Results available	n	28	23
	<50 copies/mL	n (%)	28 (100.0)	23 (100.0)
	>=50 copies/mL	n (%)	0	0
		n (%) <LLOQ	0	0

Source: Applicant's Clinical Study Report for MOCHA (Table 2.1, pages 223 and 224).
N = Number of participants in each Cohort.
n (%) = Number (percent) of participants in each subcategory in each Cohort (with respect to the number of participants with results available at that visit in each Cohort).
n (%) <LLOQ = Number (percent) of unquantifiable values where the lower limit of quantification was above 50 c/mL.
Abbreviations: LLOQ, Lower limit of quantitation

Through the full Cohort 1 analysis, no participant met CVF criteria while receiving CAB or RPV treatment. One participant (Participant (b) (6); Cohort 1C) met CVF approximately 46 weeks after the last CAB injection while receiving oral ARVs as described in Section 6.

Cohort 2

This section focuses on the Week 24 virologic and immunologic results for MOCHA Cohort 2, which provide supportive evidence of efficacy. CVF was defined as two consecutive plasma HIV-1 RNA test results ≥200 c/mL.

There were no primary efficacy endpoints in Cohort 2; the virologic activity secondary endpoints included the number of participants with HIV-1 RNA ≥50 c/mL and HIV-1 RNA ≥200 c/mL, per snapshot algorithm.

At Week 24, 139 (96.5%) participants in Cohort 2 with a HIV-1 assessment had an HIV-1 RNA value <50 c/mL (Table 12). The two participants with HIV-1 RNA ≥50 c/mL at Week 24 (Participant (b) (6) and Participant (b) (6)) returned to HIV-1 RNA values <50 c/mL at Week 32 or Week 40, and remained suppressed at subsequent visits. The three participants without a HIV-1 RNA assessment at Week 24 had discontinued study treatment prior to Week 24. At Week 24, all participants in Cohort 2 with a HIV-1 RNA assessment (n=141) had an HIV-1 RNA value below 200 c/mL. Through the Cohort 2 Week 24 analysis, no participants met CVF criteria.

Table 12. Summary of Study Outcomes at Week 24 per Snapshot algorithm (All Treated Population), MOCHA Cohort 2

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

Source: Source: Clinical Reviewer's Analysis of adeffout.xpt dataset (MOCHA); JMP 16.2.0.

Analysis of efficacy by demographic factors was generally not informative because of the small sample size in this study.

Immunologic Response

The CD4 cell count in Cohort 1 as well as CD4/Lymphocytes (%) in Cohorts 1 and 2 remained stable over time. Although the median CD4 cell count is slightly lower in Cohort 2 at Week 24 compared to baseline, these changes were assessed as not clinically relevant.

Cohort 1

The CD4 cell count and CD4/Lymphocytes (%) were collected at Baseline and at Week 16. Of the 55 participants in Cohort 1 All Treated Analysis Dataset Set, 54 participants had a median CD4 cell count of 725 cells/mm^3 (range: 397, 1808), and had median CD4/lymphocytes (%) of

36% (range: 21, 56) at baseline. At Week 16, data were available from 49 participants. The median change from baseline for CD4 count was -8 (range: -345, 338), and the median change from baseline for CD4/Lymphocytes (%) was 0.1% (range: -5, 5) at Week 16.

Cohort 2

Of the 144 participants in Cohort 2 All Treated Analysis Dataset set, 142 participants had a median CD4 cell count of 740 cells per mm^3 (range: [81, 1925]), and had median CD4/lymphocytes (%) of 36% (range: [5%, 60%]) at baseline. At Week 24, data were available from 138 participants. The median change from baseline for CD4 count was -36.0 cells/mm^3 (range: [-1164, 741]) at Week 24. The median change from baseline for CD4/Lymphocytes (%) was -0.2% (range: [-34%, 18%]) at Week 24. Of note, one participant (Participant (b) (6)) experienced a decrease in CD4 count from 1595 cells/mm^3 at baseline to 431 cells/mm^3 at Week 24; however, the CD4 count value was 993 cells/mm^3 at Week 48.

Of note, a similar change in CD4 count from Baseline was observed at Week 48 based on analyses performed by the Applicant in response to an information request.

Clinical Reviewer's Comment: Although the median CD4 cell count in Cohort 2 was lower at Week 24 compared to baseline, these changes were considered not to be clinically relevant. CD4 count changes will be further assessed when longer-term MOCHA Cohort 2 data are available from Weeks 72, and 96. Cabenuva labeling will include the median change from baseline in CD4 cell count for MOCHA Cohort 2 at Week 24 (-36.0 cells/mm^3) under 14.2 Clinical Trial in Adolescents. The inclusion of the change in CD4 cell count in labeling is consistent with our labeling practices for adolescent trials for recent INSTI-based regimens.

8. Safety

Overall, the data submitted in these sNDAs are adequate to characterize the safety profile of Vocabria and Cabenuva in adolescents. Review of the provided safety findings in adolescents from MOCHA are consistent with previous safety findings in adults and adolescents receiving CAB+RPV in the registrational Phase 3 trials and no new safety concerns were identified.

MOCHA was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in adverse (AE) incidences. Descriptive statistics were therefore applied to describe the observed findings.

8.1 Overview and Methods

The data for the safety review are the from the full Cohort 1 analysis and the Cohort 2 Week 24 primary analysis from MOCHA.

Using the Applicant's SDTM and ADaM datasets, the primary clinical reviewer verified the key safety analyses presented in this section using JMP 16.2.0, unless otherwise specified. The Applicant used MedDRA version 26.0 for coding. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.0 (November 2014) was used to determine severity of AEs. Where noted, Cohorts 1C and 1R are also referred to as subcohorts and the All Available Data Set includes data collected in the LSFU Phase.

Cohort 1

Table 13 summarizes the safety results from Cohort 1 through Week 16. Almost all participants in both Cohort 1C and Cohort 1R reported at least one AE, and approximately one-third of participants in both Cohort 1C and Cohort 1R reported at least one ISR. There were no deaths and there were no serious adverse events (SAEs) assessed as related to study intervention. In Cohort 1R, one participant discontinued oral RPV due to a related AE of hypersensitivity (see Section 8.8.2).

Table 13. Summary of Adverse Events (All Treated Population through Week 16), MOCHA Cohort 1

	Cohort 1C (N=30) n (%)	**Cohort 1R (N=25) n (%)**	**Total (N=55) n (%)**
Any AE	**26 (87)**	**23 (92)**	**49 (89)**
Any AE, excluding ISRs	26 (97)	22 (88)	48 (87)
Any ISR	9 (30)	9 (36)	18 (33)
Any ≥Grade 3 AE	7 (23)	5 (20)	12 (22)
Drug-related AE	9 (30)	12 (48)	21 (38)
Drug-related AE, excluding ISRs	3 (10)	7 (28)	10 (18)
Drug-related ≥Grade 3 AE	1 (3)	1 (4)	2 (4)
Permanently discontinued treatment because of a drug-related AE	0	1 (4)	1 (2)
Any SAE	0	0	1 (2)
Drug-related SAE	0	0	0
Fatal SAE	0	0	0

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0.
Based on DAIDS Adverse Event Grading Tables Version 2.1.
Abbreviations: AE, adverse event; ISR, injection site reaction; OLI, oral lead-in; SAE, serious adverse event.

Cohort 2

Table 14 summarizes the safety results from Cohort 2. Almost all participants (85%) in Cohort 2 reported at least one AE, and approximately one-third of participants reported at least one ISR. There were no deaths and there were no SAEs assessed as related to study intervention. No participants discontinued study drugs due to a related AE.

Table 14. Summary of Adverse Events (All Treated Population, All Available Data), MOCHA Cohort 2

	Cohort 2 Total (N=144) n (%)
Any AE	**122 (85)**
Any AE excluding ISRs	119 (83)
Any ISR AE	49 (34)
Any AE ≥Grade 3	22 (15)
Any drug-related AE	51 (35)
Any drug-related AE excluding ISRs	15 (10)
Any drug-related AE ≥Grade 3	2 (1)
Any drug-related AE causing permanent treatment discontinuation	0
Any SAE	2 (1)
Any drug-related SAE	0
Any fatal SAE	0

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0.
Based on DAIDS Adverse Event Grading Tables Version 2.1.
Abbreviations: AE, adverse event; ISR, injection site reaction; OLI, oral lead-in; SAE, serious adverse event.

Safety Update Report

On May 20, 2024, a 60-Day Safety Update report was submitted with safety information through the database lock of March 21, 2024, for MOCHA Cohort 2 only. The safety data in the 60-Day Safety Update did not raise any new safety concerns.

All participants had reached Week 48 by August 05, 2023, and most participants (108 of 144 [75%] participants) had 12 injection or 13 injection visits. The remaining participants either had <12 injections (22 of 144 [15%] participants; or had 14 or 15 injections (14 of 144 [10%] participants). As for the number of weeks on treatment, 140 of 144 (97%) participants have been on treatment for at least 72 weeks. Two additional pregnancies were reported in participants in Cohort 2; both pregnancies were ongoing at the time of the report and the outcomes were not known.

One participant discontinued CAB+RPV because of a study drug-related SAE of anaphylactic reaction (assessed as related to RPV); this was the only SAE reported as related to study drug in Cohort 2 and the only reported AE leading to discontinuation in Cohort 2. A brief description of this event is described below.

A female participant (aged 17 years at enrollment and 19 years at the time of the event) developed what was initially considered by the principal investigator as a Grade 4 anaphylactic reaction within minutes following administration of the two injections at Week 72. CAB was the first drug administered and RPV was administered approximately 1 minute later. No

complications were observed with either the CAB or RPV injection; however, approximately 1 minute after receiving RPV, the participant reported feeling "tight in the chest" and described a "choking" sensation. The participant developed a maculopapular rash on the face, chest, arms, trunk and extremities but did not lose consciousness or develop angioedema or any change in her voice. Blood pressure was recorded as 143/93 mm Hg and the pulse rate was 76 beats/minute. Approximately 9 minutes later, it was noted that chest tightness had decreased and the rash was fading. Blood pressure was 115/72 mm Hg and pulse 76 beats/min. An allergist was consulted and the participant was diagnosed as having a Grade 4 anaphylactic reaction, related to both study drugs. The participant was treated with "adrenaline and normal saline infusion." After approximately 25 minutes, blood pressure was 121/75 mm Hg and pulse was 84 beats/min. The participant was admitted to hospital for observation where her symptoms improved and she was discharged after 24 hours. Subsequently, the study site conducted skin testing using oral RPV and CAB tablets for presumed allergy (outside of the protocol recommendations). The tests resulted in a negative finding for CAB but an equivocal result for RPV. The participant was discontinued from the study drugs since the investigator did not feel anaphylaxis following study drug exposure could be ruled out.

The Applicant stated that the Clinical Management Committee (CMC) and DAIDS medical officer reviewed the case of Grade 4 anaphylactic reaction; however, the CMC and DAIDS medical officer considered the events as not strongly indicative of anaphylaxis. Instead, the CMC and DAIDS medical officer considered the events to be potentially consistent with a Grade 3 RPV post-injection reaction (PIR) and were not life threatening. The prolonged time to onset (Week 72) relative to the start of CAB+RPV in Cohort 2 and the speed of resolution despite presumed ongoing exposure to CAB+RPV together with the observed improvement in some symptoms prior to administration of "adrenaline," were considered by the DAIDS medical officer and the CMC as not strongly indicative of anaphylaxis. Post-dose PK samples were collected; however, results were not available at this time.

Clinical Reviewer's Comment: Based on the available information, the assessment by the CMC and DAIDS medical officer is reasonable; this event appears to be consistent with a PIR related to the RPV injection and not an anaphylactic reaction because of the prolonged time to onset (Week 72) relative to the start of CAB+RPV and the speed of resolution despite presumed ongoing exposure to CAB+RPV together with the observed improvement in some symptoms prior to the administration of supportive medication and care. No PK data are currently available, which could be used to determine if this event was related to an inadvertent partial intravenous administration of RPV. PIRs are prominently labeled for Cabenuva under Section 5 WARNINGS AND PRECAUTIONS, Post-Injection Reactions with the following signs and symptoms, which also overlap with anaphylaxis: dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest). No additional labeling is recommended.

8.2 Deaths

At the time of the full Cohort 1 analysis and the Week 24 analysis for Cohort 2, there were no deaths.

8.3 Serious Adverse Events (SAEs)

At the time of the full Cohort 1 analysis and the Week 24 analysis for Cohort 2, a total of three participants (one in Cohort 1 and two in Cohort 2) reported nonfatal SAEs that were all assessed as not related to study intervention and are summarized in Table 15. There were no SAEs assessed as related to study intervention at the time of the full Cohort 1 analysis and the Week 24 analysis for Cohort 2.

Table 15. Summary of Serious Adverse Events, MOCHA Cohort 1 (through Week 16) and Cohort 2 (through Week 24)

Participant ID	Preferred Term	Action Taken with Study Drug	Grade	Causality Assessment (Investigator)	Outcome
Cohort 1					
(b) (6)	Gastritis alcoholic haemorrhagic	None	3	Not related	Resolved
Cohort 2					
(b) (6)	Aspartate aminotransferase increased	None	3	Not related	Resolving*
	Blood creatine phosphokinase increased	None	4	Not related	Resolving*
	Rhabdomyolysis	None	4	Not related	Resolved
(b) (6)	Malaria	None	3	Not related	Resolved

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0.
Based on DAIDS Adverse Event Grading Tables Version 2.1.
*Outcome based on the clinical reviewer's assessment (information not reported in the dataset)

Cohort 1
One participant (Participant (b) (6) Cohort 1C) had one nonfatal SAE (hospitalization; Grade 3 gastritis alcoholic hemorrhagic) on Day 92 (duration: 2 days) that was assessed as not related to study intervention. The participant reported drinking "a lot" of alcohol on two separate days prior to the event. Other reported AEs (assessed as not related) during this event included the following: conjunctival pallor (Grade 1), dehydration (Grade 2), dyspepsia (Grade 1), melena (Grade 1), and vomiting (Grade 2). No action was taken with study intervention.

Cohort 2
Two participants had a total of four nonfatal SAEs, which were all assessed as not related to study intervention, and are summarized below.

- One participant (Participant (b) (6)) had three nonfatal SAEs of blood creatine phosphokinase increased (Grade 4) and aspartate aminotransferase increased (Grade 3) that led to hospitalization for rhabdomyolysis (Grade 4). No action was taken with the study intervention. Additional details of these events are included in Section 8.8.7.

- One participant (Participant (b) (6)) had one nonfatal SAE (Grade 3 malaria) and no action was taken with the study intervention.

The SAE assessed as related to study intervention in Cohort 2 that was included in the 60-Day Safety Update, which is also the only reported AE leading to discontinuation in Cohort 2, is described Section 8.1. Of note, a previously reported SAE (blood creatine phosphokinase increased) in Cohort 1 at the time of the Week 16 interim analysis was amended to nonserious by the investigator because the event did not meet criteria for an SAE.

8.4 Dropouts and/or Discontinuations Due to Adverse Events

At the time of the full Cohort 1 analysis and the Week 24 analysis for Cohort 2, one participant discontinued from Cohort 1R due to Grade 3 hypersensitivity following the first oral dose of RPV (see Section 8.8.2). There were no permanent discontinuations of study intervention due to AEs in Cohort 1C or Cohort 2.

The AE of anaphylactic reaction that lead to discontinuation in Cohort 2, which was included in the 60-Day Safety Update, is included in Section 8.1.

Clinical Reviewer's Comment: The Grade 3 event of hypersensitivity (Cohort 1R) that led to discontinuation is included in the Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. Edurant (oral RPV) is labeled for skin and hypersensitivity reactions, including treatment-related rashes that have led to discontinuation. No additional labeling is recommended.

8.5 Treatment Emergent Adverse Events and Adverse Drug Reactions

In this section, the term AE indicates the event occurred irrespective of causality. The term adverse drug reaction (ADR) indicates the AE was deemed at least possibly related to study drug by the investigator. All AEs and ADRs discussed in this section were treatment emergent, meaning the AE or ADR occurred while receiving study drug. This section is presented by combined oral and injection AEs, combined ≥Grade 3 AEs, combined ADRs, and then a summary of AEs and ADRs in the OLI period specifically. AEs or ADRs pertaining to laboratory abnormalities are excluded in this section and are instead discussed in Section 8.6.

Cohort 1 (through Week 16)
The majority (>85%) of participants in both Cohort 1C and Cohort 1R reported at least one AE (Table 13). As shown in Table 16, the most common AEs were injection site pain, cough, oropharyngeal pain, headache, and nasal congestion.

Table 16. Adverse Events[*†] in ≥3 Participants in Either Subcohort (All Treated Population through Week 16), MOCHA Cohort 1

Preferred Term	Cohort 1C n=30 n (%)	Cohort 1R n=25 n (%)
Injection site pain	9 (30)	9 (36)
Cough	8 (27)	4 (16)
Oropharyngeal pain	5 (17)	4 (16)
Headache	2 (7)	5 (20)
Nasal congestion	3 (10)	4 (16)
Blood pressure increased	6 (20)	0
Hypertension	6 (20)	0
Rhinorrhoea	1 (3)	3 (12)
Vomiting	1 (3)	3 (12)
Nasal mucosal disorder	0	3 (12)
Nausea	0	3 (12)

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0.
Based on DAIDS Adverse Event Grading Tables Version 2.1.
[*]Excluding laboratory findings.
[†]Includes events that occurred during the oral lead-in.

Cohort 2 (All Available Data)

The majority (85%) of participants in Cohort 2 reported ≥1 AE (Table 14). As shown in Table 17, the most common AEs were injection site pain, cough, and blood pressure increased.

Table 17. Adverse Events[*†] in ≥3 Participants (All Treated Population, All Available Data), MOCHA Cohort 2

Preferred Term	Cohort 2 total (N=144) n (%)
Injection site pain	48 (33)
Cough	28 (19)
Blood pressure increased	17 (12)
Headache	16 (11)
Nasal congestion	16 (11)
Upper respiratory tract infection	16 (11)
Pyrexia	14 (10)
Blood pressure systolic increased	13 (9)
Oropharyngeal pain	12 (8)
Rhinorrhoea	11 (8)
Blood creatine phosphokinase increased	9 (6)
COVID-19	9 (6)

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0.
Based on DAIDS Adverse Event Grading Tables Version 2.1.
[*]Excluding events related to laboratory findings.
[†]Includes events that occurred during the oral lead-in.

Grade ≥3 Adverse Events

Cohort 1 (through Week 16)
Four participants had a total of four Grade 3 AEs that included the following events (there were no Grade 4 events):

- Hypersensitivity (Cohort 1R)
  - Assessed as related to study intervention
  - See Section 8.8.2 for additional details
- Insomnia (Cohort 1C)
  - Assessed as related to study intervention
  - See Section 8.8.4
- Gastritis alcoholic hemorrhage (Cohort 1C)
  - Assessed as not related to study intervention
  - See Section 8.3 for additional details

Of note, several Grade 3 or 4 AEs pertained to laboratory abnormalities or to vital signs are discussed in Section 8.6 and Section 8.7, respectively.

Clinical Reviewer's Comment: The two Grade 3 events of hypersensitivity (Cohort 1R; led to discontinuation) and insomnia (Cohort 1C) are included in the Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. No additional labeling is recommended.

Cohort 2 (All Available Data)
Of the AEs in Table 18, only the ISRs (Grade 3 injection site pain and Grade 3 injection site abscess) were considered related to study intervention (see section 8.8.1). Additional details of the event of rhabdomyolysis (Grade 4) are included in Section 8.8.7.

Table 18. Grade 3 and 4 Adverse Events (All Treated Population, All Available Data), MOCHA Cohort 2

Preferred Term	Grade	Cohort 2 Total (N=144) n (%)
Injection site abscess	3	2 (1)
Injection site pain	3	1 (<1)
Malaria	3	1 (<1)
Rhabdomyolysis	4	1 (<1)

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0
Based on DAIDS Adverse Event Grading Tables Version 2.1
[†]Includes events that occurred during the oral lead-in

Of note, several Grade 3 or 4 AEs pertained to laboratory abnormalities or vital signs and are discussed in Section 8.6 and Section 8.7, respectively.

Clinical Reviewer's Comment: The two Grade 3 events of injection site abscess and injection site pain from Cohort 2 are included in the Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. No additional labeling is recommended.

Adverse Drug Reactions

Cohort 1 (through Week 16)

In Cohort 1C, 30% of participants reported at least one ADR through Week 16. In Cohort 1R, 48% of participants reported at least one ADR through Week 16. Most participants with ADRs in both Cohorts 1C and 1R reported ISRs, which are expected with IM administration of study intervention, therefore assessed as related, and further discussed in ISRs (See Section 8.8.1).

Other than ISRs, most ADRs were reported by single participants within either subcohort (Table 19), and most non-ISR ADRs were ≤Grade 2. ADRs reported by more than one participant in either subcohort were nausea (Cohort 1R only) and hypersensitivity (Cohort 1R only).

Table 19. Adverse Drug Reactions[*] (All Treated Population through Week 16), MOCHA Cohort 1

Preferred Term	Cohort 1C Total (N=30) n (%)	Cohort 1R Total (N=25) n (%)
Diarrhea	1 (3)	0
Nausea	0	2 (8)
Swelling	1 (3)	0
Hypersensitivity	0	2 (8)
Scar	1 (3)	0
Decreased appetite	1 (3)	0
Dizziness	0	1 (4)
Headache	1 (3)	1 (4)
Somnolence	0	1 (4)
Insomnia	1 (3)	1 (4)
Pruritus	0	1 (4)
Rash	0	1 (4)
Rash maculopapular	0	1 (4)
Rash papular	0	1 (4)

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0
Based on DAIDS Adverse Event Grading Tables Version 2.1
[*]Excluding injection site reactions

Clinical Reviewer's Comment: ADRs reported by more than one participant in Cohort 1 (regardless of severity) are included in Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. The non-ISR ADRs reported by more than one participant (regardless of severity) were headache (n=2), hypersensitivity (n=2), insomnia (n=2), and nausea (n=2). No additional labeling is recommended.

Cohort 2 (All Available Data)

In Cohort 2, 35% of participants reported at least one ADR. Most participants with ADRs reported ISRs, which are expected with IM administration of study intervention and further discussed in Section 8.8.1. Most non-ISR ADRs were reported by single participants (Table 20), and all non-ISR ADRs were ≤Grade 2.

Table 20. Adverse Drug Reactions* (All Treated Population, All Available Data), MOCHA Cohort 2

Preferred Term	Cohort 2 Total (N=144) n (%)
Headache	3 (2)
Nausea	2 (1)
Rash	2 (1)
Rash pruritic	2 (1)
Abdominal pain upper	1 (<1)
Asthenia	1 (<1)
Chest pain	1 (<1)
Chills	1 (<1)
Cough	1 (<1)
Dizziness	1 (<1)
Dyspnoea	1 (<1)
Flatulence	1 (<1)
Hyperhidrosis	1 (<1)
Myalgia	1 (<1)
Papule	1 (<1)
Presyncope	1 (<1)
Product administration error	1 (<1)
Rash maculo-papular	1 (<1)
Somnolence	1 (<1)
Vomiting	1 (<1)

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0
Based on DAIDS Adverse Event Grading Tables Version 2.1
*Excluding injection site reactions

Clinical Reviewer's Comment: ADRs reported by more than one participant in Cohort 2 (regardless of severity) are included in Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. No additional labeling is recommended.

Adverse Events During Oral Lead-In

Cohort 1

There were no deaths or SAEs in either Cohort 1C or Cohort 1R during OLI, and there were no AEs leading to permanent discontinuation of study intervention in Cohort 1C during OLI.

In Cohort 1C, one participant had an ADR of Grade 1 diarrhea during the OLI. In Cohort 1R, four participants had the following ADRs during the OLI that included the following: hypersensitivity (n=2; one Grade 3 and one Grade 2), pruritus (n=1; Grade 2), rash (n=1; Grade 2), rash maculo-papular (n=1; Grade 2), insomnia (n=1; Grade 1), and somnolence (n=1; Grade 1). One participant (Participant (b) (6) Cohort 1R) discontinued study intervention due to a nonserious Grade 3 hypersensitivity following the first oral dose of RPV (see Section 8.8.2).

Cohort 2

There were no deaths, SAEs, or AEs leading to permanent discontinuation of study intervention during OLI. Forty percent of all participants in Cohort 2 reported at least one AE during OLI; the majority of these participants reported an AE that was ≤Grade 2. Most of the AEs reported by participants during OLI were assessed as not related to study intervention.

All ADRs during OLI were Grade 1 in intensity and included the following: nausea (n=2), rash (n=2), rash pruritic (n=2), abdominal pain upper (n=1), flatulence (n=1), headache (n=1), papule (n=1), vomiting (n=1), and somnolence (n=1).

Clinical Reviewer's Comment: The safety profile of oral CAB and oral RPV during the OLI period in adolescents was consistent with the safety profile in adults and no new ADRs were identified. The hypersensitivity event during OLI in Cohort 1R that led to discontinuation is included in the Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. No additional labeling is recommended.

8.6 Laboratory Findings

Across Cohort 1 and Cohort 2, no new safety concerns were identified based on the review of laboratory abnormalities.

Chemistry

Cohort 1 Overall Assessment through Week 16
There were no clinically relevant patterns in median chemistry parameters over time (both observed and change) for participants in either Cohort 1C or Cohort 1R. The majority of participants had no changes in grade for all graded chemistry laboratory parameters through Week 16. Grade 1 or Grade 2 changes were reported in several participants for ALT, bilirubin, and lipase. Chemistry parameters for which a ≥Grade 3 change from Baseline was reported through Week 16 were creatine phosphokinase (CPK), creatinine clearance (CrCl), and/or serum creatinine.

Cohort 2 Overall Assessment through Week 24
Through Week 24, there were no clinically relevant patterns in median chemistry parameters over time (both observed and change) for participants in Cohort 2. The majority of participants had no changes in grade for all graded chemistry laboratory parameters. Grade 1 or Grade 2 changes were reported in several participants for ALT, bilirubin, and lipase. Chemistry parameters for which a ≥Grade 3 change from Baseline were reported were CPK and CrCl.

Liver Chemistry
No participants in either Cohort 1 or Cohort 2 had an adverse events of special interest (AESI) relevant to hepatotoxicity.

Cohort 1
Through Week 16, no participants met Hy's law criteria or other protocol-defined liver monitoring criteria. Increases in ALT or bilirubin were all ≤Grade 2. One of the 3 participants in Cohort 1C with a bilirubin increase through Week 16 had a Grade 2 increase (see Section 8.8.3).

Cohort 2
Through Week 24, no participants met Hy's law criteria or other protocol-defined liver monitoring criteria. Increases in ALT or bilirubin were all ≤Grade 2. One participant had an SAE

of Grade 3 aspartate aminotransferase increased concurrent with SAEs of blood creatine phosphokinase increased and rhabdomyolysis (See Section 8.8.7).

Renal Function

Cohort 1 (through Week 16)
Changes in serum creatinine were reported in several participants in both subcohorts; none had Grade 1 increases and eight participants had Grade 2 increases (six participants in Cohort 1C and two participants in Cohort 1R).

Participants in both subcohorts (two participants in Cohort 1C and one participant in Cohort 1R) had shifts to Grade 3 for serum creatinine and/or CrCl that were reported as AEs; none were assessed as related to study intervention, and there were no changes to the study intervention. In one of the Cohort 1C participants (Participant (b) (6)), although the serum creatinine was within the reference range, there were AEs of creatinine renal clearance decreased that were graded as Grade 2 or 3. The CrCl value at the time of the Grade 3 AE creatinine renal clearance decreased was 109 mL/min/1.73m^2, which was above the Grade 3 absolute value cutoff of 60 mL/min/1.73m^2; however, this represented a -30.1% change from baseline (DAIDS Grade 3 criteria: 30 to <50% decrease from participant's baseline). The CrCl value at the next study visit was 133 mL/min/1.73m^2 (representing a -14.6% change from baseline); therefore, this no longer met the criteria for a Grade 3 shift. In the other two participants with AEs of creatinine clearance decreased, the CrCl values no longer met criteria for a Grade 3 shift by the subsequent study visit.

Cohort 2 (All Available Data)
Changes in serum creatinine were reported in several participants; those that had changes were ≤Grade 2. Three participants had shifts to Grade 3 in CrCl that were reported as AEs (creatinine renal clearance decreased) but were all assessed as not related to study intervention and there were no changes to the study intervention; these three participants are described below.

- Participant (b) (6) had two Grade 3 AEs of creatinine renal clearance decreased. CrCl was below 60 mL/min/1.73 m^2 at Week 56 (56.7 mL/min/1.73 m^2) and Week 72 (52.6 mL/min/1.73 m^2) but above this threshold (Grade 2) at Week 80 (63.3 mL/min/1.73 m^2). Of note, the participant's creatinine clearance at Cohort 2 baseline was normal (95.7 mL/min/1.73 m^2) and serum creatinine was within the reference range through Week 80.
- Participant (b) (6) had three AEs of creatinine renal clearance decreased and had a medical history of blood creatinine increased (Cohort 2 baseline serum creatinine: Grade 1). This participant's CrCl was below 60 mL/min/1.73m^2 (Grade 3) at Week 24 (57.5 mL/min/1.73 m^2), Week 32 (57.0 mL/min/1.73 m^2), and Week 40 (55.2 mL/min/1.73 m^2).
- Participant (b) (6) had multiple (n=28) Grade 3 AEs of creatinine renal clearance decreased and had a history of blood creatine phosphokinase increased and serum creatinine renal clearance decreased (Cohort 2 baseline creatinine clearance: Grade 2). CrCl was below 60 mL/min/1.73m^2 at multiple timepoints through Week 64 (lowest value: 43 mL/min/1.73 m^2), which were reported as separate AEs. It was noted that this participant had Grade 3 AEs of blood creatine phosphokinase increased secondary to

Hashimoto's thyroiditis (reported as Grade 1 AE of autoimmune thyroiditis) at some of the same visits when Grade 3 creatinine renal clearance decreased was reported. This participant also had an AE of Grade 2 chronic kidney disease, considered not related to study intervention, and reported as resolved after 67 days. Per the Applicant, approximately 1 month following the treatment of Hashimoto's thyroiditis, the participant's CrCL and CPK values improved to Grade 2.

Creatine Phosphokinase

Cohort 1 (through Week 16)
One participant in Cohort 1C and two participants in Cohort 1R had Grade 4 CPK values through Week 16, all of which were also reported as Grade 4 AEs of blood creatine phosphokinase increased. All three of these participants had transient elevations in CPK that returned to the reference range at subsequent visits (resolved), All three of these participants had a relevant exercise history, and one of the three participants also had myalgia (see Section 8.8.7).

An additional participant in Cohort 1R had a Grade 4 CPK value (also reported as an AE) after Week 16, during LSFU. The nonserious Grade 4 AE of blood creatine phosphokinase increased was recorded at Day 184 (LSFU); the final dose of study intervention (600 mg of RPV LA) had been on Day 86. The AE was considered unrelated to study intervention. Of note, this AE had been reported as serious at the Week 16 interim analysis, but the investigator amended their characterization to nonserious as the event did not meet criteria for an SAE. The participant reported sore muscles on movement from vigorous exercise with an associated AE of Grade 2 myalgia. On subsequent testing (Day 190), the participant's CPK value improved to Grade 1 and remained within the reference range at subsequent visits during LSFU.

Cohort 2 (All Available Data)
Two participants had a maximum of Grade 3 CPK values and seven participants had a maximum of Grade 4 CPK values, all of which were also reported as AEs of blood creatine phosphokinase increased. Five of the nine participants had single AEs of blood creatine phosphokinase increased to Grade 3 or Grade 4, and four of the nine participants had multiple Grade 3 and/or 4 AEs of blood creatine phosphokinase increased. None of these AEs were considered related to study intervention and none were treatment limiting. Eight of the nine participants also had a relevant exercise history, and the one participant without a relevant exercise history had concurrent thyroid disease. A Grade 4 AE of blood creatine phosphokinase increased was serious for one participant, who also had an associated SAE of rhabdomyolysis (see Section 8.8.7).

Lipase

Cohort 1 through Week 16
No participants had an AE associated with pancreatitis. Increases in lipase, observed only in Cohort 1C, were all ≤Grade 2.

Cohort 2 (All Available Data)
No participants had an AE associated with pancreatitis. Increases in lipase were all ≤Grade 2.

Hematology

Across Cohort 1 and Cohort 2, no new safety concerns were identified based on the review of hematology abnormalities.

Cohort 1 (through Week 16)
Most participants did not have any graded changes in hematology parameters, where applicable; of the few who did, all shifts were ≤Grade 2 in both subcohorts.

ANC was not a protocol-required laboratory parameter under protocol Version 2.0 or 3.0. Although ANC was not a required test, sites received ANC results as part of the requested panels, and these AEs were therefore reported as incidental findings when differential white cell counts were reported as part of the scheduled leukocyte count. AEs of Grade 3 neutropenia was reported for one participant in Cohort 1C and two participants had Grade 3 neutrophil count decreased in Cohort 1R. The participant in Cohort 1C was known to have chronic neutropenia, which fluctuated over time. One of the two participants in Cohort 1R had a medical history of neutrophil count decreased; however; the Grade 3 AE of neutrophil count decreased appeared to have been reported erroneously since the recorded neutrophil counts indicated sporadic transient reductions in neutrophil count to a maximum of Grade 2. In addition, the AE began the same day as the first dose of study intervention, which suggests that it was not treatment emergent. The other Cohort 1R participant also had a history of chronic fluctuations in neutrophil counts of unknown etiology that pre-dated study participation and persisted beyond Week 48 LSFU.

Cohort 2
Through Week 24, there were no patterns in median hematology parameters over time or changes over time for participants in Cohort 2.

For All Available Data, most participants did not have any changes in grade of gradable hematology parameters (for the few participants who did, all shifts in leukocytes and platelets were ≤Grade 2). Most shifts in hemoglobin were also ≤Grade 2; however, one participant had a shift to Grade 3 hemoglobin at Week 24. This participant had concurrent iron deficiency anemia (Grade 3) and hemoglobin decreased (Grade 3). At the last two assessments available prior to the data cutoff date, hemoglobin returned to the reference range.

For All Available Data, three participants had Grade 3 AEs related to low absolute neutrophil count, which was not a protocol-required laboratory parameter at the time of event (similar to Cohort 1). One Grade 3 and two Grade 4 AEs related to decreased neutrophils were reported for three participants in Cohort 2. In two of these participants, the reports represented isolated events that resolved and were not sustained findings over time; the outcome was not known for one participant. Two of the three participants had a medical history relevant to decreased neutrophils. In one participant, viral infection was considered to be a potential alternative cause of neutropenia.

8.7 Vital Signs

Overall, no clinically important vital signs findings were noted with respect to median observed data for vital signs. AEs relevant to increased blood pressure were observed, but all were assessed as not related to study intervention.

Cohort 1 (through Week 16)
No clinically important findings were noted with respect to median observed data for vital signs in Cohort 1. AEs relevant to increased blood pressure were observed, but all AEs were assessed as not related to study intervention. Events related to hypertension were evaluated because events of hypertension (Vascular disorders SOC) were among the common AEs reported in Cohort 1C, and in the Investigations SOC, three AEs (blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased) relevant to increased blood pressure were reported as AEs in participants in Cohort 1C (Table 16).

Six participants (Cohort 1C Q8W) had an AE of hypertension (all Grade 1), which were from the same study site (5116) that did not enroll participants in Cohort 1R. In addition, eight participants had AEs in the Investigations SOC relevant to increased blood pressure, which were all from the same study site that did not enroll participants in Cohort 1R (8052). Six participants (Cohort 1C Q8W) had blood pressure increased (Grade 1 or 2), one participant (Cohort 1C Q8W) had blood pressure systolic increased (Grade 3), and one participant (Cohort 1C Q8W) had blood pressure diastolic increased (Grade 2). The participant with blood pressure systolic increased (Grade 3) had a past medical condition of blood pressure systolic increased and concurrent condition of sinus bradycardia; concomitant ARVs included lopinavir and ritonavir. All of these AEs were assessed as not related to study intervention and none of these AEs were serious or led to changes in study intervention. According to the Applicant, 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.

No participants met the defined reporting criteria for QTc prolongation.

Cohort 2
No clinically important findings were noted with respect to median observed data for vital signs in Cohort 2. Median weight at Baseline was 48.5 kg and it was 51.3 kg at Week 24. Median height at Baseline was 156.6 cm and it was 158.4 cm at Week 24. Median BMI at Baseline was 19.5 kg/m^2 and it was 20.0 kg/m^2 at Week 24. All increases over the 24 weeks as would be expected in this adolescent age group.

AEs relevant to increased blood pressure were observed, but all AEs were assessed as not related to study intervention. Events related to hypertension were further evaluated because hypertension was among the common AEs reported in Cohort 2, and in the Investigations SOC, three AEs (blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased) relevant to increased blood pressure were reported for participants in Cohort 2 (Table 17).

All AEs of hypertension were Grade 1, and most of the other AEs relevant to increased blood pressure were Grade 1 or 2. All AEs relevant to increased blood pressure were reported at three sites (including one site [8052] that had the same events in Cohort 1), and all AEs of hypertension were reported at a separate single site (5116), which is the same site that had events of hypertension in Cohort 1. Four participants reported at least one Grade 3 AE relevant to increased blood pressure (blood pressure increased or blood pressure systolic increased). All 4 of these participants were enrolled at the same study site (8052) with one participant from Cohort 1C with a Grade 3 AE blood pressure systolic increased. All four participants had concurrent medical conditions or a history of blood pressure systolic increased (n=2), hypertension (n=1), or blood pressure increased (n=1).

No participants in Cohort 2 met ECG reporting criteria for QTc prolongation.

Clinical Reviewer's Comment: The reporting of AEs relevant to increased blood pressure from only two study sites is notable and could be a reflection of the timing and/or technique of the blood pressure measurements at these study sites; in addition, some of the participants had a medical history of increased blood pressure. According to the Applicant, 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.

8.8 Adverse Events of Special Interest

This section provides an overview of the following AESI based on concerns identified from the original NDA reviews or class-related concerns:

- Injection site reactions
- Hypersensitivity reactions
- Hepatobiliary events
- Psychiatric events (including depressive disorders)
- Neurologic events (including seizure)
- Gastrointestinal events (including pancreatitis)
- Musculoskeletal events (related to injection or rhabdomyolysis)
- Weight increase
- Pregnancy and embryo-fetal toxicity

Overall, analyses of these AESIs did not reveal any concerning findings.

8.8.1 Injection Site Reactions

Cohort 1 (through Week 16)
Nine of 30 (30%) participants in Cohort 1C and 9 of 25 (36%) participants in Cohort 1R reported at least one ISR.

No participants withdrew because of ISRs, and no ISRs met the criteria for an SAE. In both cohorts, all ISRs were ≤Grade 2 and the most commonly reported ISR in both cohorts was injection site pain, which was reported by all 18 participants with ISRs. Table 21 summarizes ISRs by grade through Week 16.

Overall, 36 of 39 (92%) ISRs resolved within 7 days, and the longest duration was 14 days (Cohort 1C; Grade 1 injection site pain). One participant in Cohort 1R prematurely discontinued treatment with study drug because of procedural pain (no RPV was injected at the time of the administration attempt because the participant requested cessation of the injection due to procedural pain).

Table 21. Injection Site Reactions (All Treated Population through Week 16), MOCHA Cohort 1

Preferred Term	Cohort 1C (n=30) n (%)			Cohort 1R (n=25) n (%)		
Grade	**1**	**2**	**≥3**	**1**	**2**	**≥3**
Any ISR	5 (17)	4 (13)	0	5 (20)	4 (16)	0
Injection site hypoesthesia	0	0	0	1 (4)	0	0
Injection site nodule	0	0	0	1 (4)	0	0
Injection site pain	5 (17)	4 (13)	0	5 (20)	4 (16)	0
Injection site swelling	0	0	0	1 (4)	0	0

Source: Clinical Reviewer's Analysis of ADAE dataset (MOCHA); JMP 16.2.0.
Note: A participant may have reported an ISR more than once; for each preferred term, a participant was only counted for the worst grade.
Note: Grade: 1 = Mild, 2 = Moderate, 3 = Severe.
Based on DAIDS Adverse Event Grading Tables Version 2.1.
Abbreviations: ISR, injection site reaction.

No participants in Cohort 1 developed signs or symptoms compatible with or reported as possible PIR.

Cohort 2 (All Available Data)

In Cohort 2, only 142 of the 144 participants received at least one injection. Forty-nine of 144 (34%) participants in Cohort 2 reported at least one ISR through the data cutoff date. The most commonly reported ISR was injection site pain, both by participant (Table 22) as well as event (183 of the 209 [88%] total ISRs reported).

Overall, 64% of injection site pain ISRs resolved within 3 days, 90% of injection site pain ISRs resolved within 14 days, 2% of injection site pain ISRs had a duration of >14 days, and 5% of injection site pain ISRs were ongoing at the data cutoff date. With the exception of injection site pain, all other types of ISRs were reported in <5% of participants and most participants had ISRs that were Grade 1 or 2. Injection site nodule was reported in 6 of 144 (4%) participants; 33% of injection site nodule ISRs resolved within 7 days and all resolved within 21 days.

Grade 3 ISRs were reported in two participants; one participant with Grade 3 injection site abscess (duration: 4 days) and one participant with Grade 3 injection site abscess (duration: 16 days) and Grade 3 injection site pain (duration: 16 days). None of these events were serious and the participants continued receiving injections of the study intervention following resolution of the event(s).

Table 22. Injection Site Reactions (All Treated Population, All Available Data), MOCHA Cohort 2

Preferred Term	Cohort 2 Total N=144* n (%)			
Grade	**1**	**2**	**3**	**Total**
Injection site pain	38 (26)	9 (6)	1 (1)	48 (33)
Injection site nodule	5 (4)	1 (1)	0	6 (4)
Injection site swelling	5 (4)	0	0	5 (4)
Injection site abscess	0	0	2 (1)	2 (1)
Injection site pruritus	2 (1)	0	0	2 (1)
Injection site bruising	1 (1)	0	0	1 (1)
Injection site erythema	1 (1)	0	0	1 (1)
Injection site induration	1 (1)	0	0	1 (1)
Injection site joint pain	1 (1)	0	0	1 (1)

Source: Clinical Reviewer's Analysis of adae.xpt dataset (MOCHA); JMP 16.2.0.
*The number of participants who received an injection is different (142 of 144).
Note: A participant may have reported an ISR more than once; for each preferred term, a participant was only counted for the worst grade.
Note: Grade: 1 = Mild, 2 = Moderate, 3 = Severe.
Based on DAIDS Adverse Event Grading Tables Version 2.1.

Three participants in Cohort 2 reported nonserious AEs that were potentially consistent with a PIR and are summarized below. None of these events led to discontinuation of study intervention. Of note, PK data were not available for any of the three cases.

One participant (Participant (b) (6)) had three Grade 1 AEs on Day 290 of injection related reaction. All three events resolved on the same day that they occurred. Prior to this, on Day 170, four Grade 1 AEs (hyperhidrosis, palpitations, and two events of injection site pain) were reported. Hyperhidrosis and palpitations resolved on the same day they occurred. Of these seven events, the two injection site pain AEs were the only AEs assessed as related to study intervention.

One participant (Participant (b) (6)) had a Grade 1 immediate post-injection reaction on Day 282 that resolved the same day it occurred and was assessed as not related to study intervention. No other AEs were reported.

One participant (Participant (b) (6)) had multiple Grade 2 AEs on Day 284 including chest pain, cough, dyspnea, hyperhidrosis, and product administration error, all of which resolved on the same day they occurred and were assessed as related to study intervention.

Clinical Reviewer's Comment: The type of ISRs reported in adolescents are generally similar to adults. Information regarding ISRs from MOCHA Cohort 1 and Cohort 2 are included in Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. No additional labeling is recommended.

8.8.2. Hypersensitivity Reactions and Rash

Cohort 1 (through Week 16)
Two participants experienced hypersensitivity ADRs (both in Cohort 1R) and are described below. No suspected hypersensitivity reactions were reported in Cohort 1C.

One participant (Participant (b) (6) Cohort 1R) experienced a nonserious Grade 3 hypersensitivity (verbatim term: *acute allergic reaction*) ADR on the first day of RPV OLI leading to discontinuation of study intervention (assessed as related to RPV). Symptoms included rash and itchiness; acute symptoms began resolving within a few hours and were completely resolved within 6 days.

A second participant (Participant (b) (6) Cohort 1R) developed three rashes (all Grade 2) on Day 11 (OLI), followed by Grade 2 hypersensitivity (verbatim term: *allergic reaction*) on Day 15 (OLI); all were nonserious and assessed as ADRs. One of the rashes resolved in 1 day and the other two rashes resolved after 9 days. The resolution of the AE of hypersensitivity (duration: 5 days) was the same day as the resolution of the two rashes. No action was taken with the study intervention, and the participant remained on study.

Clinical Reviewer's Comment: The Grade 3 event of hypersensitivity (Cohort 1R) that led to discontinuation is included in the Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. Edurant (oral RPV) is labeled for skin and hypersensitivity reactions, including treatment-related rashes that have led to discontinuation. No additional labeling is recommended.

Cohort 2 (All Available Data)
No participants had events consistent with suspected hypersensitivity reactions.

Four participants had at least one AE of rash or rash-like events: rash and rash pruritic (n=2), rash (n=1), or rash maculo-papular (n=1). All events were Grade 1 in intensity, nonserious, and none led to discontinuation of study intervention. In three of the participants, the events were considered related to study intervention; rash and rash pruritic (n=2), or rash maculo-papular (n=1). The fourth participant had an event of rash during the injection phase, which was considered unrelated to study intervention.

Clinical Reviewer's Comment: The Cabenuva labeling includes rash (erythema, pruritus, pruritus generalized, purpura, rash, rash- erythematous, generalized, macular) as an ADR reported in at least 2% of participants from the Phase 3 trials FLAIR and ATLAS. The ADRs of rash (n = 2) and rash pruritic (n = 2) from Cohort 2 are included in Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. Edurant (oral RPV) is labeled for skin and hypersensitivity reactions, including treatment-related rashes that have led to discontinuation. No additional labeling is recommended.

8.8.3. Hepatobiliary Events

Cohort 1
No participants met Hy's law criteria or other protocol-defined liver monitoring criteria. Increases in ALT were all ≤Grade 2.

One participant (Participant (b) (6) Cohort 1C) had three nonserious Grade 3 AEs of blood bilirubin increased during LSFU on Days 203, 241, and 721; all AEs were considered not related to study intervention. The participant was taking an atazanavir-based regimen as part of his background cART regimen, which is associated with asymptomatic and reversible hyperbilirubinemia. Prior to Week 16, there were intermittent, transient bilirubin changes to ≤Grade 2. At the last visit before LSFU (Day 94), bilirubin was within the reference range.

Cohort 2
No participants met Hy's law criteria or other protocol-defined liver monitoring criteria. Increases in ALT or bilirubin were all ≤Grade 2.

One participant had a Grade 3 SAE of aspartate aminotransferase increased concurrent with SAEs of rhabdomyolysis and blood creatine phosphokinase increased; additional details are provided in Section 8.8.7.

8.8.4. Psychiatric Events (including depressive disorders)

Cohort 1
One participant in Cohort 1C had depression (Grade 1), anxiety (Grade 1), and post-traumatic stress disorder (Grade 1) after LSFU. These events were nonserious, not considered related to study intervention, and all reported as resolved. Although reported as Cohort 1 AEs, these events were reported after the LSFU Week 48 visit for Cohort 1 but prior to the participant's eventual enrollment in Cohort 2.

Five participants reported nonserious events of insomnia (n=4) or stress (n=1). Insomnia was assessed as related to study intervention in two participants (one Grade 1 [Cohort 1C] and one Grade 3 [Cohort 1R]). The Grade 3 insomnia event is summarized here.

One participant (Participant (b) (6) Cohort 1C) had a nonserious, Grade 3 ADR of insomnia with onset on Day 41, the same day the participant started the injection phase. The participant had not experienced prior insomnia and reported being unable to sleep the entire night after the first injection and being unable to fall asleep the following night until given diphenhydramine. Study participation continued with no change in study intervention and the event resolved in 5 days.

Clinical Reviewer's Comment: The Grade 3 insomnia ADR is included in the Cabenuva labeling under 6.1 Clinical Trials Experience, Clinical Trial Experience in Adolescents. Cabenuva labeling includes sleep disorders (insomnia, poor quality sleep, and somnolence) as adverse reactions under 6.1 Clinical Trials Experience from the Phase 3 trials FLAIR and ATLAS.

Insomnia is also included as an adverse reaction under 6.1 Clinical Trials Experience, Adverse Reactions of Vocabria in Clinical Trials for the Treatment of HIV-1 Infection. No additional labeling is recommended.

Cohort 2
There were no AEs in Cohort 2 reported in relation to depressive disorders.

Four participants reported nonserious events of insomnia (n=2), anxiety (n=1), or attention deficit hyperactivity disorder (n=1). These events were considered unrelated to study intervention by the investigator.

8.8.5. Neurologic Events (including seizure)

Cohort 1
There were no confirmed reports of seizure.

One Grade 2 event of syncope (verbatim term: *syncopal episode*) was reported in one participant (Cohort 1R) during LSFU. The event was nonserious, considered unrelated to study intervention, and resolved the same day it occurred.

Cohort 2
There were no confirmed reports of seizure.

One Grade 1 event of syncope (verbatim term: *vasovagal syncope [near syncope without loss of conscious* [sic]]) occurred in a participant after approximately 41 weeks on study. The event was nonserious, considered unrelated to study intervention by the investigator, and resolved the same day it occurred. The participant reported Grade 1 injection site pain on the same day as syncope.

8.8.6. Gastrointestinal Events (including pancreatitis)

Cohort 1 and Cohort 2
There were no significant AEs reported in relation to pancreatitis, and there were no ≥Grade 3 lipase elevations observed in any participant.

8.8.7. Musculoskeletal events (related to injection or rhabdomyolysis)

Cohort 1
Rhabdomyolysis was not reported in any participant in Cohort 1. Three participants (two participants in Cohort 1R and one participant in Cohort 1C) reported Grade 1 or 2 myositis that resolved within 7 days. The myositis events were assessed as not related to study intervention by the investigator, and none led to discontinuation of study intervention. Although two of the three participants had CPK elevations around the time of the myositis events, these events were assessed by the investigator as related to weightlifting/vigorous exercise.

Cohort 2

Rhabdomyolysis (Grade 4 SAE) was reported for one participant in Cohort 2 and is summarized below. In addition, SAEs of AST increased (Grade 3) and blood creatine phosphokinase increased (Grade 4) were also reported. These events were assessed by the investigator as not related to study intervention and did not lead to discontinuation of study intervention.

A 20-year-old male participant (Participant (b) (6); enrollment age was 17 years) was admitted to the hospital with a diagnosis of rhabdomyolysis with an elevated CPK (16,605 U/L; Grade 4 SAE) during the Week 72 study visit; in addition, ALT (124 U/L; Grade 1) and AST (405 U/L; Grade 3 SAE) were found to be elevated. Serum creatinine was normal (0.84 mg/dL). The participant was treated with intravenous normal saline. Repeat laboratory values for CPK and AST improved over the next few days, eventually to Grade 1 at the last observation (4 days after admission). In the weeks prior to the event, the participant reported an intensified weight training regime, increased intake of protein and creatine supplementation, and poor hydration. In addition, the participant also reported consuming a pre-workout supplement containing caffeine for 6 weeks prior to the events. Past medical history included perinatal infection with HIV-1 and attention deficit hyperactivity disorder. Concomitant products included creatine powder. Social history was negative for smoking, drug or alcohol use, and drug and alcohol testing at the time of admission was negative. CAB+RPV were continued with no change. According to the hospital discharge note, the diagnosis of rhabdomyolysis was likely secondary to uptake in exercise regimen with increased supplementation use of protein and creatine.

In addition, Grade 1 myositis events were reported in three participants. All three events resolved within 7 days and none of these participants had other symptoms suggestive of rhabdomyolysis. Two of the three myositis events were assessed as not related to study intervention by the investigator and none led to discontinuation of study intervention.

Clinical Reviewer's Comment: Vocabria and Cabenuva are labeled for pain (e.g., back and chest) in 5.2 Post-Injection Reactions and musculoskeletal pain in 6.1 Clinical Trials Experience, but are not labeled for rhabdomyolysis. Labeling for rhabdomyolysis is not indicated and continued pharmacovigilance is recommended.

8.8.8. Weight Increase

Three participants had AEs associated with weight gain. All events were Grade 1, none were serious, and none led to discontinuation of study intervention. Reported AEs related to weight changes were not independently analyzed in detail because of the subjective nature of reporting such events as an AE.

Cohort 1
One participant (Participant (b) (6)) in Cohort 1R had a nonserious, Grade 1 AE of weight increased at Week 14 that was not considered related to study intervention by the investigator.

Cohort 2
One participant (Participant (b) (6)) had two nonserious, Grade 1 AEs of overweight (both Grade 1, nonserious, and not related) at Weeks 38 and 41 that were not considered related to study intervention by the investigator. This participant had a medical history of "overweight."

One participant (Participant (b) (6)) had a nonserious, Grade 1 AE of obesity at Week 41 that was not considered related to study intervention by the investigator.

8.8.9. Pregnancy and Embryo-Fetal Toxicity

No new nonclinical data were submitted with this submission.

Cohort 1
No participants became pregnant in Cohort 1.

Cohort 2
In Cohort 2, one participant became pregnant during the study as of the data cut-off. The pregnancy outcome was a live birth (assisted vaginal delivery) and Apgar scores at 1, 5, and 10 minutes were 9, 10, and 10, respectively.

In the 60-Day Safety Update, two additional pregnancies were reported in Cohort 2. At the time of the data cut-off, both pregnancies were currently ongoing and the outcomes were not known.

8.9 Special Populations

The total number of participants in MOCHA was too small to ascertain any safety trends based on intrinsic factors.

9. Advisory Committee Meeting

Not applicable. There was no Advisory Committee Meeting held for these sNDA applications. No significant issues were raised to warrant a public discussion.

10. Pediatrics

The use of CAB + RPV in adolescents ≥12 years of age and older and weighing ≥35 kg is supported by the following:

- Open-label Study 208580 (MOCHA) in adolescent participants
  - Full Cohort 1 analysis and Cohort 2 Week 24 primary analysis
- CAB and RPV population PK models
- Pivotal phase 3 trials in adults (FLAIR, ATLAS, ATLAS-2M), including a supplemental analysis of adults weighing <50 kg and <55 kg
- Apretude (CAB) PrEP NDA (sponsored by ViiV); data from HPTN study 083-01 and HPTN 084-01 (adolescent CAB sub studies)

11. Other Relevant Regulatory Issues

None.

12. Labeling

The Vocabria and Cabenuva labeling have been updated with data from the MOCHA full Cohort 1 analysis and Cohort 2 Week 24 primary analysis. No changes to the USPPI are recommended. The final agreed upon USPI will be available at the time of approval.

As of the completion of this review, the following substantive labeling changes have been made:

- Vocabria
  - 6 ADVERSE REACTIONS
    - 6.1 *Clinical Trials Experience*, *Clinical Trial Experience in Adolescents*
      - Updated with safety information from MOCHA Cohort 2 Week 24
  - 8 USE IN SPECIFIC POPULATIONS
    - 8.1 *Pregnancy*
      - Removal of the statement regarding the risk of neural tube defects (NTDs) and that NTDs were associated with dolutegravir
    - 8.4 *Pediatric Use*
      - Updated and the description of MOCHA moved to Section 14
    - 8.6 *Renal Impairment*
      - Minor edit for the definition of severe renal impairment
  - 12 CLINICAL PHARMACOLOGY
    - 12.3 *Pharmacokinetics*
      - Table 4 updated with PopPK model with adolescent data
  - 14 CLINICAL STUDIES
    - 14.2 *Clinical Trials in Adolescents*
      - Updated with a description of MOCHA Cohort 2 Week 24
      - A cross reference to the Cabenuva labeling USPI has been added

- Cabenuva
  - 6 ADVERSE REACTIONS
    - 6.1 *Clinical Trials Experience, Clinical Trial Experience in Adolescents*
      - Updated with Cohort 1 Week 16 (cohort 1) and Cohort 2 Week 24 safety information from MOCHA
  - 8 USE IN SPECIFIC POPULATIONS
    - 8.1 *Pregnancy*
      - Removal of statement regarding the risk of neural tube defects (NTDs) and that NTDs were associated with dolutegravir
    - 8.4 *Pediatric Use*
      - Updated and the description of MOCHA moved to Section 14
  - 12 CLINICAL PHARMACOLOGY
    - 12.3 *Pharmacokinetics*

- Table 11 updated with PopPK model with adolescent data
- 14 CLINICAL STUDIES
  - 14.2 *Clinical Trials in Adolescents*
    - Updated with a description of MOCHA Cohort 1 Week 16 and Cohort 2 Week 24 primary analysis

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

None.

Postmarketing Requirements (PMRs)

None.

These sNDAs were reviewed at the Pediatric Review Committee (PeRC) meeting on August 20, 2024. With these sNDAs, the PeRC agreed that the following PMRs (see Section 2.2) have been fulfilled:

- Vocabria (NDA 212887): 3997-1, 4223-5
- Cabenuva (NDA 212888): 3998-1, 4221-1, 4232-1

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

We recommend approval of these sNDAs, which support continued approval of CAB+RPV dosing regiments in adolescents aged ≥12 years and weighing ≥35 kg as a complete HIV-1 ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

Our recommendation is based on review of the PK, safety, and antiviral activity data from Study 208580 (MOCHA) full Cohort 1 analysis and Cohort 2 Week 24 primary analysis; in addition, our recommendation also considered the available adult PK, safety, and efficacy data.

Benefit-Risk Assessment

Overall, Vocabria and Cabenuva continue to have a favorable benefit-risk profile in the adolescent population aged ≥12 years and older and weighing ≥35 kg.

HIV pediatric trials are predominately single-arm, uncontrolled trials with the primary aim of showing PK parameters comparable to adults, providing at least 24 weeks of safety data, and demonstrating the activity of the drug is generally within the range observed for adults. The

required data to support an indication in pediatric patients infected with HIV-1 are the PK and safety data. Efficacy data are considered supportive. The effectiveness in pediatrics is extrapolated based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adult and pediatric patients. Thus, the PK data are sufficient to extrapolate efficacy; that is, if the exposures achieved in pediatric trials are comparable to the effective exposures (AUC_{0-24}, C_{min}) from adult trials, the new drug is expected to be effective in the pediatric population.

The safety data from Study 208580 (MOCHA) full Cohort 1 analysis and Cohort 2 Week 24 primary analysis suggest that CAB+RPV are generally safe and well-tolerated in adolescent participants. There were no deaths or related SAEs in the full Cohort 1 analysis and Cohort 2 Week 24 primary analysis. Overall, ADRs were similar to those reported in adults. No new or unique safety findings in adolescents compared to adults were observed for CAB or RPV.

There was one Grade 3 ADR (drug hypersensitivity) that lead to discontinuation of RPV in Cohort 1R during the OLI. This event is included in the Cabenuva labeling under Section 6 ADVERSE REACTIONS, 6.1 *Clinical Trials Experience, Clinical Trial Experience in Adolescents.* Of note, Edurant (oral RPV) is labeled for skin and hypersensitivity reactions, including treatment-related rashes that have led to discontinuation. In addition, the 60-Day Safety Update report included a description of a likely RPV PIR (reported by the investigator as a Grade 4 SAE of anaphylactic reaction), which is already prominently labeled for Cabenuva under Section 5 WARNINGS AND PRECAUTIONS, *Post-Injection Reactions*.

The long-term success of HIV-1 treatment is dependent on sustained adherence to ART. Poor adherence to medications is a complex health behavior in children and adolescents, and adherence to ART is commonly encountered in the treatment of children and adolescents living with HIV.[d] LA injectable formulations, such as CAB+RPV, may improve adherence to ART for some individuals, particularly those with adherence barriers related to pill-fatigue associated with daily oral therapy or pill-aversion.

[d] Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed August 2, 2024.

Appendix A

Clinical Investigator Financial Disclosure Review

Application Numbers: 212887/S-009

212888/S-015

Submission Dates: March 21, 2024 and August 15, 2024 (response to information request)

Applicant: ViiV Healthcare

Products: NDA 212887 VOCABRIA (oral cabotegravir)

NDA 212888 CABENUVA (injectable cabotegravir + rilpivirine)

Reviewer: Timothy Jancel, PharmD, MHS

Date of Review: August 19, 2024

Covered Clinical Study: Study 208580 (MOCHA)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 305 (investigators and sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant adequately disclosed financial interests/arrangements with investigators and sub-investigators as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators*, and by 21 CFR 54.4.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIMOTHY J JANCEL
09/12/2024 11:10:13 AM

STEPHANIE B TROY
09/12/2024 11:33:01 AM

YODIT BELEW
09/12/2024 11:34:46 AM