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

Date	March 29, 2022
From	Timothy Jancel, PharmD, MHS (Clinical Reviewer) Sarah Connelly, 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-005 and S-006 (SDN 69 and 71) 212888/S-005 and S-006 (SDN 267 and 275)
Applicant	ViiV Healthcare
Date of Submission	S-005: September 29, 2021 S-006: October 7, 2021
PDUFA Goal Date	March 29, 2022
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
Applicant Proposed Indication(s)/ Population(s)	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: • (b) (4) oral lead-in to assess the tolerability of CAB prior to administration of CABENUVA extended-release injectable suspensions • oral therapy for patients who will miss planned injection dosing with CABENUVA 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 treatment 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 2 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*

* S-003 is currently under review (PDUFA goal date: March 27, 2022) and would allow for an *optional* oral lead-in (i.e., direct to injection)
† S-001 was approved during the review of S-005/6 on January 31, 2022, allowing every-2-month CABENUVA injections

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1. Introduction

This review summarizes the data package submitted by the Applicant (ViiV Healthcare) to support labeling changes for VOCABRIA (cabotegravir [CAB] tablets for oral use) and CABENUVA (CAB extended-release injectable suspension; rilpivirine [RPV] extended-release injectable suspension) to expand treatment to adolescent patients aged ≥12 years and weighing ≥35 kg. The data package includes the Week 16 Clinical Study Report (interim analysis) and associated data sets for study 208580 (MOCHA; IMPAACT 2017): *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.* In addition, the Applicant submitted safety data from lower-weight adults (defined as weighing ≤55 kg) enrolled in the three pivotal phase 3 trials (FLAIR, ATLAS, ATLAS-2M) to support both CAB+RPV dosing regimens (monthly [Q4W] and every 2 months [Q8W]) in adolescents ≥12 years of age and weighing ≥35 kg.

2. Background

HIV is a significant public health concern, both globally and domestically. At the end of 2020, there were an estimated 38 million people living with HIV globally, and 680,000 deaths related to HIV in 2020.[a] In the United States in 2019, 36,801 people received a new diagnosis of HIV, of whom 1,667 were 19 years or younger, and over one million adults and adolescents were living with HIV.[b] 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.

Standard of care HIV treatment 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), integrase strand transfer inhibitors (INSTIs), CCR5 antagonists, fusion/entry inhibitors, attachment inhibitors, and CD4-directed post-attachment HIV-1 inhibitors. Six of these eight classes include drugs that have been approved for treatment of HIV-1 in patients <18 years of age.[c] The long-term success of HIV-1 treatment is dependent on sustained adherence to daily antiretroviral therapy (ART), which can be especially challenging in children and adolescents living with HIV.[d] Recently, the development of multiple long-acting (LA) drugs for the treatment and prevention of HIV-1 has increased, including the approval of injectable CABENUVA for the treatment of HIV-1 infection in adults, and APRETUDE (NDA 215499; CAB extended-release injectable suspension) for HIV-1 pre-exposure

[a] "HIV/AIDS." World Health Organization, https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Accessed January 22, 2022.
[b] "Statistics Overview." Centers for Disease Control and Prevention, https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed January 22, 2022.
[c] "HIV Treatment Information for Children." U.S. Food and Drug Administration, https://www.fda.gov/drugs/hiv-treatment/hiv-treatment-information-children. Accessed January 22, 2022.
[d] "HIV and Children and Adolescents." National Institutes of Health, https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-and-children-and-adolescents. Accessed January 22, 2022.

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

The current sNDAs (212887/S-005 and S-006; 212888/S-005 and S-006) were submitted to expand the indications for VOCABRIA and CABENUVA treatment to include adolescent patients aged ≥12 years and weighing ≥35 kg. VOCABRIA and CABENUVA provide an alternative therapy for adolescent patients who may not tolerate other ARVs or have issues with treatment adherence. Of note, EDURANT is already indicated in combination with other ARV agents for the treatment of HIV-1 infection in patients aged ≥12 years and weighing ≥35 kg.

Prior to these submissions, CAB+RPV Q4W injection dosing was approved for the treatment of HIV-1 infection in adults. During this review cycle, CAB+RPV Q8W injection dosing was approved for HIV-1 treatment in adults under sNDAs 212887 S-001 and NDA 212888 S-001. In addition, VOCABRIA and APRETUDE were approved for PrEP in adults and adolescents weighing ≥35 kg with Q8W injection dosing of CAB.

The Clinical Study Report submitted in these sNDAs describes the results of an interim analysis for MOCHA. MOCHA is an ongoing phase 1/2 multicenter, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and pharmacokinetics (PK) of oral and injectable CAB and injectable RPV in virologically suppressed adolescents aged ≥12 years and weighing ≥35 kg, who are receiving stable combination antiretroviral therapy (cART) consisting of 2 or more drugs from 2 or more classes of ARV drugs. The report provided here describes the data collected from adolescents enrolled in Cohort 1 through Week 16 only (interim analysis; refer to Section 7 for details).

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 Q4W or Q8W as intragluteal intramuscular (IM) injections. CABENUVA is currently indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies per 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 an HIV-1 INSTI indicated in combination with EDURANT (RPV) tablets for oral use. The intended use of VOCABRIA in combination with EDURANT is as oral lead-in (OLI) to assess the tolerability of CAB and RPV prior to administration of CABENUVA, and as oral therapy for patients who will miss planned injection dosing with CABENUVA. Of note, sNDAs 212887/S-003 and 212888/S-003 are currently under review and would allow for an optional oral lead-in (i.e., direct to injection) before starting CABENUVA (PDUFA goal date: March 27, 2022).

[e] 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.

2.2 Summary of Regulatory Activity Related to Submission

MOCHA is a study conducted to fulfill the required pediatric assessments under the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c). The required pediatric assessments were issued in the initial approval letters for VOCABRIA and CABENUVA dated January 21, 2021.

The current application partially fulfills the PREA postmarketing requirements (PMRs) for the following two PMRs:

- 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 ARV regimen at the time of enrollment, to assess the PK, tolerability, and short-term safety of VOCABRIA after 4-week administration in combination with other ARVs.

- 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 PK, 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.

[redacted] (b) (4)

These sNDAs were reviewed at the Pediatric Review Committee (PeRC) meeting on February 1, 2022. The PeRC agreed with the assessment that these components can be labeled for treatment of HIV-1 in adolescents aged ≥12 years and weighing ≥35 kg. During the meeting, DAV clarified that although there are enough safety, tolerability, PK, and antiviral activity data for labeling from the individual components of CABENUVA (i.e., CAB and RPV) in combination with other ARVs, we have not yet reviewed any of the aforementioned data for the CABENUVA combination product; therefore, the PREA PMRs could only be considered partially fulfilled. The PeRC agreed that the PMRs will have to be reviewed and assessed for fulfillment after the CABENUVA data from MOCHA Cohort 2 have been submitted and reviewed.

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 CMC 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 Dr. Mario Sampson's Clinical Pharmacology Review for additional details. In addition to their review, which is summarized below, Clinical Pharmacology also requested inspections of two of the highest enrolling clinical sites (Emory and Johns Hopkins), and of the analytical site (b) (4)

Exposures from adolescent subjects were obtained from MOCHA Cohort 1 and the adult reference consisted of exposures from the pivotal adult phase 3 treatment trials FLAIR, ATLAS, and ATLAS-2M. Comparable PK parameters were observed among adolescents and adults administered CAB OLI followed by Q4W injections. CAB population PK models were developed from PK data collected from adolescents (Q4W dosing) and adults (Q4W and Q8W dosing) and simulations were performed to predict adolescent exposures corresponding to the Q8W regimen. Comparable exposures were predicted for adolescents compared to adults and the CAB Q8W regimen was approved for adolescents for HIV-1 prevention (NDA 215499, integrated review dated December 20, 2021). The same analysis supports approval of the CAB Q8W regimen for treatment of HIV-1 in adolescents. RPV 25 mg orally daily (the same dose as the OLI dosing regimen) was approved for adolescents prior to the conduct of MOCHA. Comparable concentration-time profiles and PK parameters were observed among adolescents and adults administered RPV OLI followed by Q4W injections. Predicted adolescent exposures for adolescents compared to the observed exposures in adults administered RPV Q8W were evaluated using a virtual adolescent population.

Because of the relatively small number of adolescents enrolled and to ensure full coverage of the ≥35 kg weight range, the Applicant also used a virtual adolescent population (n=1000) to conduct a second graphical analysis in addition to a statistical comparison of CAB and RPV exposures in adolescents and adults. Overlapping exposures were observed in adolescents compared to adults with values in adolescents not exceeding safety threshold concentrations and not below efficacy threshold concentrations.

6. Clinical Microbiology

No participant met criteria for protocol-defined confirmed virologic failure (CVF); therefore, no resistance data were available to review. CVF was defined as 2 consecutive plasma HIV-1 RNA test results ≥200 c/mL.

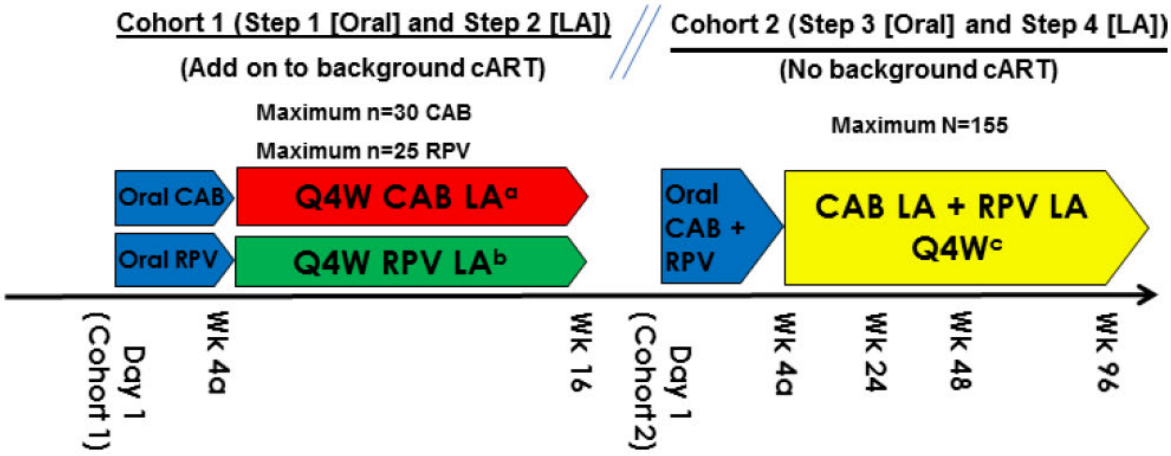
7. Clinical/Statistical- Efficacy

7.1 Overview of the Study Design

MOCHA is an ongoing phase 1/2 multicenter, open-label, non-comparative study evaluating the safety, acceptability, 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 2 or more drugs from 2 or more classes of ARV drugs.

The MOCHA study design is presented in Figure 1. The report provided here describes the data collected from adolescents enrolled in Cohort 1 through Week 16 only (interim analysis).

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



Cohort 1 participants were assigned to Cohort 1C (participants received CAB + cART) or Cohort 1R (participants received RPV + cART) based on their pre-study cART regimen.
Cohort 2 enrollment will be open to eligible participants who have completed Cohort 1 as well as eligible participants who have not been previously enrolled in the study.

a. PI/NNRTI-based cART.
b. INSTI-based cART.
c. Protocol Version 2.0 required participants to receive Q4W LA injections during the injection phases. Based on Protocol Version 3.0 (effective 13 August 2020), newly enrolled participants in Cohort 1 and Cohort 2 will receive Q8W LA injections during the injection phases.

Source: Applicant's Clinical Study Report for Study 208580 (MOCHA), Document 2020N457376_00, Page 17.
Abbreviations: CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks

Adolescent participants in Cohort 1 were assigned to receive either open-label CAB (oral CAB followed by injectable CAB Q4W) or open-label RPV (oral RPV followed by injectable RPV Q4W) while continuing their background cART. Study treatment assignments in Cohort 1 were based on their pre-study cART regimen:

- Participants on a PI-based and/or NNRTI-based cART regimen were assigned to Cohort 1C
- Participants on an INSTI-based cART regimen were assigned to Cohort 1R

Following enrollment, participants received at least 4 weeks of OLI (CAB or RPV) while continuing their background cART (Cohort 1, Step 1) for assessing tolerability before starting the injections of the assigned drug (Cohort 1, Step 2). Injections were administered Q4W for a total of 3 injections while continuing the background cART (Cohort 1, Step 2). Details of the CAB or RPV dosing for Cohort 1 are as follows:

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

Only data from participants enrolled in Cohort 1 (Step 1, Step 2, and long-term safety and washout pharmacokinetic follow-up [LSFU]) are included in the Cohort 1 Week 16 analysis. Cohort 2 (CAB+RPV) had not opened to accrual at the time of the Cohort 1 Week 16 interim analysis; therefore, data were not reviewed for the combination of oral CAB+RPV, combination of injectable CAB+RPV, or Q8W dosing of CAB+RPV.

7.2 Disposition and Baseline Demographics

In MOCHA Cohort 1, 25 participants were screened, 23 were enrolled, and 23 received at least one dose of study drug. The two participants that were screened but not enrolled did not meet inclusion criteria (documented plasma HIV-1 RNA <50 copies/mL at Screening [n=1]; Grade 2 or lower hemoglobin at Screening [n=1]). The 23 enrolled participants were assigned to either Cohort 1C (n=8, receiving CAB + cART) or Cohort 1R (n=15, receiving RPV + cART) based on their pre-study cART.

Participant baseline demographics and disease characteristics are summarized in Table 1.

Table 1. Baseline Demographics and Disease Characteristics, MOCHA Cohort 1)

Baseline Demographics and Disease Characteristics	**Cohort 1C n=8 n (%)**	**Cohort 1R n=15 n (%)**
Age (years)		
Mean (SD)	14.9 (2.0)	15.9 (1.5)
Median (IQR)	14.5 (13.3, 17.0)	17.0 (15.0, 17.0)
Range	12, 17	12, 17
Sex, n (%)		
Male	6 (75.0)	7 (47.0)
Female	2 (25.0)	8 (53)
Race, n (%)		
Black or African American	7 (87.5)	11 (73)
Asian	1 (12.5)	0
White	0	4 (27)
Ethnicity, n (%)		
Hispanic or Latino	0	3 (20.0)
Not Hispanic or Latino	8 (100)	12 (80.0)
Country, n (%)		
United States	8 (100)	15 (100)
Height (cm)		
Mean (SD)	166.2 (11.9)	162.7 (10.1)
Median (IQR)	162.4 (157.6, 176.8)	162.9 (156.0, 171.5)
Range	150.2, 185.3	140.0, 178.0
Weight (kg)		
Mean (SD)	57.8 (14.2)	65.2 (15.3)
Median (IQR)	57.2 (43.9, 72.1)	63.0 (54.0, 75.0)
Range	43.0, 73.5	44.1, 98.5
BMI (kg/m^2)		
Mean (SD)	20.7 (3.7)	24.5 (4.7)
Median (IQR)	19.6 (17.5, 23.5)	24.5 (20.5, 27.9)
Range	16.4, 27.2	17, 31.3
Plasma HIV-1 RNA (copies/mL), n (%)		
0 to <40	8 (100)	14 (93.3)
40 to <60	0	1 (6.7)
CD4 Cell Count* ($cells/mm^3$)		
Median	725	713
Range	449, 1137	84, 1397
CD4 Cell Count* Categories ($cells/mm^3$), n (%)		
350 to <500	2 (25.0)	1 (6.7)
500 to <750	6 (75.0)	5 (33.3)
≥750	0	8 (53.3)

Source: Clinical Reviewer's Analysis of ADSL dataset (MOCHA); JMP 16.1.0
*One participant in Cohort 1R had their first CD4 evaluation 4 days after the first dose of RPV; therefore, baseline CD4 count is missing
Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation

Details regarding the age and weight of the 23 participants from Cohort 1 are summarized in Table 2.

Table 2. Participants by Age, Weight, and Body Mass Index, MOCHA Cohort 1

	Cohort 1C (n=8) n (%)	**Cohort 1R (n=15) n (%)**
Age (years)		
12	1 (12.5)	1 (6.7)
13	1 (12.5)	0
14	2 (25.0)	2 (13.3)
15	1 (12.5)	1 (6.7)
16	0	3 (20.0)
17	3 (37.5)	8 (53.3)
Weight (kg)		
35 to <50	4 (50.0)	2 (13.3)
≥50	4 (50.0)	13 (86.7)
BMI (kg/m^2)		
<30	8 (100)	12 (80)
≥30	0	3 (20)

Source: Clinical Reviewer's Analysis of ADSL dataset (MOCHA); JMP 16.1.0
Abbreviations: BMI, body mass index

All participants enrolled in Cohort 1 were receiving cART at enrollment, which was continued throughout Cohort 1. All 23 participants (23 of 23 [100%]) were receiving 2 NRTIs. In Cohort 1C, 5 or 8 (63%) participants were receiving an NNRTI, and 3 of 8 (38%) were receiving a PI. In Cohort 1R, all 15 participants (15 of 15 [100%]) were receiving an INSTI. Specific details regarding cART that was continued throughout Cohort 1 are summarized in Table 3.

Table 3. Concomitant Antiretroviral Therapy, MOCHA Cohort 1

Concomitant ARV Drugs	**Cohort 1C (n=8) n (%)**	**Cohort 1R (n=15) n (%)**
Any Concomitant ARV Drug	8 (100)	15 (100)
Atazanavir, Cobicistat, Abacavir, Lamivudine	1 (12.5)	0
Bictegravir, Emtricitabine, Tenofovir alafenamide	0	7 (46.7)
Dolutegravir, Abacavir, Lamivudine	0	6 (40.0)
Dolutegravir, Emtricitabine, Tenofovir alafenamide	0	2 (13.3)
Lopinavir, Ritonavir, Abacavir, Lamivudine	1 (12.5)	0
Lopinavir, Ritonavir, Lamivudine, Zidovudine	1 (12.5)	0
Nevirapine, Lamivudine, Zidovudine	1 (12.5)	0
Rilpivirine, Emtricitabine, Tenofovir alafenamide	4 (50.0)	0

Source: Clinical Reviewer's Analysis of ADSL dataset (MOCHA); JMP 16.1.0
Abbreviations: ARV, antiretroviral

7.3 Intervention Compliance and Extent of Exposure

The median number of days of exposure to oral CAB for Cohort 1C and oral RPV for Cohort 1R was 38 and 39 days, respectively (see Table 4). The median number of days of exposure to CAB or RPV for the entire study for Cohort 1C and Cohort 1R was 137 and 134 days, respectively.

Two participants in Cohort 1R did not receive any injections of RPV; one participant experienced injection procedural pain after the needed was inserted (no study drug was administered; see Section 8.8.1), and the other participant permanently discontinued study treatment because of drug hypersensitivity following the first oral RPV dose (see Section 8.4).

Table 4. Exposure to Study Drugs, MOCHA Cohort 1

	Cohort 1C (n=8) n (%)	**Cohort 1R (n=15) n (%)**
Days of Exposure to Oral Study Drugs*		
Mean (SD)	38.3 (2.6)	36.3 (10.5)
Median (Q1,Q3)	37.5 (36.0, 40.0)	39.0 (36.0, 43.0)
Range	36, 43	1, 43
Number of Injections		
0 Injections	0	2 (13.3)
1 Injection	0	0
2 Injections	0	0
3 Injections	8 (100)	13 (86.7)
Days of Exposure to Study Drugs†		
Mean (SD)	137.6 (4.2)	120.4 (40.9)
Median (Q1,Q3)	136.5 (134.5, 141.0)	134.0 (132.0, 138.0)
Range	133, 144	1, 142

Source: Adapted from the Applicant's Clinical Study Report for Study 208580 (MOCHA), Document 2020N457376_00, Page 42.
* 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

Needle length for the CAB and RPV injections was chosen by the investigator for each participant based on guidance in the manual of procedures. A total of 63 injections of CAB or RPV were administered. The majority (51 of 63 [81%]) of injections were administered using a 1.5-inch needle, and 60 of 63 [95%] of injections were administered using a ≥1.5-inch needle; the remainder of injections (3 of 63 [5%]) were administered with a 1.0-inch needle. The majority of injections (57 of 63 [90%]) were administered using a 20- to 23-gauge needle; the remainder of injections (6 of 63 [10%]) were administered using a 25-gauge needle.

Each CABENUVA dosing kit contains 2 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 BMI ≥30 kg/m^2.

In MOCHA, 3 participants had a BMI ≥30 kg/m^2 at baseline, all were in Cohort 1R. For 2 of these participants, 2-inch, 21-gauge needles were used for each of the 3 injections, and in the third participant, 1.5-inch, 21-gauge needles were used for each of the 3 injections. In the original NDA review of CABENUVA, no statistically significant associations between the change in HIV-1 RNA from baseline and needle length or needle gauge 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).

7.5 Summary of Efficacy

This section focuses on the Week 16 virologic and immunologic results for MOCHA, which provide supportive evidence of efficacy. No formal statistical testing was conducted; descriptive statistics were used. The efficacy assessment in this study consisted of virologic outcomes based on HIV-1 RNA (<50 and <200 copies/mL). CVF was defined as 2 consecutive plasma HIV-1 RNA test results ≥200 copies/mL.

At Week 16, all participants with a viral load assessment (n=7 in Cohort 1C; n=13 in Cohort 1R) had an HIV-1 RNA value <50 c/mL. One participant in Cohort 1C had a missing HIV-1 RNA assessment at Week 16 because of the COVID-19 pandemic. Through the interim assessment period, no participant met the criteria for CVF; therefore, no resistance data were available for review. At each of the timepoints (Baseline, Week 2, 4b, 8, 12, and 16) between 88 and 100% of participants had HIV-RNA <50 copies/mL, and all participants had HIV-RNA <200 copies/mL. A summary of viral suppression (HIV-1 RNA) through Week 16 is presented in Table 5.

Table 5. Summary of Antiviral Activity, MOCHA Cohort 1

Cohort	Analysis Visit	HIV-1 RNA <50 copies/mL n (%)	HIV-1 RNA ≥50 copies/mL n (%)	Total n (%)
Cohort 1C (N=8)	Baseline	8 (100.0)	0	8 (100.0)
	Week 2	8 (100.0)	0	8 (100.0)
	Week 4b	8 (100.0)	0	8 (100.0)
	Week 8	7 (87.5)	1 (12.5)	8 (100.0)
	Week 12	8 (100.0)	0	8 (100.0)
	Week 16	7 (100.0)	0	7 (100.0)
Cohort 1R (N=15)	Baseline	14 (93.3)	1 (6.7)	15 (100.0)
	Week 2	14 (100.0)	0	14 (100.0)
	Week 4b	13 (92.9)	1 (7.1)	14 (100.0)
	Week 8	13 (100.0)	0	13 (100.0)
	Week 12	13 (100.0)	0	13 (100.0)
	Week 16	13 (100.0)	0	13 (100.0)

N = Number of participants in each cohort.
n (%) = Number (percent) of participants in each subcategory for each visit for each cohort. The number in the total column was used as the denominator.
Results after oral treatment end date + 1 for participants who discontinued treatment in the oral phase and results after final injection date + 42 for participants who received injections have been excluded from the analysis through Week 16.
Participant (b) (6) 1C) had a virtual visit for Week 16 due to COVID-19, so the Week 16 collection did not occur.
Participant 1R) discontinued study drug after the entry visit due to a drug-related adverse event and was not included following Baseline.
Participant 1R) went directly into LSFU after not receiving any injection medication due to Grade 1 procedural pain and was not included following Week 4b.
Results below the lower limit of quantification were imputed to one lower than the lower limit and were used in the calculations. Note that for such results where the lower limit was greater than 50, the actual result may not necessarily be above 50 copies/mL
Source: Applicant's Clinical Study Report for Study 208580 (MOCHA), Document 2020N457376_00, Page 103.

The median (IQR) CD4+ count decreased over 14 weeks by -45 cells/mm^3 (-156, 92) in the 1C Cohort (n=6), and increased by 41 cells/mm^3 (-198, 172) in the 1R Cohort (n=12). The median (IQR) CD4+ percent change decreased over 14 weeks by -6% (-18, 14) in the 1C Cohort (n=6), and increased 7% (-22, 25) in the 1R Cohort (n=12).

Clinical Reviewer's Comment: We will further assess CD4+ count changes when longer-term MOCHA data are available from Cohort 2 (e.g., Week 24, Week 48).

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

Patient Experience Data:
The Applicant submitted patient experience data; however, no patient experience data are included in the proposed labeling.

In Cohort 1C, the same number of participants (4 of 8 [50%]) reported "no hurt" during the first and second injections of CAB, and 6 of the 8 (75%) participants in Cohort 1C reported "no hurt" during the third injection. In Cohort 1R, the number of participants reporting "no hurt" during injections of RPV was 3 of 13 (23%) participants during the first injection, 2 of 13 (15%) participants during the second injection, and 3 of 13 (23%) during the third injection. At Week 16, 3 of 8 (38%) participants in Cohort 1C reported that their reactions to CAB injections were "totally" acceptable; the remainder reported that their reactions were "very" (1/8 [12.5%]) or "moderately" (4 of 8 [50.0%]) acceptable. In Cohort 1R, 8 of 13 (62%) participants reported that their reactions to study drug injections were "totally" acceptable. The remaining participants in Cohort 1R reported that their reactions were "very" (1 of 13 [8%]), "moderately" (2 of 13 [15%]), "a little" (1 of 13 [8%]), or "not at all" (1 of 13 [8%]) acceptable. For pain, 2 of 8 (25%) of participants in Cohort 1C and 6 of 13 (46%) participants in Cohort 1R reported that pain was "totally" acceptable. Five (63%) and 6 (46%) participants in Cohort 1C and Cohort 1R, respectively, found their pain to be "moderately" acceptable. One

(13%) participant in Cohort 1C and 1 (8%) participant in Cohort 1R found their pain to be "not at all" or "a little" acceptable, respectively.

8. Safety

8.1 Overview and Methods

The data for the safety review are the Week 16 results from the phase 1/2 study MOCHA. Using the Applicant's SDTM and ADaM datasets, the primary clinical reviewer verified the key safety analyses presented in this section using JMP 16.1.0, unless otherwise specified. The Applicant used MedDRA version 23.0 for coding. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs, version 2.0 (November 2014) was used to determine severity of AEs. Overall, the safety findings are consistent with those of the Applicant, and no new significant safety issues were identified that are not currently included in labeling.

Table 6 summarizes the major safety results from the MOCHA Week 16 data.

Table 6. Safety Overview through Week 16, MOCHA Cohort 1

	Cohort 1C (n=8) n (%)		**Cohort 1R (n=15)** n (%)	
	OLI	**Week 16**	**OLI**	**Week 16**
Any AE	3 (38)	6 (75)	12 (80)	15 (100)
Any AE, excluding ISRs	3 (38)	6 (75)	12 (80)	14 (93)
Any ISR	n/a	5 (63)	n/a	9 (60)
Any ≥Grade 3 AE	0	3 (38)	1 (7)	3 (20)
Drug-related AE	1 (13)	5 (63)	2 (13)	9 (60)
Drug-related AE, excluding ISRs	1 (13)	2 (25)	2 (13)	4 (27)
Drug-related ≥Grade 3 AE	0	1 (13)	1 (7)	1 (7)
Permanently discontinued treatment because of a drug-related AE	0	0	1 (7)	1 (7)
Any SAE	0	0	0	0
Drug-related SAE	0	0	0	0
Fatal SAE	0	0	0	0

Source: Clinical Reviewer's Analysis of ADAE dataset (MOCHA); JMP 16.1.0
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
A 60-Day Safety Update report was submitted on November 26, 2021 with safety data through the database lock of September 30, 2021. Since the data were reported in the sNDA for 212887 and 212888 (n=23 participants), 12 additional participants have been enrolled in MOCHA as summarized below:

- Cohort 1
  - 5 participants in Cohort 1C
  - 7 participants in Cohort 1R, including 1 participant who has received 1 RPV injection

- Cohort 2
    - 9 participants (all completed Cohort 1)

Nine participants who completed participation in Cohort 1 to date have been enrolled in Cohort 2, including 1 participant who completed the OLI period and received injections of both CAB and RPV.

The safety data in the 60-Day Safety Update do not raise any new safety concerns. No deaths, new SAEs, or pregnancy reports have been received during the reporting period of the 60-Day Safety Update. No pregnancy reports have been received for MOCHA to date; therefore, no follow-up on previously reported pregnancies have been received. No participants have been discontinued from the study due to adverse events, or for other reasons during the time period of this update.

Overall, the data submitted in these sNDAs are adequate to characterize the safety profile of CAB and RPV in adolescents. There were no unique safety concerns in the adolescent participants relative to safety findings seen in adult participants in the phase 3 trials.

8.2 Deaths

There were no deaths in Cohort 1C or Cohort 1R through Week 16.

8.3 Serious Adverse Events (SAEs)

There were no SAEs in Cohort 1C or Cohort 1R through Week 16.

During the LSFU, one participant in Cohort 1R had a Grade 4 SAE of increased blood creatine phosphokinase (CK) that was considered not related to study drug and is described below.

A 17-year-old male developed a Grade 4 SAE of increased blood CK at Day 184 (LSFU) in Cohort 1R, which was assessed as unrelated to RPV. The CK value at Day 184 was 156.2 µkat/L (reference range: 0.9 to 6.2 µkat/L). The participant reported sore muscles on movement because of a vigorous exercise in preparation for sports tryouts, with an associated AE of Grade 2, non-serious myalgia considered unrelated to RPV that began on Day 184 and lasted for 7 days; no other symptoms were reported. A Grade 1 ALT elevation of 1.0 µkat/L (reference range: 0.2 to 0.4 µkat/L) was also recorded beginning on Day 184; renal function and serum bilirubin were normal. The final dose of RPV 600 mg IM was on Day 86. On subsequent testing at Day 190, the participant's CK level was 22.8 µkat/L (Grade 1); the CK value was within normal range at both Day 280 and Day 342.

8.4 Dropouts and/or Discontinuations Due to Adverse Events (AEs)

Cohort 1C
There were no AEs leading to discontinuation in Cohort 1C.

Cohort 1R
Two participants had AEs leading to discontinuation in Cohort 1R. For one of the two participants, the Applicant states that a data discrepancy exists for this participant in that no AE resulting in treatment discontinuation is currently included in the database; this participant experienced procedural pain with the RPV injection and is described in Section 8.8.1. The second participant in Cohort 1R experienced an AE leading to discontinuation during the OLI and is described below.

A 17-year-old female had a non-serious, drug-related, Grade 3 AE of drug hypersensitivity (verbatim term: acute allergic reaction to oral RPV). Approximately 2 hours after taking the first oral RPV dose, the participant reported bilateral skin rash on her arms and above her knee and itching at the site of the rash (no trunk involvement). She denied having shortness of breath, wheezing, ulcers in the mouth, or swelling/puffiness of the eyes, tongue, or mouth. After approximately 1 hour, the participant reported symptoms resolving, with the rash fading and the itching improved; the symptoms completely resolved after 6 days. No medications were taken, no interventions were implemented, and treatment with RPV was permanently discontinued. The participant had a history of asthma and seasonal allergies, as well as an allergy to sulfamethoxazole/ trimethoprim with an unknown reaction. The investigator did not consider the drug hypersensitivity to have been caused by concomitant medications or food.

Clinical Reviewer's Comment: EDURANT is prominently labeled for skin and hypersensitivity reactions in Section 5 WARNINGS AND PRECAUTIONS.

8.5 Treatment Emergent Adverse Events and Adverse Drug Reactions

In this section, the term adverse event (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.

Through Week 16, 21 of 23 (91%) adolescents reported AEs. The most common AEs were injection site pain (61%), cough (39%), and headache (30%); most AEs (233 of 244 events [96%]) were Grade 1 or Grade 2. Laboratory values over time are discussed in more detail in Section 8.6, and grade 3 AEs related to laboratory abnormalities are discussed in more detail in the next paragraphs. AEs, excluding incidental laboratory abnormalities, that were seen in at least 3 participants (maximum grade of AE) are shown in Table 7.

Table 7. Adverse Events Occurring in ≥3 Participants Through Week 16, Excluding Laboratory Findings, MOCHA Cohort 1

MedDRA Preferred Term	**Cohort 1C n=8 n (%)**				**Cohort 1R n=15 n (%)**			
Grade*	**1**	**2**	**3 or 4**	**Total**	**1**	**2**	**3 or 4**	**Total**
Injection site pain	2 (25)	3 (38)	0	5 (63)	6† (40)	3 (20)	0	9 (60)
Cough	4 (50)	1 (13)	0	5 (63)	4† (27)	0	0	4 (27)
Headache	1 (13)	0	0	1 (13)	2† (13)	4† (27)	0	6 (40)
Nasal congestion	3 (38)	0	0	3 (38)	1† (7)	2† (13)	0	3 (20)
Oropharyngeal pain	2 (25)	0	0	2 (25)	4† (27)	0	0	4 (27)
Rhinorrhoea	2 (25)	0	0	2 (25)	4 (27)	0	0	4 (27)
Nasal mucosal disorder	1 (13)	0	0	1 (13)	4† (27)	0	0	4 (27)
Dizziness	1 (13)	0	0	1 (13)	1 (7)	2† (13)	0	3 (20)
Nausea	0	0	0	0	1 (7)	3† (20)	0	4 (27)
Upper respiratory tract infection	2 (25)	1 (13)	0	3 (38)	1 (7)	0	0	1 (7)
Viral upper respiratory tract infection	1 (13)	0	0	1 (13)	1 (7)	2 (13)	0	3 (20)
Back pain	0	1 (13)	0	1 (13)	2 (13)	0	0	2 (13)
Constipation	0	0	0	0	2 (13)	1 (7)	0	3 (20)
Diarrhoea	1* (13)	0	0	1 (13)	2† (13)	0	0	2 (13)

MedDRA Preferred Term	**Cohort 1C n=8 n (%)**				**Cohort 1R n=15 n (%)**			
Myalgia	1 (13)	0	0	1 (13)	1 (7)	1 (7)	0	2 (13)
Nasal mucosal discolouration	1 (13)	0	0	1 (13)	2[†] (13)	0	0	2 (13)
Sneezing	1 (13)	0	0	1 (13)	2 (13)	0	0	2 (13)
Throat irritation	1 (13)	0	0	1 (13)	2[†] (13)	0	0	2 (13)
Vomiting	0	0	0	0	2[†] (13)	1 (7)	0	3 (20)

Source: Clinical Reviewer's Analysis of ADAE dataset (MOCHA); JMP 16.1.0
Based on DAIDS Adverse Event Grading Tables Version 2.1
[*] Highest grade for each participant was reported
[†] Includes events that occurred during the oral lead-in

Grade 3 or 4 AEs through Week 16 (Including the Oral Lead-In)

Cohort 1C

There were 3 participants with one or more Grade 3 AEs; no participants had Grade 4 AEs. Only one of the Grade 3 AEs (insomnia) was considered related to CAB, and none resulted in discontinuation or interruption of CAB. The Grade 3 AEs included the following:

- Blood creatine phosphokinase increased (n=1)
  - See Section 8.8.7 for additional details.
- Insomnia (n=1)
  - This participant had a Grade 3, non-serious, ADR of insomnia on Day 41, which is the same day the participant started the first injection (Part 2). The participant had not experienced insomnia previously and reported being unable to sleep the entire night on night 1 (same night after the first injection) and being unable to fall asleep on night 2 until administered diphenhydramine. Study participation continued and insomnia resolved after 5 days.
- Neutropenia (n=1)
  - This participant (# (b) (6)) had a Grade 3 AE of neutropenia that was considered unrelated to CAB. It was noted this participant had leukocyte counts below the reference range (all Grade 0) at Baseline and all subsequent visits during treatment and LSFU except for Week 13. Because absolute neutrophil count was not a protocol-required laboratory parameter, additional details regarding the laboratory assessments is not available.

Cohort 1R

There were 4 participants with one or more Grade 3 AEs; 3 participants had Grade 4 AEs. Only one of the Grade 3 AEs (drug hypersensitivity) was considered related to RPV and resulted in discontinuation. The ≥Grade 3 AEs included the following:

- Blood creatinine phosphokinase increased (n=3)
  - See Section 8.8.7 for additional details.
- Drug hypersensitivity (n=1)
  - See Section 8.4 for additional details.
- Neutrophil count decreased (n=1)
  - This participant (# (b) (6)) had a Grade 3 AE of decreased neutrophil count that was considered unrelated to RPV. It was noted this participant had leukocyte counts below the reference range (all Grade 0) at Baseline and several subsequent visits during treatment and LSFU. Because absolute neutrophil count was not a protocol-required laboratory parameter, additional details regarding the laboratory assessments is not available.

Clinical Reviewer's Comment: CABENUVA is labeled for increased creatinine phosphokinase, hypersensitivity, and insomnia. Overall, there were no clinically significant

changes in leukocyte count from baseline to Week 16. Our plan will be to follow-up and review laboratory findings of the subsequent MOCHA submissions.

ADRs through Week 16 (Including the Oral Lead-In)

Cohort 1C
There were 5 participants with 15 non-serious ADRs, and only one ADR (insomnia) was ≥Grade 3. Injection site pain was the most frequently reported ADR reported in 5 of 8 participants (63%); all ISRs were Grade 1 or 2. The other ADRs in Cohort 1C included the following: diarrhea (n=1), headache (n=1), insomnia (n=1), and decreased appetite (n=1).

Cohort 1R
There were 9 participants with 28 non-serious ADRs, and only 1 ADR was ≥Grade 3 (drug hypersensitivity). ISRs (injection site pain [n=8], hypoesthesia [n=1], nodule [n=1], and swelling [n=1]) were the most frequently reported ADR in 8 of 13 participants (89%); all ISRs were Grade 1 or 2. The other ADRs in Cohort 1R included the following: dizziness (n=1), drug hypersensitivity (n=1), insomnia (n=1), nausea (n=1), and papular rash (n=1).

Clinical Reviewer's Comment: No new ADRs were identified for CAB or RPV. CABENUVA is labeled for ISRs, gastrointestinal disorders (abdominal pain [including upper abdominal pain], gastritis, dyspepsia, vomiting, diarrhea, and flatulence), sleep disorders (including insomnia), nausea, dizziness, hypersensitivity reactions (including rash), and headache.

Oral Lead-In (Cohort 1, Part 1): Summary of AEs and ADRs

Cohort 1C
Three of 8 (38%) participants reported at least 1 AE, and all were Grade 1. The only ADR was diarrhea (Grade 1).

Cohort 1R
Twelve of 15 (80%) participants reported at least 1 AE, and 31 of 32 (97%) AEs were Grade 1 or 2. The only Grade 3 AE (drug hypersensitivity) is described in Section 8.4. The two ADRs were drug hypersensitivity (Grade 3, see Section 8.4), and insomnia (Grade 1).

Clinical Reviewer's Comment: No new ADRs were identified during the OLI of CAB or RPV. VOCABRIA is labeled for diarrhea (6.1 Clinical Trials Experience); EDURANT is labeled for insomnia (6.1 Clinical Trials Experience) and prominently labeled for skin and hypersensitivity reactions (5 WARNINGS AND PRECAUTIONS).

8.6 Laboratory Findings

Graded laboratory events through Week 16 were reported in 15 of 22 (68%) of participants; most were Grade 1 or 2. One participant in Cohort 1R was excluded from analysis because of not having post-baseline results within 1 day of the last oral dose. The most common graded laboratory abnormalities included the following:

- Elevated creatinine kinase (5 of 22 [23%] participants; 3 of 22 [14%] participants ≥Grade 3)
- Elevated alanine aminotransferase (4 of 22 [18%] participants; none ≥Grade 3)
- Decreased creatinine clearance (3 of 22 [14%] participants; none ≥Grade 3)
- Elevated bilirubin (2 of 22 [9%] participants; none ≥Grade 3)

No participants met Hy's Law Criteria for drug-induced liver injury or other protocol-defined liver monitoring criteria. There were no ≥Grade 3 elevations in ALT or bilirubin values. One participant in Cohort 1C had a Grade 3, non-serious, unrelated AE of blood bilirubin increased during LSFU; the same participant had several Grade 1 to Grade 2 bilirubin elevations during the injection phase (Part 2) and was taking atazanavir as a component of their background cART, which provides an alternative etiology of the increased bilirubin.

There were no clinically significant changes or trends over time for laboratory parameters, vital sign measurements, or physical examination assessments in either Cohort 1C or 1R from baseline to Week 16. No participants had a post-baseline Grade 3 prolonged QTc interval (i.e., QTc >500 msec or an increase from baseline >60 msec).

8.7 Associated Safety Analyses

Lower Weight Adults from Phase 3 Trials 201584 (FLAIR), 201585 (ATLAS), and 207966 (ATLAS-2M)

The Applicant submitted supportive data from the pivotal adult trials FLAIR, ATLAS, and ATLAS-2M, which were analyzed for 2 subgroups: adults weighing <55 kg and adults weighing <50 kg. Because the safety profiles of CAB+RPV were consistent across FLAIR and ATLAS, the data from these phase 3 trials were pooled for the Maintenance Phase. Safety analyses include summaries of extent of exposure, AEs, laboratory tests (clinical chemistry), and ECGs.

In the pooled trials FLAIR and ATLAS, there were 32 adult participants who weighed <55 kg; of which, 11 adult participants weighed <50 kg. During the Maintenance Phase of these trials, the median (IQR) number of injections for adults weighing <55 kg was 13.0 (12.0, 15.0); for adults weighing <50 kg, it was 12.5 (12.0, 13.0) injections.

In trial ATLAS-2M, there were 30 adult participants (n=15, Q8W; n=15, Q4W) who weighed <55 kg; of which, 5 adult participants (n=1, Q8W; n=4, Q4W) weighed <50 kg. During the Maintenance Phase, the median (IQR) number of injections for adults weighing <55 kg was 8.0 (8.0, 9.0) for Q8W and 15.0 (13.0, 16.0) for Q4W; for adults weighing <50 kg, it was 9.0 or Q8W and 14.0 (13.0, 15.5) for Q4W.

Among the lower-weight adult participants in FLAIR, ATLAS, and ATLAS-2M, there were no SAEs, AEs leading to withdrawal, or Grade 3 or 4 AEs that occurred during the OLI period of the respective trial they were enrolled in. All events were Grade 1 except 5 events; the 5 Grade 2 AEs that were reported from 4 adult participants were vitamin D deficiency (n=1), cough (n=1), lower respiratory tract infection (n=1), and diplopia and dizziness (n=1); none of

these events were considered drug related. The drug-related AEs (all Grade 1) were reported for 3 adults: diarrhea (n=1), constipation and flatulence (n=1), and abdominal pain (n=1).

Injection site pain was the most frequently reported AE in all lower-weight adult subgroups. Other than ISRs, the most frequently reported AE was nasopharyngitis. Of lower-weight adults who reported at least 1 AE in FLAIR, ATLAS, or ATLAS-2M, few reported an AE with a maximum intensity of Grade 3, and none reported an AE with a maximum intensity of Grade 4.

AEs assessed as drug related that were reported by more than one adult weighing <55 kg in Pooled Trials FLAIR, ATLAS, or ATLAS-2M were ISRs (pain, induration, pruritus, swelling, nodule) and pyrexia. Only injection site pain was reported by more than 1 adult weighing <50 kg. AEs assessed as drug related that were reported by more than one adult weighing <55 kg in ATLAS-2M in either the Q8W or Q4W group were ISRs (pain, induration, swelling, nodule). Only injection site pain was reported by more than 1 adult weighing <50 kg.

Adolescent HIV-1 PrEP Studies (IND 122744)

The Applicant has initiated two HIV-1 PrEP sub-studies in adolescents: HPTN 083-01 and HPTN 084-01. These are both single-arm, open-label, safety, tolerability, and acceptability studies in sexually active, HIV-1-uninfected adolescent males (HPTN 083-01) and females (HPTN-084-01) that are <18 years of age and ≥35 kg. Participants first receive a 5-week CAB OLI followed by five CAB injections administered at 8-week intervals after a 4-week loading dose.

At the time of the last DSMB review (IND 122744, SDN 185; data cut-off of September 1, 2021), HPTN 083-01 had enrolled 4 male participants, all of whom had received ≥1 CAB injections. In HPTN 084-01, 55 female participants have been enrolled; of these, 50 participants have received ≥1 or more CAB injections. Across both sub-studies, there has been one treatment discontinuation; this occurred before the participant had received any doses of CAB. There have been no Grade 4 AEs. One out of four (25%) participants in HPTN 083-01 reported an ISR; in HPTN 084-01, 12 of the 50 (24%) participants who received 1 or more injection reported 1 or more ISRs. All ISRs were Grade 1 or 2 in severity. There have been no pregnancies and no HIV seroconversions.

8.8 Adverse Events of Special Interest

This section provides an overview of the following adverse events of special interest (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. The current labeling is adequate to convey the risks of injection site reactions, hypersensitivity reactions, hepatobiliary events, gastrointestinal events, and musculoskeletal events. For all other AESIs, continued pharmacovigilance is recommended and labeling is not warranted.

8.8.1 Injection Site Reactions

Five of 8 (62.5%) participants in Cohort 1C and 8 of 13 (61.5%) participants in Cohort 1R reported at least 1 ISR through Week 16. 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 14 participants with ISRs. Refer to Table 8 for ISRs by grade through Week 16. Overall, 97% of ISRs resolved in ≤7 days, and the longest duration was 13 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 due to the participant requesting cessation of the injection due to procedural pain. No other relevant AEs were reported.

Table 8. ISRs Through Week 16 in Participants with ≥1 Injection, MOCHA Cohort 1

MedDRA Preferred Term	Cohort 1C (n=8) n (%)			Cohort 1R (n=13) n (%)		
Grade*	1	2	≥3	1	2	≥3
Any ISR	2 (25)	3 (38)	0	5 (39)	3 (23)	0
Injection site hypoesthesia	0	0	0	1 (8)	0	0
Injection site nodule	0	0	0	1 (8)	0	0
Injection site pain	2 (25)	3 (38)	0	5 (39)	3 (23)	0
Injection site swelling	0	0	0	1 (8)	0	0

Source: Clinical Reviewer's Analysis of ADAE dataset (MOCHA); JMP 16.1.0
Based on DAIDS Adverse Event Grading Tables Version 2.1
Abbreviations: ISR, injection site reaction
*Highest grade for each participant was reported

8.8.2. Hypersensitivity Reactions

In Cohort 1C, one participant reported pruritus (Grade 1) and rash (Grade 1) beginning on Day 24 (during OLI); these AEs were considered not related to study drug and resolved within 5 days without a change in study drug treatment. In Cohort 1R, one participant reported rash papular (Grade 1) beginning on Day 42 during IM RPV treatment; the AE was considered related to RPV and resolved in 16 days without a change in study drug treatment. In addition, one participant in Cohort 1R experienced non-serious, drug-related, Grade 3 AE of drug hypersensitivity leading to discontinuation during the OLI and is described in Section 8.4. No other relevant AEs were reported.

8.8.3. Hepatobiliary Events

No participants met Hy's law criteria or other protocol-defined liver monitoring criteria. There were no ≥Grade 3 elevations in ALT values. One participant in Cohort 1C had a Grade 3 AE of blood bilirubin increased during LSFU (non-serious and considered unrelated to study drug); the same participant had several Grade 1 to Grade 2 bilirubin elevations during the injection phase and was taking atazanavir as a component of their background cART. No other relevant AEs were reported.

8.8.4. Psychiatric Events (including depressive disorders)

There were no AEs in Cohort 1 reported in relation to depressive disorders.

8.8.5. Neurologic Events (including seizure)

There were no AEs in Cohort 1 reported in relation to seizure or seizure like-events.

8.8.6. Gastrointestinal Events (including pancreatitis)

There were no significant AEs in Cohort 1 reported in relation to pancreatitis. There were no ≥Grade 3 lipase elevations observed in any participants, nor were any lipase-related AEs reported through Week 16. One post-baseline Grade 2 lipase elevation was observed in a participant in Cohort 1C at the Week 5 visit (2.1 µkat/L [reference range: 0.2 to 1.3 µkat/L]); treatment with CAB was continued. This participant's lipase level was slightly elevated (Grade 0; 0.7 µkat/L [reference range: 0.2 to 0.6 µkat/L]) at Baseline and was Grade 1 (1.5 µkat/L [reference range: 0.2 to 1.3 µkat/L]) at Week 12 of LSFU; all other lipase assessments during treatment and LSFU were within the reference range. No other relevant AEs were reported.

8.8.7. Musculoskeletal Events (related to injection or rhabdomyolysis)

Myositis and creatine kinase elevation are reported with other drugs in the INSTI class. 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.

Rhabdomyolysis and myositis were not reported in any participant. Ten musculoskeletal AEs were reported by 8 participants, which included back pain (n=3), myalgia (n=3), pain in extremity (n=2), arthralgia (n=1), and torticollis (n=1). No musculoskeletal AEs were assessed as related to study drug. Grade 4 AEs of increased blood CK were reported for 1 participant in Cohort 1C and 3 participants in Cohort 1R; all 4 of these participants had a relevant exercise history, including weightlifting, vigorous exercise, dance team exercise, and working out. The one serious Grade 4 AE of increased blood CK is discussed in Section 8.3. None of these AEs were considered related to study drug and none resulted in any changes to study drug dose.

8.8.8. Weight Increase

Weight (mean [SD] change from baseline at Week 16 of 1.4 kg [2.8]), height (mean [SD] change from baseline at Week 16 of 0.5 cm [1.6]), and BMI (mean [SD] change from baseline at Week 16 of 0.3 kg/m^2 [1.1]) all increased over the 16 weeks of the study as would be expected in this adolescent age group.

8.8.9. Pregnancy and Embryo-Fetal Toxicity

No new nonclinical data were submitted with this submission. No participants became pregnant during the study as of the data cut-off or in the 60-Day Safety Update.

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 and RPV in adolescent patients 12 years of age and older and weighing at least 35 kg is supported by the following:

- Open-label study (MOCHA) in adolescent participants
- 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); topline data from HPTN study 083-01 and HPTN 084-01 (adolescent CAB sub studies)

MOCHA is a study conducted to fulfil the required pediatric assessments under PREA (21 U.S.C. 355c). The required pediatric assessments were issued in the initial approval letters for VOCABRIA and CABENUVA dated January 21, 2021 (see Appendix 1).

11. Other Relevant Regulatory Issues

None.

12. Labeling

The VOCABRIA and CABENUVA labeling have been updated to extend the population to include HIV-1 infected adolescents aged 12 years and older and weighing at least 35 kg. Negotiations with the Applicant on the exact language in the VOCABRIA and CABENUVA labeling are currently ongoing.

As of the completion of this review, the Division has made the following substantive labeling changes:

- VOCABRIA
  - Inclusion of the expanded indication to adolescents ≥12 years of age and weighing ≥35 kg
  - 6.1 *Clinical Trials Experience*
    - Addition of a statement that the safety profile of oral CAB during the OLI in adolescents in MOCHA (Week 16) was consistent with the safety profile established in adults.
  - 8.4 *Pediatric Use*
    - Addition of an overview of the data supporting the safety and efficacy of oral CAB in adolescents.
    - Addition of an overview of the MOCHA study design, including the number of adolescent participants from the Week 16 interim analysis.
    - Addition of a statement that safety is expected to be similar to adults because there was no clinically significant difference in drug exposure; cross-reference Adverse Reactions (6.1) and Clinical Pharmacology (12.3).
  - 14 CLINICAL STUDIES
    - No information was included because efficacy data from MOCHA (Week 16 interim analysis of Cohort 1) are not included; efficacy in adolescents is extrapolated from adults with support from pharmacokinetic analyses showing similar drug exposure.

- CABENUVA
  - Inclusion of the expanded indication to adolescents ≥12 years of age and weighing ≥35 kg
  - 6.1 *Clinical Trials Experience*
    - Addition of a statement that based on the data from MOCHA (Week 16), the safety profile of oral CAB followed by injectable CAB or oral RPV followed by injectable RPV was consistent with the safety profile established with CAB+RPV in adults.

        - Addition of an overview of ADRs, including the two Grade 3 ADRs, and an overview of ISRs. Because CAB+RPV is the first complete injectable regimen for the treatment of HIV-1 infection, and the Pediatric Labeling Guidance recommends highlighting novel or unique adverse reactions, the Division decided this information should be included in labeling.
    - 8.4 *Pediatric Use*
        - Addition of an overview of the data supporting the safety and efficacy of oral CAB in adolescents.
        - Addition of an overview of MOCHA, including the number of adolescent participants from the Week 16 interim analysis; baseline information was also included for the adolescent participants (age, sex, race, CD4+ cell count).
        - Addition of a statement that safety is expected to be similar to adults because there was no clinically significant difference in drug exposure; efficacy in adolescents is extrapolated from adults with support from PK analyses showing similar drug exposure (cross-reference Clinical Pharmacology [12.3]).
    - 14 Clinical Studies
        - No information was included in Section 14 CLINICAL STUDIES because efficacy data from MOCHA (Week 16 interim analysis of Cohort 1) are not included; efficacy in adolescents is extrapolated from adults with support from pharmacokinetic analyses showing similar drug exposure.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

None.

Postmarketing Requirements (PMRs)

The current application partially fulfills the Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) for the following two PMRs:

- 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.

- 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.

[redacted] (b) (4)

These sNDAs were reviewed at the Pediatric Review Committee (PeRC) meeting on February 1, 2022. The PeRC agreed with the assessment and that these components can be labeled for treatment of HIV-1 in adolescents 12 to <18 years of age and weighing at least 35 kg. DAV clarified that, although there are enough data for labeling as there are safety data for each component, they have not yet reviewed safety data for the CABENUVA combination product; therefore, the PREA PMRs could only be considered partially fulfilled. The PeRC agreed that the PMRs will have to be reviewed and assessed for fulfillment after the CABENUVA combination product data have been submitted and reviewed.

14. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend approval of these sNDAs to expand the population to include adolescents aged ≥12 years and weighing ≥35 kg.

Our recommendation is based on review of the PK, safety, and efficacy (antiviral activity) data from the MOCHA study; in addition, our recommendation also considered the available adult PK, safety, and efficacy data, as well as additional safety data from the PrEP trials in adolescents. Approval of these supplements will expand the treatment options for adolescents infected with HIV-1 to include the first complete injectable regimen, which could improve treatment adherence. The long-term success of HIV-1 treatment is dependent on sustained adherence to daily ART, which can be especially challenging in children and adolescents living with HIV.

- Benefit-Risk Assessment

Overall, CAB+RPV has a favorable benefit-risk profile for the intended 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 MOCHA safety data through Week 16 (interim analysis) suggest that CAB and RPV are generally safe and well-tolerated in adolescent participants. There were no deaths or related SAEs. Although there was one related Grade 3 clinical event (drug hypersensitivity) that lead to discontinuation of RPV in Cohort 1R, RPV is prominently labeled for skin and hypersensitivity reactions (Section 5 WARNINGS AND PRECAUTIONS). Overall, ADRs were similar to those reported in adults, including the frequency and severity of ISRs. No new or unique safety findings in adolescents compared to adults were observed for CAB or RPV.

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.[f] A long-acting injectable formulation such as CABENUVA 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.

[f] 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 http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed March 23, 2022.

Appendix A

NDA 212888

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 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.
Study Completion: 7/2022
Final Report Submission: 1/2023

3998-2 Conduct a study in subjects weighing 25 kg to less than 35 kg (approximately 6 to less than 12 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.
Final Protocol Submission: 8/2022
Study Completion: 6/2023
Final Report Submission: 12/2023

3998-3 Conduct a study in subjects weighing 10 kg to less than 25 kg (approximately 2 to less than 6 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.
Final Protocol Submission: 8/2022
Study Completion: 12/2025
Final Report Submission: 6/2026

NDA 212887

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 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).
Study Completion: 7/2022
Final Report Submission: 1/2023

3997-2 Conduct a study in subjects weighing 25 kg to less than 35 kg (approximately 6 to less than 12 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).
Final Protocol Submission: 8/2022
Study Completion: 6/2023
Final Report Submission: 12/2023

3997-3 Conduct a study in subjects weighing 10 kg to less than 25 kg (approximately 2 to less than 6 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).
Final Protocol Submission: 8/2022
Study Completion: 12/2025
Final Report Submission: 6/2026

Appendix B

Clinical Investigator Financial Disclosure Review

Application Numbers: 212887/S-005 and S-006

212888/S-005 and S-006

Submission Dates: S-005: September 29, 2021

S-006: October 7, 2021

Applicant: ViiV Healthcare

Products: NDA 212887 VOCABRIA (oral cabotegravir)

NDA 212888 CABENUVA (injectable cabotegravir + rilpivirine)

Reviewer: Timothy Jancel, PharmD, MHS

Date of Review: January 25, 2022

Covered Clinical Study: 208580 (MOCHA)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **61 investigators total (8 principal investigators, 53 sub-investigators)**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): N**one**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **2 investigators (1 principal investigator, 1 sub-investigator)**		
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 clinic investigators as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators*, and by 21 CFR 54.4. None of the 61 investigators are employed by the Applicant, and all investigators returned the requested information regarding financial disclosures. Fifty-nine of the 61 investigators (97%) have no financial interests or arrangements with the Applicant, as defined in 21 CFR 54.2.

The investigator financial disclosures do not raise questions about the integrity of the data. The pharmacokinetic and virologic endpoints are objective laboratory measurements that are assessed centrally and not vulnerable to investigator bias. In addition, only 2 of the 61 investigators reported (b) (6) both investigators were from (b) (6) which recruited (b) (6) of the 23 participants (b) (6) of total enrollment) in Study 208580 (MOCHA).

In conclusion, the likelihood that study results were biased based on financial interests is minimal and should not affect the approvability of the application.

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
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SARAH M CONNELLY
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