COMBINED CLINICAL, CROSS DISCIPLINE TEAM LEADER, AND DIVISION DIRECTOR REVIEW FOR PEDIATRIC EFFICACY SUPPLEMENTS

Date	September 3, 2024	
From	Sarita Boyd (Clinical Reviewer) Kimberly Struble (Clinical Team Leader) Yodit Belew (Associate Director for Therapeutic Review)	
Subject	Clinical and Cross Discipline Team Leader Review	
Applicant	ViiV Healthcare	
NDA # **Supplement #**	NDA 212887 S-10 (SDN 147)	NDA 215499 S-8 (SDN 529)
Date of Submission	March 21, 2024	March 27, 2024
[redacted] (b) (4)		
Proprietary Name / Established (USAN) names	Vocabria (cabotegravir)	Apretude (cabotegravir extended-release injectable suspension)
Dosage forms / Strength	30 mg oral tablet	600 mg/3 mL (200 mg/mL) single-dose vial
Current Approved Indication	Indicated in at-risk adults and adolescents weighing at least 35 kg for short-term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Vocabria may be used as: • oral lead-in to assess the tolerability of cabotegravir prior to administration of Apretude. • oral PrEP for patients who will miss planned injection dosing with Apretude.	Indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.
Revised Indication	Indicated for short-term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition. Vocabria may be used as: • oral lead-in to assess the tolerability of cabotegravir prior to administration of APRETUDE (cabotegravir extended-release injectable suspension). • oral PrEP for patients who will miss planned injection dosing	Indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition.

	with APRETUDE.	
Dosing Regimen	Oral lead-in: 30 mg once daily for one month Oral PrEP to replace a planned missed injection: 30 mg once daily	600 mg IM injection given 1 month apart for 2 months, then every 2 months (with or without an oral lead-in)
Recommended:	Approval	Approval

1. Introduction

The Applicant submitted NDA efficacy supplements (sNDAs) for Vocabria (cabotegravir [CAB] tablets) and Apretude (CAB LA injectable). Both cabotegravir formulations were approved on December 20, 2021, for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk of HIV-1 acquisition. This review summarizes additional safety and pharmacokinetics (PK) data from the PrEP sub-studies HPTN 083-01 and HPTN-084-01 in adolescent males and females, respectively.

2. Background

Cabotegravir is an HIV-1 integrase strand transfer inhibitor (INSTI), and CAB LA was the first long-acting injectable product approved for HIV-1 PrEP to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk of HIV-1 acquisition. CAB tablets may be used as an oral lead-in to assess tolerability prior to administration of CAB LA injectable or as oral PrEP for patients who will miss planned injection dosing with CAB LA. CAB LA may be used with or without an oral lead-in with CAB tablets.

The basis for approval of the PrEP indication was demonstration of superiority of CAB LA compared with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada) in reducing the risk of acquiring HIV-1 infection in two clinical trials, HPTN 083 and HPTN 084, conducted in adults. Adolescents were included in the PrEP indication at the time of original approval based on safety and PK of CAB LA in adults without HIV-1 infection in HPTN 083 and HPTN 084 as well as adolescents with HIV-1 infection in the treatment trial MOCHA. In addition, the Applicant had initiated two HIV-1 PrEP sub-studies, HPTN 083-01 and HPTN 084-01, in adolescents without HIV-1 infection. Limited safety data were available from the ongoing sub-studies in 54 adolescents who received CAB tablets and CAB LA, providing additional support for approval in adolescents at the same time as adults.

Although the original NDA was approved for the adolescent population, a post-marketing requirement (PMR) was issued to conduct a trial to evaluate safety, tolerability, and acceptability of CAB LA in the indicated adolescent population. The current sNDA submissions are in response to the PMR and include clinical study reports for sub-studies HPTN 083-01 and HPTN 084-01. The Applicant proposes updating the prescribing information for CAB tablets and CAB LA with the additional PK and safety data from these sub-studies.

3. CMC/Device

The commercial formulations of CAB LA and CAB tablets were used in the clinical trials submitted in the sNDAs. The sNDA submissions contain no new CMC information.

4. Nonclinical Pharmacology/Toxicology

The sNDA submissions contain no new pharmacology/toxicology information.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Mario Sampson's clinical pharmacology review for complete details. The sNDA submissions contain PK data in adolescents from HPTN 083-01 and HPTN 084-01. In these sub-studies, following oral CAB (lead-in) and CAB LA injections every 8 weeks, geometric mean cabotegravir exposures were up to 40% higher in adolescents compared to adults but were largely within the range of adults. The clinical pharmacology team continues to agree with the labeling statement that there are no clinically relevant differences in cabotegravir exposures between adolescents and adults.

6. Clinical/Statistical- Efficacy

6.1 Study Design

HPTN 083-01, a sub-study of HPTN 083, is an ongoing single-arm, open-label, safety, tolerability, and acceptability study in sexually active, healthy adolescents (< 18 years of age and weighing ≥ 35 kg) who were assigned male sex at birth (includes MSM, TGW, and gender non-conforming people) and who do not have HIV-1 infection. Participants were required to have self-reported sexual activity with a male in the past 12 months.

HPTN 084-01, a sub-study of HPTN 084, is an ongoing single-arm, open-label, safety, tolerability, and acceptability study in sexually active, healthy adolescents (< 18 years of age and weighing ≥ 35 kg) who were assigned female sex at birth and who do not have HIV-1 infection. Participants were required to have self-reported sexual activity with a male (oral, anal, or vaginal) in the past 12 months.

Study participation in both sub-studies included three phases:

Step 1 – Oral Run-in Phase

a. Up to 5 weeks of oral CAB 30 mg once daily safety lead-in

Step 2 – Injection Phase

b. Series of 5 IM injections of 3 mL (600 mg) administered in the gluteal muscle at 8-week intervals after a 4-week loading dose (injections at Weeks 5, 9, 17, 25, and 33)
c. Safety visit after each injection to ascertain safety data, including injection site reactions
d. Participants who discontinued study product during Step 2 for any reason other than HIV infection or AE occurrence related to study product were transitioned to oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for 48 weeks.

Step 3 – Follow-up Phase

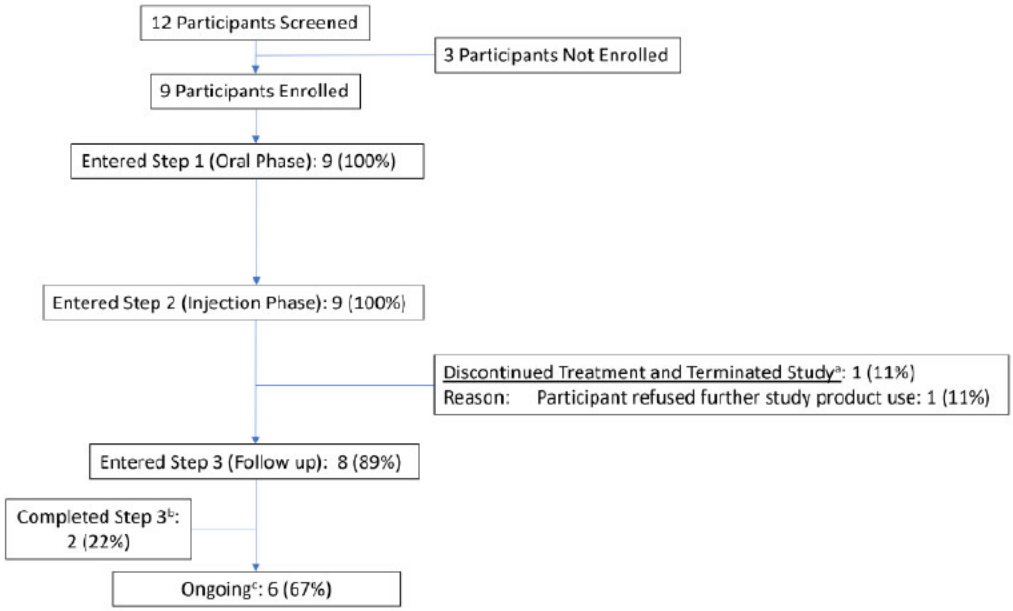
e. Cabotegravir concentrations were assessed 8 weeks after the last injection as well as 12, 24, 36, and 48 weeks after the last injection.
f. After 5 injections, participants could choose to receive oral TDF/FTC (in Step 3) or continue CAB LA (in Step 3 of HPTN 083-01 or in a separate open-label extension study HPTN 084 OLE once CAB LA was available at the site).
g. Waning concentrations of cabotegravir (PK tail) were covered with continued CAB LA (in HPTN 083 or in HPTN 084 OLE) or TDF/FTC for 48 weeks.
h. Behavioral and acceptability data were collected via computer assisted self interview (CASI).

6.2 Disposition

In HPTN 083-01, a total of 12 participants were screened, of whom 3 were not enrolled because of failure to meet inclusion or exclusion criteria. Of the 9 participants enrolled, all 9 received study drug. One participant discontinued study treatment and terminated the study after 1 injection because they refused further study product. This participant got a new job that left little time for study commitment, and the participant wanted to start medication for mental health conditions and wanted to limit the number of medications taken.

Figure 1 depicts the disposition of study participants in HPTN 083-01.

Figure 1. Participant Disposition: HPTN 083-01



Data Source: Table 1.002,Table 1.005, and Listing 16.005
Note: Participants who were followed for at least 28 weeks after their first injection in Step 2 or confirmed seroconverted were considered as having completed the the Injection Phase. Participant (b) (6) had only 4 injections during Step 2 (missed 5th scheduled injection) but was considered to have completed Step 2, entered Step 3, and continued to receive injections.

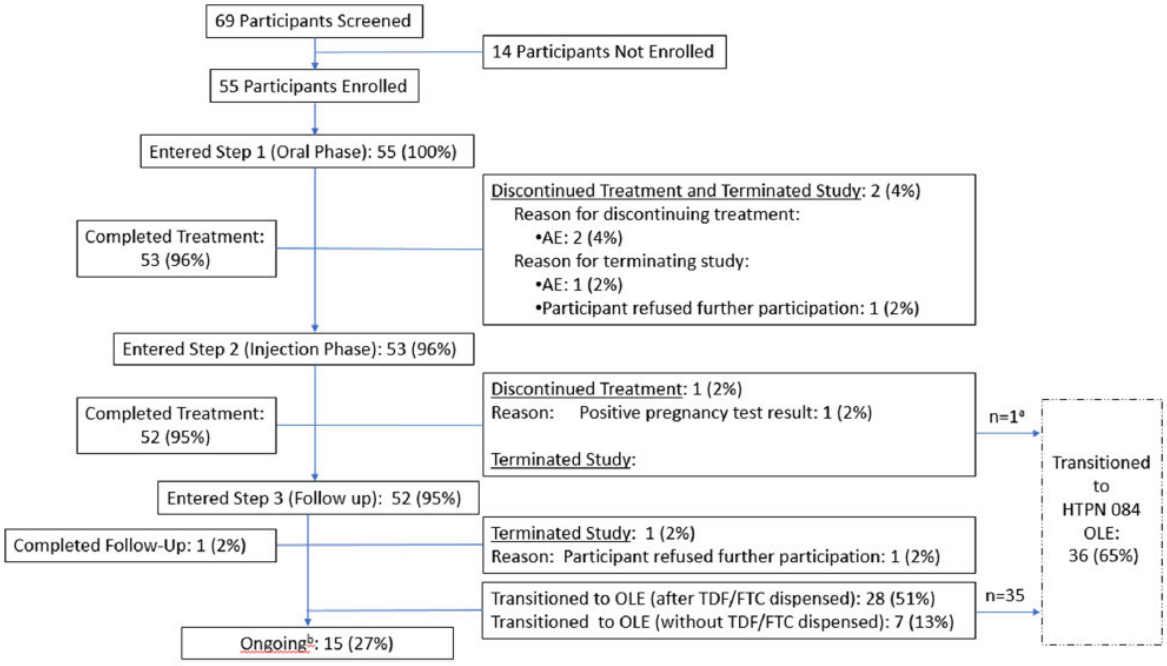
a. Participant (b) (6) discontinued treatment and terminated the study after 1 injection.
b. Participants completed all Step 3 visits and had their study exit visit.
c. Two participants (b) (6) completed their Step 3 Week +48 visit but had not completed their study exit visit at the time of the data cut-off.

Source: Applicant's Clinical Study Report for HPTN 083-01

In HPTN 084-01, a total of 69 participants were screened, of whom 14 were not enrolled; ten of the 14 participants failed to meet inclusion or exclusion criteria. Of the 55 participants enrolled, all 55 received study drug. AEs were the most common reason for treatment discontinuation, and participant refusal for further participation was the most common reason for study withdrawal.

Figure 2 depicts the disposition of study participants in HPTN 083-01.

Figure 2. Participant Disposition: HPTN 084-01



Data Source: Table 1.002 and Table 1.005

a. 1 participant became pregnant during Step 2, entered the Pregnancy Schedule and then entered the HPTN 084 OLE.
b. As of the cut-off date of 21 July 2022.

Source: Applicant's Clinical Study Report for HPTN 084-01

6.3 Baseline Demographics and Characteristics

HPTN 083-01 is a multi-center study being conducted at 4 sites in the U.S.: Aurora, CO; Boston, MA; Chicago, IL; and Memphis, TN.

HPTN 084-01 is a multi-center study being conducted at 3 sites in Africa: South Africa, Uganda, and Zimbabwe.

Participant demographics for each sub-study are presented in Table 1.

Table 1. Participant Demographics: HPTN 083-01 and HPTN 084-01

Characteristic	HPTN 083-01	HPTN 084-01
Age, years		
Mean (SD)	16.4 (0.73)	16.0 (1.12)
Median (min, max)	17.0 (15, 17)	16.0 (12, 17)
Age groups (years), n (%)		
≤16	4 (44)	15 (27)
>16	5 (56)	40 (73)
Race, n (%)		
Black or African American	3 (33)	55 (100)
White	5 (56)	-
Mixed Race	1 (11)	-

Characteristic	HPTN 083-01	HPTN 084-01
Sex Assigned at Birth, n (%)		
Male	9 (100)	-
Female	-	55 (100)
Self-Identified Gender, n (%)		
Female	1 (11)	55 (100)
Gender variant or Gender non-conforming	1 (11)	-
Male	6 (67)	-
Self-identify, Other	1 (11)	-
Sexual Orientation, n (%)		
Gay/Lesbian/Homosexual	2 (22)	-
Bisexual	6 (67)	-
Straight/Heterosexual	-	55 (100)
Additional category (Pansexual)	1 (11)	-
Cohort, n (%)		
MSM	6 (67)	N/A
TGW	2 (22)	N/A
Other	1 (11)	N/A
Weight, kg		
Mean (SD)	83.9 (32.8)	56.4 (8.9)
Median (min, max)	70.6 (63, 167)	55.7 (40, 81)

Source: FDA Reviewer, derived from the Clinical Study Reports for HPTN 083-01 and HPTN 084-01

6.4 Efficacy Results

HPTN 083-01 and HPTN 084-01 did not include any primary or secondary clinical efficacy endpoints. Efficacy of oral CAB and CAB LA for HIV-1 PrEP in adolescents was previously determined (see Section 2 for details), and PK results from HPTN 083-01 and HPTN 084-01 continue to support the initial extrapolation of efficacy from adults to adolescents.

The primary objective of both HPTN 083-01 and HPTN 084-01 was to evaluate safety, tolerability, and acceptability of CAB LA. The safety results are discussed in Section 8. Secondary objectives included adherence, patterns of sexual risk behavior, safety of oral CAB, PK of CAB LA, and HIV drug resistance among participants with confirmed HIV infection.

7. Clinical Virology

The sNDA submissions contain no new virology information. No resistance data are available in adolescents because no incident HIV infections have occurred in HPTN 083-01 or HPTN 084-01.

8. Safety

8.1 Overview and Methods

The safety review was conducted using the Applicant's Clinical Study Reports (CSRs) for HPTN 083-01 and HPTN 084-01, which include data source tables. The Applicant used MedDRA version 25.1 for coding. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs, version 2.1 (July 2017) was used to determine severity of AEs.

The safety review focuses on Steps 1 and 2, the periods during the trial when participants were administered oral CAB and injectable CAB LA, respectively. In addition, the review includes a description of notable safety events that occurred with CAB LA during Step 3, the period when participants could continue CAB LA or switch to TDF/FTC.

Overall, the safety findings in adolescents are generally consistent with the previous safety findings from adult studies, and no new significant safety issues were identified that are not currently included in the label. Table 2 displays a high-level summary of safety in both adolescent sub-studies.

Table 2. Safety Summary of AEs Steps 1 and 2: HPTN 038-01 and HPTN 084-01

	HPTN 083-01 (N=9) n (%)	**HPTN 084-01 (N=55) n (%)**
Any AE	9 (100)	55 (100)
Drug-Related AEs	5 (56)	37 (67)
≥ Grade 3 AEs	2 (22)	10 (18)
Any SAE	0	2 (4)
SAEs with fatal outcome	0	0
Drug-related SAEs	0	0
AE leading to discontinuation of study drug	0	2 (4)
Drug-related AEs leading to withdrawal	0	0
Any ISR	5 (56)	14 (26)
≥ Grade 2 ISRs	3 (33)	3 (6)
≥ Grade 3 ISRs	0	0
ISRs leading to discontinuation of study drug	0	0

Source: FDA Reviewer; derived from the Clinical Study Reports for HPTN 083-01 and HPTN 084-01
AE = adverse event, ISR = injection site reaction, SAE = serious adverse event

The Applicant submitted a safety update report on June 28, 2024. For HPTN 083-01, the report covered the period from the data cut-off of the CSR (August 26, 2022) to an end of study data cut-off (October 20, 2023). For HPTN 084-01, the report covered the period from the data cut-off of the CSR (February 10, 2023) to a data cut-off of March 10, 2024. No deaths, SAEs, or AEs leading to treatment discontinuation were reported in either sub-study during the relevant safety update period. However, the safety update report included new data on pregnancy outcomes, which are discussed in Section 8.5.5.

8.2 Deaths

No deaths have occurred in HPTN 083-01 or HPTN 084-01.

8.3 Serious Adverse Events (SAEs)

Although no participant experienced an SAE in Steps 1 or 2 of in HPTN 083-01 (Table 2), one participant had an SAE during Step 3 (Table 3). Two participants in HPTN 084-01 experienced one SAE each during Step 2 (Table 2, Table 3).

Table 3. Summary of SAEs: HPTN 083-01 and HPTN 084-01

Participant ID	Step	Preferred Term	Action Taken with Study Drug	Grade	Causality Assessment (Investigator)	Outcome
HPTN 083-01						
(b) (6)	3	Suicidal ideation	Drug interrupted	4	Not Related	Resolved
HPTN 084-01						
(b) (6)	2	Suicide attempt	Drug interrupted	4	Not Related	Resolved
	2	Ovarian cyst	None	3	Not Related	Resolved

Source: FDA Reviewer; derived from the Clinical Study Reports for HPTN 083-01 and HPTN 084-01

Narratives were provided for each SAE and are summarized below. Notably, two participants across both sub-studies had SAEs of suicidal ideation or suicide attempt. However, neither SAE was assessed as related to CAB LA, and both had a potential alternative explanation. In addition, these events are adequately captured in the current Apretude and Vocabria labels, which contain a Warning and Precaution for depressive disorders, including suicidal ideation and suicide attempt. No additional labeling is warranted.

> Participant (b) (6), a 17-year-old male, experienced Grade 4 suicidal ideation 363 days after starting CAB oral lead-in and 54 days since the last injection of CAB LA during Step 3. The participant was transported to the emergency department by the police. A psychiatric assessment revealed the presence of "harmful behaviors" and a "high expressed emotion level within family and parent-child relational problems." The participant was transferred to an inpatient behavioral facility, where he continued escitalopram (Lexapro) and was discharged with an outpatient psychiatric follow-up. The participant had no prior report of depression or suicidal ideation but had been taking escitalopram for anxiety for 2 months. The last dose was administered the day the event occurred. The participant also had a pre-existing diagnosis of ADHD for which he was taking lisdexamphetamine (Vyvance) since (b) (6). The participant has a significant family history of psychiatric conditions (not specified). The investigator assessed the event as not related to study drug and reported concurrent medication as a possible cause. The participant continued CAB LA and recovered from the SAE.
>
> Participant (b) (6), a 17-year-old female, experienced Grade 4 suicide attempt 148 days after starting CAB oral lead-in and 29 days since the last injection of CAB LA during Step 2. The participant informed the site during a visit for Depo-Provera contraceptive resupply that she took 30 tablets of Truvada (which belonged to her sister, a community peer educator for HIV prevention) in a suicide attempt following a break-up with her boyfriend and a domestic dispute at home with her sister due to an ongoing family issue. She "lavaged" at home with water within 2 hours of the overdose. No medical attention was sought at the time of the event, and she was asymptomatic. The domestic issue was ongoing. The participant was offered referral to an organization that deals with women empowerment, and she received psychosocial

counseling. The study drug was temporarily held per protocol, and the participant was scheduled for additional counseling and a formal mental health assessment. The investigator assessed the event as not related to study drug. The event resolved, and the participant completed her course of CAB LA.

Participant (b) (6), a 17-year-old female, experienced a Grade 3 ovarian cyst resulting in hospitalization approximately 3.5 months after starting CAB oral lead-in and 27 days since the last injection of CAB LA. The participant underwent an ovarian cystectomy. The investigator assessed the event as not related to study drug. The event resolved, and the participant continued CAB LA.

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

No participant in HPTN 083-01 discontinued study drug due to an AE or laboratory abnormality.

Two participants in HPTN 084-01 discontinued study drug due to non-serious Grade 3 ALT increase and Grade 3 lipase increase, respectively, both during Step 1. Neither event was considered related to study drug by the investigator. Section 8.7 contains a comprehensive review of laboratory abnormalities. Narratives are summarized below.

Participant (b) (6), a 17-year-old female, experienced Grade 3 ALT increase 29 days after starting CAB oral lead-in. Baseline ALT was reported as Grade 0. Study drug was discontinued, and the event resolved 25 days later. The investigator attributed the event to alcohol binge drinking and not to study drug.

Participant (b) (6), a 17-year-old female, experienced Grade 3 lipase increase 15 days after starting oral CAB. Baseline lipase was reported as Grade 2. Study drug was discontinued, and lipase returned to Grade 2 on Day 28. Lipase remained at Grade 2 as of the last collection of laboratory assessments (Day 32). The participant terminated study participation approximately 7 months later. The investigator assessed the event as not related to study drug. The participant had a medical history of amenorrhea (mild toxicity grade, current and prior), decreased creatinine clearance (moderate toxicity grade, prior), raised amylase (moderate toxicity grade, current), and raised lipase (moderate toxicity grade, current).

8.5 Treatment Emergent Adverse Events and Adverse Drug Reactions

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. This section focuses on AEs and ADRs that occurred during Step 1 or Step 2 because participants in Step 3 may have been receiving either CAB LA or TDF/FTC. AEs or ADRs pertaining to laboratory abnormalities are excluded in this section and are instead discussed in Section 8.7.

8.5.1 Common Adverse Events (AEs) and Adverse Drug Reactions (ADRs)

Table 4 and Table 5 display the most common AEs in HPTN 083-01 and HPTN 084-01, respectively. All AEs in both sub-studies were Grade 1 or 2, except for two SAEs that occurred in HPTN 084-01 (see Section 8.3). No new safety signals were identified from the AEs reported in the sub-studies.

Table 4. Adverse Events (AEs)[1] in Steps 1 and 2: HPTN 083-01 (n=9)

Preferred Term	n (%)
Injection site pain	5 (56)
Headache	2 (22)
Rash or Rash macular	2 (22)

[1] AEs occurring in at least 2 participants
Source: FDA Reviewer; derived from the Clinical Study Report for HPTN 083-01

Table 5. Adverse Events (AEs)[1] in Steps 1 and 2: HPTN 084-01 (n=55)

Preferred Term	n (%)
Injection site pain	13 (24)
Headache	9 (16)
Amenorrhea	14 (25)
Abnormal uterine bleeding	10 (18)
Urinary tract infection	8 (15)
Abnormal loss of weight	4 (7)
Dizziness	4 (7)
Chlamydial infection	3 (5)
Constipation	3 (5)
Dermatitis allergic	3 (5)
Genitourinary chlamydia infection	3 (5)
Genitourinary tract gonococcal infection	3 (5)
Intermenstrual bleeding	3 (5)
Nausea	3 (5)

[1] AEs occurring in at least 3 participants
Source: FDA Reviewer; derived from the Clinical Study Report for HPTN 084-01

Table 6 displays the most common ADRs that occurred in each sub-study. The most common ADRs were injection site reactions (ISRs), which are discussed in Section 8.5.2. The ADRs reported in adolescents are consistent with those reported in adult studies, as displayed in Section 6.1 of the current Apretude and Vocabria labels. A comparison of the incidence of each ADR in adolescents compared to adults is challenging because of the limited sample size of adolescents.

Table 6. Adverse Drug Reactions (ADRs)[1] in Steps 1 and 2: HPTN 083-01 and HPTN 084-01

Preferred Term	HPTN 083-01 (N=9) n (%)	HPTN 084-01 (N=55) n (%)
Injection site reactions[2]	5 (56)	14 (26)
Fatigue	1 (11)	1 (2)
Sleep disorder	1 (11)	0
Headache	0	5 (9)
Dizziness	0	4 (7)
Nausea	0	3 (5)
Abdominal pain	0	1 (2)
Abnormal loss of weight	0	1 (2)

Preferred Term	HPTN 083-01 (N=9) n (%)	HPTN 084-01 (N=55) n (%)
Depressive symptom	0	1 (2)
Vomiting	0	1 (2)

[1] ADRs occurring in at least 1 participant in HPTN 083-01 or HPTN 084-01. ADRs are listed by decreasing frequency.
[2] Injection site reactions include multiple preferred terms. Refer to Table 7 for details.
Source: FDA Reviewer; derived from the Clinical Study Reports for HPTN 083-01 and HPTN 084-01

8.5.2 Adverse Events of Special Interest (AESI): Injection Site Reactions (ISR)

In Step 2 of HPTN 083-01, a total of 40 injections were administered to 9 participants. Five (56%) of the 9 participants experienced 20 local ISRs, all of which were related to study drug. All 5 participants had injection site pain, and 1 participant also had injection site swelling (Table 7). None of the ISRs were serious or led to discontinuation of study drug. The maximum severity ISR in each participant was Grade 1 (n=2) or Grade 2 (n=3). Of the 20 ISR events, 14 were Grade 1, and 6 were Grade 2; the severity of the injection site swelling was Grade 1. The median duration of ISRs was 4 days (range 2-7 days), and all ISRs had an outcome of recovered/resolved.

In Step 2 of HPTN 084-01, a total of 263 injections were administered to the 53 participants who received injections. Note: Two participants discontinued study drug during Step 1 and did not receive any injections. Fourteen (26%) of the 53 participants experienced 20 ISRs, all of which were related to study drug. Thirteen participants had injection site pain, 2 participants had injection site induration, and 1 participant had injection site swelling (Table 7). None of the ISRs were serious or led to discontinuation of study drug. The maximum severity ISR in each participant was Grade 1 (n=11) or Grade 2 (n=3). Of the 20 ISR events, 14 were Grade 1, and 6 were Grade 2; the injection site swelling and both injection site induration events were Grade 1. The median duration of ISRs was 7 days; 11 participants had a maximum duration of < 7 days, while two participants each had a maximum duration of 8-14 days and >14 days, respectively. All ISRs had an outcome of recovered/resolved.

Table 7. Injection Site Reactions (ISRs) in Step 2: HPTN 083-01 and HPTN 084-01

Preferred Term	HPTN 083-01 (N=9) n (%)	HPTN 084-01 (N=53) n (%)
Any ISR	5 (56)	14 (26)
Injection site pain	5 (56)	13 (25)
Injection site swelling	1 (11)	1 (2)
Injection site induration	0	2 (4)

Source: FDA Reviewer; derived from the Clinical Study Reports for HPTN 083-01 and HPTN 084-01

Similar to the adolescent sub-studies, ISRs were the most frequent ADRs associated with CAB LA in adult studies; and pain, swelling, and induration were among the most frequently reported ISRs in adult studies. ISRs leading to treatment discontinuation and severe ISRs were observed in adult studies only but at relatively low rates (<1% to 3%) and from large sample sizes. The sample sizes in the adolescent studies were likely too small to detect more severe ISRs but may still occur in this population. Overall, the description of ISRs in the current

Apretude label (Section 6.1) from adult studies is comprehensive, and no additional information from the adolescent sub-studies is warranted.

8.5.2 Adverse Events of Special Interest (AESI): Hypersensitivity Reactions/Rash

Two participants in HPTN 083-01 experienced rash, both during Step 2 (summarized below). No participants in HPTN 084-01 experienced a rash event.

> Participant (b) (6) developed a non-serious Grade 1 macular rash 184 days after initiation of CAB oral lead-in and had not resolved after 214 days (as of the data cutoff date). The event was not considered related to study drug by the investigator, and no action was taken with study drug.
>
> Participant (b) (6) developed a non-serious Grade 1 rash 57 days after initiation of CAB oral lead-in. The event was upgraded to Grade 2 after 36 days and resolved after 141 days. The event was not considered related to study drug by the investigator, and no action was taken with study drug.

One participant in HPTN 084-01 (Participant (b) (6)) had non-serious Grade 2 pyrexia, which occurred 182 days after initiation of CAB oral lead-in (during Step 2) and resolved 5 days later. The event was not considered related to study drug, and no action was taken with study drug. No participants in HPTN 083-01 experienced a pyrexia event.

None of the rash or pyrexia events were indicative of a hypersensitivity reaction or any other safety concern. Furthermore, no other clinical AEs potentially indicative of a hypersensitivity reaction were reported in HPTN 083-01 or HPTN 084-01. No new labeling is warranted.

8.5.3 Adverse Events of Special Interest (AESI): Rhabdomyolysis

One participant in HPTN 084-01 (Participant (b) (6)) experienced non-serious Grade 2 myalgia in the left trapezius muscle, which occurred 7 days after initiation of CAB oral lead-in and resolved 7 days later. The event was not considered related to study drug by the investigator, and no action was taken with study drug. No other clinical AEs associated with rhabdomyolysis occurred in HPTN 083-01 or HPTN 084-01, and no new labeling is warranted. Refer to Section 8.7 for a review of CK abnormalities.

8.5.4 Adverse Events of Special Interest (AESI): Hepatotoxicity, Pancreatitis, Seizures

Other AESIs for cabotegravir include hepatotoxicity, pancreatitis, and seizures. No clinical AEs indicative of potential hepatotoxicity, pancreatitis, or seizures were reported in HPTN 083-01 or HPTN 084-01, and no new labeling is warranted. Refer to Section 8.7 for a review of ALT, AST, total bilirubin, ALP, and lipase abnormalities.

8.5.5 Adverse Events of Special Interest (AESI): Pregnancy and Embryo-Fetal Toxicity

Because HPTN 083-01 was conducted in participants assigned male sex at birth, pregnancies are not applicable for this sub-study.

The HPTN 084-01 protocol required confirmation of pregnancy at least 4 weeks after the initial positive pregnancy test. Confirmed pregnancy was reported in 1 participant in the initial CSR and in 6 participants in the safety update report. The outcome of each confirmed pregnancy was either spontaneous abortion less than 20 weeks (n=2), full term delivery (n=2), or ongoing (n=3). No fetal or congenital abnormalities were reported in either full-term delivery or in either spontaneous abortion. No additional data are available for the ongoing pregnancies. Three unconfirmed pregnancies were reported in the safety update report, all of which ended in spontaneous abortion before the confirmatory test. In the 10 collective participants who became pregnant (confirmed or unconfirmed), no other SAEs or AEs leading to discontinuation were reported during the pregnancy. No new safety concerns were identified during pregnancy based on the available data.

8.6 Vital Sign Measurements

8.6.1 Weight and Body Mass Index (BMI)

In adult trials, CAB LA was associated with greater weight increase over time compared to TDF/FTC, which is described in Section 6.1 of the current Apretude label. Adolescents in HPTN 083-01 and HPTN 084-01 had a median weight gain (Q1, Q3) from baseline to Week 34 of 2.7 kg (-1.2, 9.5; n=7) and 1.6 kg (-1.3, 4.2; n=51), respectively. However, an assessment of weight changes in the adolescent sub-studies is challenging given the expectation of weight gain in this population and the absence of a control group. In addition, a comparison of weight gain in the adolescent sub-studies compared to the adult studies is difficult because of large differences in sample sizes. No additional labeling regarding weight change is warranted based on available data.

8.7 Laboratory Findings

The current Apretude label (Section 6.1) includes laboratory abnormalities that were Grade 3 or 4 in severity in at least 1% of adults in HPTN 083 or HPTN 084; ALT, AST, CK, lipase, and serum creatinine elevations are included. The laboratory findings in HPTN 083-01 and HPTN 084-01 in adolescents are generally consistent with the findings from adult studies. Based on a review of the reported laboratory abnormalities along with a review of clinical AEs and ADRs, no new safety concerns (e.g., hepatobiliary, musculoskeletal, pancreatic, or kidney toxicities) were identified in adolescents, and no additional labeling is warranted. Pertinent laboratory abnormalities reported in each sub-study are summarized below. All results provided below are post-baseline abnormalities unless otherwise specified.

8.7.1 Chemistry Abnormalities

ALT, AST, Total bilirubin, Alkaline phosphatase (ALP)

In HPTN 083-01, AST elevations that occurred (n=2) were all Grade 1, and ALT elevations were either Grade 1 (n=2) or Grade 2 (n=1). No total bilirubin or ALP elevations of any grade were reported.

In HPTN 084-01, ALT, AST, bilirubin, and ALP elevations were mostly Grade 1 or Grade 2. One participant had a Grade 3 ALT elevation (see Section 8.4 for details). No participants met the criteria of ALT >3x ULN and total bilirubin >2x ULN on the same study day.

9. ALT elevation: Grade 1 (n=7; 13%); Grade 3 (n=1; 2%)
10. AST elevation: Grade 1 (n=5; 9%)
11. Bilirubin elevation: Grade 1 (n=5; 9%); Grade 2 (n=5; 9%)
12. ALP: Grade 1 (n=12; 22%); Grade 2 (n=2; 4%)

Creatine kinase (CK)

In HPTN 083-01, one participant had a CK elevation, which was Grade 3. This non-serious event occurred 186 days since the start of CAB oral lead-in and 10 days since the last CAB LA injection. The event was accompanied by a Grade 1 AST elevation. The events resolved after 7 days and were considered not related to study drug by the investigator. Six days later, this participant had a Grade 2 decrease in creatinine clearance, which resolved after 206 days and was considered not related to study drug by the investigator.

In HPTN 084-01, CK elevations were Grade 1 (n=6; 11%) or Grade 2 (n=1; 2%). One participant had a Grade 4 CK elevation at baseline, which declined to a Grade 3 elevation post-baseline.

Lipase

In HPTN 083-01, one participant had a lipase elevation, which was Grade 3. This non-serious event occurred 137 days since the start of CAB oral lead-in and 13 days since the last CAB LA injection. The event was accompanied by a Grade 1 amylase elevation. The events resolved after 15 days and were considered not related to study drug by the investigator. No AEs occurred proximal to these laboratory events, and no abdominal pain or other symptoms associated with pancreatitis were reported.

In HPTN 084-01, most lipase elevations were Grade 1 (n=15; 27%) or Grade 2 (n=5; 9%). One participant (2%) had a Grade 2 lipase elevation at baseline, which worsened to a Grade 3 elevation post-baseline (see Section 8.4 for details). Four additional participants had a Grade 2 lipase elevation both at baseline and post-baseline.

Serum creatinine, Creatinine clearance

In HPTN 083-01, two participants had serum creatinine elevations, which were Grade 1 (n=1) or Grade 2 (n=1). The median (Q1, Q3) creatinine clearance at baseline was 93 (77, 94) mL/min (n=9), and the median change from baseline at Week 5 and Week 34, respectively, was 3 (-3, 8) mL/min (n=9) and 8 (-6, 10) mL/min (n=7). None of the declines in creatinine clearance were Grade 3 or higher.

In HPTN 084-01, serum creatinine elevations that occurred were Grade 1 (n=1; 2%), Grade 2 (n=6; 11%), or Grade 3 (n=2; 4%). Two of these participants had graded elevations because absolute values were above the ULN, and the remaining 7 participants had graded elevations because of changes from baseline (i.e., absolute serum creatinine values remained within normal limits). The median (Q1, Q3) creatinine clearance at baseline was 110 (96, 119) mL/min (n=55), and the median change from baseline at Week 5 and Week 34, respectively, was -4 (-11, 5) mL/min (n=53) and -7 (-16, 0) mL/min (n=51). One of 2 participants with Grade 3 serum creatinine elevations (due to change from baseline) also had Grade 3 creatinine clearance declines (due to change from baseline and absolute value); AEs of influenza occurred proximal to two of these timepoints, and the events subsequently resolved without treatment discontinuation. The second participant with a Grade 3 serum creatinine elevation (due to change from baseline) had a quick resolution; Grade 3 creatinine clearance decrease also occurred and was resolving without treatment discontinuation. Also of note, proteinuria occurred in 8 participants, two of which were considered related to cabotegravir by the investigator; all were non-serious and resolved, and none led to treatment discontinuation. Overall, no clinical AEs associated with kidney toxicity (i.e., aside from laboratory abnormalities) were reported.

8.7.2 Hematologic Abnormalities

In HPTN 083-01, no treatment-emergent laboratory abnormalities occurred for hemoglobin, leukocytes, lymphocytes, neutrophils, or platelets.

In HPTN 084-01, hemoglobin (n=5; 9%) and leukocyte (n=3; 5%) abnormalities were all Grade 1; and lymphocyte (n=1; 2%) and platelet (n=2; 4%) abnormalities were all Grade 2. Neutrophil abnormalities were Grade 1 (n=4; 7%), Grade 2 (n=1; 2%), or Grade 3 (n=1; 2%). No safety signals were identified following a review of clinical AEs in both studies.

8.7.3 Changes in Lipid Values

Minimal changes in lipid parameters were observed in HPTN 083-01 and HPTN 084-01. The median changes at Week 34 in adolescents were clinically similar to the median changes at Week 57 in adults (as displayed in the Apretude label).

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

10. Pediatrics

This application is in response to PMR 4191-1 issued for Apretude with a final report submission deadline of June 2024.

4191-1
Conduct a trial to evaluate the safety, tolerability, and acceptability of cabotegravir extended-release injectable suspension (CAB LA) for pre-exposure prophylaxis (PrEP) in adolescents weighing at least 35 kg, who are at risk of sexually acquired HIV-1 infection. The trial should capture data on resistance among participants who become infected during PrEP use or within one year of discontinuing PrEP.

a) Adherence data
b) Information on adverse events and treatment discontinuations
c) Information on patterns of sexual risk behavior over time
d) Resistance analyses of viral isolates from those who acquire HIV-1, including a description of the methodologies used to evaluate resistance
e) Pharmacokinetic data

Submit Clinical Study Reports (CSR) from the HPTN adolescent sub-studies and from the MOCHA study.

The submission contains CSRs from the HPTN adolescent sub-studies (083-01 and 084-01) and from the MOCHA study. The PMR is considered fulfilled. The Pediatric Review Committee (PeRC) also agreed on August 20, 2024, that the PMR is considered fulfilled.

11. Other Relevant Regulatory Issues

None

12. Labeling

The Apretude and Vocabria labels currently include a summary statement in Clinical Trials Experience in Adolescents (6.1) that the safety data in adolescents receiving [Apretude or Vocabria] for HIV-1 PrEP were comparable to the safety data reported in adults receiving [Apretude or Vocabria] for HIV-1 PrEP. The statements remain adequate and accurate with no changes warranted.

The following terminology was updated throughout both labels in accordance with the NIAID HIV Language Guide (available at https://www.niaid.nih.gov/research/hiv-language-guide).

13. “participant” instead of “subject”
14. “with HIV-1” instead of “HIV-1 infected”
15. “without HIV-1” instead of “HIV-1 uninfected”

In addition, the Apretude and Vocabria labels were updated as follows.

INDICATIONS and USAGE (1)

The indications were rephrased to use person-first language per the NIAID HIV Language Guide (available at https://www.niaid.nih.gov/research/hiv-language-guide).

> *Apretude is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk of HIV-1 acquisition.*
>
> *Vocabria is indicated for short-term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition.*

USE IN SPECIAL POPULATIONS (8)

Pregnancy (8.1): Language pertaining to neural tube defects associated with dolutegravir, another integrase inhibitor, was removed for consistency with recent changes to the dolutegravir labels.

Lactation (8.2): Breastfeeding recommendations were rephrased for clarity and accuracy.

Pediatric Use (8.4): The number of participants enrolled and dosed in HPTN 083-01 and HPTN 084-01 was updated.

Renal Impairment (8.6): The recommendation for increased monitoring for adverse effects in individuals with severe renal impairment (creatinine clearance 15 to <30 mL/min) or end-stage renal disease (creatinine clearance <15 mL/min) was removed. This recommendation was an inadvertent carry over from the Cabenuva label related to the rilpivirine component. This change is consistent with the current Vocabria label.

CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3)

The PK parameters for cabotegravir were updated based on population PK modeling that incorporated PK data from sub-studies HPTN 083-01 and HPTN 084-01 (i.e., adolescents without HIV-1 infection [n=62]). Previously, PK parameters in labeling were based on population PK modeling using data only from HIV-1 treatment studies (i.e., adults and adolescents with HIV-1 infection). Because HIV-1 infection does not impact the PK of cabotegravir, PK data from both populations (adolescents with and without HIV-1 infection) are included in the PK model and by extension included in labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Safety and PK results from HPTN 083-01 and HPTN 084-01 support continued approval of Apretude and Vocabria for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adolescents weighing at least 35 kg who are at risk for HIV-1

acquisition. We recommend approval of both supplements with the agreed upon labeling changes.

- Benefit Risk Assessment

The safety and PK assessment of Apretude and Vocabria in adolescents is unchanged from previous assessments and remains comparable to the safety and PK assessment in adults. Overall, the benefit-risk profiles for Apretude and Vocabria in the approved adolescent population for HIV-1 PrEP remain favorable.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Requirements

None

14. References

None

Appendix A

Clinical Investigator Financial Disclosure Review

Application Number: NDA 212887 (S-10); NDA 215499 (S-8)

Submission Date(s): March 21, 2024; March 27, 2024

Applicant: ViiV Healthcare

Product: Vocabria (cabotegravir oral tablet); Apretude (cabotegravir extended-release injectable suspension)

Reviewer: Sarita Boyd, PharmD

Date of Review: 8/29/2024

Covered Clinical Study (Name and/or Number): HPTN 083-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 48		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 89		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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) 0		
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. There were no financial disclosures.

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/

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