# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215499Orig1s000

# OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** December 17, 2021

**To:** London Harrison, Regulatory Project Manager
Division of Antivirals (DAV)

**From:** Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Sam Skariah, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use

**NDA**: 215499

---

In response to DAV consult request dated August 16, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for APRETUDE (cabotegravir extended-release injectable suspension), for intramuscular use (Apretude). The proposed indication of Apretude is for use for Pre-Exposure Prophylaxis (PrEP) of HIV-1 infection in adults and adolescents.

**Labeling**: OPDP's comments on the proposed labeling (PI & IFU) are based on the draft labeling received by electronic mail from DAV (London Harrison) on December 10, 2021, and comments on the PI are provided below. We have no comments on the IFU.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on December 16, 2021.

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 14, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

51 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**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/

---

WENDY R LUBARSKY
12/17/2021 11:03:13 AM

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | December 16, 2021 |
| To: | London Harrison<br>Regulatory Project Manager<br>**Division of Antivirals (DAV)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Shawna Hutchins, MPH, BSN, RN<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Wendy Lubarsky, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Patient Package Insert (PPI) |
| Drug Name (established name): | APRETUDE (cabotegravir) |
| Dosage Form and Route: | Extended-release injectable suspension, for intramuscular use |
| Application Type/Number: | NDA 215499 |
| Applicant: | ViiV Healthcare Co. |

# 1 INTRODUCTION

On July 23, 2021, ViiV Healthcare Co. submitted for the Agency's review the final portion of a rolling review for original New Drug Application (NDA-215499) for APRETUDE (cabotegravir) extended-release injectable suspension, for intramuscular use. The proposed indication of APRETUDE (cabotegravir) extended-release injectable suspension, for intramuscular use, is for use for Pre-Exposure Prophylaxis (PrEP) of HIV-1 infection in adults and adolescents.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on August 16, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for APRETUDE (cabotegravir) extended-release injectable suspension, for intramuscular use.

# 2 MATERIAL REVIEWED

- Draft APRETUDE (cabotegravir) PPI received on July 23, 2021 and received by DMPP and OPDP on December 7, 2021.
- Draft APRETUDE (cabotegravir) Prescribing Information (PI) received on July 23, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 7, 2021.
- Approved VOCABRIA (cabotegravir) comparator labeling dated January 21, 2021.
- Approved DESCOVY (emtricitabine and tenofovir alafenamide) comparator labeling dated September 15, 2021.

# 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

## 4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**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/

---

SHAWNA L HUTCHINS
12/16/2021 10:20:05 AM

WENDY R LUBARSKY
12/16/2021 10:57:48 AM

BARBARA A FULLER
12/16/2021 11:05:36 AM

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | December 15, 2021 |
| Requesting Office or Division: | Division of Antivirals (DAV) |
| Application Type and Number: | NDA 215499 |
| Product Name and Strength: | Apretude (cabotegravir) suspension for injection, 600 mg/3 mL (200 mg/mL) |
| Applicant/Sponsor Name: | ViiV Healthcare Company (ViiV) |
| OSE RCM #: | 2021-933-1 |
| DMEPA 1 Safety Evaluator: | Melina Fanari, R.Ph |
| DMEPA 1 Team Leader: | Sevan Kolejian, PharmD, MBA, BCPPS |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 14, 2021 for Apretude. The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling for Apretude (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Fanari,M. Label and Labeling Review for Apretude (NDA 215499). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Sept 28. RCM No.: 2021-933.



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**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/

---

MELINA N FANARI
12/15/2021 10:55:03 AM

SEVAN H KOLEJIAN
12/15/2021 10:57:40 AM

**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)**

# Sufficiency of ARIA to evaluate the incidence of seroconversions and development of resistance associated with cabotegravir use for Pre-Exposure Prophylaxis of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents

| | |
|---|---|
| Date: | December 3, 2021 |
| Reviewer: | Hannah Day, PhD<br>Division of Epidemiology II |
| Acting Team Leader: | Natasha Pratt, PhD<br>Division of Epidemiology II |
| Deputy Division Director: | Monique Falconer, MD, MS<br>Division of Epidemiology II |
| OPE Deputy Director: | Michael Blum, MD, MPH |
| FDA Sentinel Program Lead: | Sarah Dutcher, PhD (designee) |
| OSE Deputy Director: | Robert Ball, MD, MPH, ScM |
| Subject: | Sufficiency of ARIA to evaluate the incidence of seroconversions and development of resistance associated with cabotegravir use for Pre-Exposure Prophylaxis of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents |
| Drug Name(s): | APRETUDE (cabotegravir) injectable suspension |
| Application Type/Number: | NDA 215499 |
| Applicant/sponsor: | ViiV Healthcare Company |
| OSE RCM #: | 2021-934 |

**EXECUTIVE SUMMARY** *(place "X" in appropriate boxes)*

| | |
|---|---|
| **Memo type** | |
| -Initial | |
| -Interim | |
| -Final | X |
| **Source of safety concern** | |
| -Peri-approval | X |
| -Post-approval | |
| **Is ARIA sufficient to help characterize the safety concern?** | |
| -Yes | |
| -No | X |
| **If "No", please identify the area(s) of concern.** | |
| -Surveillance or Study Population | X |
| -Exposure | |
| -Outcome(s) of Interest | X |
| -Covariate(s) of Interest | |
| -Surveillance Design/Analytic Tools | |

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

APRETUDE (cabotegravir, CAB) is an extended-release injectable suspension intended for use for pre-exposure prophylaxis (PrEP) of human immunodeficiency virus type 1 (HIV-1) infection. CAB, a 2-metal-binding integrase strand inhibitor (INSTI), is not a new molecular entity. It is a new indication (PrEP) and a new formulation (individual injection). It has previously been formulated as an oral tablet and long-acting (LA) suspension for intramuscular (IM) administration. VOCABRIA (CAB tablets) and CABENUVA (an extended-release, injectable, two-drug copackaged product containing CAB and rilpivirine) were approved for the treatment of HIV-1 infection on January 21, 2021.

### 1.2. Describe the Safety Concern

In clinical trials, CAB LA was highly effective in preventing HIV-1 infection in at-risk adults. However, pharmacologic failures (i.e., acquisition of HIV-1 infection despite on-time CAB injections and/or CAB exposures above the target exposure) were reported in a small number of participants. Some of these participants experienced a delay in HIV-1 diagnosis.[a] As a result of prolonged CAB monotherapy in the setting of undiagnosed HIV-1 infection, resistance to the integrase strand transfer inhibitor (INSTI) drug class developed in some cases.[b]

The Division of Anti-Virals (DAV) plans to issue a Post Market Requirement (PMR) for an observational study to provide additional information on the frequency and risk factors for pharmacologic failure, delayed HIV-1 diagnosis, and INSTI resistance among participants who receive CAB LA for HIV-1 PrEP. CAB LA will be approved for use with or without an oral lead-in. For use with an oral lead-in, approximately four weeks of oral CAB will be used prior to initiating CAB LA injections. There is no data to confirm the direct to injection approach will be as safe and effective as the oral lead in in the prevention setting, but as seroconversions were noted during the oral lead in during the HPTN trials the review team hypothesizes the oral lead in may be detrimental to some persons as adherence to the daily pill regimen may be challenging for some participants.[c] The PMR study will also provide additional evidence regarding patient and prescriber preferences, adherence, tolerability, and HIV-1 acquisition among participants who receive an oral lead-in and those

[a] Due to the possibility that use of ARV-based PrEP products by individuals infected with HIV-1 may affect the ability of HIV-1 diagnostic assays to detect infection (Donnell et al. 2017)
[b] More information about pharmacologic failures can be found in Section 7.7.1 of the integrated review of NDA 215499: "Key Risk Review Issue #1: Pharmacologic Failures"
[c] More information about the oral lead in can be found in Section 7.7.2 of the integrated review of NDA 215499: "Key Risk Review Issue #2: Optional Oral Lead-In"

who do not use the oral lead-in prior to initiating CAB LA injections.[d]

The Division of Epidemiology -II (DEPI-II) has been consulted by DAV to evaluate if Sentinel ARIA can be used to conduct this PMR study.

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

| *Purpose (place an "X" in the appropriate boxes; more than one may be chosen)* | |
|---|---|
| Assess a known serious risk | |
| Assess signals of serious risk | X |
| Identify unexpected serious risk when available data indicate potential for serious risk | |

### 1.4. Statement of Purpose

The goal of the observational study will be to provide information on the frequency and risk factors for pharmacologic failure, delayed HIV-1 diagnosis, and INSTI resistance among participants who receive CAB LA for HIV-1 PrEP, as well as to collect additional information on patients who receive an oral lead-in and patients who do not use the oral lead-in prior to initiating CAB LA injections.

### 1.5. Effect Size of Interest or Estimated Sample Size Desired

The main purpose of the study is to estimate incidence of the outcomes of interest; therefore, effect size and sample size is not applicable.

## 2. SURVEILLANCE OR DESIRED STUDY POPULATION

### 2.1 Population

The population to include in the PMR study will be adults and adolescents eligible to take CAB LA for PrEP. According to the draft label, individuals must be screened for HIV-1 infection and have a negative HIV-1 test immediately prior to initiating CAB LA or oral cabotegravir for PrEP. Information on this negative HIV-1 test is needed to identify the study population.

### 2.2 Is ARIA sufficient to assess the intended population?

ARIA is not sufficient as laboratory test results to determine HIV infection are not available in the common data model for ARIA.

## 3 EXPOSURES

### 3.1 Treatment Exposure(s)

[d] In the clinical trials for CAB LA for HIV-1 PrEP, all patients received an oral lead-in, therefore information on those who go directly to CAB LA injections is not available in the clinical trials.

The exposure of interest is CAB LA. It is supplied as a combination product with a syringe, needle and vial adapter. The product will be administered by a healthcare professional in an outpatient setting, so either NDC codes or HCPC codes will be available.

### 3.2 Comparator Exposure(s)

Does not apply.

### 3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify exposure of interest.

## 4 OUTCOMES

### 4.1 Outcomes of Interest

The key outcomes of interest include incidence of laboratory defined seroconversions (new HIV-1 infections) and INSTI resistance among CAB PrEP users.

Other outcomes include frequency and testing methods used for HIV-1 diagnosis, data indicating a delay time to initial HIV-1 diagnosis, description of subsequent antiretroviral therapy and time required to achieve virologic suppression among those with a new HIV-1 infection, as well as information on adherence, adverse events and treatment discontinuations.

### 4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient. Laboratory results to determine HIV seroconversion and the development of resistance (virology laboratory data) are not available in ARIA. ARIA also does not contain information on the time to achieve virologic suppression.

## 5 COVARIATES

### 5.1 Covariates of Interest

Several outcomes will be compared in two participant groups:

1) Patients who initiate CAB LA with an oral lead-in
2) Patients who initiate CAB LA directly with CAB LA injections

### 5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA is sufficient to identify if CAB LA PrEP users who received an oral lead-in, which should be available via NDC codes in outpatient dispensing records.

## 6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

### 6.1 Surveillance or Study Design

The intended study design for the PMR study is an observational cohort study with the collection of information on important variables, such as the laboratory test findings to determine the outcomes of interest.

### 6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The tools available in ARIA are sufficient for an observational cohort study. Issues related to the need for laboratory data collection are captured above.

## 7 NEXT STEPS

ARIA is insufficient to conduct this study due to the lack of laboratory data needed to identify the population of interest and measure the outcomes. Therefore, DAV will issue a PMR to the applicant. The current language is as follows:

Conduct a study to collect and analyze data from adults and adolescents who take cabotegravir extended-release injectable suspension (CAB LA) for pre-exposure prophylaxis (PrEP) of sexually acquired HIV-1 infection and who become infected during PrEP use or within one year of discontinuing PrEP. As part of this study, collect and provide information on adherence, risk factors for non-adherence and HIV-1 acquisition. To compare tolerability and rates of HIV-1 acquisition among patients who initiate CAB LA with an oral lead-in to those who directly initiate CAB LA injections, the following should be included in the study report:

a) Frequency of testing and methods used for HIV-1 diagnosis
b) Frequency of prevalent HIV-1 infections that were detected, including those captured during screening
c) Resistance analyses of viral isolates from those who acquire HIV-1, including a description of the methodologies used to evaluate resistance
d) Description of subsequent antiretroviral therapy, including the time required to achieve virologic suppression and the durability of the response (to cover 48-weeks from the time therapy is initiated, at minimum)
e) Information on adherence, adverse events and treatment discontinuations

---

**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/

---

HANNAH R DAY
12/03/2021 11:44:46 AM

CHIH-YING CHEN
12/03/2021 12:17:56 PM

MONIQUE FALCONER
12/03/2021 12:55:20 PM

MICHAEL D BLUM
12/03/2021 01:14:16 PM

SARAH K DUTCHER
12/03/2021 03:39:29 PM

ROBERT BALL
12/03/2021 04:42:25 PM

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | 11/05/2021 |
| **From** | Jenn Sellers, M.D., Ph.D., Medical Officer<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations (OSI) |
| **To** | London Harrison, Pharm.D., Regulatory Project Manager<br>Aimee Hodowanec, M.D., Clinical Reviewer<br>Kim Struble, Pharm. D., Clinical Team Leader<br>Division of Antiviral Products (DAV) |
| **NDA #** | 215499 |
| **Applicant** | ViiV Healthcare Company |
| **Drug** | Cabotegravir (CAB, GSK1265744) |
| **NME** | No |
| **Therapeutic Classification** | HIV-1 Integrase Strand Transfer Inhibitor |
| **Proposed Indication** | (b) (4) |
| **Consultation Request Dates** | 07/08/2021 for Protocol HPTN 083 |
| | 08/10/2021 for Protocol HPTN 084 |
| **Summary Goal Date** | November 10, 2021 |
| **Action Goal Date** | December 10, 2021 |
| **PDUFA Date** | January 23, 2022 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators (CIs) Drs. Kelley, Mayer, and Landovitz (all in the U.S.) were inspected for Protocol 201738/HPTN 083. For Drs. Mokgoro and Bekker in South Africa, Remote Regulatory Assessments (RRAs) were performed for Protocol 201738/HPTN 084 as an alternative to onsite inspections due to pandemic travel restrictions.

Based on the results of the on-site CI inspections and RRAs, the studies (Protocols 201738/HPTN 083 and 201738/HPTN 084) appear to have been conducted adequately, and the data appears to be acceptable in support of this NDA. Of note, there was no evidence of missed HIV seroconversions at any of these sites.

Also of note, the RRA results for Drs. Mokgoro and Bekker are based on summaries provided by the FDA field investigators via emails and are therefore preliminary. If significantly new or different information is contained in the final RRA Report, an addendum to this clinical inspection summary will be filed.

## II. BACKGROUND

Cabotegravir (CAB, GSK1265744) is an HIV-1 integrase strand transfer inhibitor (INSTI). The combination of CAB tablets and the (b) (4) rilpivirine ((b) (4)) has recently been approved in countries including the US, EU, Canada, and Australia for the treatment of HIV-1 infection in adults.

The Applicant, ViiV Healthcare, developed oral CAB tablets and CAB LA extended-release

suspension for injection for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals (adults and adolescents) weighing at least 35 kg. The NDA includes trial data from the following two pivotal randomized Phase IIb/III studies:

> **Protocol 201738/HPTN 083** in men who have sex with men (MSM) and transgender women (TGW) who have sex with men. The trial data of HPTN 083 was submitted on May 27, 2021.
>
> **Protocol 201739/HPTN 084** for pre-exposure prophylaxis in HIV-uninfected in cisgender women. The trial data of HPTN 084 was submitted on July 23, 2021.

Both studies 201738/HPTN 083 and 201739/HPTN 084 were sponsored by the HIV Prevention Trials Network (HPTN) under the sponsorship of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH).

Clinical investigator (CI) inspections (two of which had to be converted to remote regulatory assessments [RRAs]) of CIs were conducted for these studies at the request of the Division of Antiviral Products for this rolling submission. The following is a brief description of the studies.

**Protocol 201738/HPTN 083**

*Title:* "A Phase IIb/III Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men."

*Subjects:* 2283 in Cabotegravir group and 2287 in TDF/FTC group were randomized

*Study Sites:* 43 HPTN-affiliated centers in: United States (27 centers), Peru (5 centers), Brazil (4 centers), Argentina (2 centers), Thailand (3 centers), Vietnam (1 center), and South Africa (1 center).

*Study Initiation and Completion Dates:* 19-Dec-2016 and 14-May-2020

The primary study objective was to compare HIV incidence among participants randomized to oral cabotegravir (CAB)/CAB long-acting (LA) (oral lead in and injections) vs. oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as well as to further assess the safety of CAB LA (Steps 1 and 2).

This was a Phase IIb/III, multi-center, double-blind, two-arm, randomized (1:1), active controlled non-inferiority study in HIV-uninfected cisgender men and transgender women who have sex with men. Eligible participants were randomized 1:1 to one of two arms and moved through the following steps:

***Step 1- Oral Run-in Phase:***

- **Arm A** – **Daily oral CAB** (30 mg tablets) and **oral TDF/FTC placebo** for up to five Weeks (to allow for any delays in return of Week 4 testing results).
- **Arm B** – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and **oral CAB placebo** for up to five weeks.

Participants who became HIV-infected during Step 1 of the study were permanently discontinued from the investigational product and terminated from the study, with a referral for HIV-related care.

***Step 2 - Injection Phase:***

- **Arm A – CAB LA** (600 mg as a single intramuscular [IM] injection at two time points 4 weeks apart and every 8 weeks thereafter) and **daily oral TDF/FTC placebo** to Week 153.
- **Arm B – Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and **IM placebo** at two time points 4 weeks apart and every 8 weeks thereafter (identical volume as active injectable product in Arm A) to Week 153.

Participants who became HIV-infected during Step 2 of the study were permanently discontinued from the investigational product and were referred for immediate suppressive antiretroviral therapy (ART). They were followed at quarterly intervals for 52 weeks after their last injection prior to diagnosis of HIV in order to evaluate a number of safety parameters as well as $CD_4$ cell count and HIV viral load. After 52 weeks, they were terminated from the study and transitioned to continued HIV-related care.

***Step 3 - Follow-up Phase:***

Both arms: Open-label daily oral TDF/FTC was offered at Week 153 (last day of Step 2)/Day 0 (first day of Step 3) and continued for 48 weeks.

The ***Primary Efficacy Endpoint*** was number of documented incidences of HIV infection in Step 1 and Step 2.

**Protocol 201739/HPTN-084**

*Title:* "A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women (HPTN 084)."

*Subjects:* 3224 were randomized

*Study Sites:* 20 centers in 7 countries: Botswana (1 center), Kenya (1 center), Malawi (2 centers), South Africa (7 centers), eSwatini [formerly Swaziland] (1 center), Uganda (3 centers), and Zimbabwe (5 centers).

*Study Initiation and Completion Dates:* 27-NOV-2017; study is still ongoing.

The primary study objective was to evaluate the relative efficacy of oral Cabotegravir/Cabotegravir long-acting injectable extended-release suspension (CAB/CAB LA) (oral run-in and injections) vs. daily oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) for human immunodeficiency virus (HIV) prevention (Steps 1 and 2). This is an ongoing Phase 3 randomized, multi-site, two-arm, double-blind study of the safety and efficacy of CAB LA vs. TDF/FTC for prevention of HIV-acquisition in HIV- uninfected women in Sub-Saharan Africa (SSA). Eligible participants were randomized 1:1 to one of two arms and moved through the following steps:

***Step 1- Oral Run-in Phase:***

- **Arm A – Daily oral CAB** and **oral TDF/FTC placebo** for up to 5 weeks plus an HIV

prevention package including behavioral risk reduction, adherence counseling, and offer of condoms.

- **Arm B** – Daily **TDF/FTC** and **oral CAB placebo** for up to 5 weeks plus an HIV prevention package including behavioral risk reduction, adherence counseling, and offer of condoms.

***Step 2 - Injection Phase:***

- **Arm A** – Injections of **CAB LA** at 2 time points 4 weeks apart and every 8 weeks thereafter and **daily oral TDF/FTC placebo** beginning at Week 5 plus an HIV prevention package as in Step 1. Injections consisted of 600 mg of CAB LA administered as one 3 mL IM injection.
- **Arm B** – Daily **oral TDF/FTC** and **IM placebo** (matching vehicle, identical volume as active injectable product in Arm A) beginning at Week 5 plus an HIV prevention package as in Step 1.

***Step 3 - Follow-up Phase:***

Both arms – Open-label daily TDF/FTC (to cover the PK tail for Arm A participants) was provided no later than 8 weeks after the last injection visit, for up to 48 weeks, plus an HIV prevention package as in Steps 1 and 2.

The ***Primary Efficacy Endpoint*** was number of documented incidences of HIV infection in Step 1 and Step 2.

## III. RESULTS

1. **Colleen F. Kelley, M.D.**
   Center number: 31440
   Site number: 787
   500 Irvin Court, Suite 200
   Decatur, GA 30030
   Inspection dates: August 30 - September 23, 2021

At this site for Protocol 201738/HPTN 083, a total of 109 subjects were screened and 86 were enrolled. There were 23 screen failures. Among all the enrollers, a total of 79 subjects completed Step 1 (Oral Run-in Phase) and 35 subjects completed Step 2 (Injection Phase). All discontinuations were verifiable, i.e., there were no discrepancies between the source records and the data line listings submitted by the sponsor for discontinuations.

The inspection reviewed the records of all 23 screen failures, the 30 out of 35 enrolled subjects who completed Step 2 (the Injection Phase), and subjects who were lost to follow up. The records reviewed included, but not limited to, the informed consent forms (ICFs), the study worksheets, electronic case report forms (eCRFs), eligibility records, efficacy endpoint data (HIV test results), adverse event reports, concomitant medications, the pharmacy records, investigational product storage and shipment, IRB and monitor correspondence, and training records.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor. All the HIV tests results were reviewed, and there was no evidence of missed seroconversions. There was also no evidence of underreporting of adverse events. One adverse event was misreported: Subject # (b) (6) (in TDF/FTC treatment group) had "rectal gonorrhea" in the source records but was reported to eCRF and FDA as "rectal chlamydia".

**2. Kenneth H. Mayer, M.D.**
Center number: 31785
Site number: 819
1340 Boylston Street
Boston, MA 02215
Inspection dates: August 23-26, 2021

At this site for Protocol 201738/HPTN 083, 110 subjects were screened, 82 were enrolled, and 62 subjects completed the study. All discontinuations were verifiable, i.e., there were no discrepancies between the source records and the data line listings submitted by the sponsor for discontinuations.

The inspection reviewed all 110 screened subjects' informed consent forms, all 82 enrolled subjects' laboratory records of HIV test results, and 21 of the 82 enrolled subjects' eligibility criteria. Other study records reviewed included, but were not limited to, adverse event records, protocol deviations, correspondence between the CI and the Sponsor/Contract Research Organization, correspondence between the CI and the Institutional Review Board (IRB), the sponsor monitoring log, study drug accountability, and Form FDA 1572.

The primary efficacy data were verifiable. There was no incidence of seroconversion for any of the 82 enrolled subjects, i.e., all subject source records were reviewed for HIV seroconversion. There was no evidence of underreporting of adverse events.

**3. Raphael J. Landovitz, M.D.**
Center number: 00601
Site number: 701
1399 S. Roxbury Dr. Suite 100
Los Angeles, California, 90035
Inspection dates: July 26-30, 2021

At this site for Protocol 201738/HPTN 083, 78 subjects were screened, 65 were enrolled, and 50 subjects completed Step 2. All discontinuations were verifiable, i.e., there were no discrepancies between the source records and the data line listings submitted by the sponsor for discontinuations.

The inspection reviewed informed consent forms for all 78 screened subjects and HIV test results for all 65 enrolled subjects. The inspection also reviewed study eligibility, randomization, adverse events, protocol deviations, concomitant medications, treatment with the investigational product for 26 enrolled subjects. Other records audited included, but were not limited to, home health care reports, electronic medical records, eCRFs, investigational product accountability, site correspondence, FDA form 1572, financial disclosure, study monitoring report and staff training records.

The primary efficacy data were verifiable. There was no evidence of missed seroconversions, as the HIV test results for all 65 enrolled subjects were reviewed.

The inspection found that the following adverse events for two subjects (both in TDF/FTC group) were not reported by the CI:

- Chills and sweating (Subject # (b) (6))
- Hemorrhoid and lymphadenopathy (Subject # (b) (6))

*Reviewer's comment: Since these two subjects were in the control group, these unreported adverse events would not impact the safety profile of the study drug.*

**4. Linda-Gail Bekker, Ph.D.**

Center number: 30346
Site number: 779
14 Sonwabile Road
Old Crossroads Klipfontein, Cape Town
Western Cape, 7750, South Africa
RRA dates: September 27 - October 8, 2021

At this site for Protocol 201739/HPTN-084, a Remote Regulatory Assessment (RRA) was used as an alternative to onsite inspection when an onsite inspection was not possible due to the COVID-19 pandemic. The RRA was conducted using video conferencing via Zoom and document sharing via an online platform (Box.com) to exchange information.

This site had three CIs over the course of Protocol HPTN 084: Dr. Gonasagrie Nair from 15-Oct-2018 to 26-Feb-2021, Dr. Linda-Gail Bekker from 26-Feb-2021 to 20-Jul-2021, and Dr. Steven Innes from 20-Jul-2021 to present.

At this site for Protocol HPTN 084, 347 subjects were screened and 223 subjects were enrolled. Three subjects were transferred from other sites; therefore, the site enrolled a total of 226 subjects. The study is currently ongoing.

The RRA reviewed 101 of 223 enrolled subjects for study eligibility and 215 of 226 subjects for the primary efficacy endpoint (documented HIV infection in Step 1 and Step 2). The RRA also reviewed and verified 5 of 5 serious adverse events; 2 of 2 pregnancies; 23 randomly selected subject source records for adverse events; and 8 subjects listed as Treatment/Study Withdrawal in the data listings. No issues were observed with the subject records, reporting, or general study conduct.

The primary efficacy endpoint data were verifiable. The inspection verified against source records the three seroconversions in the data listings prior to the data cutoff date of 05-Nov-2020; there have been three seroconversions since the cutoff. There was no evidence of underreporting of adverse events.

5. **Mammekwa Mokgoro, M.D.**
   Center number: 31445
   Site number: 789
   No. 1 Zulu Road
   Valley Trust
   Botha's Hill, Kwa-Zulu Natal, 3660
   South Africa
   RRA dates: October 18-29, 2021

At this site for Protocol 201739/HPTN-084, a Remote Regulatory Assessment (RRA) was used as an alternative to onsite inspection when an onsite inspection was not possible due to the COVID-19 pandemic. The RRA was conducted using video conferencing via Zoom and document sharing via an online platform (Box.com) to exchange information.

There were 319 subjects screened, 223 subjects were enrolled, and 190 subjects completed Part 1 and 2 and are currently in Part 3. Thirty-three subjects were discontinued for various reasons. The RRA found all documentation of discontinuations to be sufficient and verifiable.

The RRA reviewed 31 subjects for study inclusion/exclusion, adverse events, chart notes (clinic notes), dosing logs, communication folder, and notes to file. The RRA found that subjects were properly determined to be eligible for enrollment and did not find other significant non-compliance.

The primary efficacy endpoint data were verifiable. That is, the RRA reviewed the primary efficacy endpoint (HIV test results) for all 223 subjects enrolled. Eight subjects seroconverted, 6 of which were verified against the data line listing provided by the sponsor, and two subjects seroconverted after the data cut-off (Subject # (b) (6) in TDF/FTC group and # (b) (6) in CAB group). There was no evidence of unreported seroconversions or underreporting of adverse events.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

**cc:**
DARRTS: NDA 215499
DAV/Project Manager/London Harrison
DAV/Medical Officer/Aimee Hodowanec
DAV/Clinical Team Leader/Kim Struble
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

---

**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/

---

JENN W SELLERS
11/05/2021 12:11:37 PM

PHILLIP D KRONSTEIN
11/05/2021 12:21:54 PM

KASSA AYALEW
11/05/2021 01:27:27 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | September 28, 2021 |
| Requesting Office or Division: | Division of Antivirals (DAV) |
| Application Type and Number: | NDA 215499 |
| Product Name and Strength: | Apretude (cabotegravir) suspension for injection, 600 mg/3 mL (200 mg/mL) |
| Product Type: | Combination Product (Drug-Device) |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | ViiV Healthcare Company (ViiV) |
| FDA Received Date: | July 23, 2021 |
| OSE RCM #: | 2021-933 |
| DMEPA 1 Safety Evaluator: | Melina Fanari, R.Ph |
| DMEPA 1 Team Leader: | Sevan Kolejian, PharmD, MBA, BCPPS |

## 1 REASON FOR REVIEW

As part of the approval process for Apretude (cabotegravir) suspension for injection, the Division of Antivirals (DAV) requested that we review the proposed Apretude prescribing information (PI), patient prescribing information (PPI), instruction for use (IFU), container label and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B-N/A |
| ISMP Newsletters* | C-N/A |
| FDA Adverse Event Reporting System (FAERS)* | D-N/A |
| Other | E-N/A |
| Labels and Labeling | F |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 CONCLUSION AND RECOMMENDATIONS

We note that the proposed Apretude IFU and PPI are in alignment with the marketed Cabenuva IFU and PPI with the exception that Apretude is for monotherapy and provide a recommendation in Section 4 below to ensure this alignment. In addition, we collaborated with DAV to revise the PI to improve the readability of the Dosage and Administration section. Further, the proposed container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for ViiV Healthcare Company (ViiV).

## 4 RECOMMEDATIONS FOR DIVISION OF ANTIVIRALS (DAV)

| Table 2. Identified Issues and Recommendations for Division of Antivirals (DAV) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Patient Prescribing Information | | | |
| 1. | Proprietary name is missing. | The Applicant submitted a request for proprietary name, Apretude, which DMEPA reviewed and has concluded that it is conditionally acceptable based on the proposed product characteristics received on July 23, 2021. | Place the conditionally acceptable proprietary name, Apretude throughout the Prescribing information (PI), patient prescribing information (PPI)and instruction for use (IFU). |
| 2. | The section 'How will I receive Apretude' should state injections are provided by healthcare provider. | Improve clarity on product administration. | Revise bullet 1 in this section to read as follows:<br><br>APRETUDE is given as an injection by your healthcare provider 1 time every 2 months into the muscle of your buttock. |

## 5 RECOMMENDATIONS FOR VIIV HEALTHCARE COMPANY (VIIV)

| Table 3. Identified Issues and Recommendations for ViiV Healthcare Company (ViiV) (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| All Container label and Carton Labeling | | | |
| 1. | As currently presented the tradename is missing. | Unable to review the tradename placement. | If you plan on utilizing a tradename for your product, place the conditionally acceptable proprietary name Apretude on container label, backing card and carton labeling; and submit revised labels for Agency review. |
| 2. | Total drug content strength statement is of | Minimize risk of wrong dose medication errors. | The prominence of the total drug content statement (600 |

| Table 3. Identified Issues and Recommendations for ViiV Healthcare Company (ViiV) (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | equal prominence to mg/mL strength statement. | | mg/3 mL) should be increased in prominence in comparison to the 200 mg/mL strength statement. |
| Container Label | | | |
| 1. | Lot number and expiration date are missing. | Ensure proper product identification and reduce risk for deteriorated drug medication errors. | Please update label with a lot number and expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. |
| Carton Labeling | | | |
| 1. | Healthcare Professional administration statement missing. | Ensure proper product administrations. | The following statement should be added to the principal display panel of the carton labeling: |

| Table 3. Identified Issues and Recommendations for ViiV Healthcare Company (ViiV) (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | | "HealthCare Professional Administration Only"<br><br>In addition, this statement should be added to the backing card. |

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Apretude that ViiV Healthcare Company (ViiV) submitted on July 23, 2021, and the listed drug (Vocabria).

Table 4. Relevant Product Information for Listed Drug and Apretude

| Product Name | Vocabria | Apretude |
|---|---|---|
| Initial Approval Date | 1/21/2021 | N/A |
| Active Ingredient | cabotegravir | cabotegravir |
| Indication | (b) (4) for the prevention of HIV (PrEP [preexposure prophylaxis]) | (b) (4) |
| Route of Administration | oral | intramuscular |
| Dosage Form | tablet | Suspension for injection |
| Strength | 30 mg | 600 mg/3 mL (200 mg/mL) |
| Dose and Frequency | One tablet of Vocabria 30 mg taken orally once daily for approximately 1 month in combination with one tablet of Edurant (rilpivirine) 25 mg | (b) (4) |

| | | |
|---|---|---|
| | taken orally once daily with a meal. | |
| How Supplied | Bottles of 30 tablets | One single-use vial of cabotegravir Injectable Suspension, 200 mg/mL (600 mg/3 mL fill presentation) is co-packaged with:<br>• Sterile, single-use vial adaptor<br>• 5-mL sterile, single-use syringe<br>Sterile, single-use 23 gauge, 1.5-inch safety needle |
| Storage | Store below 30°C (86°F) | Store at [redacted] (b) (4). Do not freeze. |

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Apretude labels and labeling submitted by ViiV Healthcare Company (ViiV).

- Container label(s) received on July 23, 2021
- Carton labeling received on July 23, 2021
- Instructions for Use, Patients Prescribing Information and Prescribing Information (Images not shown) received on July 23, 2021, available from \\CDSESUB1\evsprod\NDA215499\0012\m1\us\114-labeling\1141-draft

F.2 Label and Labeling Images

Container label

Vial

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

**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/

---

MELINA N FANARI
09/28/2021 04:07:44 PM

SEVAN H KOLEJIAN
09/28/2021 05:34:45 PM