CLINICAL PHARMACOLOGY REVIEW

NDA/SDN (Supplement #)	212887/69 (S-5) 212887/71 (S-6) 212888/267 (S-5) 212888/275 (S-6) 202022/492 (S-17) 202022/493 (S-18)
Submission Type	Efficacy supplement
Applicant Name	ViiV
Submission Date	NDA 212887 S5: 9/29/2021 NDA 212887 S6: 10/7/2021 NDA 212888 S5: 9/29/2021 NDA 212888 S6: 10/7/2021 NDA 202022 S17: 10/15/2021 NDA 202022 S18: 10/15/2021
Generic Name	Cabotegravir (CAB) and Rilpivirine (RPV)
Brand Name	NDA 212887: Vocabria NDA 212888: Cabenuva NDA 202022: Edurant
Dosage Form (Strength)	NDA 212887: CAB tablet NDA 212888: -CAB 200 mg/mL vial -RPV 300 mg/mL vial
Indication	Treatment of HIV-1 Infection
Review Team	Mario Sampson, PharmD, Vikram Arya, PhD, FCP

This is an addendum to the NDA 212887 Clinical Pharmacology review dated 3/8/2022. The purpose of this addendum is to address the clinical and analytical site inspection reviews, which were received after March 8. We find that the objectionable conditions identified in the clinical site inspections have no impact on the PK analysis. We continue to recommend approval.

Clinical site inspections

The clinical site inspection review identified objectionable findings that did not warrant issuance of an FDA Form 483, but recommended the review division assess the impact of four findings (NDA 212888, OSIS reviews dated 3/11/2022 and 3/15/2022):

- Site Emory, subject (b) (6): Not being on stable antiretroviral therapy (ART) for 180 days and changing therapy before enrollment
- Site Emory, subject (b) (6): Incorrect dosing of RPV 900 mg instead of 600 mg
- Site Emory, subject AE of Grade 4 elevated CPK

- Site Johns Hopkins, subject [redacted]: Not being on stable ART for 180 days and changing therapy before enrollment

Not on stable ARV for 180 days before enrollment
An inclusion criterion stated a subject should be on the same ART for six consecutive months before enrollment. Subject [redacted] changed ART ~4.5 months before enrollment and subject [redacted] changed ART 82 days before enrollment. As there are no antiretrovirals that cannot be coadministered with injectable CAB/RPV, these findings have no impact on the PK results.

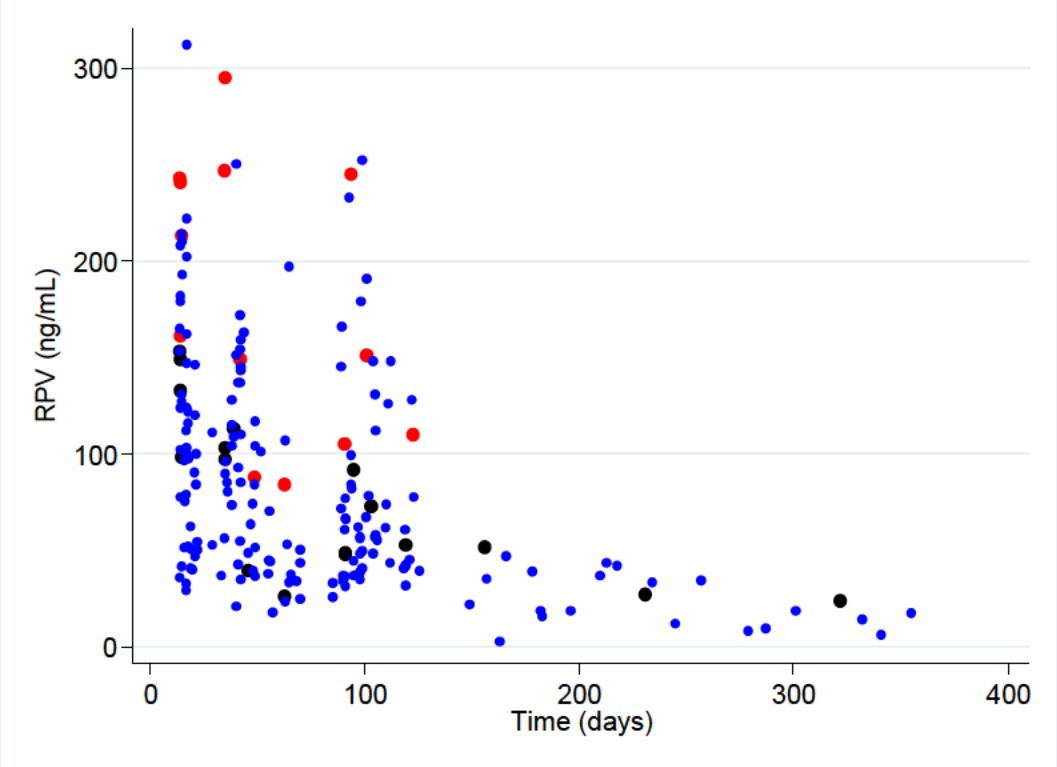
Incorrect RPV dosing
Subject [redacted] received RPV 900 mg instead of 600 mg at week 8. RPV exposures in subject [redacted] did not significantly differ from other subjects. RPV geometric mean AUC is almost identical for all subjects (80101 ng*h/mL) vs when excluding subject [redacted] (79557 ng*h/mL) (Table 1). Also, RPV exposures do not noticeably differ for subject [redacted] vs others in study 208580 (Figure 1). No changes are necessary to the previously discussed PK analyses in the NDA 212888 Clinical Pharmacology review dated 3/8/2022.

Table 1. Study 208580 RPV AUCtau values.

Subject ID	RPV Q4W AUCtau (ng*h/mL)
[redacted]	119116
	50630
	53949
	54427
	44753
	73159
	92321
	68911
	73314
	Not reported
	155165
	128601
	71097
	133317

Source: RPV popPK report (p92).

Figure 1. Study 208580 RPV concentration-time profiles in subjects [redacted] vs other subjects.



Source: Plotted by reviewer. Black dots = [redacted]; red dots = [redacted] blue dots = other subjects.

Grade 4 elevated CPK

Subject [redacted] was enrolled in the RPV arm and had an AE of Grade 4 elevated CPK. RPV exposures were relatively high in subject [redacted] but not outside the range of exposures observed in other study 208580 subjects (Figure 1). Elevated CPK is described in the Adverse Reactions section of approved Cabenuva labeling, where it was reported for 8% of adults in a pooled analysis of trials FLAIR and ATLAS vs 4% of subjects receiving active control.

Analytical site inspection

OSIS conducted a remote record review of the analytical site at [redacted] and found no objectional conditions (NDA 212888, OSIS review dated 2/9/2022).

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/

MARIO SAMPSON
03/18/2022 03:37:26 PM

VIKRAM ARYA
03/18/2022 03:44:11 PM