CLINICAL PHARMACOLOGY REVIEW

NDA/SDN	212887/147 (S-9, S-10) 212888/752 (S-15) 215499/529 (S-8)
Submission Type	Efficacy supplement
Applicant Name	Viiv
Submission Date	NDA 212887 and NDA 212888: 3/21/2024 NDA 215499: 3/27/2024
Generic Name	Cabotegravir (CAB) and rilpivirine (RPV)
Brand Name	NDA 212887: Vocabria NDA 212888: Cabenuva NDA 215499: Apretude
Dosage Form (Strength)	Vocabria: CAB tablet (30 mg) Cabenuva: CAB suspension (200 mg/mL) and RPV suspension (300 mg/mL) Apretude: CAB suspension
Indication	Treatment of HIV-1
Review Team	Mario Sampson, PharmD, Justin Earp, PhD, Su-Young Choi, PharmD, PhD

1 Executive summary

CAB for HIV prevention

CAB for HIV prevention was previously approved for adolescents based on observed PK from adolescents receiving CAB oral lead-in (OLI) then every four week (Q4W) IM injections in HIV treatment study MOCHA, and modeling and simulation to predict exposures for the HIV prevention dosing regimen (every eight week [Q8W] maintenance injections). This supplement includes PK data for adolescents enrolled in HIV prevention studies HPTN 083-01 and HPTN 084-01. Based on the updated CAB PK parameters for adolescents, we continue to agree with the labeling statement that there are no clinically relevant differences in CAB exposure between adolescents and adults.

CAB + RPV for HIV treatment

CAB + RPV for HIV treatment as either monthly or every-two-month maintenance injections was previously approved for adolescents based on observed PK from adolescents receiving CAB OLI then Q4W IM injections or RPV OLI then Q4W IM injections in HIV treatment study MOCHA, and modeling and simulation to predict exposures for the Q8W regimen. This

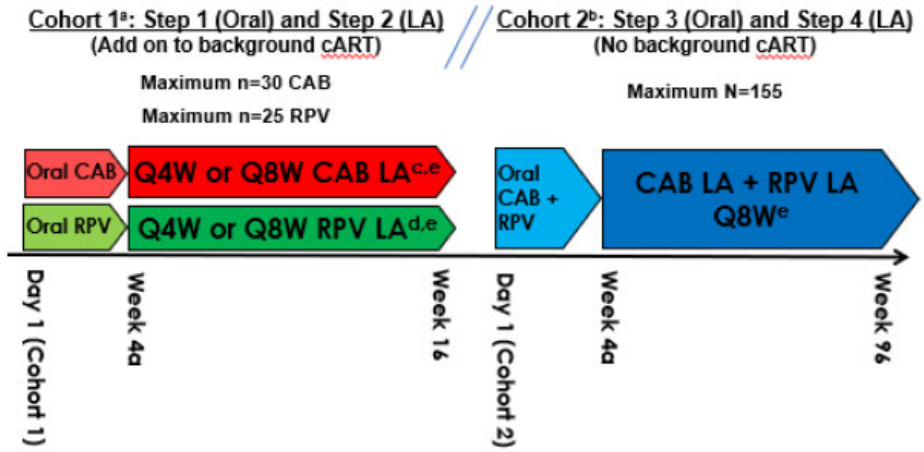
supplement includes the additional PK data for adolescents enrolled in MOCHA. Based on the updated CAB and RPV PK parameters for adolescents, we continue to agree with the labeling statement that there are no clinically relevant differences in CAB or RPV exposure between adolescents and adults.

2 Background

CAB for HIV prevention

CAB for HIV prevention was previously approved for adolescents. From study MOCHA, observed PK were available from eight adolescents with HIV receiving CAB OLI followed by Q4W IM dosing (Figure 1). Using modeling and simulation, exposures were predicted for adolescents receiving CAB Q8W injections (NDA 215499, Integrated review dated 12/20/2021). Approved dosing for adults and adolescents weighing ≥35 kg included an optional OLI period (oral CAB 30 mg daily for ≥28 days), initiation injections of 600 mg IM administered on months one and two, followed by continuation injections of 600 mg IM administered on months four and every two months onwards.

Figure 1. MOCHA design



Source: MOCHA CSR, p26.
CAB dosing was 30 mg daily orally for 4-6 weeks followed by 600 mg IM on week four and 400 mg IM on weeks eight and 12.
RPV dosing was 25 mg daily orally for 4-6 weeks followed by 900 mg IM on week four and 600 mg IM on weeks eight and 12.

The current supplement contains observed PK data from adolescents receiving CAB OLI followed by Q8W IM injections for HIV prevention in studies HPTN 083-01 (n=9) and HPTN 084-01 (n=62), along with CAB PK data for cohorts 1C and 2 in MOCHA (Table 1).

Table 1. PK sample size by cohort in MOCHA in the current supplement

Cohort	Dosing	PK sample size
1C	CAB Q4W	8
1C	CAB Q8W	22
1R	RPV Q4W	15
1R	RPV Q8W	10
2	CAB + RPV Q8W	144

Source: MOCHA CSR, section 8.

CAB + RPV for HIV treatment

CAB + RPV for HIV treatment was previously approved for adolescents. PK data were submitted from adolescents with HIV in cohort 1 of MOCHA receiving CAB oral lead-in (OLI, 30 mg orally daily for 4-6 weeks) followed by Q4W IM dosing (n=8) or RPV OLI (25 mg orally daily for 4-6 weeks) followed by Q4W IM dosing (n=14) as add-on to current antiretroviral treatment. Using modeling and simulation, exposures were predicted for adolescents receiving CAB Q8W (NDA 212887, Clinical pharmacology reviews dated 3/8/2022 and 3/18/2022). Approved dosing for adults and adolescents weighing ≥35 kg included an optional OLI period (oral CAB 30 mg daily + oral RPV 25 mg daily for ≥28 days) followed by either once monthly or every-two-month IM injections:

- Monthly IM injections: CAB 600 mg and RPV 900 mg on month one, CAB 400 mg and RPV 600 mg on month two and monthly onwards
- Every-two-month IM injections: CAB 600 mg and RPV 900 mg on months one, two, and then every two months onwards

The current supplement contains the cohort 1 Q8W data and cohort 2 data (Table 1).

3 Exposure comparison in adolescents vs adults

3.1 CAB IM for prevention

In adolescent studies HPTN 083-01 and HPTN 084-01, geometric mean CAB exposures after OLI and Q8W injections were up to 40% higher than adults but were largely within the range of adults (Table 2, Figure 2). We agree with the statement in proposed labeling that there are no clinically relevant differences in CAB exposure between adolescents and adults.

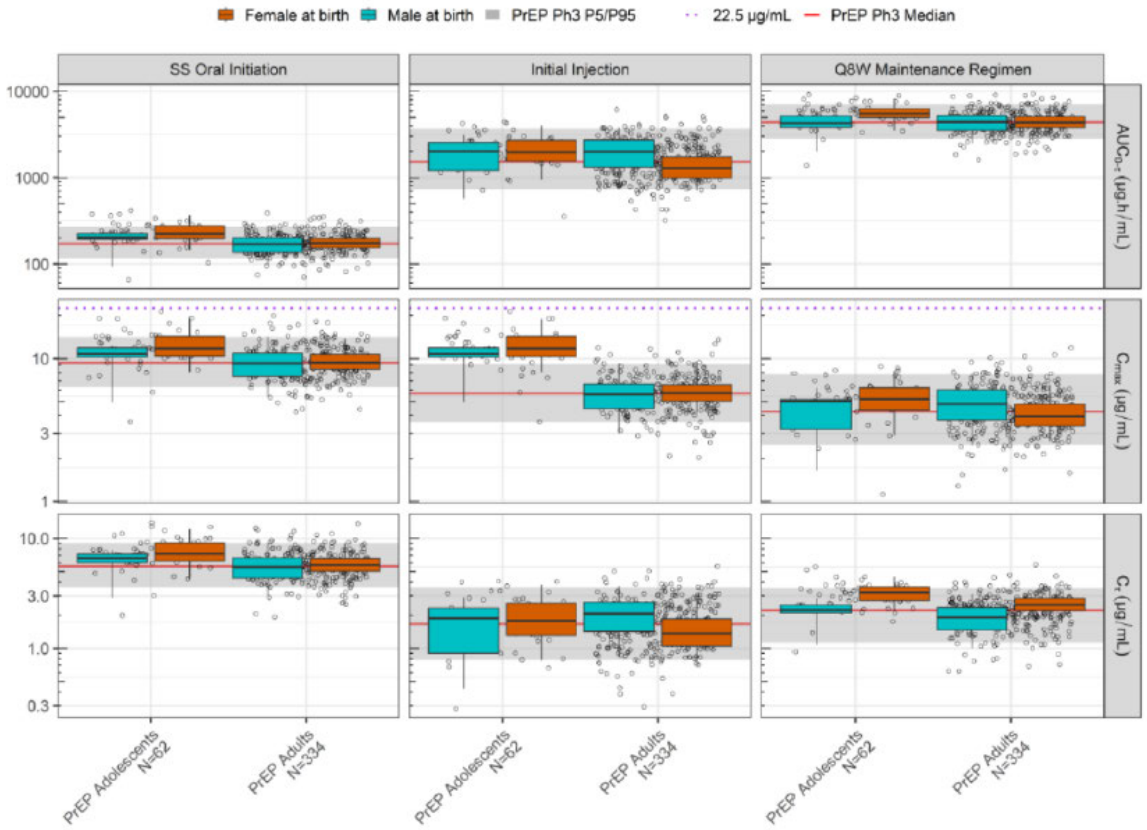
Table 2. Geometric mean (95% CI) of post-hoc estimates of CAB exposures in adolescents and adults by indication.

Dosing	Population	N	AUC0-τ (µg•h/mL)	Cmax (µg/mL)	Cτ (µg/mL)
30 mg PO once daily steady state	PrEP adolescents	62	221 (205-238)	11.6 (10.8-12.5)	7.15 (6.59-7.76)
	Ph3 treatment	740	149 (146-152)	7.98 (7.83-8.13)	4.65 (4.54-4.75)
	PrEP adults	334	172 (167-177)	9.29 (9.04-9.54)	5.59 (5.42-5.76)
CAB LA initial injection	PrEP adolescents	62	1960 (1750-2200)	11.6[a] (10.8-12.5)	1.73 (1.52-1.97)
	Ph3 treatment	740	1610 (1560-1660)	7.99[a] (7.84-8.14)	1.44 (1.39-1.49)
	PrEP adults	334	1590 (1500-1670)	5.63[a] (5.46-5.81)	1.65 (1.57-1.74)
CAB LA Q8W steady state	PrEP adolescents	62	5350 (4960-5770)	4.90 (4.49-5.35)	2.96 (2.75-3.18)
	Ph3 treatment	740	3670 (3600-3740)	3.79 (3.70-3.88)	1.66 (1.61-1.71)
	PrEP adults	334	4380 (4250-4510)	4.34 (4.18-4.51)	2.12 (2.05-2.21)

Source: NDA 215499, Clinical Pharmacology Summary submitted 3/27/2024, p20.

Reviewer's comment:
Geometric mean ratio (PrEP adolescent / PrEP adult) of PK parameters ranges for OLI, initial injection, and Q8W maintenance are 1.25-1.28, 1.05-2.06, and 1.13-1.4, respectively.
The larger difference (~2-fold) between adolescents and adults for C_{max} after initial injection is due to giving the initial injection on the same day as last OLI dose in adolescents but 24 hours after last OLI dose in adults.

Figure 2. CAB exposures after Q8W IM administration for HIV prevention in adolescents vs adults.

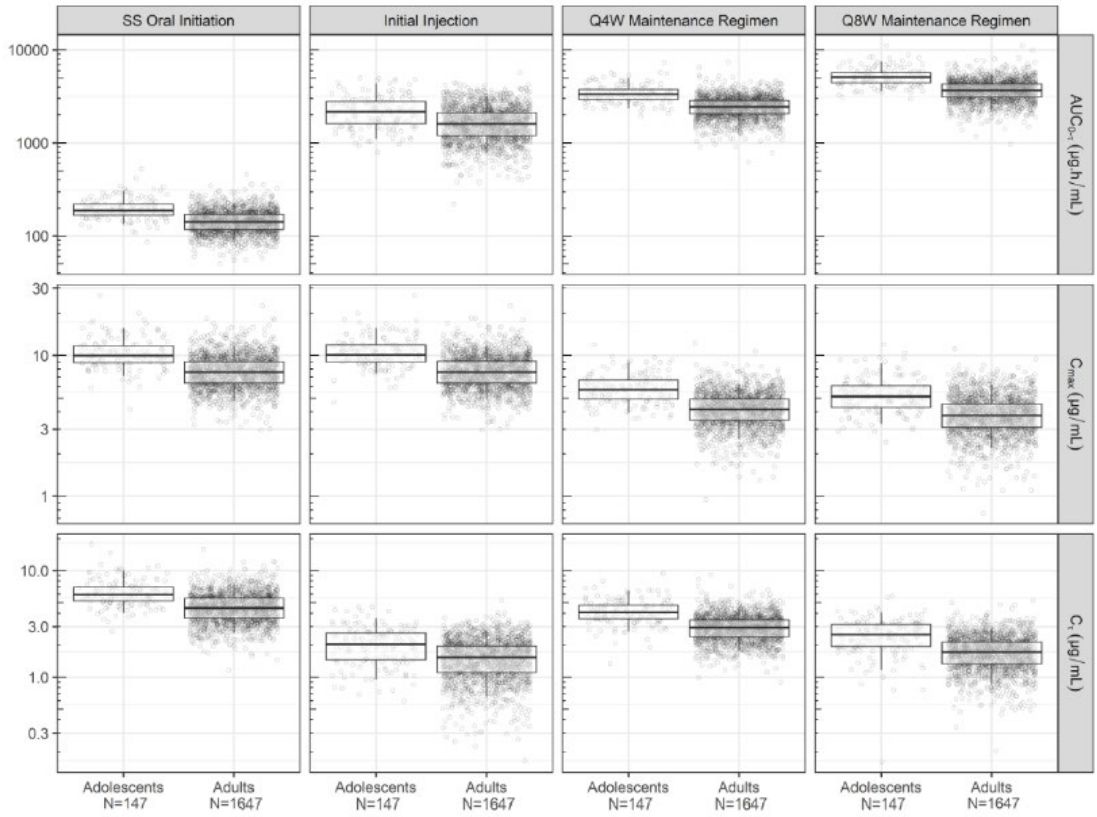


Source: NDA 215499, Response to IR dated 6/10/2024, p1.
For box plots, the horizontal center solid line in each box represents the median value, the box represents the 25th to 75th percentiles, and the whiskers represent the 5th and 95th percentiles.
The standard Q8W dosing regimens were simulated with PO lead-in: PO lead-in of CAB PO once daily for 4 weeks, followed by 600 mg CAB LA IM 2 hours after the last PO dose, followed by CAB LA IM 600 mg Q8W thereafter.

3.2 CAB/RPV IM for treatment

In MOCHA, geometric mean CAB exposures after OLI, Q4W, and Q8W injections in adolescents were 29-43% higher than adults but largely within the range of adults (Figure 3, Table 3). We agree with the statement in proposed labeling that there are no clinically relevant differences in CAB exposure between adolescents and adults.

Figure 3. CAB post hoc exposure metrics in adolescents and adults.



Source: NDA 212887, Response to IR submitted 6/5/24, p1.

Table 3. CAB post hoc exposure metrics in adolescents and adults.

Dosing phase		Adult participants			Adolescent participants from Study 208580 (MOCHA) only		
		AUC0-τ,ss (µg×h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)	AUC0-τ,ss (µg×h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)
OLI	N	1647	1647	1647	147	147	147
	Geomean [95% CI]	142 [140, 144]	7.59 [7.49, 7.69]	4.43 [4.37, 4.50]	195 [187, 204]	10.3 [9.92, 10.8]	6.14 [5.87, 6.43]
	%CV	87.1	83.7	93.5	83.0	81.8	87.0
	Median [min, max]	142 [49.5, 452]	7.59 [2.96, 22.6]	4.46 [1.16, 15.9]	189 [85.8, 523]	9.98 [4.15, 26.7]	5.92 [2.69, 17.7]
	Percentiles						
	5th	89.2	4.92	2.61	135	7.11	4.01
	25th	118	6.37	3.61	168	8.87	5.18
	50th	142	7.59	4.46	189	9.98	5.92
	75th	172	9.05	5.50	222	11.7	7.00
	95th	222	11.6	7.23	306	15.7	10.0
Dosing phase		**Adult participants**			**Adolescent participants from Study 208580 (MOCHA) only**		
		AUC0-τ (µg×h/mL)	Cmax[a] (µg/mL)	Cτ (µg/mL)	AUC0-τ (µg×h/mL)	Cmax[a] (µg/mL)	Cτ (µg/mL)
Initial injection	Geomean [95% CI]	1577 [1545, 1609]	7.60 [7.50, 7.70]	1.45 [1.42, 1.48]	2138 [2004, 2281]	10.4 [10.0, 10.8]	1.95 [1.82, 2.08]
	%CV	116	83.5	120	111	80.6	116
	Median [min, max]	1609 [223, 5739]	7.59 [2.97, 22.6]	1.54 [0.164, 5.25]	2155 [792, 4981]	10.1 [4.64, 26.7]	2.04 [0.598, 4.58]
	Percentiles						
	5th	773	4.93	0.654	1104	7.42	0.951
	25th	1204	6.37	1.11	1620	8.98	1.46
	50th	1609	7.59	1.54	2155	10.1	2.04
	75th	2109	9.10	1.97	2782	11.9	2.61
	95th	3158	11.6	2.72	4342	15.7	3.62
Dosing phase		**Adult participants**			**Adolescent participants from Study 208580 (MOCHA) only**		
		AUC0-τ,ss (µg×h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)	AUC0-τ,ss (µg×h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)
Q4W maintenance regimen (11th LA IM injection)	Geomean [95% CI]	2395 [2365, 2426]	4.09 [4.04, 4.15]	2.89 [2.85, 2.93]	3376 [3255, 3501]	5.74 [5.52, 5.97]	4.09 [3.92, 4.28]
	%CV	83.3	86.4	86.3	75.5	78.6	85.0
	Median [min, max]	2427 [619, 7390]	4.15 [0.947, 12.3]	2.93 [0.895, 9.10]	3336 [1932, 7331]	5.69 [2.98, 11.9]	4.09 [1.34, 9.41]
	Percentiles						
	5th	1510	2.54	1.80	2333	3.90	2.69
	25th	2053	3.48	2.42	2937	4.91	3.56
	50th	2427	4.15	2.93	3336	5.69	4.09
	75th	2846	4.91	3.47	3752	6.68	4.75
	95th	3562	6.22	4.44	5001	8.89	6.42
Dosing phase		**Adult participants**			**Adolescent participants from Study 208580 (MOCHA) only**		
		AUC0-τ,ss (µg×h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)	AUC0-τ,ss (µg×h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)
Q8W maintenance regimen (6th LA IM injection)	Geomean [95% CI]	3625 [3580, 3672]	3.72 [3.66, 3.78]	1.67 [1.64, 1.70]	5116 [4935, 5305]	5.18 [4.95, 5.43]	2.38 [2.22, 2.55]
	%CV	82.9	94.4	105	75.1	87.9	117
	Median [min, max]	3673 [961, 11 131]	3.77 [0.759, 11.1]	1.72 [0.203, 5.23]	5084 [2986, 11 078]	5.12 [2.42, 12.0]	2.52 [0.160, 5.75]

	Percentiles					
	5th	2282	2.20	0.858	3594	3.26	1.17
	25th	3106	3.09	1.34	4441	4.28	1.95
	50th	3673	3.77	1.72	5084	5.12	2.52
	75th	4300	4.54	2.15	5724	6.08	3.15
	95th	5384	6.23	2.87	7576	8.78	4.07

Source: Document No. TMF-16443596 Table 11.
a. The Cmax following the first CAB LA injection is likely determined by the last oral dose instead of the initiation LA dose.
Notes: Adolescent participants consist of participants from Study 208580 only. AUC0-τ and Cτ, τ is different for different regimens. For time-varying BMI (designated as PBMI in the dataset), BMI at time = 0 was used for simulations. Post hoc simulations were performed without residual variability. Numeric values are presented as 3 significant figures.
PK sampling schedule in the simulation:
Following oral doses: one sample every 0.1 hour within 6 hours and one sample every 2 hours after 6 hours. This sampling schedule is more intensive than the previous adult tNDA PopPK analysis.
Following IM injections: one sample every 24 hours.
The standard Q4W and Q8W dosing regimens were simulated with OLI: OLI of CAB QD for 4 weeks, followed by 600 mg CAB LA IM 2 hour after the last oral dose, followed by CAB LA IM 400 mg Q4W or 600 mg Q8W thereafter.

Source: NDA 212887, Clinical pharmacology summary submitted 3/21/2024, p25.
Geometric mean ratios (adolescent / adult) of PK parameters ranged from 1.29-1.43 (NDA 212887, Response to IR submitted 6/12/2024).

Geometric mean RPV exposures after OLI, Q4W, and Q8W injections in adolescents were 21% lower to 27% higher than adults and within the range of adults (Table 4, Figure 4). We agree with the statement in proposed labeling that there are no clinically relevant differences in RPV exposure between adolescents and adults.

Table 4. RPV post hoc exposure metrics in adolescents and adults.

Exposure parameter	Adolescents (Study 208580) (5th-95th %) (n)	Adults (Studies ATLAS, FLAIR, ATLAS-2M) (5th-95th %) (n)	GMR adolescents to adults (90% CI)
AUCtau initial injection (ng.h/mL)[a]	35259 (20301 - 63047) (n=148)	44842 (21712 - 87575) (n=1359)	0.79 (0.74-0.83)
Ctau initial injection (ng/mL)[a]	36.5 (22.4 - 59.4) (n=148)	41.9 (21.7 – 78.9) (n=1359)	0.87 (0.82-0.92)
Cmax initial injection (ng/mL)[a]	135 (85.8 - 211) (n=148)	144 (93.9 - 221) (n=1359)	0.94 (0.890-0.97)
AUCtau Q4W maintenance regimen Week 48 (ng.h/mL)[b]	84280 (49444 - 156987 (n=13)	68324 (39042 - 118111) (n=969)	1.23 (1.05-1.45)
Ctau Q4W maintenance regimen Week 48 (ng/mL)[b]	109 (64.8 - 202) (n=13)	85.8 (49.6 - 147) (n=969)	1.27 (1.08-1.48)
Cmax Q4W maintenance regimen Week 48 (ng/mL)[b]	146 (84.8 - 269) (n=13)	121 (68.1 - 210) (n=969)	1.21 (1.03-1.42)
AUCtau Q8W maintenance regimen Week 48 (ng.h/mL)[c]	110686 (78480 - 151744) (n=125)	132450 (76638 - 221783) (n=390)	0.84 (0.79-0.88)
Ctau Q8W maintenance regimen Week 48 (ng/mL)[c]	61.8 (44.5 – 88.0) (n=125)	68.9 (38.0 - 119) (n=390)	0.90 (0.85-0.95)
Cmax Q8W maintenance regimen Week 48 (ng/mL)[c]	108 (68.0 - 164) (n=125)	138 (80.6 - 228) (n=390)	0.79 (0.75-0.83)

Note: Values are shown as geometric mean (5^{th} and 95^{th} percentiles) and sample size (n); the adults' individual parameters are computed from the previously developed adult PopPK model.[19,21]

GMR: geometric mean ratio. CI: confidence interval. IM: intramuscular. Q4W: every 4 weeks. Q8W: every 8 weeks

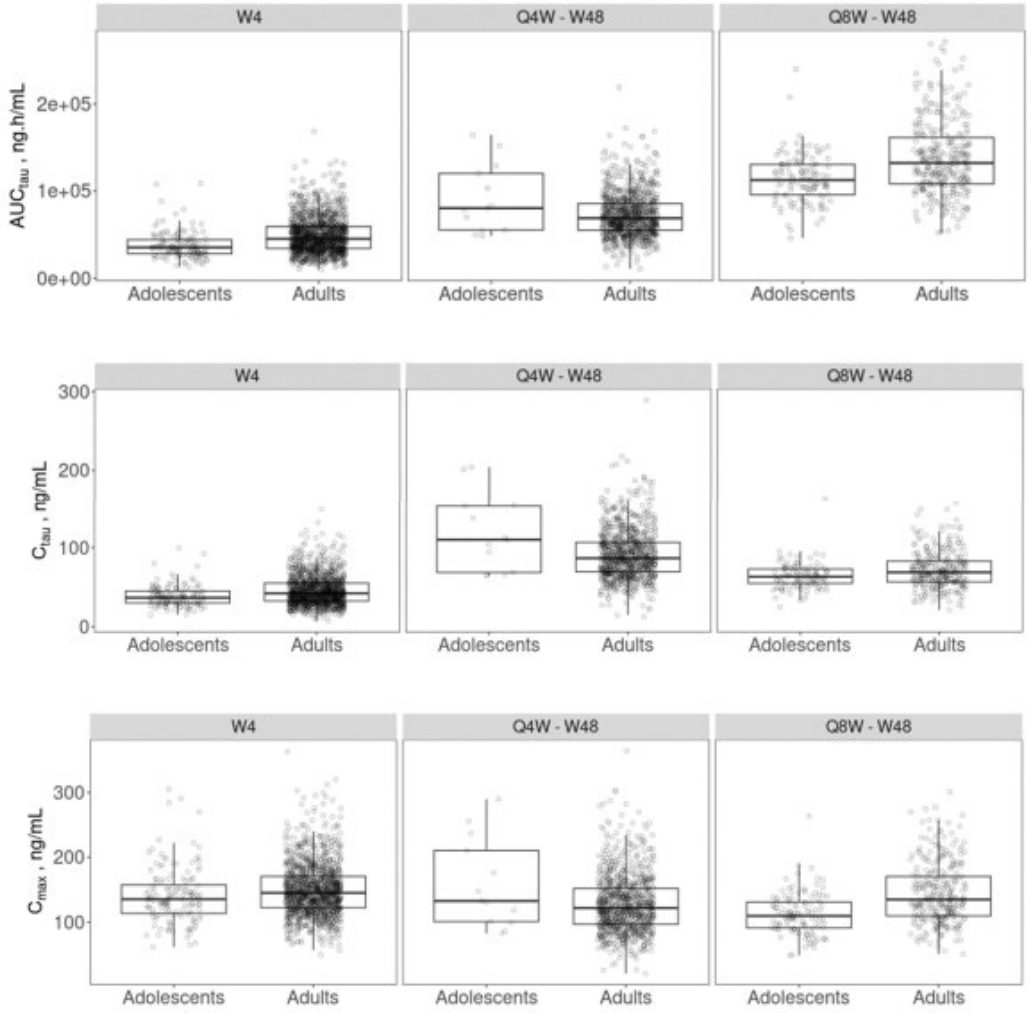
[a] All data is pooled irrespective of regimen: visit after single IM 900 mg injection.

[b] For Study ATLAS-2M, only participants in the RPV LA 600 mg Q4W arm, and with no prior exposure, are shown

[c] For Study ATLAS-2M, only participants in the RPV LA 900 mg Q8W arm, and with no prior exposure, are shown

Source: NDA 212887 SDN 147, RPV popPK report, p37.

Figure 4. RPV post hoc exposure metrics in adolescents and adults.



Gray dots overlaid on the boxplots represent the individual data. For Study ATLAS-2M, participants in the RPV LA 600 mg IM Q4W arm, and with no prior exposure, are shown in the central panels; while participants in the RPV LA 900 mg IM Q8W arm, and with no prior exposure, are shown in the right panels. The adults' individual parameters are computed from the previously developed adult PopPK model[12,13].

Source: NDA 212887 SDN 147, RPV popPK report, p118.

4 Adolescent study summaries

Study 208580 (MOCHA)

MOCHA enrolled adolescents weighing ≥35 kg with HIV infection and on stable antiretroviral therapy (ART). In cohort 1, participants received oral CAB or RPV for 4-6 weeks followed by either Q4W or Q8W injections as add-on to ART. In cohort 2, participants received CAB + RPV orally for 4-6 weeks followed by Q8W injections without ART (Figure 1). PK sample sizes by cohort ranged from 8-22 in cohort 1 and PK sample size in cohort 2 was 144.

Prohibited concomitant medications included the following:

- Entire study: included systemically administered immunomodulators (such as interleukin and interferon agents), chronic systemic glucocorticoids, and HCV therapy.
- Steps 1-4: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifampin, rifapentine, St. John's Wort
- Cohort 1, entire study:
    - Cohort 1R: Cobicistat, ritonavir, any NNRTI other than the study drug rilpivirine
    - Cohort 1C: any INSTI other than the study drug cabotegravir
- Cohort 1R and Cohort 2 Step 3 while receiving oral RPV: PPIs and systemic dexamethasone (more than a single dose)
- Cohort 1 Step 2 and Cohort 2 Step 4: Use of anticoagulants >14 days except for DVT prophylaxis or low dose acetylsalicylic acid

Reviewer's comment: There were no reported uses of contraindicated medications listed in labeling (Vocabria, Cabenuva, Edurant). Use of a PPI was reported for one participant, but this was during follow-up (Concomitant medication dataset).

The Applicant reported protocol deviations for 42 participants in Cohort 1 and 81 participants in Cohort 2 (MOCHA CSR, p43). None were identified by the Applicant as being significant. *Reviewer's comment: Deviations related to the PK analysis included deviations for shipping of PK samples reported for three participants, and for number and type of cryovials for PK storage samples reported for 10 participants (ICH Data Listings, p9). We do not consider these to be significant deviations.*

Study 213002 (HPTN 083-01)

HPTN 083-01 enrolled sexually active participants assigned male at birth, with age <18 years, weighing ≥35 kg, and without HIV infection. The study targeted men who have sex with men in the US. Study dosing was oral CAB 30 mg daily for five weeks (Step 1) followed by 600 mg IM injections at weeks 5 (loading dose), 9, 17, 25, and 33 (Step 2). Nine participants were enrolled and contributed PK samples.

Prohibited concomitant medications included the following:

- Cytotoxic chemotherapy or radiation
- Systemically administered immunomodulators, chronic systemic glucocorticoids, and HCV therapy

- Certain enzyme inducers: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifampin, rifapentine, St. John's Wort
- Anticoagulants within seven days before or after an injection

Reviewer's comment: There were no reported uses of contraindicated medications listed in labeling (Vocabria, Cabenuva) (CSR, p88).

Protocol deviations were reported for eight of nine participants. None were identified by the Applicant as being significant.
Reviewer's comment: The majority of reported protocol deviations were unrelated to dosing or PK sample collection, with the exception of one participant who missed a blood draw timepoint (ICH data listings, p30).

Study 213003 (HPTN 084-01)

HPTN 084-01 females (assigned at birth) who reported sex with a male in the last 12 months, with age <18 years, weighing ≥50 kg, and without HIV infection. The study was conducted in Sub-Saharan Africa. Study dosing was oral CAB 30 mg daily for five weeks (Step 1) followed by 600 mg IM injections at weeks 5 (loading dose), 9, 17, 25, and 33 (Step 2). Fifty-three participants contributed PK samples.

Prohibited concomitant medications included the following:

- Cytotoxic chemotherapy or radiation
- Systemically administered immunomodulators, chronic systemic glucocorticoids, and HCV therapy
- Certain enzyme inducers: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampicin, rifampin, rifapentine, St. John's Wort
- Anticoagulants within seven days before or after an injection

Reviewer's comment: There were no reported uses of contraindicated medications listed in labeling (Vocabria, Cabenuva) (CSR, p127).

Protocol deviations were reported for 46 of 55 enrolled participants. None were identified by the Applicant as being significant.
Reviewer's comment: The majority of reported protocol deviations were unrelated to dosing or PK sample collection, with the exception of two out of window injections for one participant (ICH data listings, p152).

5 Bioanalytical methods

Concentrations of CAB (calibration curve: 25-25000 ng/mL [0.025-25 mcg/mL]) and RPV (calibration curve: 1-5000 ng/mL) were measured in human plasma using validated LC/MS-MS methods. Most validation and study sample analysis runs were acceptable with calibration curve, QC sample, and incurred sample reanalysis assessments meeting acceptance criteria. Study samples were analyzed within the documented duration of stability. No significant protocol deviations were reported (Table 5, Table 6).

Table 5. Validation reports

Analyte	**Validation report**
CAB	Validation v6 dated 6/2/20, p44
CAB	Validation v8 dated 3/9/22, p74
CAB	Validation v9 dated 3/7/23
RPV	Validation v3 dated 4/6/20, p45
RPV	Validation v5 dated 5/17/22

Table 6. MOCHA study sample analysis reports

Study	Analyte	# samples analyzed	Analysis dates	Sample analysis report
MOCHA	CAB	153	5/19 – 7/20	CAB
MOCHA	CAB	1512	11/21 – 3/23	CAB part 3A
MOCHA	RPV	210	5/19 – 8/20	RPV part 1
MOCHA	RPV	1349	11/21 – 6/23	RPV part 2
HPTN 083-01	CAB	88	10/22 – 11/22	CAB
HPTN 084-01	CAB	572	6/22 – 8/22	CAB

Note: NDA 212888, response to IR submitted 8/26/24 confirms that RPV samples from MOCHA were analyzed within the duration of stability.

6 Population PK models

6.1 CAB popPK report

Review Summary
The Applicant's population PK (popPK) analysis is acceptable for the purpose of deriving CAB and metabolite exposure metrics (C_{max}, AUC, C_{tau}) for labeling. The Applicant's final model parameters and individual exposure estimates (C_{max}, AUC, C_{tau}) were verified by the reviewer.

Introduction
In prior submissions, CAB popPK modeling objectives were to characterize the PK of CAB in the general adult population (NDA 212887, Integrated review dated 12/19/2019) and subsequently among a subset of the adolescent population (NDA 212887, Clinical pharmacology reviews dated 3/8/2022 and 3/18/2022). The objective of the current popPK analysis was to characterize the disposition of CAB using the full adolescent dataset.

Model development

New data for this analysis are from adolescent studies MOCHA, HPTN 083-01, and HPTN 084-01 (Table 7). Model parameters had acceptable precision and interindividual variability parameters had acceptable shrinkages (Table 8). The models demonstrated acceptable performance in goodness-of-fit and visual predictive check plots (Figure 5, Figure 6).

Table 7. Studies included in the CAB popPK analysis

Study No.	Study Description	CAB Dose and Administration	PK Population	PK Sampling
Lal116585	Oral relative bioavailability study – single dose, healthy subjects. Cohort A: (b) (4); (b) (4)	30 mg ((b) (4) tablets) PO single dose	18 healthy subjects (10 M, 8 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose
Lal117010	Rifampin DDI study with CAB as victim in healthy subjects Period 1 only (single dose without rifampin)	30 mg ((b) (4) tablets) PO single dose	15 healthy subjects (10 M, 5 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose
Lal117011	Oral contraceptive DDI study with CAB as perpetrator in healthy subjects	30 mg ((b) (4) tablets) PO QD × 11 days	19 healthy subjects (19 F)	Pre-dose and 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose
Lal117020	Oral, single-dose, relative bioavailability study in healthy subjects Fasted 800-mg (b) (4)	30 mg ((b) (4) tablets) PO single dose	22 healthy subjects (13 M, 9 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose
201741	Oral, single-dose, relative bioavailability study in healthy subjects 500- and 800-mg (b) (4)	30 mg ((b) (4) tablets) PO single dose	37 healthy subjects (27 M, 10 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose
201479	Hepatic impairment, single-dose study in both healthy and hepatically impaired subjects	30 mg ((b) (4) tablets) PO single dose	16 healthy subjects (12 M, 4 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose
201480	Renal impairment, single-dose study in both healthy and renally impaired subjects	30 mg ((b) (4) tablets) PO single dose	16 subjects (12 M, 4 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose

Study No.	Study Description	CAB Dose and Administration	PK Population	PK Sampling
205696	Food effect on CAB PK; single dose; fasted period only, 500-mg (b) (4); Phase 3 formulation	30 mg (b) (4) tablets) PO single dose	23 healthy subjects (16 M, 7 F)	Pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours post-dose
Lal116482 (LATTE)	Phase 2b, dose ranging in HIV-infected subjects (with 2 nucleoside reverse transcriptase inhibitors [NRTIs]): induction phase	10 mg tablet PO QD × 24 weeks 30 mg tablet PO QD × 24 weeks 60 mg (2 × 30 mg) PO QD × 24 weeks	176 HIV subjects 10 mg: n = 60 (57 M, 3 F) 30 mg: n = 57 (55 M, 2 F) 60 mg: n = 59 (55 M, 4 F)	Sparse PK: Pre-dose and 2 to 4 hours on Weeks 2 and 12 Intensive PK: Pre-dose and 1, 2, 3, 4, 8, and, 24 hours post-dose on Week 2 only; pre-dose on Week 12
Lal115428	Phase 1, repeat-dose escalation of CAB LA, PO lead-in phase only	30 mg PO QD × 14 days	43 healthy subjects (27 M, 16 F)	Pre-dose and 1, 2, 3, 4, 8, and 24 hours post-dose
Lal116815	LA relative bioavailability, single-dose study in healthy subjects with PO lead-in Cohort A: (b) (4) data only; (b) (4) (b) (4), formulations in Cohorts B and C excluded	30 mg PO QD, at steady state LA 400 mg IM single dose (b) (4) (b) (4) only)	21 healthy subjects (15 M, 6 F)	PO (Day -15): pre-dose and 1, 2, 3, 4, 8, and 24 hours post-dose. LA: Pre-dose and 4 hours post-dose on Days 3, 5, and 7, Weeks 2, 3, 4, 6, 8, and 12.
200056 (LATTE-2)	Phase 2b treatment study in HIV-infected subjects	Lead-in/induction 30 mg PO QD × 20 weeks, then switch to 1) 800 mg IM × 1, then 400 mg IM Q4W or 2) 800 mg IM × 1, then 600 mg IM at Week 4, then 600 mg IM Q8W starting at Week 8	286 HIV subjects (262 M, 24 F)	Day 1: Pre-dose (pre-last PO dose/pre-first IM injection) and 2 hours post-IM injection Weeks 1, 4, 8, 12, 16, 20, 24, 25, 28, 32 pre-dose and 2 hours post-dose, 36, 40, and 41 PK sampling scheme same regardless of dosing regimen
201103 (HPTN077)	Phase 2a PrEP study of safety, tolerability, and PK of CAB LA in healthy subjects	Lead-in 30 mg PO QD × 4 weeks, 1-week washout, then Arm 1: 800 mg IM Q12W × 3 Arm 2: 600 mg IM at Weeks 5 and 9, and then Q8W × 3	134 healthy subjects (89 M, 45 F)	Arm 1: Week 1 pre-dose, 2, 4 (24 h trough after the last oral dose), 5 pre-dose (pre-first IM injection), 6, 9, 13, 17 pre-dose (pre-second IM injection), 18, 23, 29 pre-dose (pre-third IM injection), 30, 35, 41, 53, 65, 77, 89, 101, and 105.

Study No.	Study Description	CAB Dose and Administration	PK Population	PK Sampling
				Arm 2: Week 1 pre-dose, 2, 4 (24 h trough after the last oral dose), 5 pre-dose (pre first IM injection), 6, 9 pre-dose (pre-second IM injection), 10, 13, 17 pre-dose (pre-third IM injection), 18, 21, 25 pre-dose (pre-fourth IM injection), 26, 29, 33 pre-dose (pre-fifth IM injection), 34, 38, 41, 53, 65, 77, 89, 101, and 109.
201120 (ECLAIR)	Phase 2a PrEP-enabling study of CAB LA in male healthy subjects at low risk of contracting HIV	Lead-in 30 mg PO QD × 4 weeks, 1-week washout, then 800 mg IM Q12W × 3	102 healthy subjects (102 M)	Weeks 5 pre-dose (pre-first IM injection), 6, 9, 13, 17 pre-dose (pre-second IM injection), 18, 23, 29 pre-dose (pre-third IM injection), 30, 35, and 41, and follow-up (Week 53 through Week 81)
201584 (FLAIR)	Phase 3 treatment study in HIV-infected, antiretroviral (ARV)-naive subjects (switch from an integrase inhibitor [INI] single-tablet regimen)	Induction ABC/DTG/3TC 1 tablet QD × 20 weeks, followed by lead-in 30 mg PO QD × 4 weeks, then switch to 600 mg IM × 1, then 400 mg IM Q4W	283 HIV subjects (220 M, 63 F)	Weeks 4 (prior to the last PO dose, prior to the first IM injection), 5, 8, 12, 16, 20, 24, 28, 32, 36, 40, 41, 44, 48, 52, 56, 60, 96, 100, 104, and 108 Note: Samples are taken prior to IM injection at the time points above except for Weeks 4 and 104 (subjects switching from comparator arm), where the PK sample was taken prior to the last PO dose. In addition, a PK sample at 2 hours post-IM injection is taken at Weeks 4, 48, 96, and 104. Samples beyond Week 64 were available in no subject at the time of the adult analysis.
201585 (ATLAS)	Phase 3 treatment study in HIV-infected, virologically suppressed, treatment-experienced subjects (switch current INI-, non-NRTI-, or protease inhibitor-based ARV regimen)	Lead-in 30 mg PO QD × 4 weeks, then switch to 600 mg IM × 1, then 400 mg IM Q4W	308 HIV subjects (209 M, 99 F)	Weeks 4 (last PO dose, first IM injection), 5, 8, 12, 16, 20, 24, 28, 32, 36, 40, 41, 44, 48, 52, 56, 60, and 96 Note: Samples are taken prior to IM injection at the time points above except for Weeks 4 and 56 (subjects

Study No.	Study Description	CAB Dose and Administration	PK Population	PK Sampling
				switching from comparator arm), where the PK sample was taken prior to the last PO dose. In addition, a PK sample at 2 hours post-IM injection is taken at Weeks 4, 48, 56, and 96. Samples beyond Week 72 were available in no subject at the time of the adult analysis.
208580 (MOCHA)	Phase 1/2, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of PO CAB, CAB LA, and RPV LA in virologically suppressed HIV-1-infected children and adolescents aged 12 to <18 years	CAB dose and administration: Q4W regimen was implemented for the data included in this analysis. The study protocol was updated wherein Q8W regimen was to be implemented for any new subjects enrolled in 2021 and thereafter.	Up to 155	For patients who were recruited under clinical protocol V2, PK samples were: Cohort 1 • Wk 2 oral dosing: pre-dose and 1, 2, 3, 4, 8 and 24 hours post-dose. • LA injection: Wk 4b: Pre-dose and 2h post dose, Wk 5: Day 3-7 post-dose, Wk 6: Day 10-14 post-dose, Wk 8: pre-dose, Wk 12: Pre-dose and 2h post dose, Wk 13: Day 3-7 post-dose, Wk 14: Day 10-14 post-dose, Wk 16: Day 28 post-dose. Cohort 2 • Wk 2 - oral dosing: Pre-dose and between 2-7h post dose • LA dosing: Wk 4b: Pre-dose and 2h post dose, Wk 5: Day 3-7 post-dose, predose prior to every injection at Wk 8, Wk 12, Wk 16, Wk 20, Wk 24, Wk 25 (Day 3-7 post-W24 dose), Wk 36, Wk 48, Wk 60, Wk 72, Wk 84, Wk 96.

Study No.	Study Description	CAB Dose and Administration	PK Population	PK Sampling
				For patients who were recruited under clinical protocol V3, PK samples were: Cohort 1 • Wk 2 oral dosing: Pre-dose, 1, 2, 3, 4 and 8h post dose • LA dosing: Wk. 4b: Pre-dose and 2h post dose, Wk. 5: Day 3-7 post-dose, Wk. 8: pre-dose, Wk. 9: Day 3-7 post-dose, Wk. 12: Day 28 post dose, Wk. 16: Day 56 postdose Cohort 2 • Wk. 2 oral dosing: Pre-dose and 3h post dose • LA dosing: Wk. 4b: Pre-dose and 2h post dose, Wk. 5 and Wk. 25: Day 3-7 post-dose, pre-dose prior to every injection at Wk. 8, Wk. 16, Wk. 24, Wk. 32, Wk. 40, Wk. 48, Wk. 64, Wk. 80, Wk. 88, Wk. 96.
213002 (HPTN 083-01)	Phase 2B, single arm, open label; safety, tolerability, and acceptability of CAB LA injection for the prevention of HIV among sexually active healthy male adolescents aged <18 years	5-week CAB 30 mg PO QD safety lead-in, followed by a series of 5 IM injections of 600 mg administered at 8-week intervals after a 4-week loading dose (i.e., IM injection at 5, 9, 17, 25, and 33 weeks)	50	Pre-dose trough samples at 5, 9, 17, 25, and 33 weeks (final concentration in injection phase). 1-week post-injection samples at 6, 10, 18, 26, and 34 weeks. Follow-up samples at +8, +12, +24, +36, and +48 weeks following the final injection and at the HIV confirmatory visit.
213003 (HPTN 084-01)	Phase 2B, single arm, open label; safety, tolerability, and acceptability of CAB LA injection for the prevention of HIV among sexually	5-week CAB 30 mg PO QD safety lead-in, followed by a series of 5 IM injections of 600 mg administered at 8-week intervals after a 4-week	50	Pre-dose trough samples at 5, 9, 17, 25, and 33 weeks (final concentration in injection phase).

Study No.	Study Description	CAB Dose and Administration	PK Population	PK Sampling
	active, healthy female adolescents aged <18 years	loading dose (i.e., IM injection at 5, 9, 17, 25, and 33 weeks)		1-week post-injection samples at 6, 10, 18, 26, and 34 weeks. Follow-up samples at +8, +24, +36, and +48 weeks following the final injection and at HIV confirmatory visit.

Source: CAB popPK report, p97.

Reviewer's comment: For adolescent studies, the PK population appears to be the planned sample size as the actual enrollment differs compared to the CSRs (Adolescent study summaries). Further the sample size is acceptable for estimating the pharmacokinetics of cabotegravir in adolescents.

Table 8. Final CAB population PK model parameters

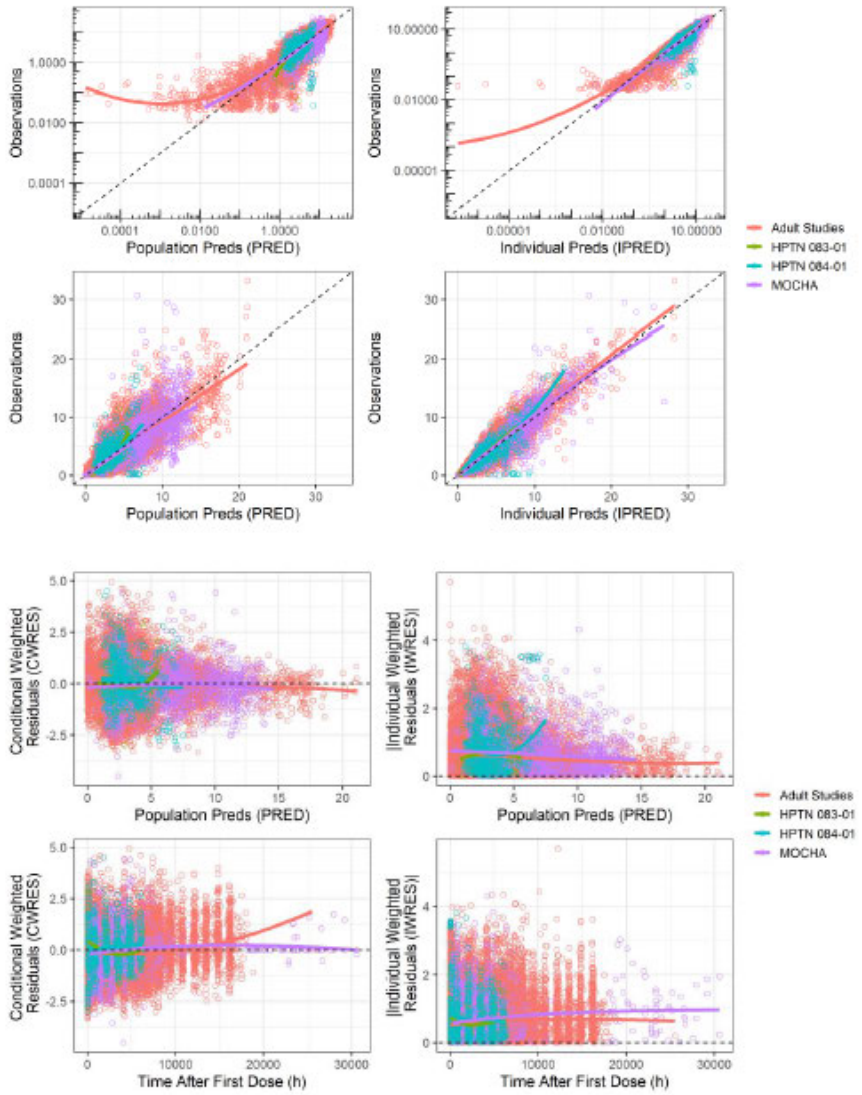
Parameter	Estimate	%RSE[a]	95% CI (SIR)	IIV (variance)	95% CI (SIR)	IIV (%CV)[b]	%RSE of IIV[a,c]	Shrinkage (%)	Equation expression
CL/F (L/h)	0.145	0.829	[0.143, 0.147]	0.0549	[0.0509, 0.0603]	23.8	2.43	10.8	$\frac{CL}{F} = 0.145 \times \left(\frac{BWT}{74.8}\right)^{0.676} \times (1 + 19.3\% \; if \; current \; smoker)$
V2/F (L)	5.15	2.01	[4.85, 5.43]	0.0354	[0.0225, 0.0501]	19.0	10.9	30.6	$\frac{V2}{F} = 5.15 \times \left(\frac{BWT}{74.8}\right)^{0.752}$
KA1 (1/h)	1.38	4.54	[1.21, 1.54]	0.768	[0.550, 0.993]	108	5.38	69.4	
Q/F (L/h)	0.481	6.91	[0.375, 0.603]						$\frac{Q}{F} = 0.481 \times \left(\frac{BWT}{74.8}\right)^{0.676}$
V3/F (L)	2.32	5.09	[2.06, 2.63]						$\frac{V3}{F} = 2.32 \times \left(\frac{BWT}{74.8}\right)^{0.752}$
KA2 (1/h)	0.000730	2.24	[0.000700, 0.000762]	0.327	[0.302, 0.357]	62.2	2.29	16.6	$KA2 = 0.000730 \times \left(\frac{BMI}{24.8}\right)^{-0.823} \times \left(\frac{NDL}{1.5}\right)^{0.539} \times (1 - 50.9\% \; if \; female) \times (1 + 49.5\% \; if \; split \; injection)$
F1	0.745	0.912	[0.734, 0.755]	0.0355	[0.0298, 0.0412]	19.0	4.89	36.8	
Additive error (µg/mL)	0.0313	19.4	[0.0277, 0.0357]					6.80	
Proportional error	0.277	1.06	[0.274, 0.280]						

Parameter	Estimate	%RSE[a]	95% CI (SIR)	IIV (variance)	95% CI (SIR)	IIV (%CV)[b]	%RSE of IIV[a,c]	Shrinkage (%)	Equation expression
BWT on CL/F and Q/F	0.676	4.03	[0.629, 0.726]						
BWT on V2/F and V3/F	0.752	5.73	[0.672, 0.831]						
Current smoking status on CL/F	0.193	8.44	[0.162, 0.225]						
BMI on KA2	-0.823	10.8	[-0.941, -0.698]						
NDL on KA2	0.539	30.4	[0.371, 0.718]						
Gender (if female) on KA2	-0.509	3.72	[-0.541, -0.471]						
Split injection on KA2	0.495	13.5	[0.432, 0.561]						
Covariance									
Parameter	**Estimate**	**%RSE**	**95% CI (SIR)**						
Covariance (KA2, CL/F)	0.00700	71.1	[-0.00172, 0.0163]						
Covariance (KA2, V2/F)	0.0341	29.4	[0.0160, 0.0507]						
Covariance (CL/F, V2/F)	0.0328	13.1	[0.0251, 0.0406]						

Source: GOF_Run11.Rmd → GOF_Run11.html.
a Obtained from the $COV step.
b IIV in %CV calculated using $\sqrt{e^{\omega^2} - 1} \times 100$.
c %RSE of IIV expressed on approximate standard deviation scale calculated using (SE/ω²)/2 ×100.
Notes: Parameters are expressed as median (95% CI). The reference population for CL/F is a 74.8 kg non-smoker participant. The reference population for V2/F, V3/F, and Q/F is a 74.8 kg participant. The reference population for KA2 is a male participant (BMI=24.8 kg/m²) using an NDL of 1.5 inches with unsplit injection.
MOCHA=Study 208580; HPTN 083-01=Study 213002; HPTN 084-01=Study 213003.

Source: CAB popPK report, p51. Note IM and oral PK data were co-modelled and CL/F is the systemic clearance (oral and IM route) (NDA 212888, response to IR submitted 8/26/2024).

Figure 5. CAB final model GOF plots.

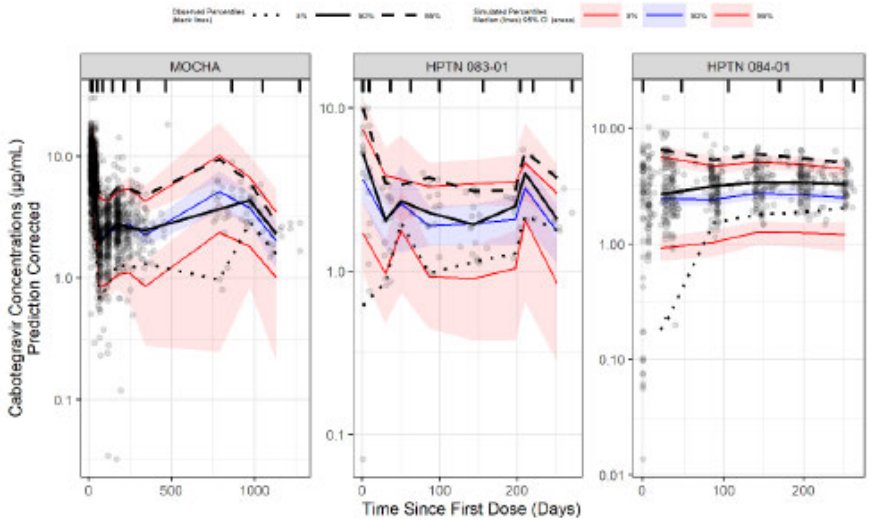


Source: GOF_Run11.Rmd → GOF_Run11.html
Notes: The colored symbols represent the individual observations. The solid lines represent the LOESS lines of the presented data: red represents PK observations for adult studies, green represents PK observations for Study HPTN 083-01, cyan represents PK observations for Study HPTN 084-01, and violet represents PK observations for the MOCHA study.
MOCHA=Study 208580; HPTN 083-01=Study 213002; HPTN 084-01=Study 213003.

Abbreviations: CAB=cabotegravir; GoF=goodness-of-fit; LOESS=locally estimated scatterplot smoothing; PK=pharmacokinetic; PopPK=population pharmacokinetic(s); Preds=predictions

Source: CAB popPK report, p54.

Figure 6. CAB VPC by study



Source: VPC_Run11.Rmd → VPC_Run11.html.
Notes: The open circles represent the observed data. The solid black lines represent the median of the observed data, and the dashed lines represent the 5th and 95th percentiles of the observed data. The blue solid lines represent the median of the simulated data, and the pink solid lines represent the 5th and 95th percentiles of the simulated data. The blue and pink shaded areas represent the 95% CI of the median and the 5th and 95th percentiles of the simulated data, respectively.
MOCHA=Study 208580; HPTN 083-01=Study 213002; HPTN 084-01=Study 213003.
Abbreviations: CAB=cabotegravir; CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PopPK=population pharmacokinetic(s)

Source: CAB popPK report, p58.

Results

The final model was used to derive individual CAB exposure metrics (C_{max}, AUC, C_{tau}). Individual estimates of exposure metrics were obtained by simulation of the concentration-time profiles following treatment with the CAB Q4W and Q8W dosing regimens (with OLI) for respective individuals using their individual parameter values and without residual variability. C_{max} and C_{tau} were directly obtained from the simulated concentration-time profiles. AUC was obtained from the final model using an empirical Bayes estimation by integrating the concentration-time profile within NONMEM (Table 9) (NDA 212888, response to IR submitted 8/26/2024).

Table 9. CAB individual exposures in adolescents.

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
			$AUC_{(0\text{-}tau)}$[b] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau}[b] (mcg/mL)
Cabotegravir	Oral lead-in[c]	30 mg once daily	203 (136, 320)	10.7 (7.36, 16.6)	6.43 (4.15, 10.5)
	Initial injection[d]	600 mg IM initial dose	2,085 (1,056; 4,259)	10.8 (7.42, 16.6)	1.88 (0.801, 3.71)
	Every-1-month injection[e]	400 mg IM every 1 month	3,416 (2,303; 5,109)	5.73 (3.76, 8.90)	4.24 (2.74, 6.45)
	Every-2-months injection[e]	600 mg IM every 2 months	5,184 (3,511; 7,677)	5.10 (3,06, 8.24)	2.54 (1.25, 4.19)

[a] Pharmacokinetic parameter values for cabotegravir were based on individual post-hoc estimates from population pharmacokinetic models in both adolescents with HIV-1 (n = 147) weighing 35.2 to 98.5 kg and adolescents without HIV-1 (n = 62) weighing 39.9 to 167 kg.

[b] tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection and monthly intramuscular injections, and 2 months for every-2-months intramuscular injections of extended-release injectable suspension.

[c] Oral lead-in pharmacokinetic parameter values represent steady-state.

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection.

[e] Monthly and every-2-month injection pharmacokinetic parameter values represent Week 48 data.

Source: NDA 212888 SDN 851, Proposed labeling submitted 7/23/2024.
Reviewer's Comments: The PK parameters shown are from proposed CABENUVA labeling. The same values are shown in VOCABRIA (OLI only) and APRETUDE.

Reviewer's Comments: Overall, the Applicant's model is acceptable as demonstrated by GOF and VPC plots. We ran the Applicant's model and no discordance was identified with the objective function, model parameters, or individual exposure estimates.

6.2 RPV popPK report

Review Summary
The Applicant's population PK (popPK) analysis is acceptable for the purpose of deriving RPV and metabolite exposure metrics (C_{max}, AUC, C_{tau}) for labeling. The Applicant's final model parameters and individual exposure estimates (C_{max}, AUC, C_{tau}) were verified by the reviewer.

Introduction
In prior submissions, RPV popPK modeling objectives were to characterize the PK of RPV in the general adult population and subsequently among a subset of the adolescent population. The objective of the current popPK analysis was to characterize the disposition of RPV using the full adolescent dataset.

Model development

New data for this analysis are from adolescent study MOCHA (Table 10). Model parameters had acceptable precision and interindividual variability parameters had acceptable shrinkages (Table 11). The models demonstrated acceptable performance in goodness-of-fit and visual predictive check plots (Figure 7, Figure 8, Figure 9).

Table 10. Studies included in the RPV popPK analysis

Study No.	Study Title	Dose (mg), Volume (mL), Regimen, Route of Administration, Formulation	No. of Participants with PK Data Available	PK Sampling
Study 208580 (IMPAACT 2017, MOCHA), Cohort 1R and 2 only	Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents	Cohort 1R Step 1: RPV 25 mg q.d., oral (4 weeks), Edurant Cohort 1R Step 2: RPV LA 900 mg (3 mL, 1x), RPV LA 600 mg (2 mL, 2x), Q4W, IM, G001; or RPV LA 900 mg (3 mL, 1x), RPV LA 900 mg (3 mL, 1x), Q8W, IM, G001	Cohort 1R: Up to 25 adolescents planned to be enrolled in order to achieve approximately 15 adolescents evaluable for RPV.	Oral dosing Cohort 1R, Step 1: - Week 2: Pre-dose, 4, 8, and 24 hours (24 hours for Q4W only) post dose IM dosing Cohort 1R, Step 2: - Week 4b: pre-dose and 2 hours post-dose - Week 5, 9 & 13 (Week 13 Q4W only): 1 week post-dose (3-7 days) - Week 6 & 14 (Q4W only): 2 weeks post-dose (10-14 days) - Week 8: pre-dose (same as 4 weeks post-dose) - Week 12: 4 weeks post-dose (pre-dose for Q4W) and 2 hours post-dose (Q4W only) - Week 16: 4 (Q4W) or 8 (Q8W) weeks post-dose
		Cohort 2 Step 3: oral CAB 30 mg + RPV 25 mg q.d. (4 weeks), RPV: Edurant Cohort 2 Step 4: CAB LA 600 mg (3 mL, 1x) and RPV LA 900 mg (3 mL,	Cohort 2: Up to 155 adolescents planned. Up to 100 adolescents who had not previously participated in Cohort 1, to achieve approximately 70 evaluable, who had not previously participated in Cohort 1, receiving the final recommended oral doses	Oral dosing Cohort 2, Step 3: - Week 2: Pre-dose, 3 hours post dose IM dosing Cohort 2, Step 4: - Week 4b: pre-dose and 2 hours post-dose - Week 5: 1 week post-dose (3-7 days) - Week 8, 16, 24: pre-dose

		1x), followed by CAB LA 600 mg (3 mL) and RPV LA 900 mg (3 mL) Q8W, IM, RPV LA: G001	followed by LA doses of CAB and RPV. Adolescents who participated in Cohort 1 (up to 55 participants), if eligible, in additional to the up to 100 adolescents.	- Week 25: 1 week post-dose 3-7 days) - Week 32, 40, 48, 64, 80, 88, 96: pre-dose
TMC278-C158	Phase 1 study in healthy volunteers to examine in an open-label part the safety, tolerability and plasma pharmacokinetics of a single intramuscular injection of a novel TMC278 LA (long acting) formulation at 2 different doses, followed by a double blind, randomized, placebo-controlled part of multiple intramuscular injections of this novel formulation at a selected dose	300 mg (1 mL) single dose, 600 mg (2 mL) single dose, 1200 mg (4 mL), then 600 mg (2 mL), then 600 mg (2 mL)/Q4W, IM, G001	Planned 17 healthy participants	Panel 1 and 2: Predose and postdose at 1, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264, 336, 408, 528, 672h Panel 3, 1st dose: Predose Day1 and postdose at 1, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264; 2nd injection (Day 15): Predose and postdose at 0, 1, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 336, 408, 528; 3rd injection (Day 43):, Predose and postdose at 1, 4, 8, 12, 24, 48, 72, 120, 168, 216, 336, 408, 528, 672h Additional follow-up samples were taken 8 and 12 weeks after injection in Panel 1 and 2 and after last injection in Panel 3. Thereafter, every 12 weeks a sample was taken until the individual RPV plasma concentration was below 20 ng/mL.
TMC278LAHTX1001	A Phase I open-label, randomized, parallel-group study in healthy participants to investigate the effect of different storage conditions of a long-acting (b) (4) of rilpivirine on the single-dose plasma pharmacokinetics of rilpivirine after intramuscular injection	600 mg (2 mL) single dose, IM, G001	Planned 61 healthy participants	Predose and postdose at 0, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264, 336, 408, 528, 672h and at Day 57, 85, 113, 141, 169 and in case of drop out at time of dropout or the following morning
TMC278LAHTX1002	A Phase I, Open-label, Randomized, Parallel-group Study in Healthy Participants to Investigate the Effect of Different Particle Sizes on the Single-dose Pharmacokinetics of Rilpivirine After Intramuscular Injection of a Long-acting (b) (4)	600 mg (2 mL) single dose, IM, G001	Planned 110 healthy participants	Predose and postdose at 0, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264, 336, 408, 528, 672h and at Day 57, 85, 113, 141, 169, 197, 225, 253. In case of drop-out at the time of dropout
LAI115428	A Randomized, Open Label Study to Investigate the Safety, Tolerability and Pharmacokinetics of Repeat Dose Administration of Long Acting GSK1265744 and Long-Acting TMC278 Intramuscular and Subcutaneous Injections in Healthy Adult Participants	1200 mg (4 mL), then 900 mg (3 mL)/Q4W 1200 mg (4 mL), then 600 mg (2 mL)/Q4W, IM, G001	Planned 19 healthy participants	Predose and at 4 hours post dose on Day 1 and at each outpatient visit at days 1, 3, 7, 14, 21 during Months 3 and 4 and at Day 28 for the 4th month.
LATTE-2 (200056)	A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 for the Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Participants	25 mg oral QD 600 mg (2 mL) Q4W 900 mg (3 mL) Q8W, IM, G001	Planned 286 participants	Maintenance Period: Predose (Q8W): Day 1, Weeks 4, 8, 16, 24, 32, 40 and 48 Predose (Q4W): Day 1, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 2 Hours Post Dose (Q4W and Q8W): Day 1 1 Week Post Dose (Q4W and Q8W): Week 1, Week 25 and Week 41 4 Weeks Post Dose (Q8W): Weeks 12, 20, 28, 36 and 44 Additional PK samples were collected predose at Weeks 56, 64, 72, 88, 88 and 96. Extension Period: Q8W: PK samples collected predose at Weeks 104, 112, 128, 144, 160, 176, 192 and continue every 16 weeks. Q4W: PK samples collected predose at Weeks 100, 104 108, 124, 140 and continue every 16 weeks.

FLAIR (201584)	A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naive Adult Participants	25mg oral QD 900 mg (3 mL, 1st dose), then 600 mg (2 mL)/Q4W, IM, G001	Planned 570 HIV-1 infected antiretroviral therapy naive adult participants	CAB LA + RPV LA IM arm: Predose: Week 4b, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 96, 100, 108, Withdrawal 2 Hours postdose: Week 4, Week 48, Week 96 1 Week postdose: Week 5 and Week 41 PK samples for storage only: Pre-dose: Week 64, 72, 80, and 88 ABC/DTG/3TC[a] Arm Transitioning to CAB LA + RPV LA at Week 100: Predose: Week 104, Week 108, Withdrawal 2 Hours postdose: Week 104 Long-term follow-up Period (off-drug; storage samples): Months 1, 3, 6, 9, and 12
ATLAS (201585)	A Phase III, randomized, multicenter, parallel-group, noninferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting RPV from current INI- NNRTI-, or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed	25 mg oral QD 900 mg (3 mL, 1st IM dose), then 600 mg (2 mL)/Q4W, IM, G001	Must have been on CAB LA 400 mg + RPV LA 600 mg Q4W or "Current ART" regimen through at minimum Week 52 of the ATLAS study as per ATLAS protocol dosing requirements and until Day 1 of the ATLAS-2M study.	All participants receiving CAB LA + RPV LA: Predose: Week 4b, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 96, and Withdrawal. 2 Hours postdose: Week 4, Week 48, Week 96 1 Week postdose: Week 5 and Week 41 PK samples for storage only: Predose: Week 64, 72, 80 and 88 Long-term follow-up Period (off-drug): Months 1, 3, 6, 9, and 12 Current ART Arm (Control Arm) Transitioning to CAB LA + RPV LA following Week 48 analysis: Predose: Week 56b, Week 60, and Withdrawal 2 Hours postdose: Week 56 Long-term follow-up Period (off-drug): Months 1, 3, 6, 9, and 12
ATLAS-2M (207966)	A Phase IIIb, Randomized, Multicenter, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every 8 Weeks or Every 4 Weeks in HIV-1-infected Adults who are Virologically Suppressed. Sub-study to the ATLAS-2M study to Evaluate the Pharmacokinetics, Tolerability and Efficacy of Cabotegravir and Rilpivirine Long-Acting Injections Following Intramuscular Administration in the Vastus Lateralis Muscle (thigh) in HIV-infected Adult Participants who have Received at Least Three Years of Gluteal Injections in the ATLAS-2M Study.	Participants transitioning from oral SOC: -25mg oral QD 900mg (1st IM dose), then 600mg IM/Q4W -25mg oral QD 900mg IM/Q8W (with only 4 weeks in between first 2 doses) Participants transitioning from RPV LA Q4W: -continue 600mg IM Q4W -switch to 900mg IM Q8W	Patients (n= 1020 planned) Participants will be randomly assigned to receive treatment with CAB LA + RPV LA either Q4W or Q8W. Patients transitioning from oral standard of care therapy will initiate their randomized treatment regimen with Oral CAB 30 mg + RPV 25 mg once daily for 4 to 5 weeks during the Oral Phase, followed by CAB LA + RPV LA IM injections initiating at Week 4b. Patients transitioning from the ATLAS study and on CAB LA + RPV LA Q4W treatment will be randomized at Day 1 to either continue Q4W administration or transition to Q8W administration of CAB LA + RPV LA. Regardless of treatment arm assignment.	One blood sample for CAB and RPV each to be collected at each PK timepoint. At Day 1, for participants from the ATLAS Q4W arm, PK samples are to be collected pre-dose relative to IM administration. At Week 4b, for participants randomized from SOC, Pre dose PK samples are to be collected prior to the first IM injection. Week: 4B, 8,16,24,32,40,48,96, at withdrawal Only for Participants entering CAB + RPV Oral Treatment Day 1 and Week 4A

CAB = Cabotegravir; LA= Long Acting; IM= Intramuscular; OLI= Oral lead in; RPV= Rilpivirine.

Source: NDA 212888 SDN 752, RPV popPK report, p14.

Table 11. Final RPV population PK model parameters

Structural Model Parameters		*Inter-individual Variability (CV%)*	
Parameter	Estimate (RSE%)[d]	Parameter	Estimate (RSE%,[d] Shrinkage%[f])
Frac	0.396 FIX	ω *Frac*	0.168 FIX, 48.6
KA1 (1/d)	0.00346 FIX		
KA2 (1/d)	0.0322 FIX	ω *KA2*	36.6 FIX, 50.4
D2 (h)	2.68 FIX	ω *D2*	107.7 FIX, 90.0
ALAG1/D1 (d)	14.8 FIX		
K (1/d)	0.922 FIX		
K_{el} (1/d)[a]	0.925	ω K_{el}	25.2 FIX, 48.3
V_c/F (L)	132 FIX		
RELF	1 FIX	ω *RELF*	23.5 FIX, 52.3
F4	1.23 (1.21)		
KA4 (1/h)	2.54[e] FIX	ω KA4	102[e] FIX, 69.5
ALAG4 (h)	0.8[e] FIX		
D4 (h)	2.61[e] FIX		
V5/F (L)	417[e] FIX	ω *V5/F*	88[e] FIX, 43.5
Q/F (L/h)	35.7[e] FIX		
V6/F (L)	410[e] FIX		
CL/F (L/h)	13.3[e] FIX	ω *CL/F*	32[e] FIX, 58.7
Correlation ω V5/F vs ω CL/F	0.512 FIX		
WT on KA2[b]	0.439 (19.6)		
WT on CL_{IM}/F[b]	0.262 (16.4)		
WT on V_c/F[b]	1.03 (20.6)		
Phase 2 on RELF[c]	-0.185 FIX		
ATLAS and FLAIR on RELF[c]	-0.346 FIX		
600 mg ATLAS-2M on RELF[c]	-0.248 FIX		
900 mg ATLAS-2M on RELF[c]	-0.110 FIX		
Study 208580 on RELF[c]	-0.376 (8.3)		
Objective Function Value	-37928.98	*Inter-occasion Variability (CV%)*	
		ω *CL/F*	46[e] FIX, 40.0
		Residual Variability (CV%)	
		σ_1	24.3 FIX
		σ_2	26.4 (4.24)

ALAG1 (d), lag time before the slow first-order absorption starts and equal to the zero-order duration of the slow absorption pathway after IM injections; *ALAG4* (h), lag time before the oral absorption starts after IM injection; CV, coefficient of variation; *D2* (h), zero-order absorption duration via the fast absorption pathway after IM injections; *D4* (h), zero-order absorption duration after oral administration; *F4*, relative bioavailability after oral administration; *KA4* (1/h) absorption rate for the oral dose records; *V5/F* (L) and *V6/F* (L) apparent volume of distribution of the central and peripheral compartments, respectively, after the oral administration; CL/F (L/h) and Q/F (L/h), apparent oral clearance from the central compartment and intercompartmental clearance, respectively; *Frac*, fraction of the IM dose absorbed via a fast absorption pathway; IM, intramuscular; *K* (1/d), first-order elimination rate constant after IM injection; *KA1* (1/d), slow first-order absorption rate constant after IM injection; *KA2* (1/d), fast first-order absorption rate constant after IM injection; K_{el}, elimination rate constant after IM injection; *RELF*, relative bioavailability with Phase 1 as reference (ie, 1 or 100%); RPV, rilpivirine; RSE, relative standard error; WT, body weight; V_c/F (L), apparent volume of distribution of the central compartment after IM injection; σ_1 and σ_2, IM and oral residual variability.

[a] K_{el}=*KA1*+*K* with *K* >0.

[b] Power function on *KA2*: $(WT/75)^{0.439}$. Power function on K_{el}: $(WT/75)^{-0.768} = (WT/75)^{0.262-1.03}$, where 1.03 is the power coefficient of Vc/F. Power function on V_c/F: $(WT/75)^{1.03}$.

[c] Implemented as EXP (covariate), with Phase I studies as reference of 100% (i.e. 83.1%, 70.8%, 78.0%, 89.6% and 68.7% for Phase II, pooled ATLAS and FLAIR, 600mg ATLAS-2M, 900mg ATLAS-2M and Study 208580, respectively).

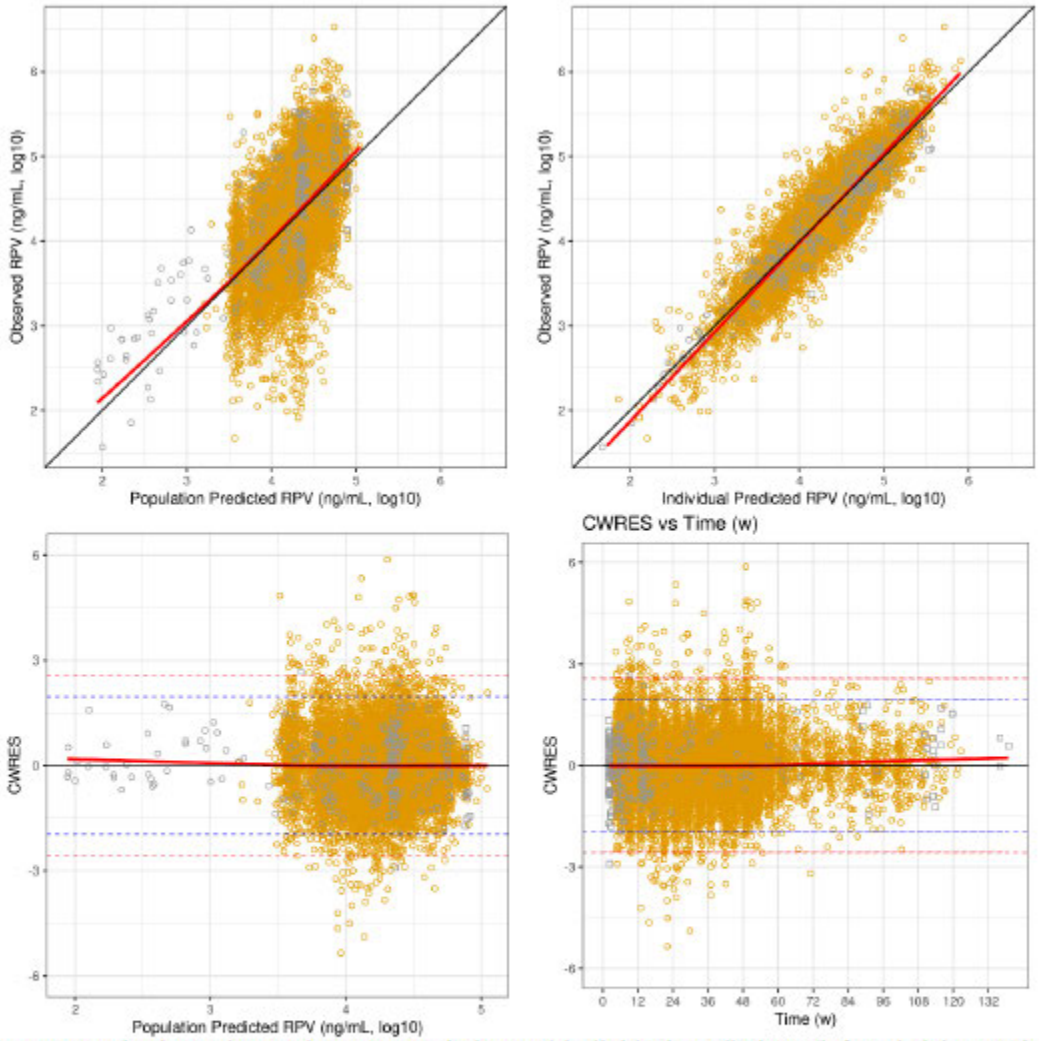
[d] RSE% is reported on newly re-estimated parameters.

[e] Parameters obtained from oral popPK model in adolescents aged ≥12 to <18 years

[f] Shrinkage derived as 1 – $SD(\eta_i)/sqrt(\omega^2)$ and computed for the Study 208580 data.

Source: NDA 212887, response to IR dated 7/15/2024, p58. The CL/F shown in the table is apparent clearance after oral administration. $CL_{IM}/F = K_{el}*V/F$ = 5.08 L/h (NDA 212888, response to IR submitted 8/26/2024).

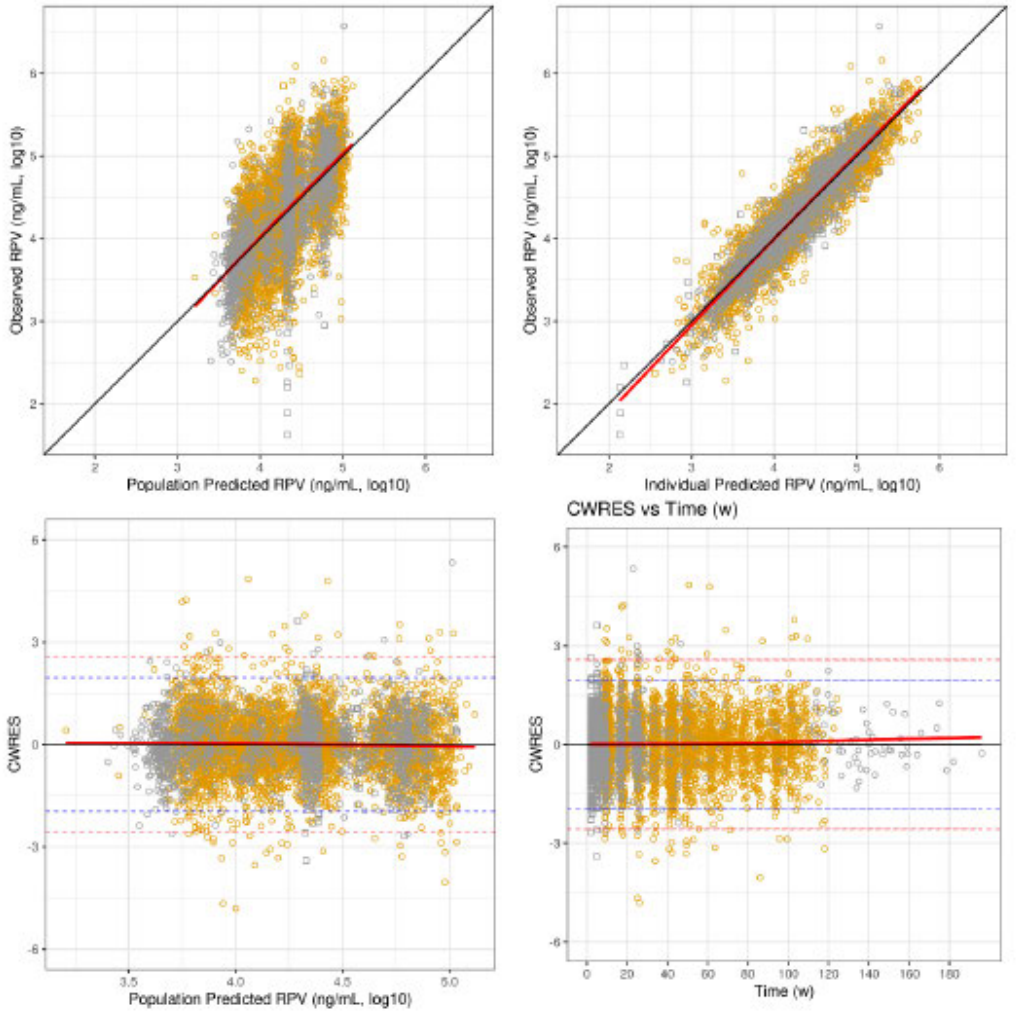
Figure 7. RPV final model GOF plots after 600 mg IM Q4W administration to adults and adolescents



Upper panels show observations vs population and individual predictions (left and right panels, respectively). Lower panels show conditional weighted residuals (CWRES) vs population predictions and time since first oral RPV dose in the oral lead-in phase (left and right panels, respectively). Gray and orange squared dots represent samples in the oral lead-in phase for the adolescents and adults' data, respectively. Gray and orange circles represent samples in the IM phase for the adolescents and adults' data, respectively. Solid red line represents the trend line (lowess, locally weighted scatterplot smoothing). Blue and red dashed lines represent the 95% CI and 99% CI respectively.

Source: NDA 212888 SDN 752, RPV popPK report, p89.

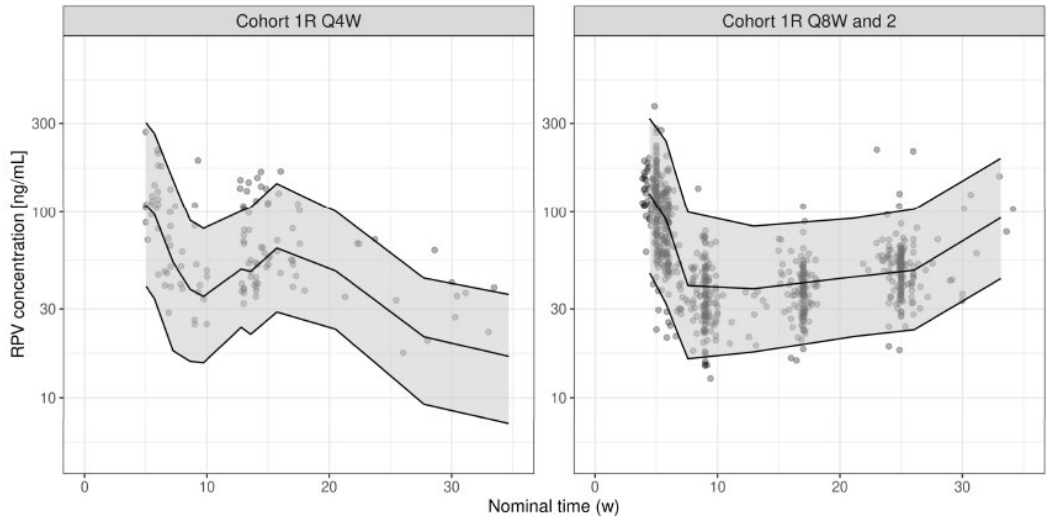
Figure 8. RPV final model GOF plots after 900 mg IM Q4W administration to adults and adolescents



Upper panels show observations vs population and individual predictions (left and right panels, respectively). Lower panels show conditional weighted residuals (CWRES) vs population predictions and time since first oral RPV dose in the oral lead-in phase (left and right panels, respectively). Gray and orange squared dots represent samples in the oral lead-in phase for the adolescents and adults' data, respectively. Gray and orange circles represent samples in the IM phase for the adolescents and adults' data, respectively. Solid red line represents the trend line (lowess, locally weighted scatterplot smoothing). Blue and red dashed lines represent the 95% CI and 99% CI respectively.

Source: NDA 212888 SDN 752, RPV popPK report, p91.

Figure 9. RPV VPC for MOCHA



Gray dots represent observed RPV plasma concentrations versus time since first IM injection from Study 208580, overlaid on the 90% prediction interval (light gray band, with black lines denoting the 5th, 50th, and 95th percentiles of the 500 simulations of the analysis dataset). Left panel represents adolescents in Study 208580 cohort 1R receiving RPV LA 600 mg IM Q4W; right panel represents adolescents in Study 208580 cohort 2 receiving RPV LA 900 mg IM Q8W.

Source: NDA 212888 SDN 752, RPV popPK report, p36.

Results

The final model was used to derive individual RPV exposure metrics (C_{max}, AUC, C_{tau}) (Table 12).

Table 12. RPV individual exposures in adolescents.

Drug	Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
			$AUC_{(0\text{-}tau)}$[b] (ng•h/mL)	C_{max} (ng/mL)	C_{tau}[b] (ng/mL)
Rilpivirine	Oral lead-in[c]	25 mg PO once daily	2,389 (1,259; 4,414)	144 (80.8, 234)	76.1 (27.9, 184)
	Initial injection[d]	900 mg IM initial dose	35,259 (20,301; 63,047)	135 (85.8, 211)	36.5 (22.4, 59.4)
	Every-1-month injection[e]	600 mg IM every month	84,280 (49,444; 156,987)	146 (84.8, 269)	109 (64.8, 202)
	Every-2-months injection[e]	900 mg IM every 2 months	110,686 (78,480; 151,744)	108 (68.0, 164)	61.8 (44.5, 88.0)

Source: NDA 212888 SDN 851, Proposed labeling submitted 7/23/2024.

[a] Pharmacokinetic parameter values for rilpivirine were based on individual post-hoc estimates from a population pharmacokinetic model in adolescents with HIV-1 (n = 148) weighing 35.2 to 98.5 kg.

[b] tau is dosing interval: 24 hours for oral administration, 1 month for the initial injection and monthly intramuscular injections, and 2 months for every-2-months intramuscular injections of extended-release injectable suspension.

[c] Oral lead-in pharmacokinetic parameter values represent steady-state.

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection.

[e] Monthly and every-2-month injection pharmacokinetic parameter values represent Week 48 data.

Reviewer's Comments: *Overall, the Applicant's model is acceptable as demonstrated by GOF and VPC plots. We ran the Applicant's model and no discordance was identified with the objective function, model parameters, or individual exposure estimates.*

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/s/

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