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, Justin Earp, PhD, Vikram Arya, PhD, FCP

1 Executive summary

Prior to this submission, CAB/RPV every four-week injections (Q4W) was approved for treatment of HIV-1 infection in adults. During the review cycle, CAB/RPV Q8W injection dosing was approved for HIV-1 treatment in adults under NDA 212887 S-1 and NDA 212888 S-1, and CAB was approved for HIV-1 prevention for adults and adolescents weighing ≥35 kg under NDA 215499.

This submission contains the Week 16 interim CSR for cohort 1 of study 208580 (MOCHA). Cohort 1 enrolled virologically suppressed, HIV-infected subjects aged ≥12 years and weighing ≥35 kg. The data in the interim CSR were collected under protocol version 2.0. Proposed

Reference ID: 4949193

labeling modifies the indication to include treatment of HIV-1 for patients aged ≥12 years and weighing ≥35 kg receiving either CAB/RPV Q4W or Q8W dosing.

Twenty-three subjects were enrolled in cohort 1. Among individual subject concentration-time profiles, no outlier subjects were observed (Figure 10, Figure 11). We requested inspection of two of the highest enrolling clinical sites (Emory and Johns Hopkins), which enrolled thirteen subjects. We also requested inspection of the analytical site (b) (4) The results of these inspections will be described in an addendum to this review.

The clinical pharmacology review focused on comparison of exposures in adolescents (defined as ≥12 years of age and weighing ≥35 kg in this review) vs adults. Exposures in adolescents generally overlapped with exposures in adults (see section 2). Assuming favorable inspection outcomes, we support approval of the CAB/RPV adult Q4W and Q8W dosing regimen for adolescents.

2 Exposure comparison in adolescents vs adults

As detailed below in graphical and statistical analyses, comparable exposures in adolescents vs adults supports approval of the adult dosing regimen for adolescents.

2.1 Graphical comparison of CAB and RPV exposures from adolescents and adults enrolled in CAB/RPV trials

Exposures from adolescent subjects were obtained from study 208580. The weight range of enrolled adolescents was ~40-100 kg. The adult reference consisted of exposures from pivotal adult Phase 3 treatment studies FLAIR, ATLAS, and ATLAS-2M.

Comparable PK parameters were observed among adolescents and adults administered CAB oral lead in (OLI) followed by Q4W IM injections (Figure 1).

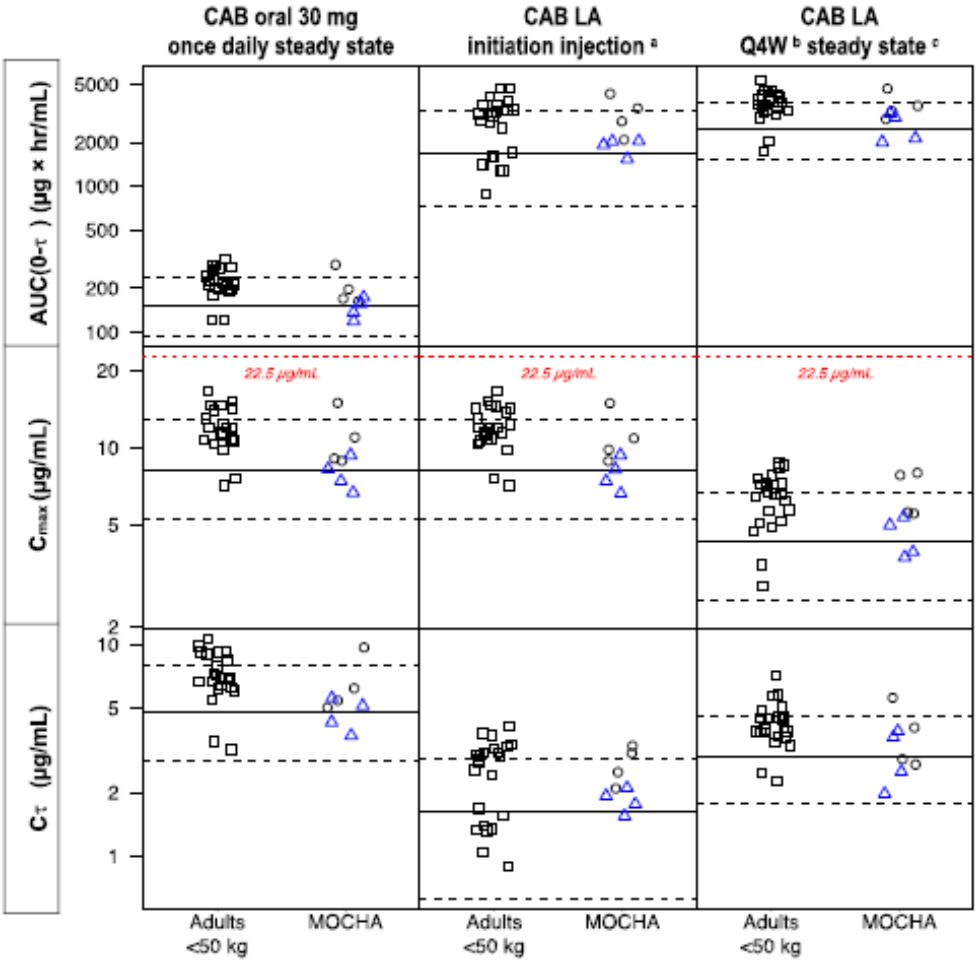
While no adolescents were enrolled in the 35-<40 kg weight range in study 208580, approval of the adolescent dosing regimen for subjects weighing 35-<40 kg is supported by the analysis using a virtual adolescent (≥35 kg) population (section 2.2).

CAB population PK models were developed from PK data collected from adolescents (Q4W IM dosing) and adults (Q4W IM and Q8W IM dosing) and simulations were performed to predict adolescent exposures corresponding to the Q8W IM regimen. Comparable exposures were predicted for adolescents (≥35 kg) vs adults and the CAB Q8W IM regimen was approved for adolescents for HIV-1 prevention (NDA 215499, integrated review dated 12/20/21). The same analysis supports approval of the CAB Q8W IM regimen for treatment of HIV-1 in adolescents.

RPV 25 mg orally daily (OLI dosing regimen) was approved for adolescents prior to the conduct of study 208580. Comparable concentration-time profiles and PK parameters were observed among adolescents and adults administered RPV OLI followed by Q4W IM injections (Figure 2, Figure 3).

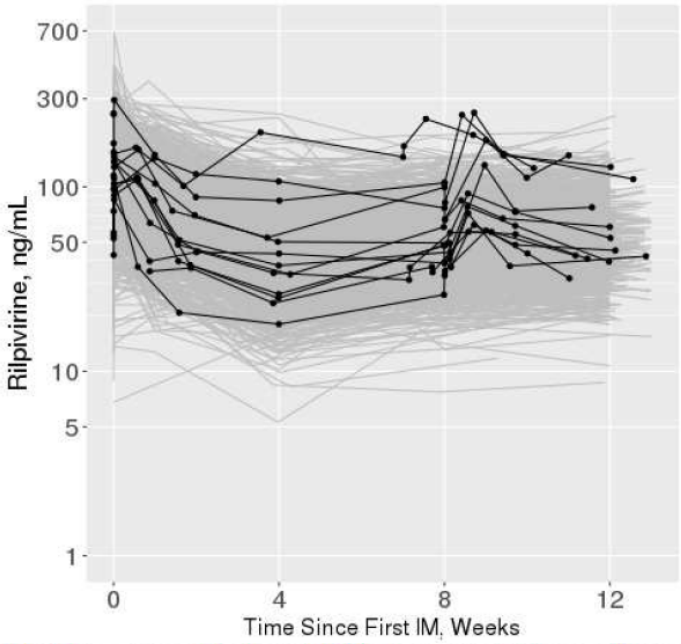
Predicted exposures for adolescents vs observed exposures in adults administered RPV Q8W IM were evaluated using a virtual adolescent population consisting of subjects weighing ≥35 kg (section 2.2).

Figure 1. CAB PK parameters in adolescents and adults administered OLI then Q4W IM injections.



Source: CAB popPK report, p25.
Solid (dashed) lines = median (5th and 95th percentiles) of exposure in 1387 adults from Phase 3 studies.
Black square = 23 adults with body weight of <50 kg (15 from Phase 3 studies).
Black circle = 4 adolescents in the MOCHA study with body weight of <50 kg.
Blue triangle = 4 adolescents in the MOCHA study with body weight of ≥50 kg.

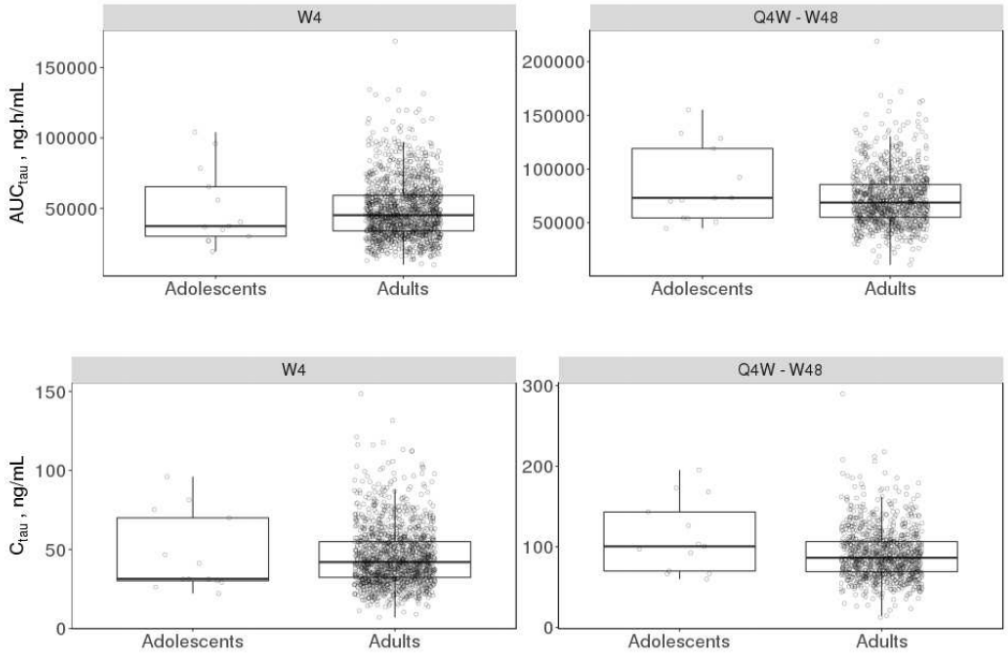
Figure 2. RPV plasma concentration-time profiles adolescents and adults administered OLI (data not shown) then Q4W IM injections.



Black lines represent the observed RPV plasma concentrations profiles versus time since first IM dose from Study 208580, overlaid on the observed plasma concentration profiles from Studies ATLAS, FLAIR, and ATLAS-2M (for which only subjects in the RPV LA 600 mg Q4W arm without prior exposure are shown) (gray lines).

Source: RPV popPK report, p21.

Figure 3. RPV PK parameters in adolescents and adults administered OLI followed by Q4W IM injections.



Source: RPV popPK report, p33. Magenta dots = adolescents; gray dots = adults in Phase 3 studies.

2.2 Graphical and statistical PK analysis using an adolescent virtual population compared to adults enrolled in Phase 3 trials

Due to the relatively small number of adolescents enrolled and to ensure full coverage of the adolescent (≥35 kg) weight range, the Applicant also used a virtual adolescent population (n=1000) to conduct a second graphical analysis in addition to a statistical comparison of CAB and RPV exposures in adolescents and adults.

In the graphical analysis, generally overlapping exposures of CAB and RPV were observed in adolescents vs adults with values in adolescents not exceeding safety threshold concentrations and not below efficacy threshold concentrations (Figure 4, Figure 6, Figure 7, Figure 9).

In a statistical analysis, geometric mean ratios (GMR) and 90% confidence intervals (CI) were computed for CAB and RPV PK parameters in adolescents vs adults. CAB exposures were comparable in adolescents vs adults, with GMRs 14-34% higher in adolescents vs adults (Table 1; referring to results when including residual variability for both populations). Similar RPV PK parameter distributions were observed in adolescents vs adults, with GMRs within 20% (Table 2).

PK parameters from the virtual adolescent population will be included in section 12.3 of labeling (Table 3).

Table 1. Statistical comparison of CAB PK parameters in adolescents vs adults.

Dosing Phase PK Parameter	CAB				
	Geometric Mean			Geometric Mean Ratio (90% CI)	
	Adolescent (+RV) (N=22876)	Adult (N=1387)		Adolescent +RV vs. Adult +RV[1]	Adolescent +RV: vs. Adult -RV[3]
		+RV[1]	-RV[2]		
Steady state oral					
AUC(0-tau) (h*µg/mL)	193	149	149	1.30 (1.28, 1.32)	1.29 (1.27, 1.32)
Cmax (µg/mL)	14.4	12.6	8.14	1.14 (1.13, 1.16)	1.77 (1.74, 1.80)
Ctau (µg/mL)	5.79	4.52	4.75	1.28 (1.25, 1.31)	1.22 (1.19, 1.25)
Initial injection					
AUC(0-tau) (h*µg/mL)	2123	1632	1633	1.30 (1.27, 1.33)	1.30 (1.27, 1.33)
Cmax (µg/mL)	11.2	8.31	8.13	1.34 (1.32, 1.37)	1.37 (1.35, 1.40)
Ctau (µg/mL)	1.84	1.46	1.51	1.26 (1.23, 1.30)	1.22 (1.18, 1.25)
Q4W maintenance at week 48					
AUC(0-tau) (h*µg/mL)	3222	2439	2443	1.32 (1.30, 1.34)	1.32 (1.30, 1.34)
Cmax (µg/mL)	7.88	5.96	4.22	1.32 (1.30, 1.34)	1.87 (1.84, 1.90)
Ctau (µg/mL)	3.65	2.76	2.90	1.32 (1.29, 1.35)	1.26 (1.23, 1.29)
Q8W maintenance at week 48					
AUC(0-tau) (h*µg/mL)	4871	3694	3695	1.32 (1.30, 1.34)	1.32 (1.30, 1.34)
Cmax (µg/mL)	7.23	5.50	3.87	1.31 (1.29, 1.34)	1.87 (1.83, 1.90)
Ctau (µg/mL)	2.01	1.55	1.63	1.29 (1.26, 1.33)	1.24 (1.20, 1.27)

[1] RV (residual variability) was included in calculations of adult exposure parameters to enable direct comparison to adolescent values that were simulated with residual variability.
[2] Adult exposure parameters without RV are consistent with adult product labels
[3] Geometric mean ratios of adolescent exposure simulated with RV vs. adult exposure simulated without RV are provided here only for completeness

Source: NDA 212888, SN 0262, p3.

Table 2. Statistical comparison of RPV PK parameters in adolescents vs adults.

Q4W injections

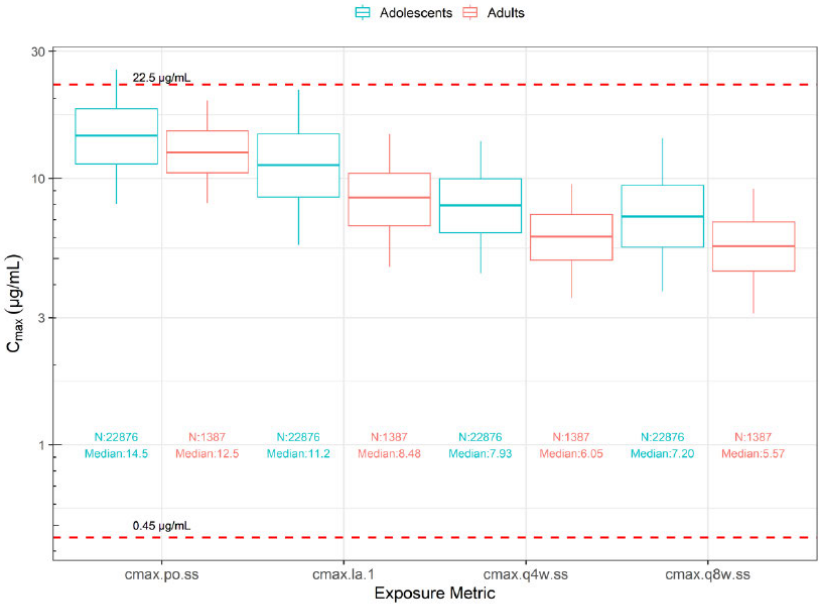
Drug	Dosing Phase	Dosage Regimen	GMR (90%CI) adolescents/adults		
			AUC(0-tau) (ng*h/mL)	Cmax (ng/mL)	Ctau (ng/mL)
RPV	Initial Injection	900 mg IM initial dose	1.01 (0.97-1.05)	1.12 (1.09-1.14)	1.07 (1.03-1.11)
	Monthly injection	600 mg IM every month	1.14 (1.10-1.17)	1.10 (1.07-1.14)	1.18 (1.15-1.22)

Q8W injections

Drug	Dosing Phase	Dosage Regimen	GMR (90%CI) adolescents/adults		
			AUC(0-tau) (ng*h/mL)	Cmax (ng/mL)	Ctau (ng/mL)
RPV	Initial Injection	900 mg IM initial dose	0.93 (0.90-0.95)	1.08 (1.06-1.10)	0.95 (0.92-0.97)
	Monthly injection	600 mg IM every month	1.09 (1.07-1.12)	1.06 (1.03-1.09)	1.13 (1.10-1.16)
	Every-2-months injection[e]	900 mg IM every 2 months	0.86 (0.83-0.89)	0.80 (0.77-0.83)	0.92 (0.88-0.95)

Source: NDA 212888, SN 0262, p4.

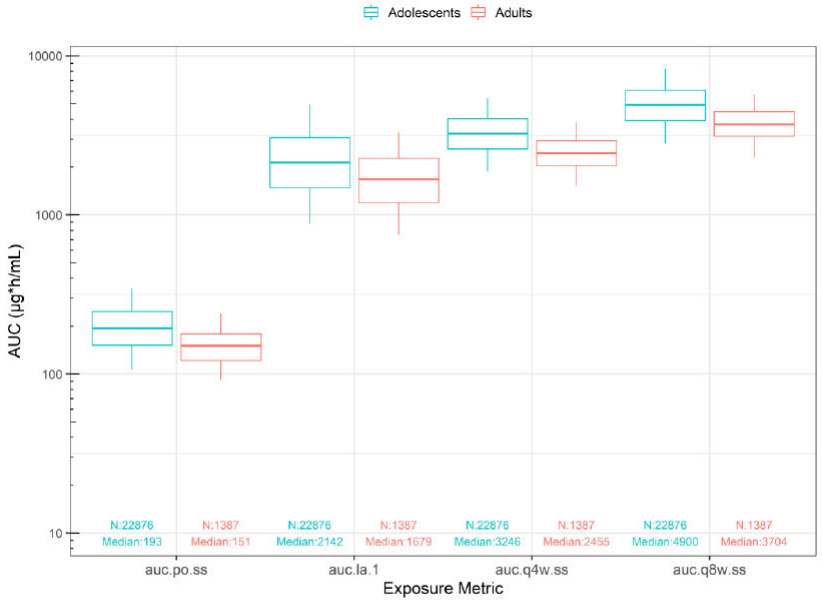
Figure 4. CAB Cmax in a virtual adolescent population vs adults in Phase 3 trials.



Where cmax.po.ss denotes Cmax following 30mg once daily, cmax.la.1 denotes Cmax at initial injection (includes final oral dose of OLI), cmax.q4w.ss denotes Cmax at Q4W maintenance regimen week 48 and cmax.q8w.ss denotes Cmax at Q8W maintenance regimen week. The horizontal dotted lines denotes safety threshold: 22.5 µg/mL and efficacy threshold is 0.45 µg/mL correspondingly.

Source: NDA 212888, SN 0262, p6.

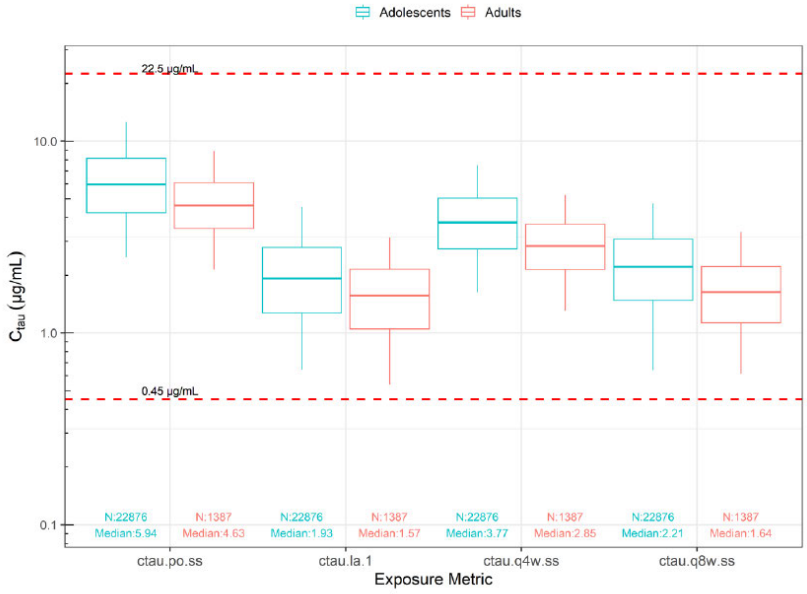
Figure 5. CAB AUC in a virtual adolescent population vs adults in Phase 3 trials.



Where auc.po.ss denotes AUC(0-tau) following 30mg once daily, auc.la.1 denotes AUC(0-tau) for the initial injection, cmax.q4w.ss denotes AUC(0-tau) following Q4W maintenance regimen at week 48 and cmax.q8w.ss denotes AUC(0-tau), following Q8W maintenance regimen at week 48. The horizontal dotted lines denotes safety threshold: 22.5 µg/mL and efficacy threshold is 0.45 µg/mL correspondingly. Tau = the dosing interval, which is 24h for oral dosing, 4 weeks for the initiation injection and Q4W steady state, and 8 weeks for the Q8W steady state.

Source: NDA 212888, SN 0262, p7.

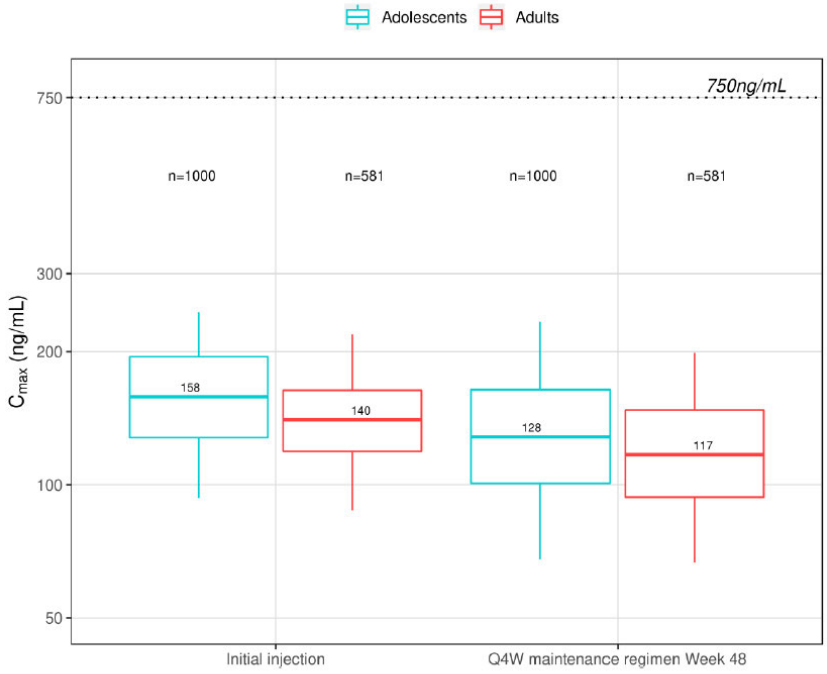
Figure 6. CAB Ctau in a virtual adolescent population vs adults in Phase 3 trials.



Where ctau.po.ss denotes Ctau at SS oral initiating, ctau.la.1 denotes Ctau at initial injection, ctau.q4w.ss denotes Ctau at Q4W maintenance regimen week 48 and ctau.q8w.ss denotes Ctau at Q4W maintenance regimen week. The horizontal dotted lines denotes safety threshold: 22.5 µg/mL and efficacy threshold is 0.45 µg/mL correspondingly.

Source: NDA 212888, SN 0262, p8.

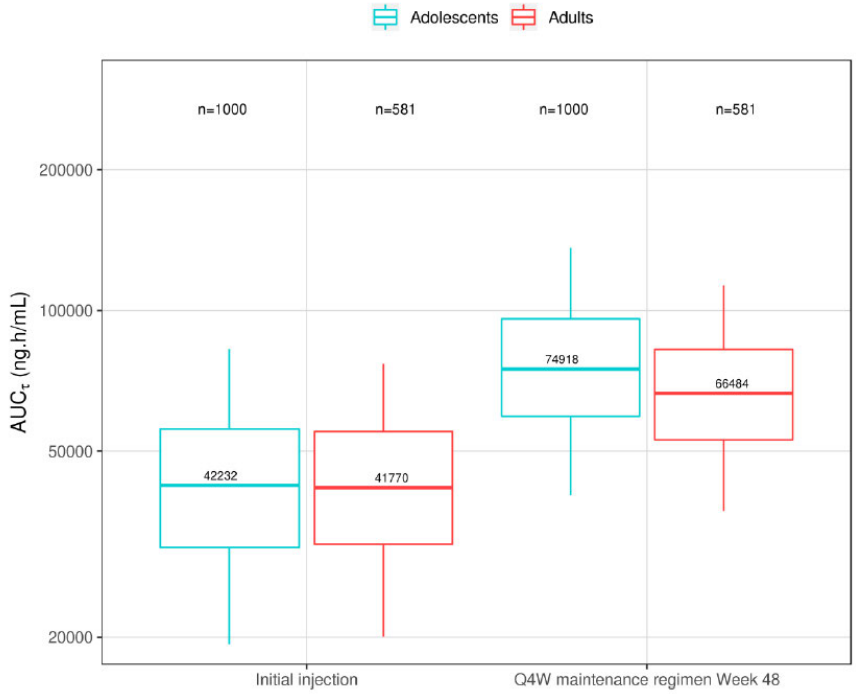
Figure 7. RPV Cmax in a virtual adolescent population vs adults in Phase 3 trials.



1 The horizontal dotted lines denotes safety threshold: 750 ng/mL

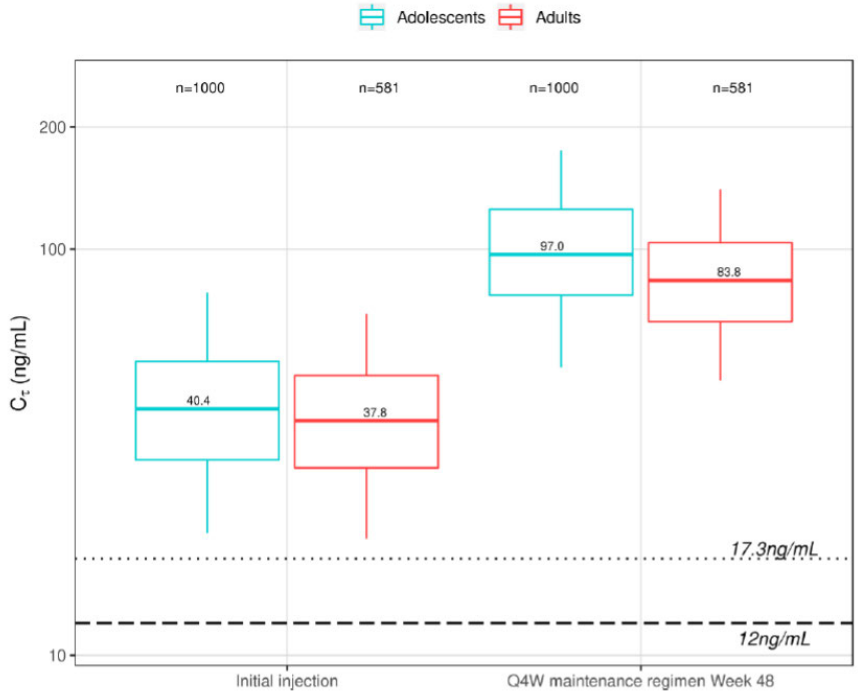
Source: NDA 212888, SN 0262, p9.

Figure 8. RPV AUC in a virtual adolescent population vs adults in Phase 3 trials.



Source: NDA 212888, SN 0262, p10.

Figure 9. RPV Ctau in a virtual adolescent population vs adults in Phase 3 trials.



2 The horizontal dotted lines denotes PAIC90: 12 ng/mL and efficacy threshold is 17.3 ng/mL

Source: NDA 212888, SN 0262, p11.

Table 3. Adolescent CAB and RPV PK parameters to be included in section 12.3 of labeling.

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} (mcg/mL)
Cabotegravir	Oral lead-in[c]	30 mg once daily	193 (106, 346)	14.4 (8.02, 25.5)	5.79 (2.48, 12.6)
	Initial injection[d]	600 mg IM initial dose	2,123 (881; 4,938)	11.2 (5.63, 21.5)	1.84 (0.64, 4.52)
	Every-1-month injection[e]	400 mg IM every 1 month	3,222 (1,879; 5,406)	7.88 (4.41, 13.8)	3.65 (1.63, 7.49)
	Every-2-months injection[e]	600 mg IM every 2 months	4,871 (2,827; 8,232)	7.23 (3.76, 14.1)	2.01 (0.64, 4.73)
Drug	**Dosing Phase**	**Dosage Regimen**	**Geometric Mean (5th, 95th Percentile)**		
			$AUC_{(0\text{-}tau)}$[b] (ng•h/mL)	**C_{max} (ng/mL)**	**C_{tau} (ng/mL)**
Rilpivirine	Oral lead-in[c]	25 mg PO once daily	2,389 (1,259; 4,414)	144 (80.8, 234)	82.5 (37.5, 167)
	Initial injection[d]	900 mg IM initial dose	41,515 (19,301; 82,646)	156 (93.4, 246)	39.7 (20.0, 78.2)
	Every-1-month injection[e]	600 mg IM every month	74,717 (40,243; 136,114)	128 (67.8, 233)	97.3 (51.1, 175)
	Every-2-months injection[e]	900 mg IM every 2 months	114,139 (61,432; 206,214)	111 (57.6, 212)	63.1 (32.9, 117)

IM = intramuscular, PO = by mouth.

[a] Pharmacokinetic parameter values were based on population pharmacokinetic model simulations in a virtual HIV-1–infected adolescent population weighing 35 to 156 kg.

[b] tau is dosing interval: 24 hours for oral administration; 1 month for the initial injection and monthly IM injections and 2 months for every 2 months for IM 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 267.

3 Study 208580 (MOCHA) summary

Design
Cohort 1 of study 208580 enrolled virologically-suppressed, HIV-infected subjects aged ≥12 years and weighing ≥35 kg who were on stable current antiretroviral therapy (cART). Subjects were randomized to add-on either CAB or RPV to cART.

The approved adult dosing regimen was administered:

- 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

Blood samples for PK were collected through week 16 as follows:

- Cohort 1C (CAB)
    - Step 1 (oral dosing): Wk 2: Pre-dose, 1, 2, 3, 4, 8, and 24 h post dose (7 samples)
    - Step 2 (LA dosing): 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 1R (RPV)
    - Step 1 (oral dosing): Wk 2: Pre-dose, 4, 8, and 24 h post dose (4 samples)
    - Step 2 (LA dosing): 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 (CAB and RPV)
    - Step 3 (oral dosing): Wk 2: Pre-dose and between 2-7h post dose (2 samples)
    - Step 4 (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.
- Long-term Safety and Washout PK Follow-Up
    - Samples collected 4, 12, 24, 36 and 48 weeks after the final injection (random PK samples).

Results
Twenty-three subjects were enrolled in cohort 1; eight in the CAB arm and 15 in the RPV arm.

Eight protocol deviations were reported. Two had the potential to affect the PK analysis; one where an incorrect dose was administered (this subject was excluded) and one where a 24-hour PK sample was processed incorrectly (due to the large number of PK samples, incorrect processing of one sample would not affect the analysis). The protocol deviations did not affect the study results.

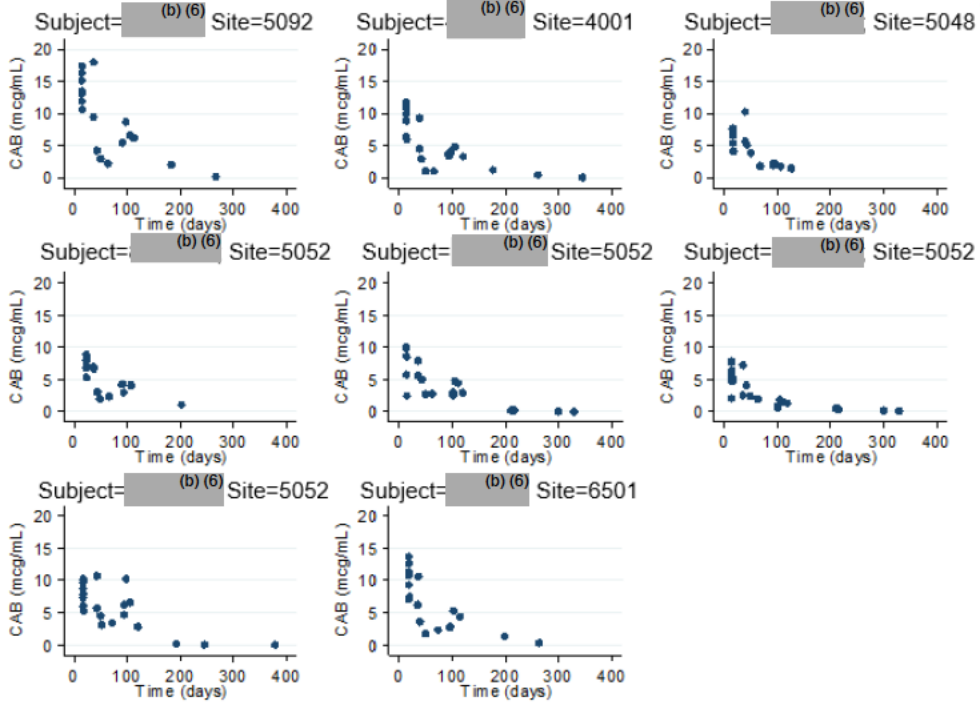
There were no reported uses of prohibited concomitant medications.

Plasma CAB (25-25000 ng/mL) and RPV (1-5000 ng/mL) bioanalytical methods were validated and were acceptable (Bioanalytical report). 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.

Week 16 antiviral activity data were available for 20 subjects (n=7 for CAB, n=13 for RPV); all subjects had HIV-1 RNA <50 copies/mL.

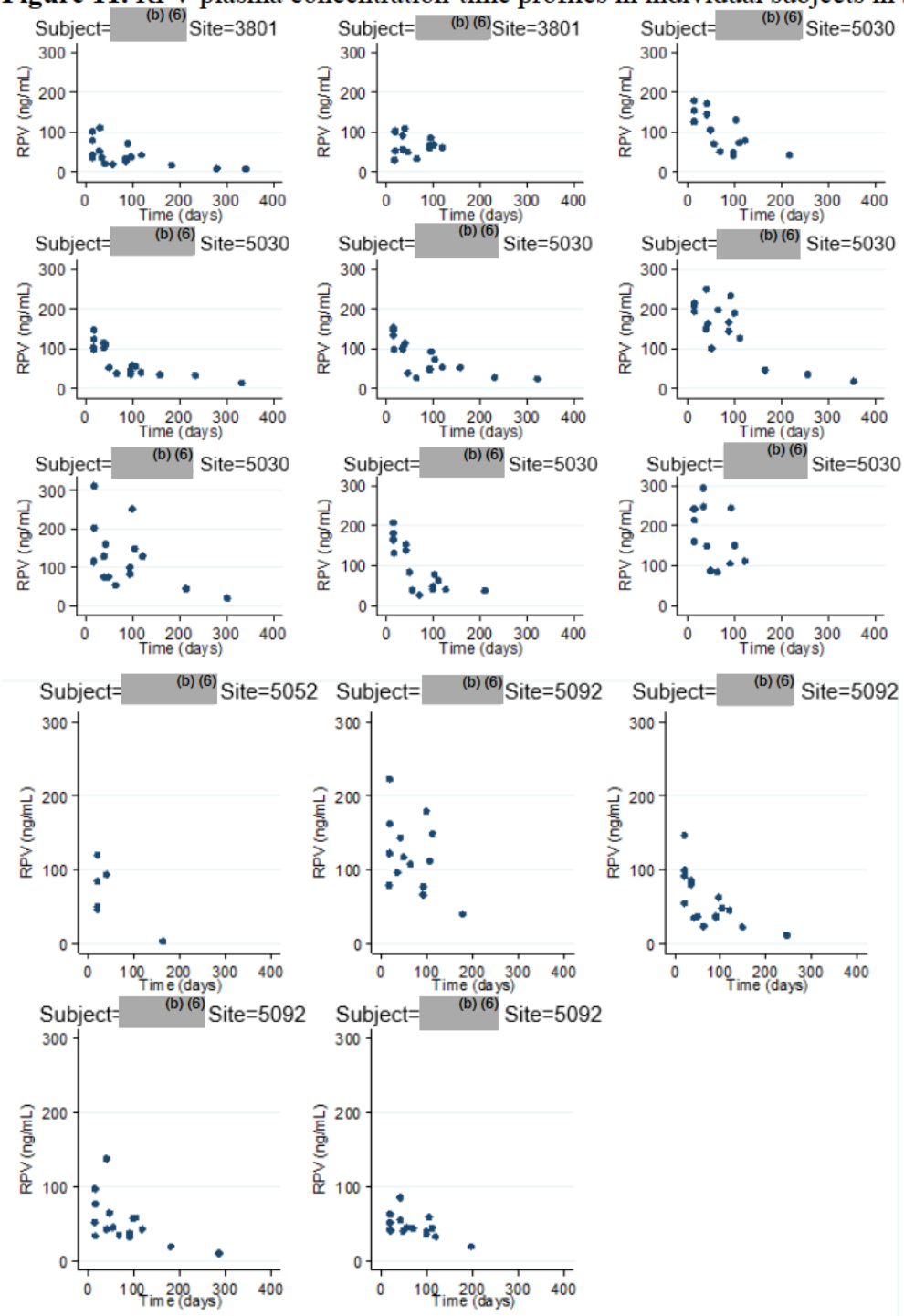
PK data were available for eight subjects in the CAB arm and 14 subjects in the RPV arm; no outliers were observed (Figure 10, Figure 11). PK data corresponded to an age range of 12-17 years (for RPV, less representation of ages 12-14 years vs 15-17 years) and weight range of ~40-100 kg (Figure 12). Exposures in adolescents generally overlapped exposures in adults, supporting approval of the adult dosing regimen for adolescents (see section 2).

Figure 10. CAB plasma concentration-time profiles in individual subjects in study 208580.



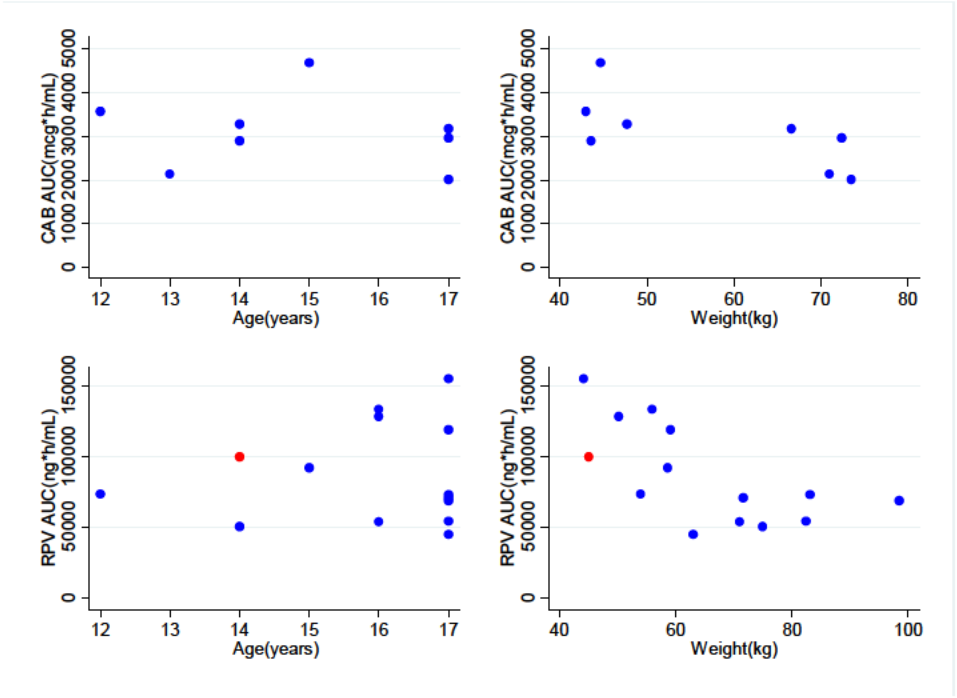
Source: Plotted by reviewer from the CAB popPK dataset.

Figure 11. RPV plasma concentration-time profiles in individual subjects in study 208580.



Source: Plotted by reviewer from the RPV popPK dataset.

Figure 12. CAB and RPV PK AUC values in study 208580 by age and weight.



Source: Plotted by reviewer. AUC values were obtained from the CAB popPK report (p24) and RPV popPK report (p92). The RPV AUC value was missing from the dataset for one subject (b) (6) shown in red), and was arbitrarily set to 100000 ng*h/mL in these plots.

4 Population PK models

CAB

The initial CAB popPK model was developed from a dataset containing numerous Phase 1-2 studies in addition to Phase 3 Q4W injection studies ATLAS and FLAIR. FDA found the model to be acceptable (NDA 212887, integrated review dated 12/19/19). As part of S-1 to support approval of Q8W dosing for treatment in adults, the model was externally evaluated using Phase 3 Q8W study ATLAS-2M. Based on model performance, the Applicant made no changes to the model. The CAB adolescent popPK report describes the model used to support approval of CAB Q8W dosing for prevention of HIV-1 in adolescents. The existing CAB popPK model was modified a priori by fixing allometric exponents to 0.75 for clearance and 1 for volume, which lead to minimal changes in model parameters. The updated model was used to estimate PK parameters for adolescents in study 208580 and to predict exposures for a virtual adolescent population. The report was previously reviewed and considered acceptable (NDA 215499, integrated review dated 12/20/21).

RPV

The initial RPV popPK model was developed from a dataset containing numerous Phase 1-2 studies in addition to Phase 3 Q4W injection studies ATLAS and FLAIR. FDA found the model to be acceptable (NDA 212887, integrated review dated 12/19/19). As part of S-1 to support approval of Q8W dosing for treatment, the model was externally evaluated using Phase 3 Q8W study ATLAS-2M. Due to higher than expected exposures predicted in ATLAS-2M HIV-infected patients, two new parameters were added to estimate relative bioavailability for 600 mg and 900 mg injection doses in ATLAS-2M.

The RPV adolescent popPK report was submitted to support approval of Q4W and Q8W dosing in adolescents. (b) (4) was removed due to a limited number of adolescent subjects. This updated model resulted in good model performance as seen in goodness-of-fit plots and visual predictive check. The updated model is acceptable as used for this supplement to estimate PK parameters for adolescents in study 208580 and to predict exposures for a virtual adolescent population.

Table 4. Parameter estimates of the updated RPV popPK model.

Structural Model Parameters		*Inter-individual Variability (CV%)*	
Parameter	Estimate (RSE%)	Parameter	Estimate (RSE%)
Frac	0.396 FIX	ω *Frac*	0.168 FIX
KA1 (1/d)	0.00346 FIX		
KA2 (1/d)	0.0237 (13.0)	ω *KA2*	36.6 FIX
D2 (h)	2.68 FIX	ω *D2*	107.7 FIX
ALAG1/D1 (d)	14.8 FIX		
K (1/d)	0.922 FIX		
K_{el} (1/d)[a]	0.924	ω K_{el}	25.2 FIX
V_c/F (L)	132 FIX		
RELF	1 FIX	ω *RELF*	23.5 FIX
F4	1.14 FIX		
Phase 2 on RELF[c]	-0.185 FIX		
ATLAS and FLAIR on RELF[b]	-0.346 FIX		
600 mg ATLAS-2M on RELF[b]	-0.248 FIX		
900 mg ATLAS-2M on RELF[b]	-0.110 FIX		
		Residual Variability (CV%)	
		σ_1	24.3 FIX

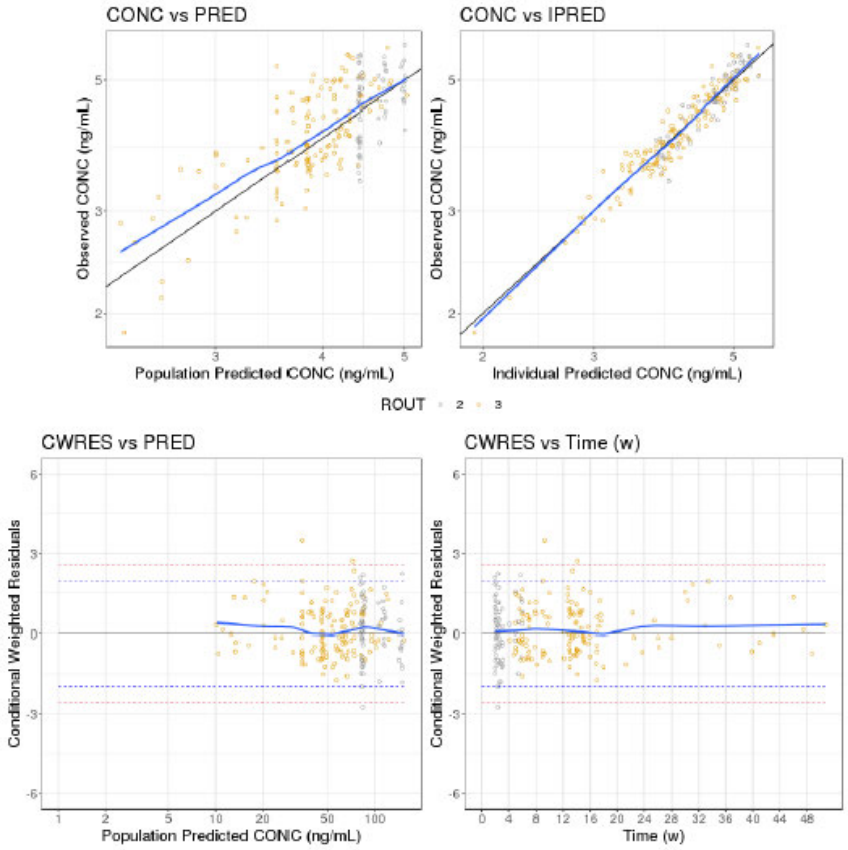
ALAG1 (h), lag time before the slow first-order absorption starts and equal to the zero-order duration of the slow absorption pathway; age effect, age-dependent fast first-order absorption rate; CV, coefficient of variation; *D2* (h), zero-order absorption duration via the fast absorption pathway; *F4*, relative bioavailability after oral administration; *Frac*, fraction of the IM dose absorbed via a fast absorption pathway; IM, intramuscular; *K* (1/h), first-order elimination rate constant; *KA1* (1/d), slow first-order absorption rate constant; *KA2* (1/d), fast first-order absorption rate constant; K_{el}, elimination rate constant; *RELF*, relative bioavailability with Phase 1 as reference (ie, 1 or 100%); RPV, rilpivirine; RSE, relative standard error; V_c/F (L), apparent volume of distribution of the central compartment.

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

[b] Implemented as EXP (covariate), with Phase 1 studies as reference of 100% (i.e. 83.1%, 70.8%, 78.0% and 89.6% for Phase 2, pooled ATLAS and FLAIR, 600mg ATLAS-2M and 900mg ATLAS-2M, respectively)

Source: RPV popPK report, p28.

Table 5. Goodness-of-fit plots for the updated RPV popPK model.



Source: RPV popPK report, p30.

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