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Pharmacokinetics of Cabotegravir and Rilpivirine Long-Acting Injectables in HIV-Infected Individuals Through 48 Weeks in the FLAIR and ATLAS Phase 3 Studies

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Introduction

- Cabotegravir (CAB), an HIV-1 integrase inhibitor, and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor, have been developed as novel, long-acting (LA) antiretrovirals for maintenance of HIV virologic suppression.
- CAB and RPV are separately formulated as suspensions of crystalline drug in aqueous vehicles for infrequent intramuscular (IM) dosing and as oral tablets for daily administration.[1,2]
  - CAB 30 mg tabs, $t_{1/2}$ = 41 hr; CAB LA 200 mg/mL susp, $t_{1/2}$ app = 5.6 to 11.5 weeks.
  - RPV 25 mg tabs, $t_{1/2}$ = 50 hr; RPV LA 300 mg/mL susp, $t_{1/2}$ app = 13 to 28 weeks.
- Sustained plasma concentrations of CAB and RPV after gluteal IM injection of LA formulations result from slow absorption from the muscle depot.
- Phase 3 studies in HIV-infected adults demonstrated non-inferiority of monthly IM CAB + RPV LA to daily oral standard of care at 48 weeks (ATLAS[1] [NCT02951052] and FLAIR[2] [NCT02938520] designs shown in Figure 1).

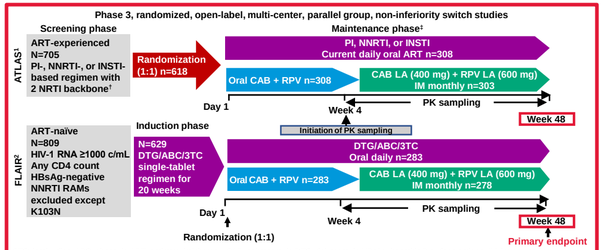
Objective

- CAB and RPV pharmacokinetics (PK) through 48 weeks from ATLAS and FLAIR were descriptively summarized in the pooled population of HIV-infected individuals and categorized by select baseline demographics associated with PK variability.

Methods

- ATLAS and FLAIR are identically designed in the maintenance phase from Day 1 through Week 48 (Figure 1 and Table 1).

Figure 1. ATLAS and FLAIR Study Designs



3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; HBsAg, hepatitis B surface antigen; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetics; RAM, resistance-associated mutation; RPV, rilpivirine. [1]Uninterrupted ART ≥ 6 months and VL <50 c/mL at screening. 2× VL <50 c/mL ≤12 months. [2]The maintenance phase included the period from the first oral dose to the Week 48 primary endpoint.

Table 1. CAB + RPV Dosing and Plasma PK Sampling

Oral lead-in period	Initiation dose (Week 4b)	Continuation dose Week 8 and every 4 weeks thereafter
CAB 30 mg once daily	CAB LA 600 mg IM (3 mL x 1)	CAB LA 400 mg IM (2 mL x 1)[§]
RPV 25 mg once daily	RPV LA 900 mg IM (3 mL x 1)	RPV LA 600 mg IM (2 mL x 1)[§]

CAB, cabotegravir; IM, intramuscular; LA, long-acting; RPV, rilpivirine.
CAB and RPV PK samples collected pre-dose prior to each injection at Week 4b (immediately prior to last oral dose and to first LA injection) and every 4 weeks up to Week 48, 2 hr post dose (Week 4b, 48), and 1 week post dose (Week 5 and 41).
[§]442/581 (76%) participants with evaluable PK data received injections using a 1.5" needle length. Use of variable needle lengths and/or needle gauges to accommodate individual body type to ensure IM injection was permitted; individuals with body mass index >30 kg/m^2 are recommended to use longer needles.[3]

Results

- PK data were available for 581/591 (98%) participants (303 ATLAS; 278 FLAIR) comprising a combined total of 14,682 injections of CAB LA and RPV LA through 48 weeks.
  - PK was unavailable for 10 participants, but the overall demographics in the PK population were the same as for the intent-to-treat population, and therefore did not impact the evaluation of covariates for the PK of CAB LA and RPV LA (Table 2).

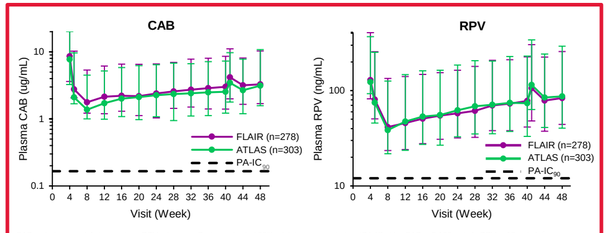
Table 2. Baseline Characteristics: Intent-to-Treat–Exposed Population

	FLAIR CAB LA + RPV LA n=283	ATLAS CAB LA + RPV LA n=308
Median age, years (range)	34 (19–68)	40 (21–74)
Age ≥50 years, n (%)	33 (12)	66 (21)
Female, n (%)	63 (22)	99 (32)
Race, n (%)		
White	216 (76)	214 (69)
Black or African American	47 (17)	62 (20)
Other	20 (7)	32 (10)
Median BMI (range), kg/m^2	24.1 (17.3–44.9)	25.5 (15.3–50.9)

BMI, body mass index; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

- Median (5th and 95th percentile) plasma CAB and RPV concentrations were consistent between studies (Figure 2).
- RPV exposures, including 95th percentile, were well below those associated with QT interval changes.

Figure 2. Median (5th and 95th Percentile) Plasma CAB and RPV PK Profiles Following CAB LA 400 mg + RPV LA 600 mg IM Every 4 Weeks



CAB, cabotegravir; LA, long-acting; RPV, rilpivirine. Protein-adjusted 90% inhibitory concentration (PA-IC$_{90}$) for CAB is 0.166 µg/mL; RPV is 12 ng/mL.[4]

- After initial IM doses, mean CAB and RPV troughs were well above their respective *in vitro* protein-adjusted 90% inhibitory concentration (PA-IC$_{90}$) values (CAB, 0.166 µg/mL; RPV, 12 ng/mL)[4] (Figure 2).

Time to Steady State

- CAB:
  - Achieved by 44 weeks.
- RPV:
  - Approximately 80% of the RPV steady-state exposure was reached after 48 weeks.
    - After Week 48, there was limited further accumulation, with RPV steady-state exposure predicted to be about 20% higher than that observed at Week 48 in ATLAS/FLAIR (Figure 2 and Table 3).

- FLAIR and ATLAS pooled geometric mean data show that CAB and RPV trough plasma levels remained above their respective PA-IC$_{90}$ and within the exposure range observed following daily oral CAB 10 mg and 30 mg (>1.35 µg/mL and <4.2 µg/mL) and daily oral RPV 25 mg regimens (79 ng/mL) (Table 3).

Table 3. CAB and RPV Trough Plasma Concentrations at Select Visits

Geometric mean [95% CI] plasma CAB and RPV C_{tau} at select visits	CAB (µg/mL)	RPV (ng/mL)
Visit	**FLAIR and ATLAS pooled**	**FLAIR and ATLAS pooled**
Week 4b (after last oral dose [30 mg/25 mg])	4.94 [4.74, 5.14]	77.13 [73.78, 80.64]
Week 8 (4 weeks after initial IM dose)	1.38 [1.31, 1.46]	39.88 [38.05, 41.8]
Week 48 (after 12 monthly IM doses)	2.97 [2.85, 3.10]	86.42 [82.87, 90.14]

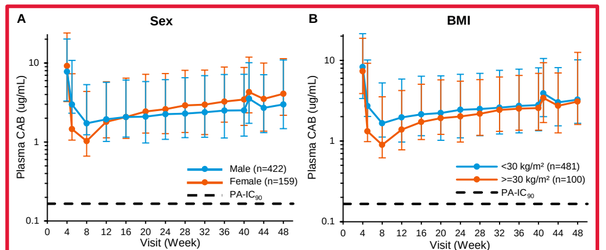
CAB, cabotegravir; CI, confidence interval; IM, intramuscular; RPV, rilpivirine; C_{tau}, trough concentration.

CAB and RPV PK Profile by Sex at Birth and Baseline BMI

CAB

- 4 weeks following the first injection, median CAB levels were lower in females than males by 40% (Figure 3A).
- CAB troughs at Week 48 were slightly higher in females than males (Figure 3A).
- 4 weeks following the first injection, median CAB levels were lower in individuals with body mass index (BMI) ≥30 kg/m^2 by 46% vs. those with BMI <30 kg/m^2 (Figure 3B).
- CAB troughs at Week 48 were similar regardless of BMI (Figure 3B).

Figure 3. Median (5th and 95th Percentile) Pooled CAB PK Profiles in ATLAS and FLAIR Through Week 4–48 by Sex at Birth (A) and Baseline BMI (B)

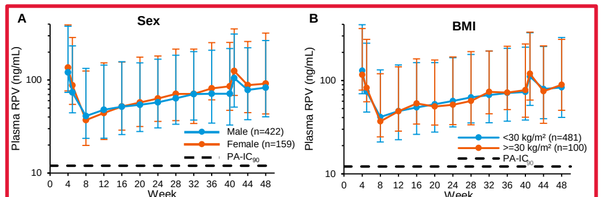


BMI, body mass index; CAB, cabotegravir; CI, confidence interval. Protein-adjusted 90% inhibitory concentration (PA-IC$_{90}$) for CAB is 0.166 µg/mL.[4]
Week 41 = 1-week post-dose timepoint.

RPV

- There were no differences in RPV concentrations by sex or BMI over the 48-week study period (Figure 4A and B, respectively).

Figure 4. Median (5th and 95th Percentile) Pooled RPV PK Profiles in ATLAS and FLAIR Through Week 4–48 by Sex at Birth (A) and Baseline BMI (B)



BMI, body mass index; CI, confidence interval; RPV, rilpivirine. Protein-adjusted 90% inhibitory concentration (PA-IC$_{90}$) for RPV is 12 ng/mL.[4]
Week 41 = 1-week post-dose timepoint.

Discussion

- The plasma concentration over time profiles are characterized by flip-flop PK whereby the elimination of the drug is limited by the slower rates of absorption.
- Within the first few days after initial IM injections, CAB and RPV concentrations were all above 1x PA-IC$_{90}$.
- Median CAB troughs pooled from ATLAS and FLAIR remained within the exposure range observed following daily oral CAB 10 mg and 30 mg regimens (>1.35 µg/mL and <4.2 µg/mL).
- Median RPV troughs remained within the exposure range observed after daily oral RPV 25 mg regimen.
- Females and individuals with BMI ≥ 30 kg/m^2 were associated with slower absorption following CAB LA administration, resulting in initially lower median troughs that steadily increased over time with somewhat higher median troughs by Week 48. These PK differences did not appear to be clinically significant through Week 48 in ATLAS and FLAIR with combined 27% female enrolment and ~17% with BMI >30 kg/m^2.

Conclusions

- Median plasma CAB and RPV concentrations were consistent between studies with therapeutic concentrations reached within the first few days and with at least 80% of steady state achieved by Week 48 in the majority of participants.
- Median CAB exposures remained between oral CAB 10 mg and 30 mg efficacious exposures while median RPV exposures were comparable to those after the marketed oral 25 mg dose.
- Sex and BMI were covariates associated with slower absorption following IM CAB LA administration only.

Acknowledgments

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