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Pharmacokinetics and Tolerability of Cabotegravir and Rilpivirine Long-Acting Intramuscular Injections to the *Vastus Lateralis* (Lateral Thigh) Muscles of Healthy Adult Participants

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Key Takeaways

- **We present the results of a Phase 1 study evaluating pharmacokinetics (PK) and tolerability following single intramuscular (IM) injections of cabotegravir + rilpivirine long-acting (CAB + RPV LA) to the lateral thigh of healthy participants – a potential alternative site of administration.**
- **CAB and RPV IM injections into lateral thigh muscle were well tolerated, with mostly mild-to-moderate injection site reactions (ISRs), and showed plasma PK profiles that support further evaluation of thigh IM injections in target populations.**

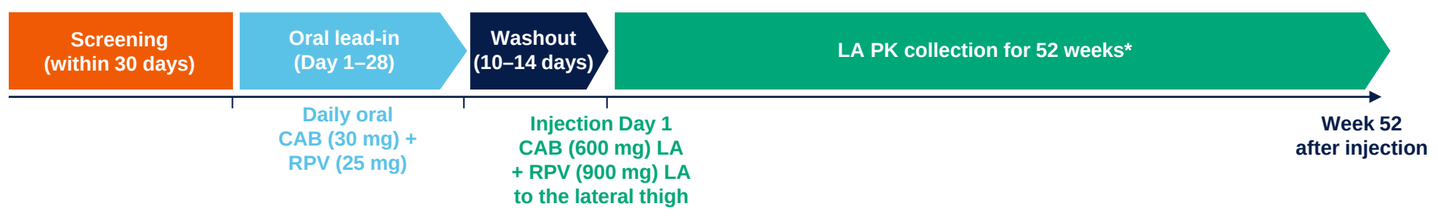
Background

- CAB + RPV is the first complete LA injectable regimen recommended by treatment guidelines for the maintenance of HIV-1 virologic suppression.[1,2]
- In the Phase 3 development program, CAB + RPV LA demonstrated noninferiority to daily oral therapy when dosed every 4 weeks (Q4W) in the FLAIR and ATLAS studies,[3,4] and when dosed every 8 weeks (Q8W) compared with Q4W dosing in the ATLAS-2M study.[5]
- CAB + RPV LA is currently administered monthly or every 2 months via IM injections into the ventrogluteal or dorsogluteal muscle.
- The *vastus lateralis* (lateral thigh) muscle could be a potential alternative site of administration, helping to alleviate injection site fatigue, intolerability, or inaccessibility of the gluteal muscle (e.g. buttock implants).
- Here, we present the results of a Phase 1 study (NCT04371380) evaluating PK and tolerability following single IM injections of CAB + RPV LA to the lateral thigh.

Methods

- Healthy adult participants without HIV infection received 4 weeks of daily oral CAB 30 mg and RPV 25 mg oral lead-in, followed by a 10–14-day washout and single 3 mL IM injections of CAB LA 600 mg and RPV LA 900 mg to contralateral *vastus lateralis* muscles (**Figure 1**).
- Safety, tolerability, and PK were collected through 52 weeks post-injection.
  - PK parameters were estimated using non-compartmental analysis.
  - Participant-reported maximum level of pain following injections at Days 1, 2, 4, 5, and 8 was assessed by the Numerical Rating Scale (NRS), ranking pain from 0 “no pain” to 10 “extreme pain.”
  - Acceptability of ISRs was measured using the acceptance domain of the Perception of Injection (PIN) Questionnaire, ranking acceptance of injections from 1 “totally acceptable” to 5 “not at all acceptable.”

Figure 1. Study Design



*PK collection at pre-injection, 1 hr and 2 hr post-injection, on Days 2, 4, 5, 7/8, 10, 15, 17, and 22 post-injection, and at Weeks 4 (Day 28), 8, 12, 24, 36, and 52, and at withdrawal visit.
CAB, cabotegravir; LA, long-acting; PK, pharmacokinetics; RPV, rilpivirine.

Results

Table 1. Baseline Characteristics

Parameter	CAB + RPV LA (N=15)
Median age (range), years	33 (21–49)
Female (sex at birth), n (%)	6 (40)
Male (sex at birth), n (%)	9 (60)
Race, n (%)	
White	7 (47)
Black or African American	7 (47)
Asian	1 (7)
Hispanic/Latinx, n (%)	5 (33)
Median BMI (range), kg/m^2	31.40 (24.3–34.4)
Median weight (range), kg	93.6 (67.9–107.7)

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

- Overall, 15 participants were enrolled; six (40%) were female (sex at birth), seven (47%) were White, and the median age was 33 years (**Table 1**).
- All participants completed the study, except for one participant who withdrew during oral dosing due to pregnancy, resulting in 14 participants with LA PK data.

Figure 2. Plasma Concentration–Time Profiles of CAB and RPV

Error bars represent minimum and maximum observed concentrations. Non-quantifiable concentrations were imputed as LLOQ for the purpose of calculating statistics.
CAB, cabotegravir; IM, intramuscular; LA, long-acting; LLOQ, lower limit of quantitation; PA-IC$_{90}$, *in vitro* protein-adjusted concentration resulting in 90% of the maximum inhibition of viral growth; RPV, rilpivirine.

- Geometric mean plasma concentrations at Weeks 4 and 8 were 15.4- and 5.3-fold above the PA-IC$_{90}$ for CAB and 4.7- and 2.4-fold for RPV, respectively (**Figure 2**; PA-IC$_{90}$, CAB 0.166 µg/mL; RPV 12 ng/mL).

Table 2. Preliminary Plasma PK Parameters of CAB and RPV

	C_{max}	T_{max}	AUC_{last}	Concentration at Week 4
CAB LA (n=13)	3.38 µg/mL (66.0) [1.02, 9.60]	7 days (7, 55)	3.61 h×mg/mL (23.0) [3.15, 4.14]	2.56 µg/mL (38.9) [1.17, 4.39]
RPV LA (n=14)	93.47 ng/mL (37.7) [35.40, 155]	5 days (3, 27)	143.89 h×µg/mL (33.0) [84.14, 283.23]	56.7 ng/mL (28.5) [47.47, 67.74]

Values are displayed as geometric mean (CV%) [minimum, maximum], except for T_{max}, which is displayed as median (minimum, maximum). Plasma concentrations below the lower limit of quantitation were omitted for estimating PK parameters.
AUC_{last}, area under the concentration–time curve from time 0 to last quantifiable time point; CAB, cabotegravir; C_{max}, maximum plasma concentration post-IM injection; CV, coefficient of variation; IM, intramuscular; LA, long-acting; PK, pharmacokinetics; RPV, rilpivirine; T_{max}, time at which C_{max} occurs.

- CAB and RPV PK parameter estimates following IM thigh injection (**Table 2**) are within the ranges that support further evaluation of thigh IM injections in target populations.

Table 3. Safety Overview

Parameter, n (%)	CAB + RPV LA (N=15)
Any AE	15 (100)
Excluding ISRs	9 (60)
Any drug-related AE	14 (93)
Excluding ISRs	3 (20)
Grade ≥3 AE	3 (20)
Excluding ISRs	0
Serious AEs	0
AEs leading to withdrawal	0

AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

- All participants reported at least one AE during the study (**Table 3**).
- Excluding ISRs, drug-related AEs were chills (n=3), headache, feeling hot, musculoskeletal stiffness, and insomnia (all n=1); all were Grade 1 or 2, and none were classified as serious.
  - The only drug-related AE occurring in the oral lead-in phase was headache (n=1).
- There were no clinically meaningful changes from baseline in chemistry and hematology parameters.

Table 4. ISR Summary (Subject-Level)

Parameter	CAB + RPV LA (N=15)
Participants who received ≥1 injection, n (%)	14 (93)
Participants with ISRs, n (% of participants with injections)	14 (100)
Injection site pain	14 (100)
Injection site erythema	8 (57)
Injection site induration	7 (50)
Injection site swelling	6 (43)
Injection site bruising	4 (29)
Injection site warmth	3 (21)
Injection site pruritus	2 (14)
Participants with Grade 3 ISRs (maximum grade), n (% of participants with injections)	3 (21)

CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

- ISRs were reported in all 14 participants who received an injection.
  - 5/14 (36%) had maximum Grade 1, 6/14 (43%) had Grade 2, and 3/14 (21%) had Grade 3 ISRs (**Table 4**).
  - All Grade 3 ISRs were injection site pain; no Grade 4 or 5 ISRs were reported.
  - ISR frequency, type, and severity were generally comparable by drug (CAB/RPV).

Table 5. ISR Summary (Event-Level)

Parameter	CAB + RPV LA (N=15)
Participants who received ≥1 injection, n (%)	14 (93)
Number of injections	28
ISR events, n	81
Injection site pain, n (% of injections)	28 (100)
Injection site induration, n (% of injections)	15 (54)
Injection site swelling, n (% of injections)	12 (42)
Injection site erythema, n (% of injections)	11 (39)
Injection site bruising, n (% of injections)	6 (21)
Injection site warmth, n (% of injections)	5 (18)
Injection site pruritus, n (% of injections)	4 (14)
Grade 3 ISR events, n (% of ISRs)	5 (6)
Median duration (IQR), days	8 (7–11)

CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

- Most (94%) ISRs were Grade 1 (79%, n=64/81) or 2 (15%, n=12/81), with a median duration of 8 days (**Table 5**).
- Participant-reported level of pain of injections at Days 1, 2, and 4 post-injection were numerically higher for RPV LA, indicating higher levels of post-injection pain compared with CAB LA. By Day 8, the results were similar (mean [standard deviation (SD)] NRS scores, CAB/RPV: Day 1, 0.5 [0.76]/2.1 [2.51]; Day 2, 2.1 [2.28]/4.4 [2.59]; Day 4, 2.0 [2.25]/2.6 [2.90]; Day 8, 0.9 [1.90]/0.9 [2.16]).
- Mean (SD) PIN scores for the acceptance domain at Day 8 post-injection were 2.57 (1.24) for CAB LA and 2.61 (1.04) for RPV LA, indicating similarly moderate acceptance of pain for both drugs.

Conclusions

- CAB and RPV IM injections into lateral thigh muscle resulted in plasma PK profiles that support further evaluation of thigh IM injections in target populations.
- The safety and tolerability profiles of CAB and RPV LA IM injections to the *lateral thigh* muscle were acceptable, with most ISRs reported as mild to moderate in severity.

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