Thigh (*Vastus Lateralis*) Administration of Long-Acting Cabotegravir Plus Rilpivirine

Summary

- Long-acting cabotegravir plus rilpivirine (CAB + RPV LA, *Cabenuva*) is approved for gluteal intramuscular injection only.[1] Pharmacokinetic data is available for thigh (*vastus lateralis*) administration.

ATLAS-2M Thigh Pharmacokinetics (PK) Study[2]

  - Cabotegravir (CAB) and rilpivirine (RPV) pharmacokinetic (PK) parameters following 16 weeks of thigh injections in participants with at least 3 years of gluteal injection experience was similar to those after gluteal administration, with no clinically significant differences observed.
  - These results support short-term CAB + RPV LA lateral thigh administration within an established gluteal regimen.
  - Additional analyses are needed to assess the potential for early or chronic thigh administration for those unable to receive gluteal injections.

Phase 1 Study (NCT04371380)[3]

  - Plasma trough concentrations remained above the protein-adjusted 90% inhibitory concentrations (PA-IC_{90}) throughout the thigh injection phase for CAB + RPV LA. The difference in plasma concentrations between gluteal and thigh administration were not considered clinically relevant.

- Important Safety Information can be found in the Prescribing Information and can also be accessed from the Our HIV Medicines

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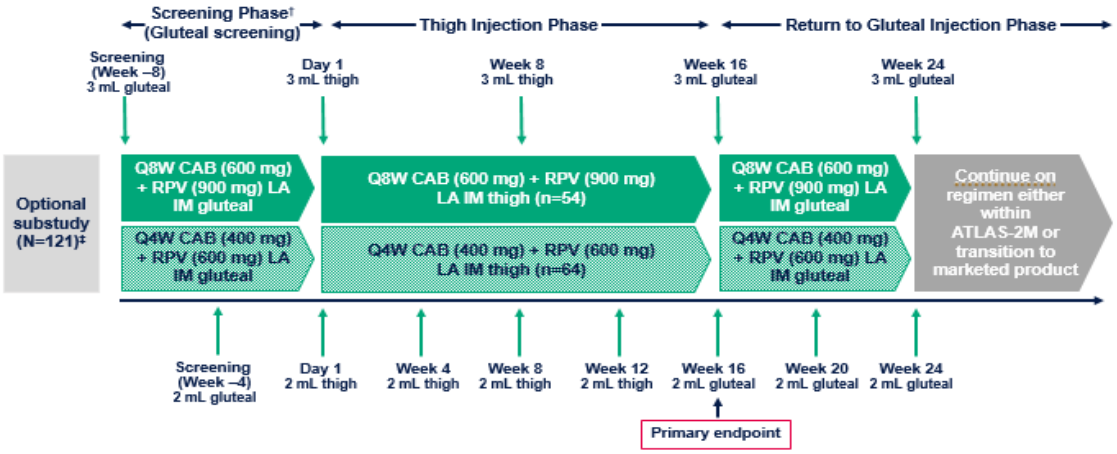
Long-acting cabotegravir plus rilpivirine (CAB + RPV LA) is approved for gluteal intramuscular injection only.[1] Pharmacokinetic data is available for thigh (*vastus* lateralis) administration.

ATLAS-2M THIGH PK STUDY

For further information on the Phase 3 ATLAS-2M study, please click here.

CAB + RPV LA is administered every-4-weeks (Q4W) or every-8-weeks (Q8W) via gluteal intramuscular (IM) injections. The PK, safety, and efficacy of CAB + RPV LA following short-term repeat intramuscular (IM) thigh administration was evaluated in an optional ATLAS-2M sub-study. PK samples were collected in eligible participants who had received ≥3 years of gluteal injections. In total, 118 participants (Q8W, n=54; Q4W, n=64) enrolled; median age (range) was 48 years (24, 71), 38 % were female sex at birth, and median body mass index (BMI) was 25 kg/m^2.[2] See Figure 1 for the study design.

Figure 1. ATLAS-2M Thigh PK Study Design*[2]



*PK samples were collected pre-dose at screening (Week –8), Day 1, Weeks 8, and 16; 2 hours post dose at Day 1 and Week 8; 1 week post dose at Weeks –7, 1, and 9; 4 weeks post dose at Weeks –4, 4, and 12. PK samples for Q4W dosing were collected: pre-dose at screening (Week –4), Day 1, Weeks 4, 8, 12, and 16; 2 hours post dose at Day 1, Weeks 4, 8, and 12; 1 week post dose at Weeks –3, 1, and 13. †Gluteal injection pre-thigh phase (control).). ‡Eligible participants had received ≥3 years of gluteal injections.

The injection schedule was unchanged during the thigh injection phase; participants continued CAB + RPV LA Q4W (n=64) or Q8W (n=54) dosing intervals.[2]

Healthcare professionals administered CAB and RPV injections into the *vastus lateralis*: RPV was injected in the right thigh and CAB into the left thigh. Injections were administered with 1.5 inch needles at a 90° angle.[2]

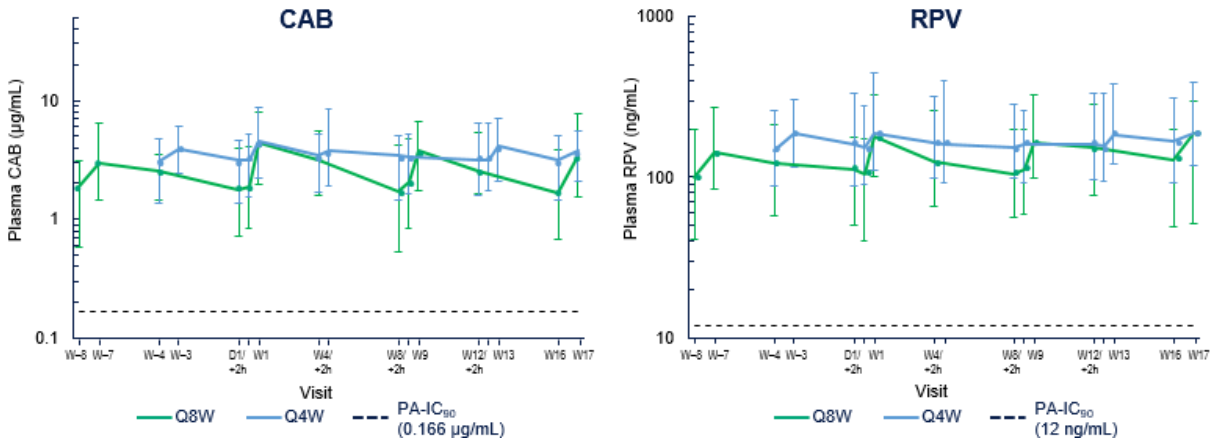
Administration Technique

Healthcare professionals administered CAB and RPV injections intramuscularly into the lateral thigh (*vastus lateralis*) using the Z tracking technique. RPV was injected in the right thigh and CAB into the left thigh. Injections were administered with 1.5 inch needles at a 90° angle. Participants were in a supine, semi-supine, or sitting position and remained in this position for approximately 15 minutes to avert any syncopal episodes.[2,4]

PK Results

Plasma trough concentrations remained above the protein-adjusted 90% inhibitory concentrations (PA-IC_{90}) throughout the thigh injection phase for both regimens. The difference in plasma concentrations between gluteal and thigh administration were not considered clinically relevant.[2] See Figure 2.

Figure 2. Median (5th, 95th Percentiles) Plasma CAB and RPV Time Plots[2]



CAB = cabotegravir; Cτ = concentration at dosing interval; D = day; Q4W = every 4 weeks; Q8W = every 8 weeks; PA-IC_{90} = protein-adjusted 90% inhibitory concentration; PO = oral therapy; RPV = rilpivirine; W = week.

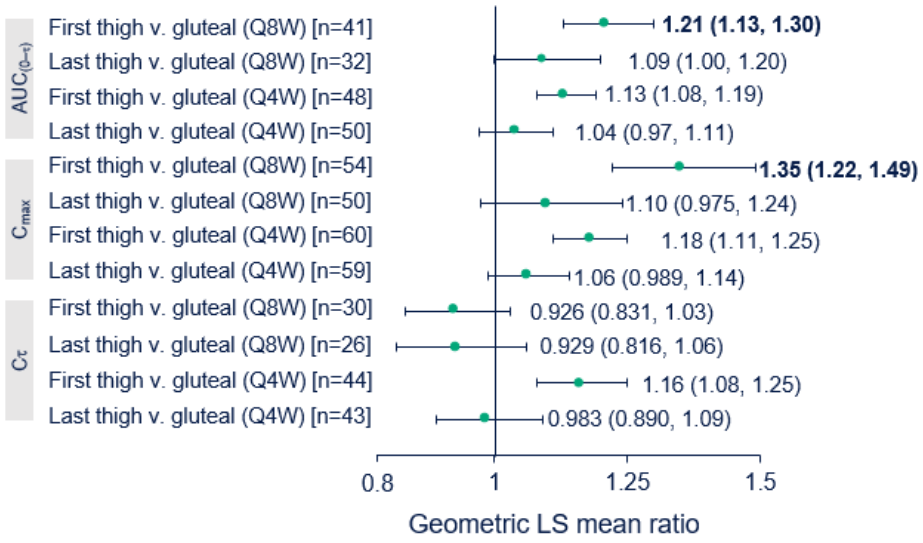
One participant had an observed plasma CAB concentration of 60.9 µg/mL at the 2-hour post-dose time point, which met the project-defined high 2-hour PK criterion (>22.5 µg/mL), consistent with potential inadvertent partial intravenous administration; the corresponding RPV concentration was 80.8 ng/mL (similar to the pre-dose RPV concentration of 84 ng/mL).[2]

In the Q8W arm, the first CAB thigh injection $AUC_{(0-\tau)}$ and C_{max} were statistically higher vs. gluteal injections. No statistically significant differences occurred in the Q4W arm.[2] See Figures 3 and 4 below for CAB PK parameters following gluteal and thigh administration.

Figure 3. CAB Geometric Least Square Means[2]

Regimen	Parameter	First thigh	Gluteal (paired)*	Last thigh	Gluteal (paired)*
Q8W	$AUC_{(0-\tau)}$ (µg × h/mL)	4062	3354	3416	3124
	C_{max} (µg/mL)	4.52	3.36	3.70	3.36
	Cτ (µg/mL)	1.70	1.83	1.62	1.74
Q4W	$AUC_{(0-\tau)}$ (µg × h/mL)	2504	2210	2343	2259
	C_{max} (µg/mL)	4.64	3.93	4.09	3.86
	Cτ (µg/mL)	3.26	2.81	2.90	2.95

Figure 4. CAB Geometric Least Square Ratios†[2]



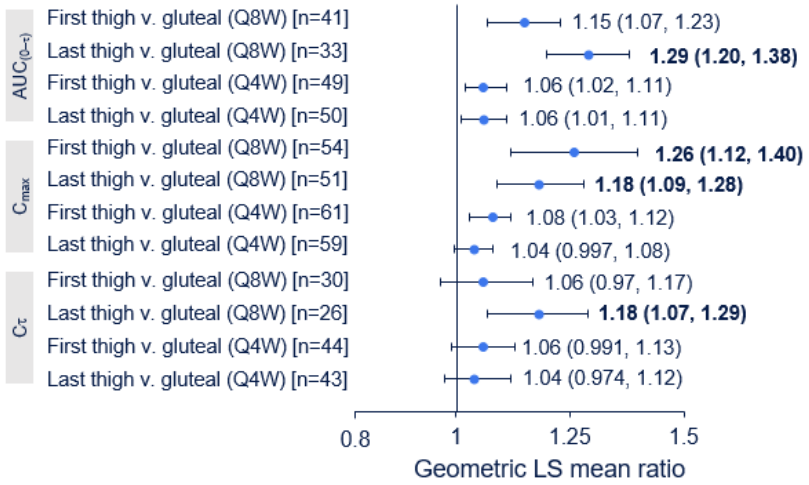
*Individuals with both test and reference (thigh and gluteal) parameters included in geometric LS mean ratio calculations. †Bolded numbers are statistically significant. Significance was determined when the 90% CIs of the GMR falls outside of the 0.8–1.25 range. AUC = area under the concentration–time curve from time 0 to last quantifiable time point; CAB = cabotegravir; CI = confidence interval; C_{max} = maximum plasma concentration post-IM injection; Cτ = concentration at dosing interval; GMR = geometric mean ratio; IM = intramuscular; LS = least squares; PK = pharmacokinetics; Q4W = every 4 weeks; Q8W = every 8 weeks; RPV = rilpivirine.

In the Q8W arm, the first RPV thigh injection Cmax and all last RPV thigh injection parameters were statistically higher vs. gluteal injections. No statistically significant differences occurred in the Q4W arm.[2] See Figures 5 and 6 below for RPV PK parameters following gluteal and thigh administration.

Figure 5. RPV Geometric Least Square Means[2]

Regimen	Parameter	First thigh	Gluteal (paired)*	Last thigh	Gluteal (paired)*
Q8W	$AUC_{(0-\tau)}$ (ng × h/mL)	184,311	160,755	205,973	160,178
	C_{max} (ng/mL)	184	146	172	146
	$C\tau$ (ng/mL)	109	103	123	104
Q4W	$AUC_{(0-\tau)}$ (ng × h/mL)	121,245	114,073	123,246	116,112
	C_{max} (ng/mL)	212	197	205	197
	$C\tau$ (ng/mL)	167	159	168	161

Figure 6. RPV Geometric Lease Square Ratios†[2]



*Individuals with both test and reference (thigh and gluteal) parameters included in geometric LS mean ratio calculations. †Bolded numbers are statistically significant. Significance was determined when the 90% CIs of the GMR falls outside of the 0.8–1.25 range. AUC = area under the concentration–time curve from time 0 to last quantifiable time point; CAB = cabotegravir; CI = confidence interval; C_{max} = maximum plasma concentration post-IM injection; Cτ = concentration at dosing interval; GMR = geometric mean ratio; IM = intramuscular; LS = least squares; PK = pharmacokinetics; Q4W = every 4 weeks; Q8W = every 8 weeks; RPV = rilpivirine.

Safety

During the thigh injection phase, injection site reactions (ISRs) accounted for the majority of adverse events (AEs); no serious AEs occurred. Across both arms, excluding ISRs, drug-related AEs were pyrexia (n=2), feeling hot, nasopharyngitis, odynophagia, arthralgia, headache, choking sensation, and flushing (all n=1).[2]

Pain was the most common ISR (52% of injections in the Q8W arm, and 33% in the Q4W arm). Most ISRs were Grade 1 or 2 (93–96%), and the median duration was 3–3.5 days. One participant withdrew due to injection site pain (Grade 2; Q8W arm).[2]

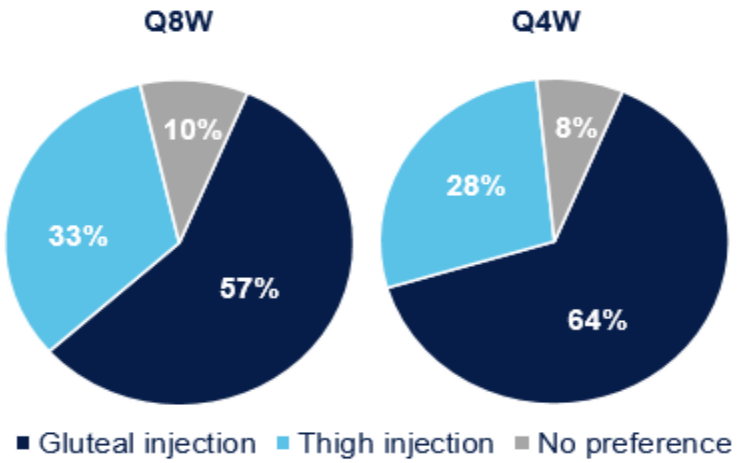
Snapshot Outcomes at Week 16

Virologic suppression were observed across both arms (Q8W, 94.4% [n=51/54]; Q4W, 95.3% [n=61/64]) at sub-study Week 16. There were no cases of confirmed virologic failure (CVF) and no patient had plasma HIV-1 RNA ≥50 during the sub-study. Three participants had no virologic data (discontinuation due to AE [Q8W, n=1) and discontinuation due to other reasons [Q8W, n=2; Q4W, n=3).[2]

Injection Site Preference

Overall, 30% of participants preferred thigh injections over gluteal injections.[2] See Figure 7.

Figure 7. Preference of Thigh Injection vs. Gluteal Injection*[2]

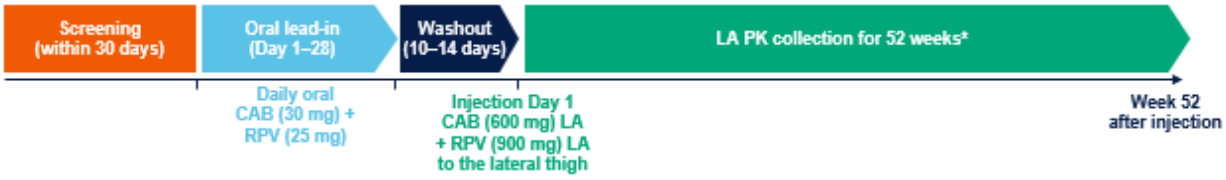


*return to gluteal injection phase
Q4W = every 4 weeks; Q8W = every 8 weeks

PHASE 1 STUDY (NCT04371380)

A Phase 1 study was conducted to evaluate PK and tolerability following single IM injections of CAB + RPV LA into the lateral thigh. Healthy adult participants (n=15), not HIV positive, received daily oral CAB 30 mg and RPV 25 mg for 4 weeks, 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. See Figure 8. The median age (range) was 33 years (21-49), 6 were female (sex at birth), and median BMI (range) was 31.40 kg/m^2 (24.3-34.4). Safety and PK parameters were collected through 52 weeks after injection.[3]

Figure 8. Phase 1 PK Study Design[3]

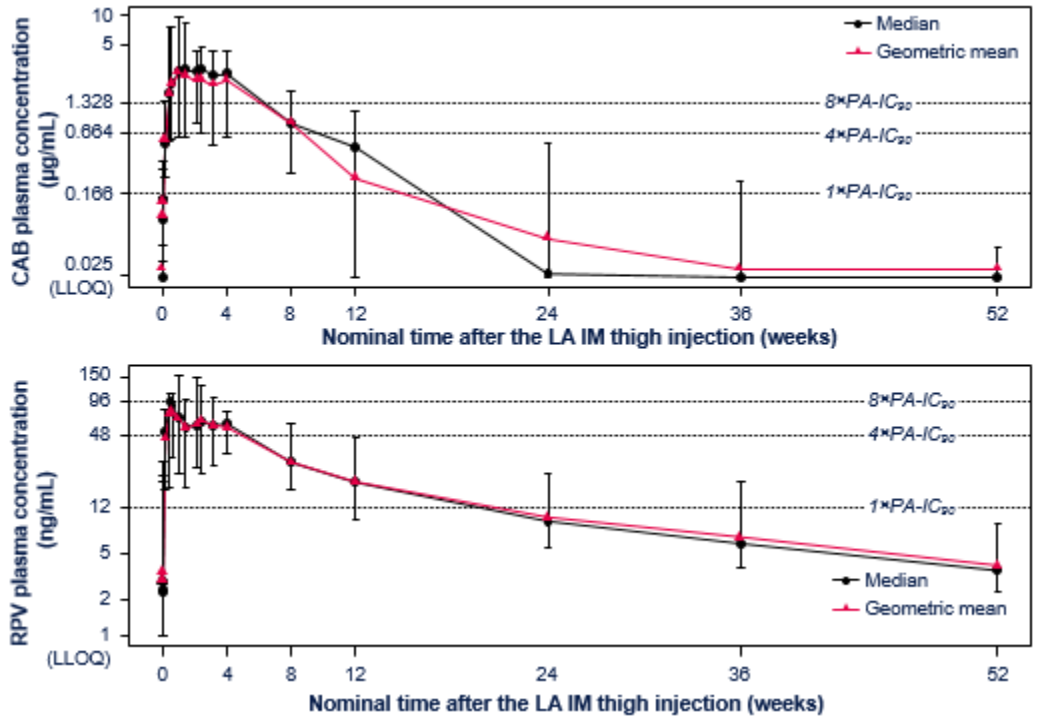


*PK collection at pre-injection, 1 hr and 2 hr post-injection, on Days 2, 4, 5, 7/8, 10, 15, 17, and 22 post-injection, and at Weeks 4 (Day 28), 8, 12, 24, 36, and 52, and at withdrawal visit.
CAB, cabotegravir; LA, long-acting; PK, pharmacokinetics; RPV, rilpivirine.

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 (PA-IC$_{90}$, CAB 0.166 µg/mL; RPV 12 ng/mL).[3]

See Figure 9.

Figure 9. Plasma Concentration-Time Profiles for CAB and RPV[3]



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.

CAB and RPV PK parameter estimates following IM thigh injection were within target ranges. See Table 1.

Table 1. CAB + RPV PK Parameter Estimates Following IM Thigh Injections[3]

	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)	93.7 ng/mg (37.7) [35.40, 55}	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.

Safety

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. ISRs were reported in all 14 participants who received an injection, with a median duration of 8 days (Grade 1, n=5; Grade 2, n=6, Grade 3, n=3). No Grade 4/5 ISRs were reported.[3]

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product in a manner inconsistent with its approved labeling. Please note that reports of adverse events in the published literature often lack causality assessments and may contain incomplete information; therefore, conclusions about causality generally cannot be drawn.

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This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCES

1. ViiV Healthcare Local Label.
2. Felizarta F, et al. Thigh Injections of Cabotegravir+Rilpivirine in Virally Suppressed Adults with HIV-1. Presented at the 30th Conference on Retroviruses and Opportunistic Infections (CROI), February 19-22, 2023, Seattle, Washington. TBD.
3. Han K, et al. Pharmacokinetics (PK) and Tolerability of Cabotegravir (CAB) and Rilpivirine (RPV) Long-Acting (LA) Intramuscular (IM) Injections to the Vastus Lateralis (Lateral Thigh) Muscles of Healthy Adult Participants. Presented at AIDS 2022, July 29-August 2, 2022, Montreal, Canada, and virtually. E-poster. EPB176.
4. ViiV Healthcare. Study Reference Manual for Protocol 208832 (Cabotegravir LA and Rilpivirine LA Thigh PK Study), September 4, 2020.