Thigh Injections of Cabotegravir + Rilpivirine in Virally Suppressed Adults With HIV-1

Franco Felizarta[1], Ronald D'Amico[2], Kehui Wang[3], Herta Crauwels[4], Mar Masia[5], Miguel Garcia Deltoro[6], Olaf Degen[7], Jonathan Angel[8], Chiu-Bin Hsiao[9], Vasiliki Chounta[2], Kelong Han[3], Conn Harrington[2], Kelly Rimler[3], William R. Spreen[2], Susan L. Ford[10]

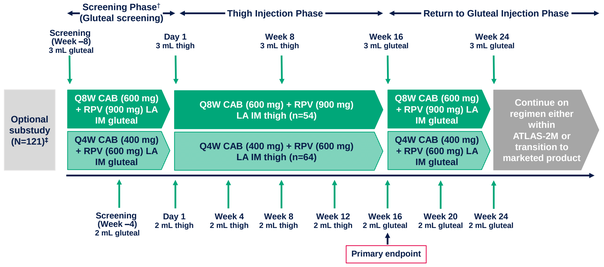
[1]Private Practice, Bakersfield, California, United States; [2]ViiV Healthcare, Durham, NC, United States; [3]GSK, Collegeville, PA, United States; [4]Janssen Research & Development, Beerse, Belgium; [5]Hospital General Universitario de Elche, Alicante, Spain; [6]Consorcio Hospital General Universitario de Valencia, Valencia, Spain; [7]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [8]University of Ottawa, Ottawa, ON, Canada; [9]Medicine Institute, School of Medicine, Infectious Diseases, Drexel University, Positive Health Clinic, Allegheny General Hospital, Allegheny Health Network, Pittsburgh, PA, United States; [10]GSK, Durham, NC, United States

Introduction

- Cabotegravir (CAB) + rilpivirine (RPV) is the first and only complete long-acting (LA) injectable regimen administered monthly or every 2 months via gluteal intramuscular (IM) injections recommended by treatment guidelines for maintaining HIV-1 virologic suppression.[1,2]
- An alternative large muscle, such as the thigh muscle, could be a potential site of administration for participants experiencing injection site fatigue or intolerability, or having contraindication for gluteal muscle administration (e.g. buttock implants).
- Previous data in healthy volunteers receiving single CAB + RPV LA IM injections to the *vastus lateralis* (lateral thigh) muscle were supportive of further evaluations.[3]
- Here, we present the pharmacokinetics (PK), safety, tolerability, and efficacy of CAB + RPV LA following short-term repeat IM thigh administration in a substudy of adults living with HIV-1 who had received ≥3 years of gluteal injections while participating in the ongoing Phase 3b ATLAS-2M study (NCT03299049).

Methods

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



*PK samples for Q8W dosing 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. 20% female (sex at birth) enrollment target. §Three participants failed screening.
CAB, cabotegravir; IM, intramuscular; LA, long-acting; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- ATLAS-2M participants volunteered and consented for the substudy (**Figure 1**).
- The injection schedule was unchanged during the thigh injection phase, with participants continuing CAB + RPV LA at every 4 weeks (Q4W) or every 8 weeks (Q8W) dosing intervals.
- CAB and RPV injections were administered by healthcare professionals intramuscularly into the *vastus lateralis*; generally, RPV injections were administered to the right thigh, CAB to the left thigh.
  - Injections were administered with 1.5-inch needles inserted at a 90-degree angle.
- Following the gluteal dose in the screening period (control), CAB and RPV PK parameters were assessed after the first and last thigh dose received (2nd Q8W dose or the 4th Q4W dose) and determined by non-compartmental analysis (linear up/log down application of the trapezoidal rule); they were then compared to CAB and RPV PK parameters after the gluteal dose by mixed effects modelling

Endpoints

- The primary analysis was to compare the PK parameters after thigh injections with those following gluteal injections, determining the ratio of the geometric least squares mean of thigh injection vs. gluteal injection and associated 90% confidence intervals (CIs) for a PK parameter within each arm (Q8W, Q4W) and for each drug (CAB, RPV).
- Other outcomes assessed included:
  - Safety and tolerability.
  - Efficacy (FDA Snapshot algorithm).
  - Participant-reported outcomes: participants completed questionnaires at Weeks 8 and 24 in the Q8W arm and Weeks 12 and 20 in the Q4W arm to understand preference between thigh injection and their previous gluteal injection. Assessments at Weeks 20 and 24 investigated whether participants' selected preferences from Weeks 8 and 12 were maintained upon return to gluteal injections.

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- **CAB and RPV PK parameters following 16 weeks of thigh injections in participants with ≥3 years' experience of gluteal injections were similar to those after gluteal administration, with no clinically significant differences observed.**
- **Additional analyses will assess the potential for early or chronic thigh administration.**

Results

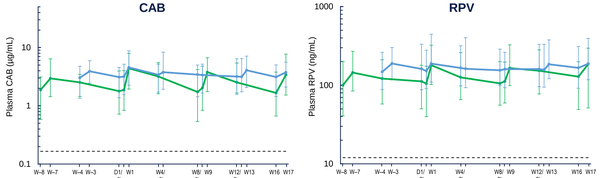
Table 1. Baseline Characteristics

Parameter	Q8W (n=54)	Q4W (n=64)	Total (N=118)
Median age, years (range)	50 (24, 71)	46 (26, 65)	48 (24, 71)
Female (sex at birth), n (%)	19 (35)	26 (41)	45 (38)
Male (sex at birth), n (%)	35 (65)	38 (59)	73 (62)
Race, n (%)			
White	43 (80)	54 (84)	97 (82)
Black or African American	11 (20)	7 (11)	18 (15)
Other	0	3 (5)	3 (3)
Hispanic/Latinx, n (%)	3 (6)	8 (13)	11 (9)
Median BMI, kg/m^2 (range)	25.54 (17.88, 51.04)	25.21 (19.63, 52.69)	25.43 (17.88, 52.69)

BMI, body mass index; Q4W, every 4 weeks; Q8W, every 8 weeks.

- 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 BMI was 25 kg/m^2 (**Table 1**).
- Baseline characteristics were similar between arms.

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



CAB, cabotegravir; C_T, 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.

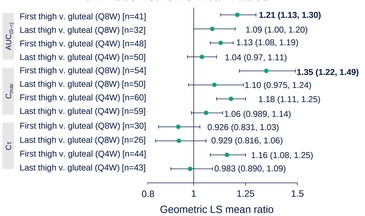
- Plasma trough concentrations remained well above protein-adjusted 90% inhibitory concentrations throughout the thigh injection phase for both regimens (**Figure 2**).
- The difference in plasma concentrations between gluteal and thigh administration were not considered clinically relevant.
- One participant 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).
  - No injection site reactions (ISRs) were reported for this participant. Three Grade 1 adverse events (AEs) (choking sensation, feeling hot, and flushing) considered to be related to study intervention were reported on the same day as the high CAB concentration. The reaction was reported as occurring within seconds of the CAB injection; the RPV injection was administered 7 minutes later, after symptoms resolved. While a possible post-injection reaction following CAB administration cannot be ruled out, the investigator considered the AEs to be a vasovagal reaction related to the use of a needle, with an operation for myopia 3 days prior as a contributing factor. Of note, no relevant changes in blood pressure, heart rate, or oxygen saturation were observed and on three separate occasions, the participant had also experienced similar Grade 1 AEs with gluteal injections of hot flush 3 days after the Week 64 visit, erythema and feeling warm on the day of the Week 104 visit, and feeling hot on the day of the Week 176 visit.

Figure 3. CAB and RPV PK Parameters Following Thigh and Gluteal Administration

CAB Geometric LS Means

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
	C_τ (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
	C_τ (μg/mL)	3.26	2.81	2.90	2.95

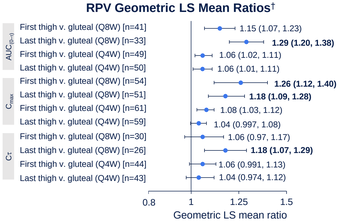
CAB Geometric LS Mean Ratios†



RPV Geometric LS Means

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_τ (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_τ (ng/mL)	167	159	168	161

RPV Geometric LS Mean Ratios†



*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; C_T, 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 CAB thigh injection $AUC_{(0-\tau)}$ and C_{max}, first RPV thigh injection C_{max}, and all last RPV thigh injection parameters were statistically higher vs. gluteal injections (**Figure 3**).
- No statistically significant differences occurred in the Q4W arm.

Table 3. Safety Summary (Thigh Injection Phase)

Parameter, n (%)	Q8W (n=54)	Q4W (n=64)	Total (N=118)
Any AE	45 (83)	49 (77)	94 (80)
Excluding ISRs	26 (48)	26 (41)	52 (44)
Any drug-related AE	39 (72)	43 (67)	82 (69)
Excluding ISRs	2 (4)	2 (3)	4 (3)
Grade ≥3 AE	4 (7)	9 (14)	13 (11)
Excluding ISRs	0	4 (6)	4 (3)
Any drug-related Grade ≥3 AE*	4 (7)	6 (9)	10 (8)
Serious AEs	0	0	0
AEs leading to withdrawal	1 (2)†	0	1 (<1)

*All were injection site pain. †Grade 2 injection site pain.
AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

- ISRs accounted for the majority of AEs; no serious AEs occurred (**Table 3**).
- 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).

Table 4. ISR Event-Level Summary (Thigh Injection Phase)

Parameter, n (%)	Q8W (n=54)	Q4W (n=64)	Total (N=118)
Number of injections, n	210	494	704
ISR events, n	132	195	327
Injection site pain, n (% of injections)*	110 (52)	163 (33)	273 (39)
Injection site discomfort, n (% of injections)*	6 (3)	8 (2)	14 (2)
Injection site induration, n (% of injections)*	4 (2)	5 (1)	9 (1)
Injection site swelling, n (% of injections)*	2 (<1)	5 (1)	7 (1)
Injection site erythema, n (% of injections)*	3 (1)	2 (<1)	5 (<1)
Grade 3 ISR events, n (% of ISRs)†	9 (7)	8 (4)	17 (5)
Median duration, days (IQR)	3.5 (3.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)

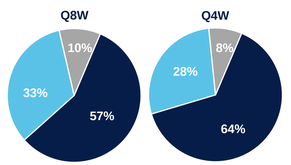
*Those occurring with ≥1% of injections in either arm are shown. †All were injection site pain events. No Grade 4 or 5 ISRs occurred.
IQR, interquartile range; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

- Pain was the most common ISR, occurring with 52% of injections in the Q8W arm, and 33% in the Q4W arm (**Table 4**).
- Most ISRs were Grade 1 or 2 (93–96%), 4–7% were Grade 3, and the median duration was 3–3.5 days.
- One participant withdrew due to injection site pain (Grade 2; Q8W arm).

Snapshot Outcomes at Week 16

- Among participants with ≥3 years of prior CAB + RPV LA gluteal IM dosing experience, no participants had confirmed virologic failure (CVF, two consecutive HIV-1 RNA ≥200 copies/mL) or plasma HIV-1 RNA ≥50 copies/mL during the substudy.
- Similarly, high rates of virologic suppression were observed across both arms (Q8W, 94.4% [n=51/54]; Q4W, 95.3% [n=61/64]) at substudy Week 16.
- Three participants in each arm had no virologic data (discontinuation due to AE [Q8W, n=1]; discontinuation due to other reasons [Q8W, n=2; Q4W, n=3]).

Figure 5. Preference of Thigh Injection vs. Gluteal Injection*



*Return to gluteal injection phase.
Q4W, every 4 weeks; Q8W, every 8 weeks.

- Overall, 30% of participants preferred thigh injections (**Figure 5**).
- The most common reasons for preferring thigh injections were: convenience/easy access (Q8W/Q4W, 71%); less bothered by pain following injection (Q8W, 65%; Q4W, 59%); less bothered by pain during injection (Q8W, 47%; Q4W, 65%).
- The most common reasons for preferring gluteal injections were: less bothered by pain following injection (Q8W, 66%; Q4W, 64%); less bothered by pain during injection (Q8W, 72%; Q4W, 46%); less bothered by muscular pain/stiffness when walking or doing physical activity (Q8W, 41%; Q4W, 49%).

Conclusions

- CAB and RPV PK parameters following 16 weeks of thigh injections in participants with ≥3 years' experience of gluteal injections were similar to those after gluteal administration, with no clinically significant differences observed.
  - The statistical differences between thigh and gluteal PK parameters observed in the Q8W arm may be due to changes in absorption rate between administration routes.
- The safety and tolerability of CAB + RPV LA IM injections to the lateral thigh muscle was acceptable, with most ISRs reported as mild to moderate in severity.
- There was one case of potential maladministration with a participant who had a high CAB concentration 2 hours post dose.
- Rates of virologic suppression at Week 16 were high, with no participants having CVF or HIV-1 RNA ≥50 copies/mL during the substudy.
- Overall, 30% preferred thigh injections, citing ease of access to injection site as the top reason.
- These results support rotational/short-term CAB + RPV LA IM lateral thigh administration within an established gluteal regimen, particularly for those experiencing gluteal injection site fatigue.
- Additional analyses are needed to assess the potential for early or chronic thigh administration for those unable to receive gluteal injections.

References: 1. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available from: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed December 2022.
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Presenting author: Franco Felizarta; francofelizarta@gmail.com

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