

A Study Evaluating the Safety, Tolerability, and Pharmacokinetics of a High-Concentration (CAB 400 mg/mL) Cabotegravir Long-Acting Injectable Formulation Following Subcutaneous and Intramuscular Administration in Healthy Adult Participants

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Key Takeaways

- A cabotegravir (CAB) 400 mg/mL formulation was developed to support the potential for less frequent dosing and/or self-administration via subcutaneous (SC) or thigh injections.
- CAB 400 mg/mL was absorbed faster than CAB 200 mg/mL, resulting in a shorter terminal half-life; every 4 week (Q4W) dosing of CAB 400 mg/mL, regardless of route, resulted in plasma concentrations within the range of approved CAB 200 mg/mL regimens.
- Overall, the safety profile of CAB 400 mg/mL was similar to CAB 200 mg/mL; injection site reactions (ISRs) were commonly reported following intramuscular (IM) and SC administration, and most were Grade 1–2 and were generally short-lived.

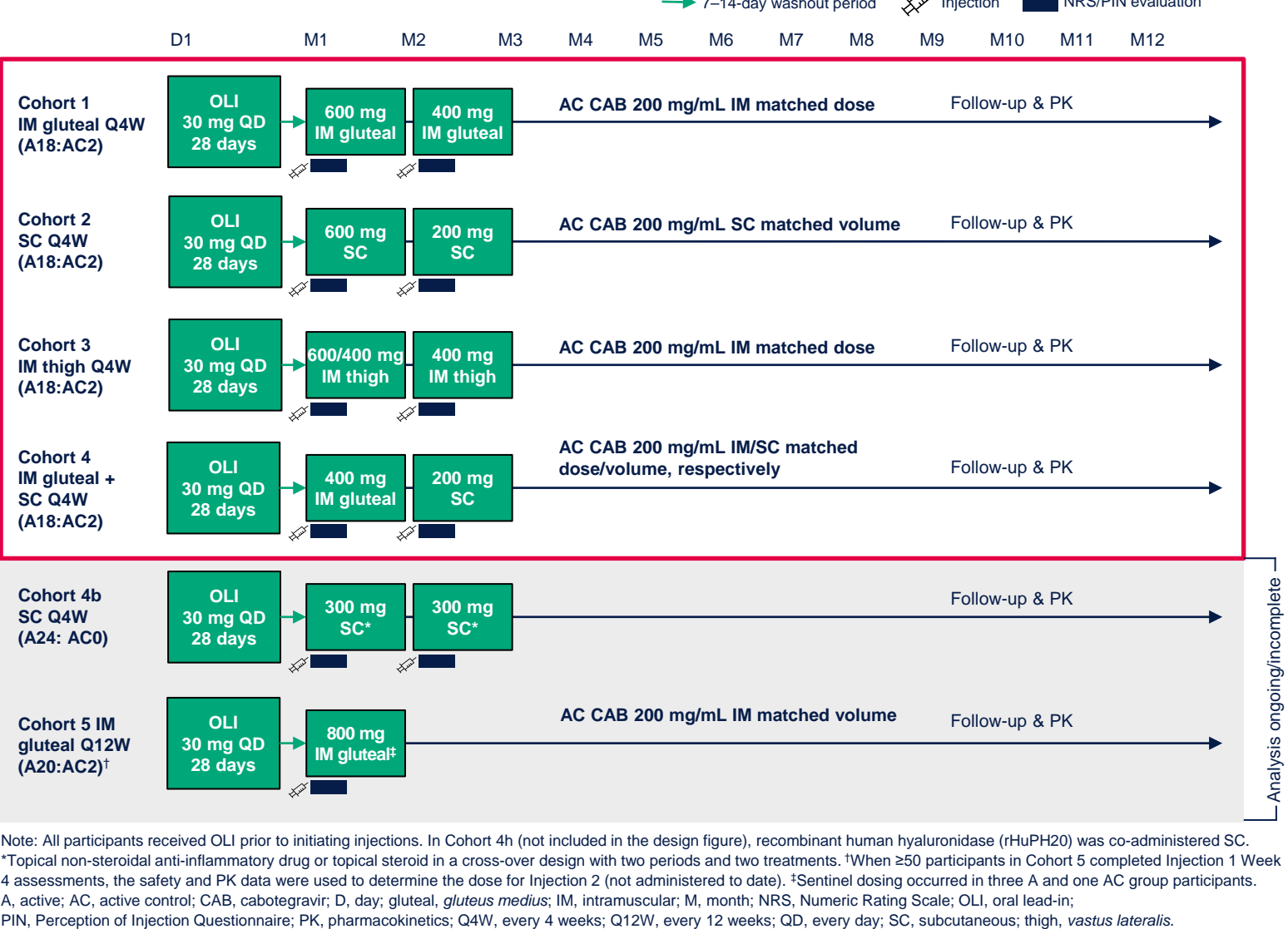
Background

- Long-acting (LA) CAB (200 mg/mL) administered IM is approved for HIV-1 prevention (every 2 months) and, in combination with rilpivirine, HIV-1 treatment in virologically suppressed individuals.^{1,2}
- With efficacious and well-tolerated antiretroviral therapy (ART) widely available, the focus of HIV care has shifted towards treatment simplification/convenience and patient satisfaction.
- A CAB 400 mg/mL formulation was developed to support the potential for less frequent dosing and/or self-administration via SC or thigh injections.
- We present interim results from the Phase 1 study (NCT04484337) investigating the pharmacokinetics (PK), safety, and tolerability of CAB 400 mg/mL in healthy adult participants.

Methods

- The PK and safety of single/repeat administration of CAB 400 mg/mL 200–800 mg (Cohorts 1–4, 4b, 4h, 5) IM (*gluteus medius*, *vastus lateralis*) or SC (abdominal) in healthy adults was evaluated in this ongoing Phase 1 study (**Figure 1**).
 - Analyses for Cohorts 4b, 4h, and 5 are ongoing, with incomplete data presented for Cohorts 4b and 5; data for Cohort 4h to be presented in future communications.
- CAB 200 mg/mL active controls (n=1–2 per cohort) were matched by dose or volume in Cohorts 1–4 and 5.
- PK parameters were estimated via non-compartmental analysis.
- A CAB 200 mg/mL population PK (PPK) model was previously built. Assuming that the only difference between CAB 400 mg/mL PK and CAB 200 mg/mL PK is that the CAB 400 mg/mL LA absorption rate is 160% faster than CAB 200 mg/mL, as observed in this study, CAB 400 mg/mL PK was simulated in 5000 virtual subjects using the CAB 200 mg/mL PPK model without residual variability by multiplying the LA absorption rate constant of all virtual participants by 2.6 while keeping all other PPK parameters, including inter-individual variabilities, unchanged.
- Patient-reported outcome measures (PROMs) assessed were the Numeric Rating Scale (NRS) and Perception of Injection Questionnaire (PIN).

Figure 1. Study Design



Note: All participants received OLI prior to initiating injections. In Cohort 4h (not included in the design figure), recombinant human hyaluronidase (rHuPH20) was co-administered SC. *Typical non-steroidal anti-inflammatory drug or topical steroid in a cross-over design with two periods and two treatments. *When 250 participants in Cohort 5 completed Injection 1 Week 4 assessments, the safety and PK data were used to determine the dose for Injection 2 (not administered to date). *Sentinel dosing occurred in three A and one AC group participants. A, active; AC, active control; CAB, cabotegravir; D, day; gluteal, *gluteus medius*; IM, intramuscular; M, month; NRS, Numeric Rating Scale; OLI, oral lead-in; PIN, Perception of Injection Questionnaire; PK, pharmacokinetics; Q4W, every 4 weeks; Q12W, every 12 weeks; QD, every day; SC, subcutaneous; thigh, *vastus lateralis*.

Results

Table 1. Baseline Characteristics for CAB 400 mg/mL Groups

Parameter	Cohort 1 IM gluteal (n=18)	Cohort 2* SC abdominal (n=9)	Cohort 3* IM thigh (n=13)	Cohort 4 IM gluteal + SC abdominal (n=18)	Cohort 4b† SC abdominal (n=20)	Cohort 5*† IM gluteal (n=10)
Median age (range), years	39 (21–50)	33 (25–50)	40 (23–49)	26 (18–47)	36 (20–49)	29 (23–44)
Female (sex at birth), n (%)	6 (33)	3 (33)	6 (46)	9 (50)	9 (45)	2 (20)
Race, n (%)						
White	9 (50)	5 (56)	8 (62)	11 (61)	9 (45)	4 (40)
Black or African American	6 (33)	3 (33)	2 (15)	2 (11)	7 (35)	5 (50)
Other race	3 (17)	1 (11)	3 (23)	5 (28)	4 (20)	1 (10)
Median BMI (IQR), kg/m ²	27 (24–30)	27 (23–29)	26 (25–29)	26 (22–30)	26 (23–29)	26 (25–28)
≥30 kg/m ² , n (%)	4 (22)	2 (22)	0	5 (28)	2 (10)	1 (10)

*In Cohorts 2, 3, and 5, the number of participants and/or injections was modified based upon emergent data. †Complete data from these cohorts will be the subject of future presentations. BMI, body mass index; CAB, cabotegravir; gluteal, *gluteus medius*; IM, intramuscular; IQR, interquartile range; SC, subcutaneous; thigh, *vastus lateralis*.

- Overall, 40% were female (sex at birth), 48% were non-White, and 16% had BMI ≥30 kg/m² (**Table 1**).
- Of the eight active control participants (gluteal, n=3; thigh, n=2; gluteal/SC, n=2, SC, n=1) who received CAB 200 mg/mL, 50% (n=4) were female, 38% (n=3) were non-White, and 13% (n=1) had a BMI ≥30 kg/m².
 - Median age/weight/BMI across the active control participants ranged 23–45 years/43–90 kg/19–29 kg/m², respectively.

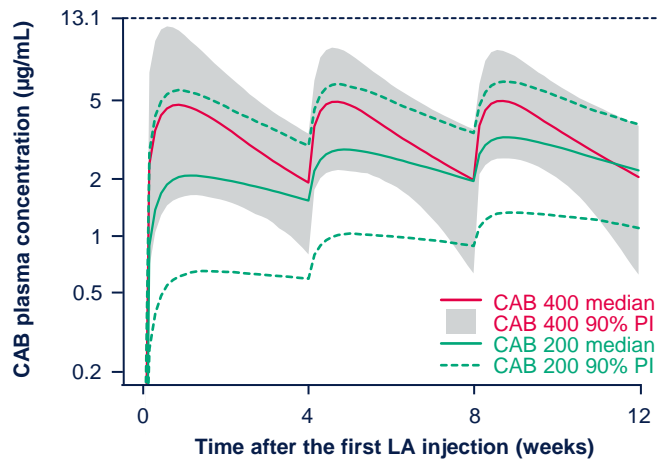
Table 2. CAB Plasma PK Parameters for CAB 400 mg/mL Groups

Parameter	Cohort 1 IM gluteal		Cohort 2 SC		Cohort 3 IM thigh		Cohort 4 IM gluteal		Cohort 4 SC		Cohort 4b SC		Cohort 5 IM gluteal	
	Inj. 1	Inj. 2	Inj. 1	Inj. 2	Inj. 1	Inj. 2	Inj. 1	Inj. 2	Inj. 1	Inj. 2	Inj. 1	Inj. 2	Inj. 1	Inj. 1
	600 mg [1.5 mL] (n=18)	400 mg [1 mL] (n=16)	600 mg [1.5 mL] (n=9)	200 mg [0.5 mL] (n=8)	600 mg [1.5 mL] (n=13)*	400 mg [1 mL] (n=10)	400 mg [1 mL] (n=18)	200 mg [0.5 mL] (n=16)	300 mg [0.75 mL] (n=20)	300 mg [0.75 mL] (n=16)	800 mg [2 mL] (n=10)		800 mg [2 mL] (n=10)	
C _{max} (µg/mL)	6.51 (28.7%) [4.20,12.2]	7.31 (23.5%) [4.30,11.5]	6.76 (37.7%) [3.88,12.2]	3.54 (51.6%) [1.46,7.02]	7.14 (69.4%) [1.73,16.7]	5.47 (75.1%) [1.57,9.93]	3.77 (53.2%) [1.71,10.1]	3.07 (23.8%) [0.94,8.45]	2.69 (41.8%) [0.94,5.78]	4.07 (28.9%) [1.92,6.53]	6.17 (38.6%) [3.05,11.6]			
Concentration at Week 4 (µg/mL)	2.51 (36.8%) [1.19,4.40]	2.85 (40.0%) [1.40,5.45]	1.96 (38.2%) [1.23,3.02]	1.33 (60.4%) [0.64,2.89]	1.86 (45.7%) [1.16,4.67]	1.54 (51.6%) [0.85,3.28]	1.27 (29.8%) [0.73,1.90]	1.29 (31.0%) [0.70,1.94]	1.05 (46.3%) [0.50,2.07]	1.75 (32.3%) [1.00,3.11]	3.06 (34.7%) [2.09,5.06]			
Terminal half-life (weeks)	N/A	2.57 (55.2%) [0.76,5.85]	N/A	1.92 (46.3%) [1.02,3.96]	N/A	2.23 (120.6%) [0.64,9.35]	N/A	3.35 (52.2%) [0.94,8.45]	N/A	2.25 (58.1%) [0.92,5.92]	N/A			
LA absorption rate constant (h ⁻¹)		0.001605 (55.2%) [0.000705, 0.00503]		0.002149 (46.3%) [0.00104, 0.00405]	N/A	0.001847 (120.6%) [0.000441, 0.00640]	N/A	0.01233 (52.3%) [0.000486, 0.00440]	N/A	0.001834 (58.1%) [0.000696, 0.00447]	N/A			

PK parameters were estimated using non-compartmental analysis. Values displayed are geometric mean (CV%) [minimum, maximum]. Note: Injection 2 was administered 4 weeks after Injection 1, and 4 weeks are insufficient to estimate t_{1/2} or KA-LA. Cohort 5 data are incomplete for estimating t_{1/2} or KA-LA. *Two participants in Cohort 3 received 400 mg instead of 600 mg for Injection 1, and their plasma concentrations were increased by 50% (dose normalized to 600 mg) for estimating PK parameters. CAB, cabotegravir; C_{max}, maximum plasma concentration; gluteal, *gluteus medius*; IM, intramuscular; Inj., injection; KA-LA, LA absorption rate constant; LA, long-acting; N/A, not applicable; PK, pharmacokinetics; t_{1/2}, terminal half-life; thigh, *vastus lateralis*.

- Dose-normalized PK parameters for CAB 400 mg/mL were similar across administration routes of IM gluteal, IM thigh, and SC abdominal and across all dose levels tested (**Table 2**).
- The terminal half-life of CAB 400 mg/mL was 62% shorter (CAB 200 mg/mL 6.4 weeks),³ and the absorption rate constant 160% higher (CAB 200 mg/mL 0.000642 h⁻¹),³ than that of CAB 200 mg/mL.

Figure 2. Predicted CAB Q4W Concentration–Time Profiles



Long-term safety threshold of 13.1 µg/mL is the observed median steady-state C_{max} following oral CAB 60 mg daily, the highest dose evaluated in the LATTE study, and was not associated with any toxicity. CAB, cabotegravir; C_{max}, maximum plasma concentration; LA, long-acting; PI, prediction interval; Q4W, every 4 weeks.

Acknowledgments: The authors thank all study participants and their families, and the clinical investigators and their staff. The study was funded by ViiV Healthcare. Editorial assistance was provided by Daniel Williams of Scimantum (Nucleus Global), with funding provided by ViiV Healthcare.

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Table 3. Safety Overview of CAB 400 mg/mL Groups (Including ISRs)*

Parameter, n (%)	IM gluteal			IM thigh		SC abdominal		
	400 mg [1.0 mL] (n=34)	600 mg [1.5 mL] (n=18)	800 mg [2.0 mL] (n=10)	400 mg [1.0 mL] (n=12)*	600 mg [1.5 mL] (n=11)	200 mg [0.5 mL] (n=24)	300 mg [0.75 mL] (n=40)	600 mg [1.5 mL] (n=9)
Any AE	33 (97)	17 (94)	10 (100)	12 (100)	11 (100)	24 (100)	35 (88)	9 (100)
Drug-related AE	33 (97)	17 (94)	10 (100)	12 (100)	11 (100)	24 (100)	34 (85)	9 (100)
Serious	0	0	0	0	0	0	0	0
Grade 3†	4 (12)	1 (6)	2 (20)	1 (8)	1 (9)	2 (8)	0	1 (11)
Leading to study drug discontinuation following Injection 1§	1 (6)	2 (11)	N/A	0	1 (9)	N/A	0	1 (11)

*Data are based on the number (%) of injections leading to any event, combined across cohorts. †One participant received two injections at the indicated dose/volume for Injection 1 and 2 and is therefore counted twice. ‡Gluteal 400 mg: injection site erythema (n=3), pyrexia (n=1); gluteal 600 mg: injection site induration and injection site swelling (n=1); gluteal 800 mg: injection site erythema (n=2); thigh 400 mg: injection site erythema (n=1); thigh 600 mg: injection site erythema (n=1); abdominal 200 mg: injection site pain (n=1), injection site erythema and injection site swelling (n=1); abdominal 600 mg: injection site erythema (n=1). There were no Grade 4 or 5 AEs. §Gluteal 400 mg: injection site erythema and injection site swelling (n=1); gluteal 600 mg: injection site pain and injection site nodule (n=1), injection site erythema and injection site induration (n=1); thigh 600 mg: injection site swelling, injection site erythema, injection site warmth, and pyrexia (n=1); abdominal 600 mg: increased hepatic enzymes (n=1). Percentage based on number of first injections. AE, adverse event; CAB, cabotegravir; gluteal, *gluteus medius*; IM, intramuscular; ISR, injection site reaction; N/A, not applicable; SC, subcutaneous; thigh, *vastus lateralis*.

- AEs occurred in 94–100% of participants; 80–100% of drug-related AEs were Grade 1 or 2 (**Table 3**).
- ISRs were the most common AEs, occurring in 99% (n=87/88) of participants.
- Overall, safety profiles were similar between formulations.

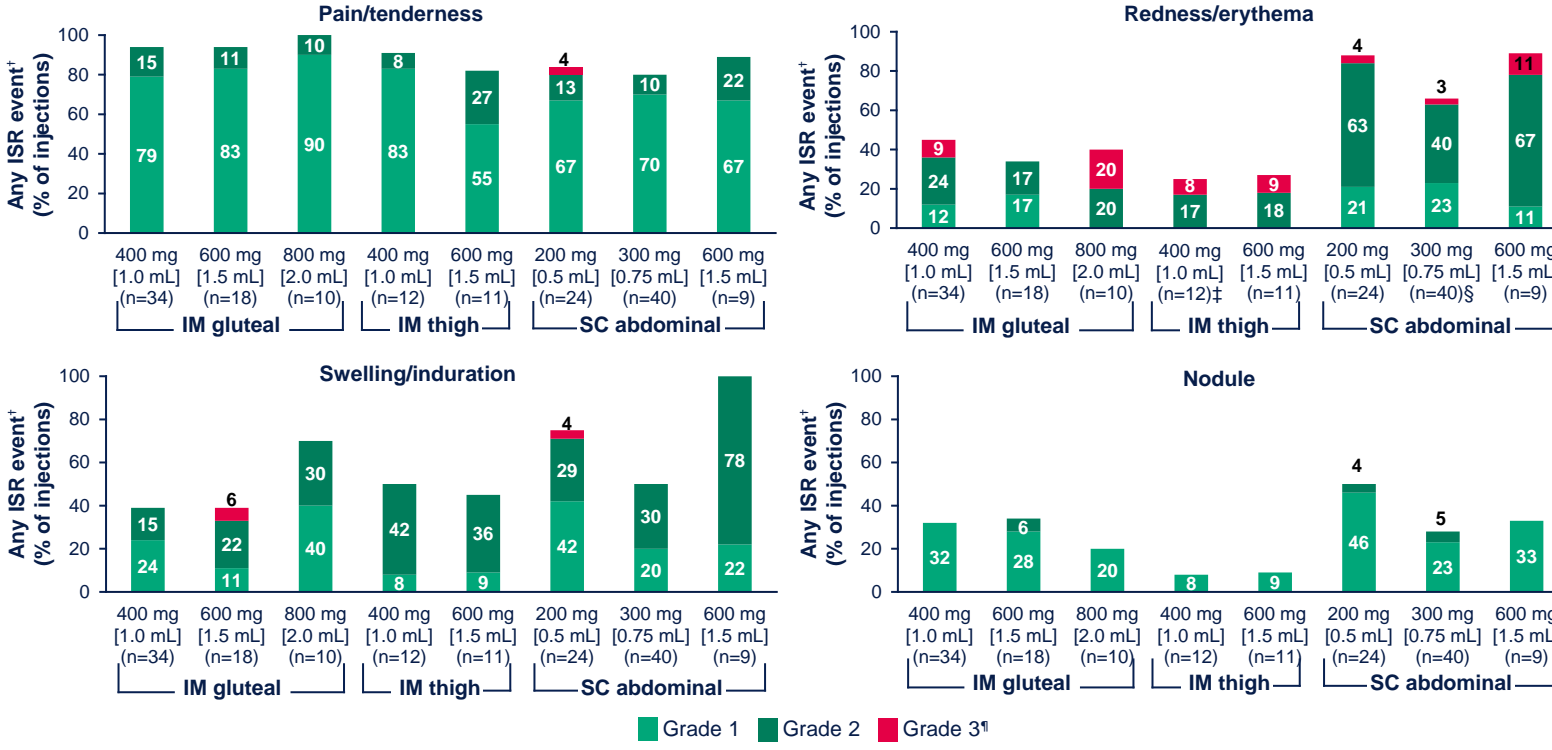
Table 4. Summary of ISR Events

Parameter	IM gluteal			IM thigh		SC abdominal		
	400 mg [1.0 mL] (n=34)	600 mg [1.5 mL] (n=18)	800 mg [2.0 mL] (n=10)	400 mg [1.0 mL] (n=12)*	600 mg [1.5 mL] (n=11)	200 mg [0.5 mL] (n=24)	300 mg [0.75 mL] (n=40)†	600 mg [1.5 mL] (n=9)
Maximum grade of ISR, n (% of injections)								
Grade 1	19 (56)	8 (44)	4 (40)	4 (33)	4 (36)	6 (25)	12 (30)	2 (22)
Grade 2	11 (32)	8 (44)	4 (40)	6 (50)	6 (55)	16 (67)	21 (53)	6 (67)
Grade 3‡	3 (9)	1 (6)	2 (20)	1 (8)	1 (9)	2 (8)	1 (3)	1 (11)
Median duration (IQR), days	8 (5–15)	8 (5–14)	7 (5–10)	9 (6–20)	7 (3–11)	12 (7–26)	9 (6–24)	13 (9–29)

*One participant received two injections at the indicated dose/volume for Injection 1 and 2 and is therefore counted twice. †Includes 20 participants who received two injections each. ‡There were no Grade 4 or 5 ISRs. Gluteal, *gluteus medius*; IM, intramuscular; IQR, interquartile range; ISR, injection site reaction; SC, subcutaneous; thigh, *vastus lateralis*.

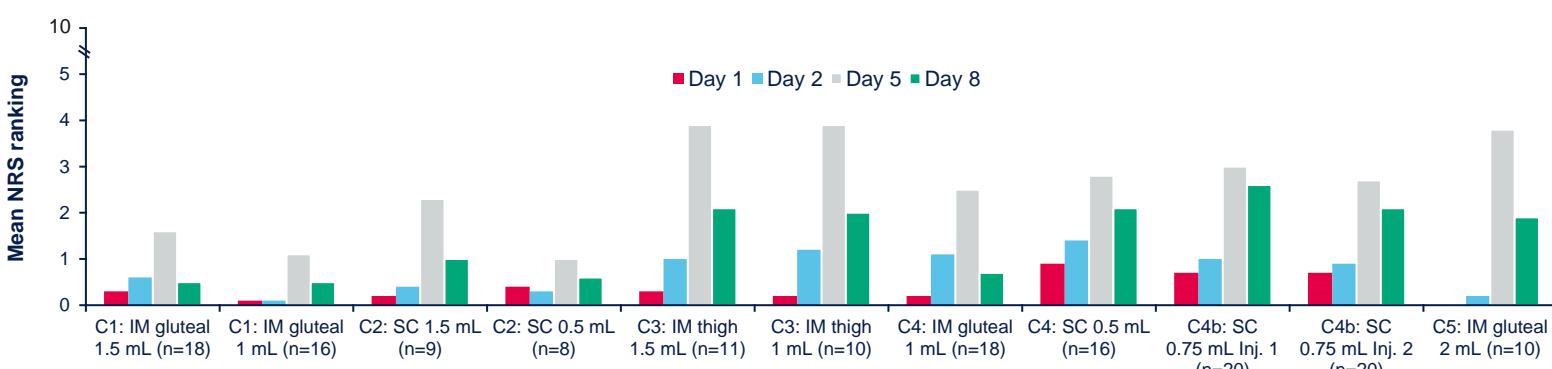
- CAB 400 mg/mL ISRs occurred with 86–100% of injections; most were Grade 1 or 2 (80–97%, maximum grade per injection) (**Table 4**).
- Injection site pain was the most common ISR event, occurring with 82–100% of injections (**Figure 3**).

Figure 3. Reported ISR Types*



*The most commonly occurring are shown. †Maximum grade reported following each injection. The denominator is the total number of injections. ‡One participant received two injections at the indicated dose/volume for Injection 1 and 2 and is therefore counted twice. §Includes 20 participants who received two injections each. †There were no Grade 4 or 5 ISRs. Gluteal, *gluteus medius*; IM, intramuscular; ISR, injection site reaction; SC, subcutaneous; thigh, *vastus lateralis*.

Figure 4. The NRS Through Day 8 (400 mg/mL Groups)*



Two participants in C3 received a first injection of CAB 400 mg/mL 1 mL via the lateral thigh; NRS rankings were: Day 1, 0; Day 2, 1.0; Day 5, 2.5; Day 8, 2.0. *The NRS ranks pain after injection from 0 “no pain” to 10 “extreme pain.” C, cohort; CAB, cabotegravir; gluteal, *gluteus medius*; IM, intramuscular; Inj., injection; NRS, Numeric Rating Scale; SC, subcutaneous; thigh, *vastus lateralis*.

- Mean NRS rankings were comparable across the SC and IM administration routes, with scores generally higher on Day 5. Day 5 scores were somewhat higher for IM thigh and SC routes versus IM gluteal, although the numbers are small (**Figure 4**).
- Median PIN scores of 1–2 were observed in the domain evaluating how bothersome pain was during the injection (ranked from 1 [not at all] to 5 [extremely]), indicating that most participants found injections to be only a little bothersome.
- Median PIN scores for the acceptability of pain (ranked from 1 [totally acceptable] to 5 [not at all acceptable]) and local reactions domains were 1.25–3 across cohorts, indicating very high to moderate acceptability, despite injection site pain being reported by most participants.

Conclusions

- CAB 400 mg/mL administered Q4W (600 mg initial injection, 400 mg for subsequent injections), regardless of route, resulted in plasma concentrations within the range of approved CAB 200 mg/mL regimens.
- Overall, safety profiles were similar between CAB 400 mg/mL and CAB 200 mg/mL formulations.^{4–8}
 - CAB 400 mg/mL ISRs were commonly reported following IM and SC administration and were mostly Grade 1 or 2 in severity and self-limited.
 - Erythema, swelling/induration and nodule occurred more commonly after SC versus IM injections with CAB 400 mg/mL.
- PROMs suggest that pain and ISRs were broadly acceptable and generally similar across administration routes, and not dissimilar to PROMs from historical data for CAB 200 mg/mL.⁹
- CAB 400 mg/mL could potentially expand options for LA injectable ART, and these interim safety and PK data support further clinical evaluation.