PESUB24

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.**

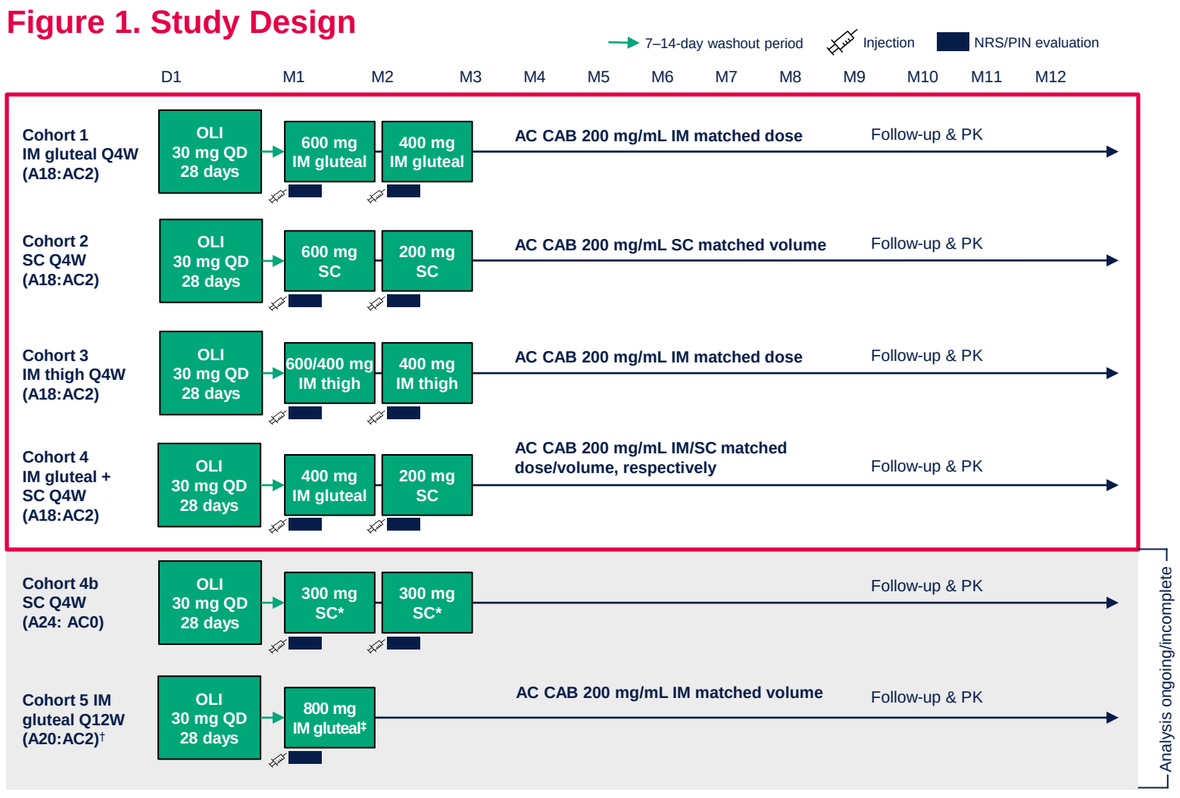
Background

- 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.
*Topical non-steroidal anti-inflammatory drug or topical steroid in a cross-over design with two periods and two treatments. †When ≥50 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 a BMI ≥30 kg/m^2 (**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/m^2.
  - Median age/weight/BMI across the active control participants ranged 23–45 years/43–90 kg/19–29 kg/m^2, respectively.

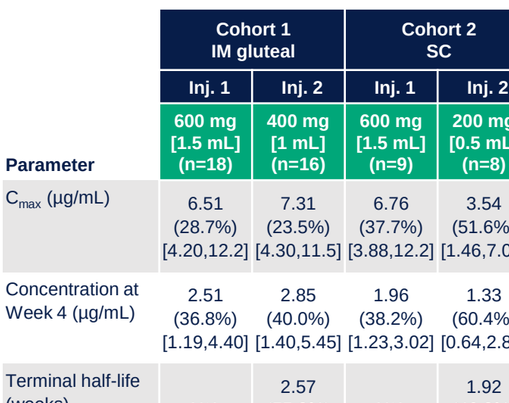
Table 2. CAB Plasma PK Parameters for CAB 400 mg/mL Groups

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
	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)
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%) [1.98,4.70]	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})	N/A	0.001605 (55.2%) [0.000705, 0.00503]	N/A	0.002149 (46.3%) [0.00104, 0.00405]	N/A	0.001847 (120.6%) [0.000441, 0.00640]	N/A	0.001233 (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; SC, subcutaneous; $t_{1/2}$, 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,

- Observed plasma concentrations for CAB 400 mg/mL administered Q4W (600 mg for initial injection, 400 mg for second injection) were within the range of the plasma concentrations of approved CAB 200 mg/mL regimens (IM gluteal):
  - C_{max} was lower than steady-state C_{max} observed in the CAB 200 mg/mL Phase 3 FLAIR, ATLAS, and ATLAS-2M studies.[4–6]
  - Trough concentrations were higher than that after the first injection observed in CAB 200 mg/mL dosed Q4W in the Phase 3 FLAIR and ATLAS studies,[4,5] and higher than that at steady state in CAB 200 mg/mL Q8W in the Phase 3 ATLAS-2M study.[6]
- Simulated plasma concentrations for CAB 400 mg/mL administered Q4W (600 mg for initial injection, 400 mg for subsequent injections), regardless of route, were within the range of approved CAB 200 mg/mL regimens (**Figure 2**).
- Dosing intervals longer than 4 weeks were predicted to require a high dosing volume that is impractical.

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.

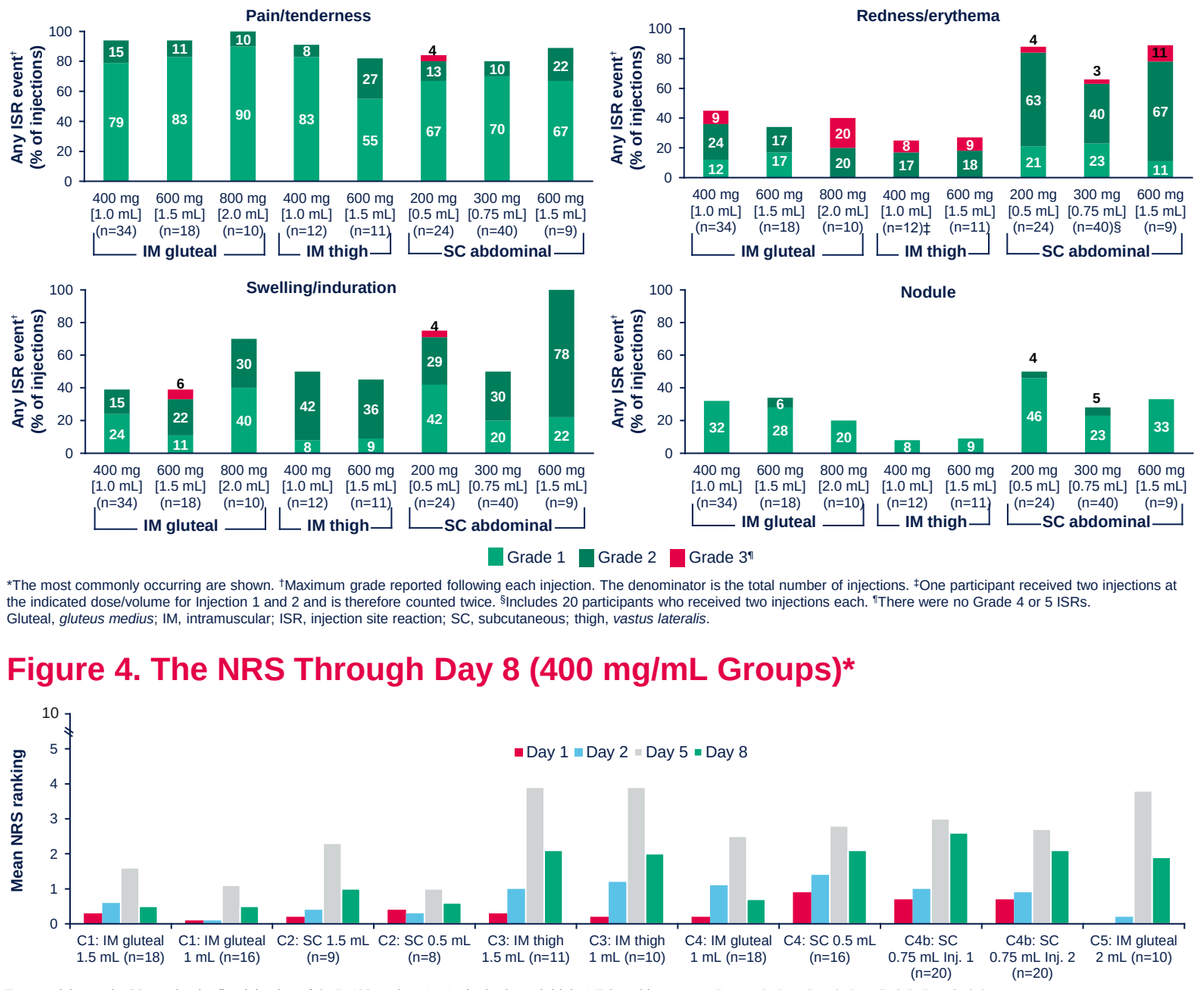
Table 4. Summary of ISR Events

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.

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*Division of AIDS assessment criteria for ISRs used in these Phase 1 studies differ from the current (2017) criteria.

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