SUBCUTANEOUS INJECTIONS OF CABOTEGRAVIR + RILPIVIRINE IN VIRALLY SUPPRESSED ADULTS WITH HIV-1: A SUBSTUDY OF THE PHASE 3 FLAIR STUDY

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Disclosures

- The FLAIR substudy was funded by ViiV Healthcare
- Ronald D’Amico is an employee of ViiV Healthcare and holds GSK stocks

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Background

- 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, as recommended by treatment guidelines for the maintenance of HIV-1 virologic suppression[1–3]
- There is an increased interest in exploring alternative methods of LA administration, including subcutaneous (SC) administration as an option that could potentially enable self-administration at home
- Previous data in healthy volunteers receiving single CAB SC injections were supportive of further evaluations[4,5]
- The Phase 3 FLAIR study (NCT02938520) demonstrated noninferior efficacy of switching from daily oral therapy to monthly CAB + RPV LA at Week 48, with 91% of participants preferring LA therapy[6]
- Here, we present pharmacokinetics (PK), efficacy, safety, tolerability, and patient-reported outcomes from the optional substudy of FLAIR evaluating SC injections of CAB + RPV LA

1. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2024. Available from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf . Accessed April 2024. 2. European AIDS Clinical Society. Guidelines Version 11.1. 2022. Available from: https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf. Accessed April 2024.
3. Ghandi RT, et al. *JAMA*. 2023;329(1):63–84. 4. Spreen W, et al. *J Acquir Immune Defic Syndr*. 2014;67(5):481–486. 5. Spreen W, et al. *J Acquir Immune Defic Syndr*. 2014;67(5):487–492.
6. Orkin, C, et al. *N Engl J Med*. 2020;382(12):1124–1135.

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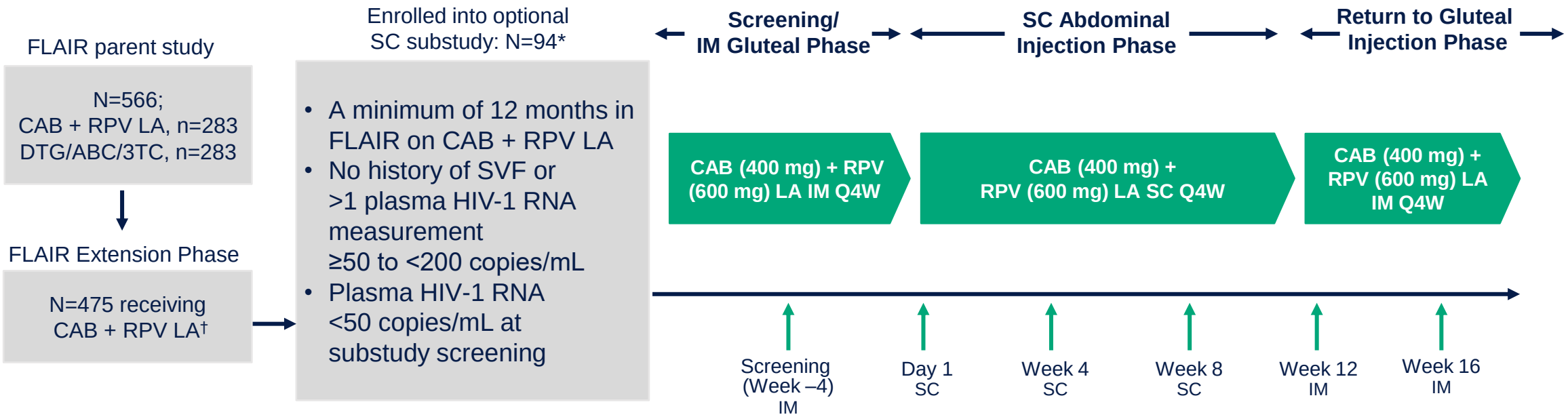
FLAIR SC Substudy Design



- Participants received IM injections during screening, three SC injections from substudy Day 1 to Week 8, and returned to IM injections at substudy Week 12
  - During the SC substudy, the formulation, volume, and injection frequency remained unchanged (Q4W) from the parent study but with a switch from IM gluteal to SC abdominal injections

*Prior to substudy, participants were receiving LA therapy for 3–6 years (40 injections minimum; 73 injections maximum). Includes one participant who enrolled but passed away from unknown reasons during the Screening Phase prior to receiving an SC dose.
†Comprises 243 participants originally randomized to CAB + RPV LA and 232 participants originally randomized to DTG/ABC/3TC who switched to CAB + RPV LA in the Extension Phase.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; IM, intramuscular; LA, long-acting; Q4W, every 4 weeks; RPV, rilpivirine; SC, subcutaneous, SVF, suspected virologic failure.

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Objective and Endpoints

- The primary objective was to compare the PK parameters after SC abdominal injections vs. IM gluteal injections
  - 90% confidence intervals (CIs) for the geometric least squares mean (LSM) ratios of each PK parameter and for each drug (CAB, RPV) were compared to the standard 80–125% boundary of no significant effect
- Secondary endpoints assessed at substudy Week 12 included:
  - The proportion of participants with HIV-1 RNA ≥50 copies/mL and HIV-1 RNA <50 copies/mL (FDA Snapshot algorithm)
  - The proportion of participants with protocol-defined confirmed virologic failure (CVF; two consecutive HIV-1 RNA ≥200 copies/mL)
  - Safety and tolerability
  - Acceptability domain of the Perception of Injection (PIN) questionnaire
  - HIV Treatment Satisfaction Questionnaire status version (HIVTSQs)
  - Treatment preference (preference questionnaire [single question])

CAB, cabotegravir; FDA, U.S. Food and Drug Administration; IM, intramuscular; LA, long-acting; PK, pharmacokinetics; RPV, rilpivirine; SC, subcutaneous.

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Baseline Characteristics of Substudy Participants

Parameter	CAB + RPV LA (N=93)*
Median age, years (range)	42 (25–69)
≥50 years, n (%)	21 (23)
Female (sex at birth), n (%)	18 (19)
Race, n (%)	
Black or African American	19 (20)
White	64 (69)
Other races†	10 (11)
Hispanic/Latinx, n (%)	10 (11)
Median BMI, kg/m^2 (range)	26.20 (18.19–44.86)

- Baseline characteristics of the substudy were representative of the FLAIR parent study
- Overall, 93 participants received SC injections; 19% were female (sex at birth), 23% were ≥50 years, and 20% were Black or African American

*Excludes one participant who enrolled but passed away before receiving an SC dose.
†Other race participants: American Indian or Alaska Native, n=2; Asian, n=6; multiple, n=2.
BMI, body mass index; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; SC, subcutaneous.

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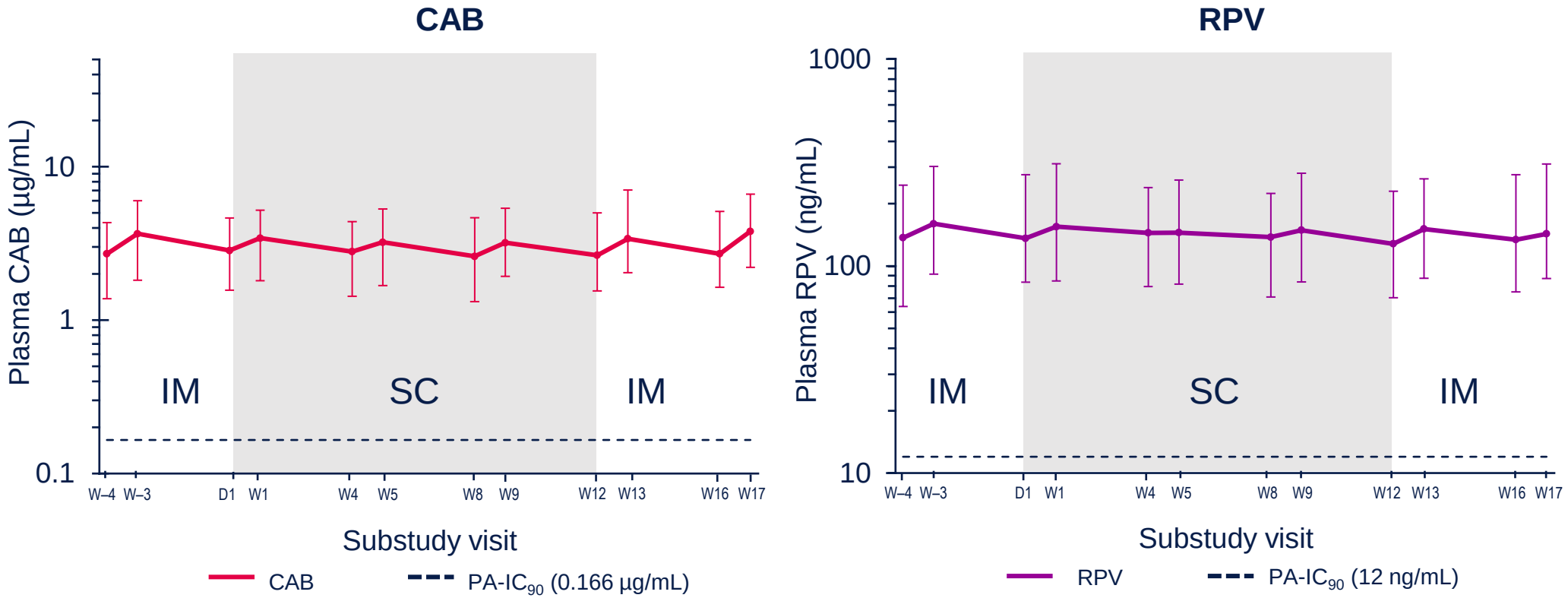
CAB and RPV Plasma Concentration–Time Plots*



- Throughout SC dosing, plasma trough concentrations for CAB and RPV remained similar to trough concentrations during IM dosing

*The graphs show median (5th and 95th percentile) CAB and RPV plasma concentrations through Week 17. CAB: W–4, W–3, and D1, n=92; W1, n=93; W4, n=89; W5, n=91; W8, W9, W12, W13, and W16, n=87; W17, n=86. RPV: W–4 and W1, n=93; W–3, D1, and W5, n=91; W4, n=90; W8, W9, and W12, n=87; W13 and W16, n=86; W17, n=85. Grey shaded area corresponds to SC Injection Phase.
CAB, cabotegravir; D, day; IM, intramuscular; PA-IC_{90}, protein-adjusted 90% inhibitory concentration; RPV, rilpivirine; SC, subcutaneous; W, week.

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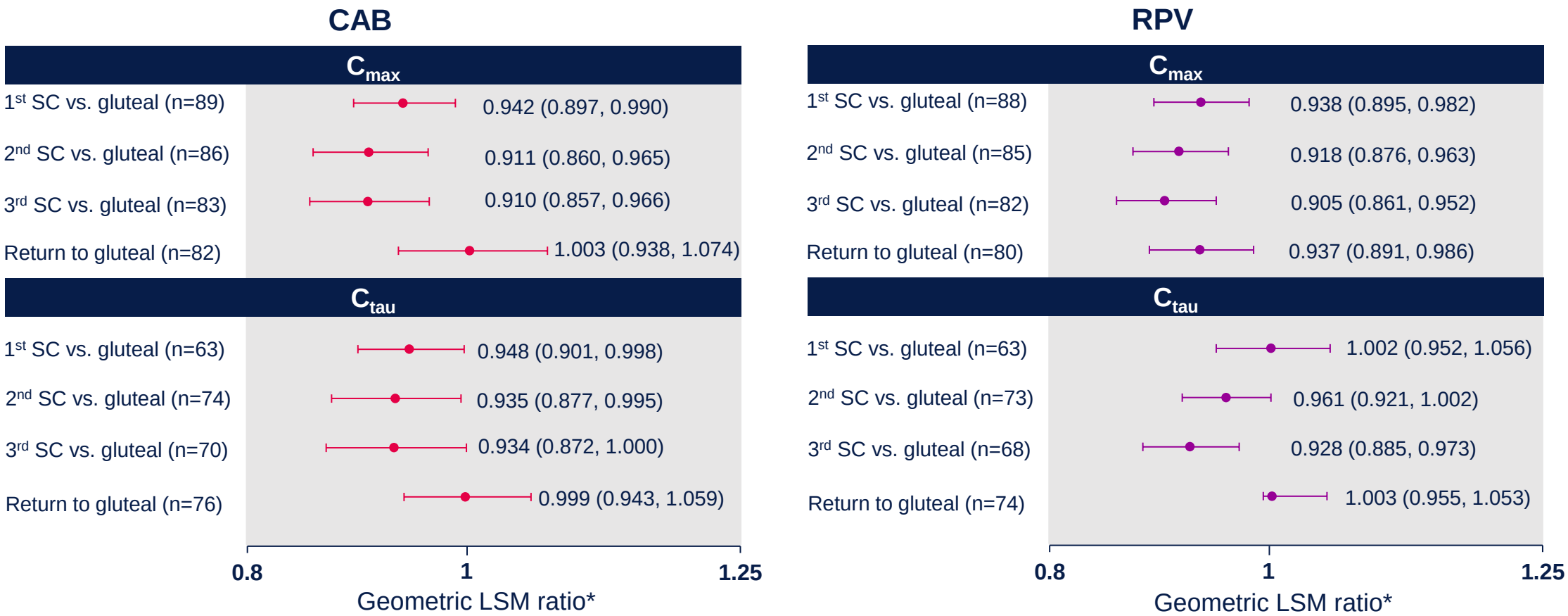
Comparable PK Exposures with SC vs. IM Administration



- CAB and RPV plasma exposures were generally comparable between SC and IM injections, with 90% CIs of geometric LSM ratios all contained within 0.80–1.25 range

*Values displayed are geometric LSM ratios (90% CIs) between each injection vs. the IM injection immediately prior to the first SC injection. Return to gluteal: the IM injection immediately following the third (final) SC injection vs. the IM injection immediately prior to the first SC injection. CAB, cabotegravir; CI, confidence interval; C_{max}, plasma concentration approximately 1 week post injection; C_{tau}, plasma concentration at the end of the dosing interval; IM, intramuscular; LSM, least squares mean; PK, pharmacokinetics; RPV, rilpivirine; SC, subcutaneous.

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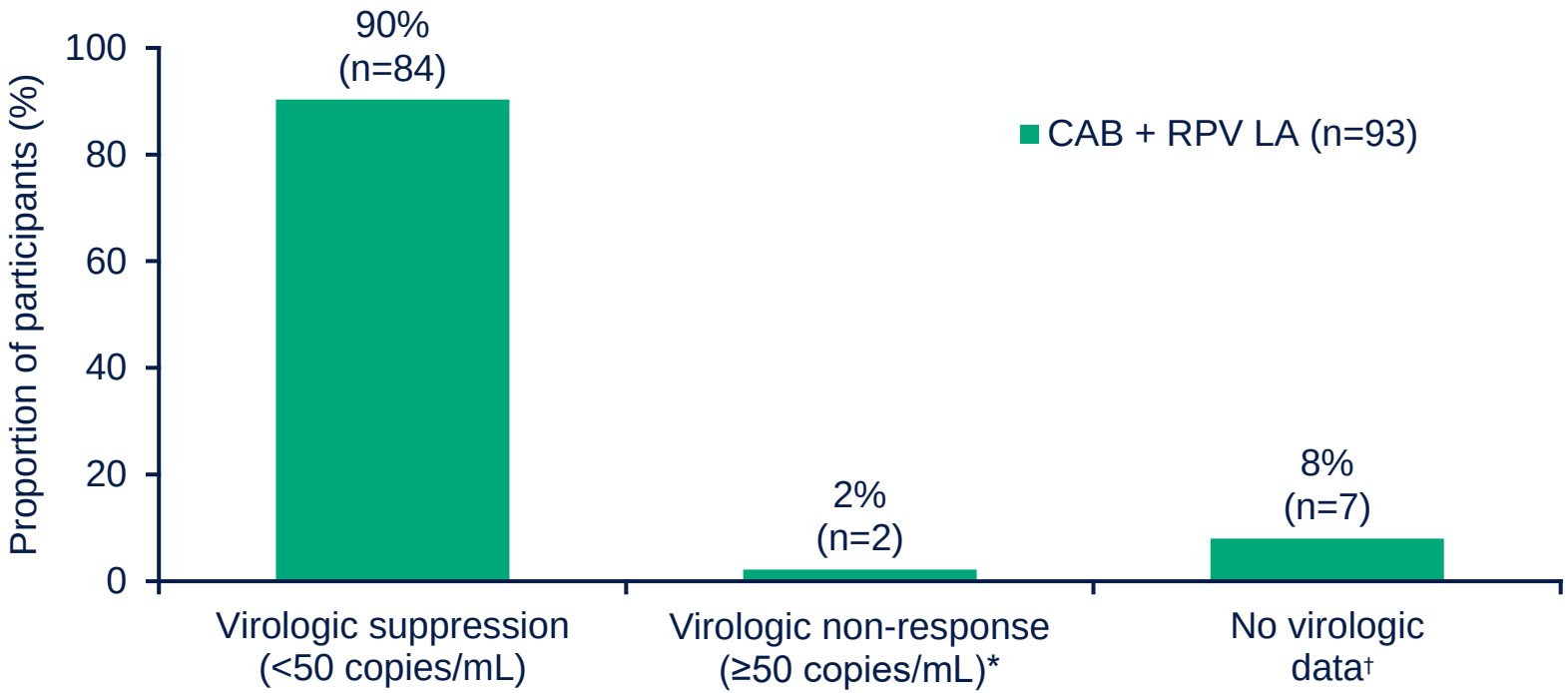
Virologic Outcomes (Snapshot) at Week 12



- At the end of the SC Injection Phase (substudy Week 12), 90% of participants maintained virologic suppression, with 2% having HIV-1 RNA ≥50 copies/mL
- No participants met the CVF criterion (two consecutive HIV-1 RNA ≥200 copies/mL) during the substudy

*One participant had plasma HIV-1 RNA ≥50 copies/mL at substudy Week 12 (81 copies/mL) and resuppressed at the subsequent visit (substudy Week 16); the participant transitioned to commercial CAB + RPV LA after substudy completion. The second participant had plasma HIV ≥50 copies/mL at substudy Week 8 (86 copies/mL), Week 12 (54 copies/mL), and Week 16 (148 copies/mL); after completing the substudy, the participant transitioned to darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

†Discontinued due to AE, n=2; discontinued for other reason, n=4 (protocol deviation, n=2; withdrawal by participant, n=2); on study but missing data in window, n=1.

AE, adverse event; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; RPV, rilpivirine; SC, subcutaneous.

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Safety Summary (SC Injection Phase)

Parameter	CAB + RPV LA (n=93)
Number of injections, n	542
ISR events, n*	816
Pain, n (% of injections)	260 (48)
Nodule, n (% of injections)	183 (34)
Erythema, n (% of injections)	142 (26)
Induration, n (% of injections)	66 (12)
Swelling, n (% of injections)	66 (12)
Grade 3, n (% of ISR events)†	17 (2)
Median duration, days (IQR)	10 (4, 29)
Participant withdrawal due to injection-related reasons, n (% of participants with injections)‡	5 (5)

- Most injection site reactions (ISRs) were Grade 1–2 (98%) and had a median duration of 10 days, with five participants withdrawing from the substudy due to injection-related reasons (5%)
- The median duration of nodule, induration, and erythema ISRs was longer with SC injections vs. IM injections (39 vs. 9 days, 33 vs. 26 days, and 11 vs. 4 days, respectively)
- Excluding ISRs, drug-related adverse events (AEs) were acute sinusitis/viral gastroenteritis (n=1), respiratory tract infection (n=1), fatigue (n=1), and scar (n=1) (all Grade 1); no serious AEs occurred and no non-ISR AEs led to withdrawal

*Top five most commonly reported ISRs are listed. Participants may have multiple ISR events following a single injection. †No Grade 4 or 5 ISRs occurred. ‡Includes: erythema, n=3; nodule, n=3; pain, n=3; swelling, n=2; warmth, n=2; discoloration, n=1; hematoma, n=1; induration, n=1; pruritus, n=1. Participants may have discontinued due to more than one ISR. Also includes an additional participant who withdrew from the study citing injection intolerability.
AE, adverse event; CAB, cabotegravir; IM, intramuscular; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine; SC, subcutaneous.

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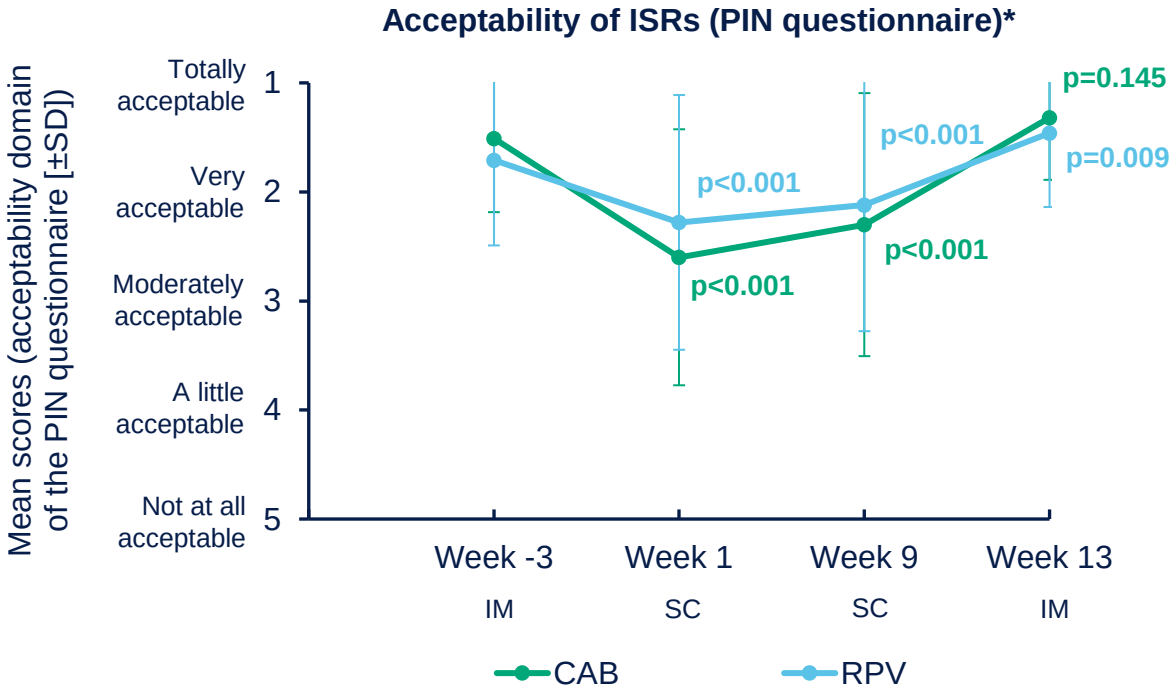
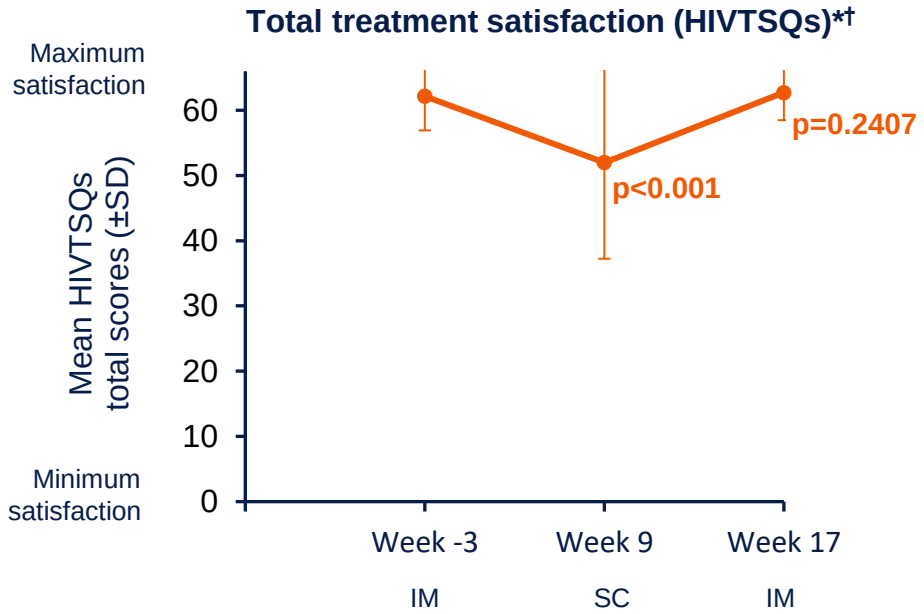
Patient-Reported Outcomes





- Participants reported statistically lower acceptance (acceptability domain of PIN; at Weeks 1 and 9) and treatment satisfaction (HIVTSQs; at Week 9) scores with SC administration compared with IM administration at baseline (Week –3)
  - This is consistent with the high percentage of pain, nodule, and erythema ISR events reported with SC administration, as well as high overall treatment satisfaction with IM administration

*Week –3 and Week 1, n=93; Week 9 and Week 13, n=87; Week 17, n=86.
†HIVTSQs: 12-item version; range per item 0–6, in which 0 = "very dissatisfied" and 6 = "very satisfied." Total score = sum of items 1–11; range for total score 0 (minimum) to 66 (maximum).
CAB, cabotegravir; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; IM, intramuscular; ISR, injection site reaction; PIN, Perception of Injection; RPV, rilpivirine; SC, subcutaneous; SD, standard deviation.

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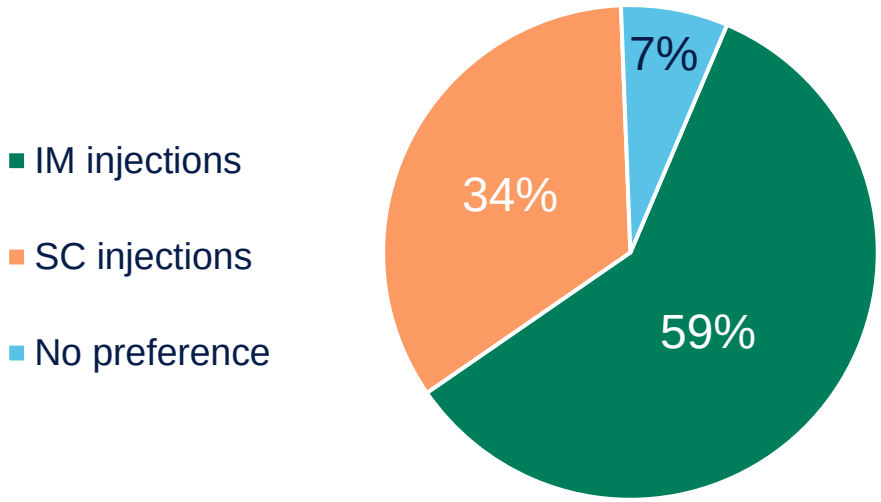
Patient-Reported Outcomes

"Which injection site do you prefer"
(1 week following 3rd SC injection)
(n=85)



Common reasons given for preference

IM injections:
- Less injection site swelling (58%, n=29/50), nodules (58%, n=29/50), and pain (54%, n=27/50)

SC injections:
- Convenience (86%, n=25/29) and injections not interfering with daily activities (59%, n=17/29)

- One week after receiving three SC injections (at substudy Week 9), 59% (n=50/85) of participants preferred IM injections and 34% (n=29/85) preferred SC injections

IM, intramuscular; SC, subcutaneous.

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Conclusions

- CAB and RPV PK parameters following 12 weeks of SC abdominal injections were similar to those following IM gluteal injections
- Efficacy results were consistent with the overall FLAIR study[1]
- SC injections led to a higher incidence and longer duration of ISRs, resulting in lower acceptability of, and satisfaction with, SC injections compared with IM injections
- Most participants (59%) favored IM administration over SC administration
- Further development of this treatment regimen for SC self-administration will not be pursued
- ViiV Healthcare remains committed to evaluating alternative assets for the potential for self-administration

1. Orkin, C, et al. *N Engl J Med*. 2020;382(12):1124–1135.
CAB, cabotegravir; IM, intramuscular; ISR, injection site reaction; LA, long-acting; PK, pharmacokinetics; RPV, rilpivirine; SC, subcutaneous.

Acknowledgments

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Backup slides

Safety Summary (SC Injection Phase)

Parameter, n (%)	CAB + RPV LA (n=93)
Any AE	90 (97)
Excluding ISRs	46 (49)
Any drug-related AE	84 (90)
Excluding ISRs	4 (4)
Any Grade ≥3 AE	7 (8)
Excluding ISRs*	1 (1)
Any drug-related Grade ≥3 AE†	6 (6)
Any serious AEs	0
AEs leading to withdrawal	5 (5)
Excluding ISRs	0

- ISRs accounted for the majority of AEs; no serious AEs occurred
- Excluding ISRs, drug-related AEs were acute sinusitis/viral gastroenteritis (n=1), respiratory tract infection (n=1), fatigue (n=1), and scar (n=1) (all Grade 1)

*A lab abnormality (lipase increased, n=1) that the investigator chose to report as an AE.
†Drug-related Grade ≥3 AEs included injection site erythema (n=5), injection site pain (n=2), injection site induration (n=2), injection site nodule (n=1), injection site swelling (n=1), and injection site warmth (n=1); participants may have had more than one event. No Grade 4 or Grade 5 AEs were reported.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine; SC, subcutaneous.

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