EPB182

Long-Acting Cabotegravir + Rilpivirine Injection Site Reactions: Pooled Week 96 Results

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Key Takeaways

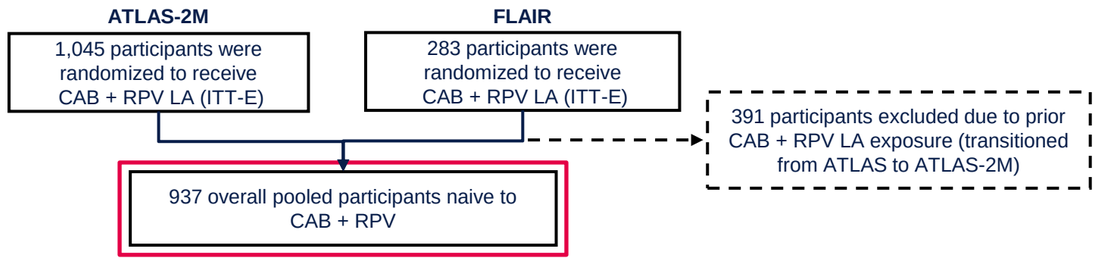
- This work evaluated the characteristics of injection site reactions (ISRs) including type, duration, severity, and outcome through Week 96, stratified by patient demographics for participants receiving long-acting cabotegravir + rilpivirine (CAB + RPV LA) dosed every 4 weeks (Q4W) or every 8 weeks (Q8W) across two Phase 3/3b trials.
- In total, 8,453 ISRs were reported across 34,939 injections; the incidence, type, and severity of ISRs reported were generally comparable by dosing regimen, drug, sex at birth, baseline body mass index (BMI) category, and race.
- Most ISRs were mild to moderate in severity, short-lived, decreased in frequency over time, and rarely led to withdrawal, demonstrating favorable tolerability with injections dosed monthly and every 2 months over the long term.

Introduction

- CAB + RPV is the first complete, LA injectable regimen recommended by treatment guidelines[1–3] for the maintenance of HIV-1 virologic suppression.
- In the Phase 3/3b development program, CAB + RPV LA dosed Q4W was noninferior to daily oral therapy, and CAB + RPV LA dosed Q8W was noninferior to Q4W dosing.[4–8]
- Across the Phase 3/3b trials, the most frequently reported adverse events were ISRs.[4–8]
- Here, we present long-term pooled ISR outcomes from the Phase 3/3b trials, evaluated by dosing regimen and participant demographics from the ATLAS-2M (NCT03299049)[7,8] and FLAIR (NCT02938520)[5,6] studies through Week 96.

Methods

Figure 1. Analysis Schematic



CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

- Pooled ISR data from ATLAS-2M (n=654) and FLAIR (n=283) were evaluated by dosing regimen, drug, sex at birth, BMI, and race (**Figure 1**).
  - Participants in ATLAS-2M who transitioned from the ATLAS CAB + RPV LA arm were excluded to ensure all participants included in the analysis had only 96 weeks of CAB + RPV LA follow-up.
- Healthcare providers (HCPs) were required to identify and report any new or resolving ISRs prior to and following administration of intramuscular LA therapy, from a pre-identified list or as free text.
- In this analysis, we evaluated the characteristics of ISRs including type, duration, and severity using the Division of Acquired Immunodeficiency Syndrome grading system (Grades 1–5), and outcome through Week 96.
  - Each ISR event was counted separately; a participant may have had multiple ISR events following a single injection.

Results

Table 1. Baseline Characteristics by Dosing Regimen

	CAB + RPV LA		
	Total (N=937)	Q8W (n=327)	Q4W (n=610)
Number of participants receiving ≥1 injection (%)	920 (98)	321 (98)	599 (98)
Age, mean years (SD)	40.3 (11.2)	42.6 (11.5)	39.1 (10.9)
Age group, n (%)			
<50 years	715 (78)	234 (73)	481 (80)
50–64 years	188 (20)	75 (23)	113 (19)
≥65 years	17 (2)	12 (4)	5 (<1)
Sex at birth, n (%)			
Female	201 (22)	70 (22)	131 (22)
Male	719 (78)	251 (78)	468 (78)
Race, n (%)			
Black or African American	147 (16)	57 (18)	90 (15)
White	698 (76)	234 (73)	464 (77)
Asian	39 (4)	16 (5)	23 (4)
Other race*	36 (4)	14 (4)	22 (4)
BMI at baseline, median kg/m^2 (IQR)	24.9 (22.6–28.0)	25.3 (22.8–28.6)	24.8 (22.5–27.8)
<30 kg/m^2, n (%)	770 (84)	262 (82)	508 (85)
≥30 kg/m^2, n (%)	150 (16)	59 (18)	91 (15)

*"Other race" category included participants who were American Indian or Alaska Natives (n=23/36, 64%), Native Hawaiian or other Pacific Islanders (n=4/36, 11%), or of multiple races (n=9/36, 25%).
BMI, body mass index; CAB, cabotegravir; IQR, interquartile range; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SD, standard deviation.

- Most participants were <50 years of age (78%), male (sex at birth) (78%), White (76%), with a BMI <30 kg/m^2 (84%) (**Table 1**).
- Baseline characteristics were broadly similar between treatment groups.

Table 2. ISR Events Through Week 96 by Dosing Regimen and Drug

	CAB + RPV LA Dosing Regimen		Drug*	
Parameter	Q8W (n=327)	Q4W (n=610)	CAB (n=937)	RPV (n=937)
Number of participants receiving ≥1 injection (%)	321 (98)	599 (98)	920 (98)	920 (98)
Number of injections	7,954	26,985	17,468	17,471
ISR events,† n	2,345	6,108	3,836	4,606
Pain, n (% of injections)	1,904 (24)	5,035 (19)	3,142 (18)	3,789 (22)
Nodule, n (% of injections)	107 (1)	355 (1)	213 (1)	249 (1)
Induration, n (% of injections)	61 (<1)	208 (<1)	130 (<1)	139 (<1)
Discomfort, n (% of injections)	113 (2)	107 (<1)	112 (<1)	107 (<1)
Swelling, n (% of injections)	56 (<1)	85 (<1)	65 (<1)	76 (<1)

*As per the trial protocols, HCPs were advised to administer CAB and RPV injections on different sides of the body (e.g. left or right *gluteus medius*), or spaced approximately 2 cm from one another, from the site of any previous injection, or from any previous ISRs. The time, side, and location of CAB and RPV injections were reported. †Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. Top five most common ISRs reported. Less common ISR events reported included: pruritus (n=131), warmth (n=81), erythema (n=67), bruising (n=43), anesthesia (n=21), hematoma (n=21), reaction (n=18), discoloration (n=10), hemorrhage (n=5), abscess (n=4), rash (n=3), necrosis (n=3), fibrosis (n=2), discharge (n=2), papule (n=2), cyst (n=2), movement impairment (n=2), scar (n=2), mass (n=1), hypoesthesia (n=1), granuloma (n=1).
CAB, cabotegravir; HCP, healthcare provider; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- The most commonly reported ISRs (% of injections) were: injection site pain (20%), nodule (1%), and induration (1%).
  - Injection site necrosis (<1%, n=3), injection site fibrosis (<1%, n=2), and injection site scars (<1%, n=2) were very rarely reported.
- The frequency of ISRs was generally comparable by drug, with slightly numerically more injection site pain events reported with RPV compared with CAB.
- Most ISRs were mild to moderate in severity (Grade 1, 83%; Grade 2, 16%; Grade 3, 1%); the few Grade 3 ISRs included pain (1%), induration (<1%), swelling (<1%), and discomfort (3%). There were no Grade 4 or 5 ISR events reported.
- The 462 injection site nodule events were reported by 19% (n=178/920) of all participants who received ≥1 injection.
  - Of all nodule events reported, 80% (n=373/462) occurred in the same 89 participants.

Table 3. ISR Events Through Week 96 by Demographics

	Sex at Birth		Baseline BMI Category		Race			
Parameter	Female (n=211)	Male (n=726)	BMI <30 kg/m^2 (n=786)	BMI ≥30 kg/m^2 (n=151)	White (n=711)	Black or African American (n=149)	Asian (n=41)	Other race* (n=36)
Number of participants receiving ≥1 injection (%)	201 (95)	719 (99)	770 (98)	150 (99)	698 (98)	147 (99)	39 (95)	36 (100)
Number of injections	7,617	27,322	29,428	5,511	26,587	5,630	1,360	1,362
ISR events,† n	1,840	6,613	7,304	1,149	6,655	911	435	452
Pain, n (% of injections)	1,322 (17)	5,617 (21)	6,062 (21)	877 (16)	5,520 (21)	705 (13)	378 (28)	336 (25)
Nodule, n (% of injections)	121 (2)	341 (1)	381(1)	81 (1)	286 (1)	88 (2)	30 (2)	58 (4)
Induration, n (% of injections)	156 (2)	113 (<1)	235 (<1)	34 (<1)	246 (<1)	11 (<1)	4 (<1)	8 (<1)
Discomfort, n (% of injections)	18 (<1)	202 (<1)	162 (<1)	58 (1)	192 (<1)	18 (<1)	5 (<1)	5 (<1)
Swelling, n (% of injections)	45 (<1)	96 (<1)	119 (<1)	22 (<1)	94 (<1)	36 (1)	2 (<1)	9 (<1)

*"Other race" category included participants who were American Indian or Alaska Natives (n=23/36, 64%), Native Hawaiian or other Pacific Islanders (n=4/36, 11%), or of multiple races (n=9/36, 25%). †Top five most common ISRs overall reported. Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection.
BMI, body mass index; ISR, injection site reaction.

- Frequency and type of ISRs reported were generally similar across groups, with slightly numerically fewer injection site pain events reported in female (sex at birth) participants, participants with BMI ≥30 kg/m^2, and Black or African American participants (**Table 3**).
- The severity of ISRs reported was generally similar across regimen, sex at birth, BMI, and race, with 97–99% of ISRs being Grade 1 or Grade 2.

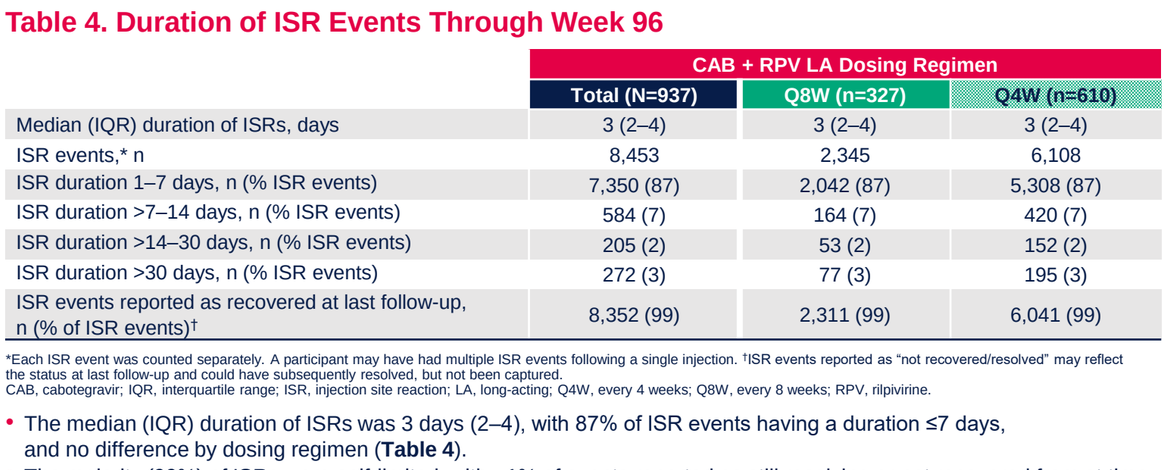
Table 4. Duration of ISR Events Through Week 96

	CAB + RPV LA Dosing Regimen		
	Total (N=937)	Q8W (n=327)	Q4W (n=610)
Median (IQR) duration of ISRs, days	3 (2–4)	3 (2–4)	3 (2–4)
ISR events,* n	8,453	2,345	6,108
ISR duration 1–7 days, n (% ISR events)	7,350 (87)	2,042 (87)	5,308 (87)
ISR duration >7–14 days, n (% ISR events)	584 (7)	164 (7)	420 (7)
ISR duration >14–30 days, n (% ISR events)	205 (2)	53 (2)	152 (2)
ISR duration >30 days, n (% ISR events)	272 (3)	77 (3)	195 (3)
ISR events reported as recovered at last follow-up, n (% of ISR events)†	8,352 (99)	2,311 (99)	6,041 (99)

*Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. †ISR events reported as "not recovered/resolved" may reflect the status at last follow-up and could have subsequently resolved, but not been captured.
CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- The median (IQR) duration of ISRs was 3 days (2–4), with 87% of ISR events having a duration ≤7 days, and no difference by dosing regimen (**Table 4**).
- The majority (99%) of ISRs were self-limited, with ~1% of events reported as still resolving or not recovered from at time of data analysis.
  - ISR events reported as "not recovered/resolved" (n=28) consisted of pain (n=9), pruritus (n=7), nodule (n=6), discomfort (n=2), fibrosis (n=2), induration (n=1), and necrosis (n=1).
  - ISR events reported as "recovered with sequelae" consisted of pain (69%, n=41/59), induration (10%, n=6/59), nodule (5%, n=3/59), swelling (5%, n=3/59), and discomfort (2%, n=1/59).

Figure 2. Duration of ISR Events Through Week 96 by ISR*



*Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. Top five most common ISRs reported. †"Other race" category included participants who were American Indian or Alaska Natives (n=23/36, 64%), Native Hawaiian or other Pacific Islanders (n=4/36, 11%), or of multiple races (n=9/36, 25%). The proportion of participants reporting injection site nodule events was higher in participants of "Other race" compared with Black or African American, White, and Asian participants; however, the number of participants of "Other race" in the analysis was low (n=36/937).
ISR, injection site reaction.

- Among injection site pain (accounting for 82% of all ISRs) and discomfort events (3% of all ISRs), most (92%) resolved in ≤7 days; among injection site swelling (2% of all ISRs), induration (3% of all ISRs), and nodule events (5% of all ISRs), 41–67% recovered in ≤7 days (**Figure 2**).
- Injection site nodule and injection site induration events were reported to have taken the longest to resolve; most of these events were Grade 1 or 2 in severity, with a single Grade 3 event of injection site induration reported.
  - The median time to resolution of injection site nodule and injection site induration events was 9 and 8 days, respectively.
  - Of the 462 injection site nodule events, which were reported by 19% (n=178/920) of all participants, reporting was similar by BMI and drug; however, nodule events were reported by a slightly higher proportion of female vs. male (sex at birth) participants (24% vs. 18%, respectively), participants of Other race (44%†), and numerically more participants receiving Q4W vs. Q8W dosing (23% vs. 13%, respectively).

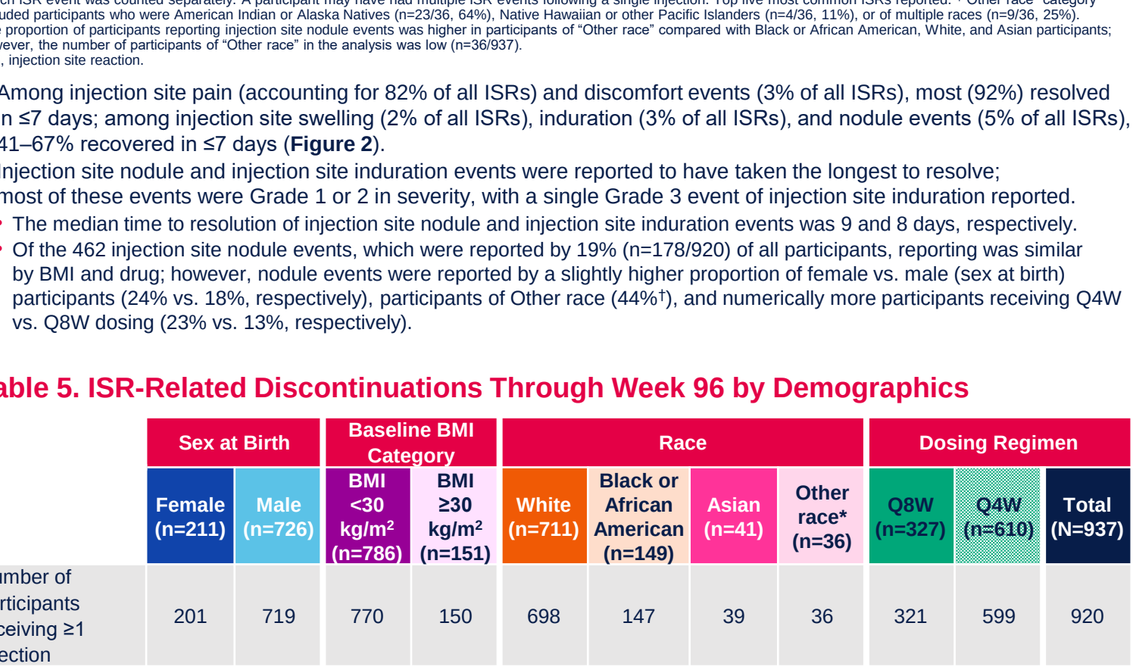
Table 5. ISR-Related Discontinuations Through Week 96 by Demographics

	Sex at Birth		Baseline BMI Category		Race				Dosing Regimen		
	Female (n=211)	Male (n=726)	BMI <30 kg/m^2 (n=786)	BMI ≥30 kg/m^2 (n=151)	White (n=711)	Black or African American (n=149)	Asian (n=41)	Other race* (n=36)	Q8W (n=327)	Q4W (n=610)	Total (N=937)
Number of participants receiving ≥1 injection	201	719	770	150	698	147	39	36	321	599	920
Participants withdrawing due to injection-related reasons, n (% of participants with injections)†	2 (<1)	18 (2)	19 (2)	1 (<1)	15 (2)	1 (<1)	4 (10)‡	0	5 (2)	15 (3)	20 (2)

*"Other race" category included participants who were American Indian or Alaska Natives (n=23/36, 64%), Native Hawaiian or other Pacific Islanders (n=4/36, 11%), or of multiple races (n=9/36, 25%). †Calculated as the percentage of participants receiving ≥1 injection. ‡The rate of withdrawals due to injection-related reasons was numerically higher in Asian participants than in other race categories; however, the number of Asian participants in the analysis was low (n=41/937).
BMI, body mass index; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

- Withdrawals due to injection-related reasons (due to one or more ISR events [n=10] or due to injection intolerability [n=10]) were infrequent (2%, n=20/920) and comparable between dosing regimens (**Table 5**).

Figure 3. ISRs Over Time by CAB + RPV Dosing Regimen Through Week 96*



*Incidence is derived relative to the number of participants who received injections at each respective study visit. Adverse event grade is the maximum grade reported by the participant at each visit.
CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

- ISRs decreased in incidence over time, being reported by 71%, 24%, and 15% of participants at Week 4, Week 48, and Week 96, respectively, and were comparable between dosing regimens (**Figure 3**).

Conclusions*

- Among 34,939 CAB + RPV LA injections administered in the ATLAS-2M and FLAIR trials, 8,453 ISR events were reported through Week 96.
- Injection site pain was the most commonly reported ISR (20% of injections), followed by nodules, induration, discomfort, and swelling (all ≤1%).
- The incidence, type, and severity of ISRs reported were generally comparable by dosing regimen, drug, sex at birth, baseline BMI category, and race.
- The incidence of ISR events decreased over time through Week 96; the majority of ISRs were mild to moderate in severity, short-lived, and infrequently a cause of treatment discontinuation, and most participants recovered fully within 7 days.
- This analysis further supports the use of CAB + RPV LA monthly or every 2 months as a complete regimen for the maintenance of HIV-1 virologic suppression, and favorable tolerability with injections dosed monthly and every 2 months over the long term.

*For tips on optimal administration of CAB + RPV LA injections, please refer to Poster EPB181: "Give it a shot: Best practices from HCPs for administering long-acting cabotegravir and rilpivirine."

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References: 1. Saag MS, et al. *JAMA*. 2020;324(16):1651–1669. **2.** 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. Accessed June 2022. **3.** European AIDS Clinical Society. Guidelines Version 11.0. 2021. Available from: https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf. Accessed June 2022. **4.** Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123. **5.** Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135. **6.** Orkin C, et al. *Lancet HIV*. 2021;8(4):e185–e196. **7.** Overton ET, et al. *Lancet*. 2021;396(10267):1994–2005. **8.** Jaeger H, et al. *Lancet HIV*. 2021;8(11):e679–e689.

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