Phase 3/3b Experience With Long-Acting Cabotegravir and Rilpivirine: Efficacy and Safety Outcomes Through Week 96 by Race

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Introduction

- Long-acting cabotegravir + rilpivirine (CAB + RPV LA) administered monthly[1,2] or every 2 months (Q2M)[3] is the first and only complete LA injectable maintenance regimen recommended by treatment guidelines for people living with HIV-1 with virological suppression[4,5]
- CAB + RPV LA dosed every 4 weeks (Q4W) was noninferior to daily oral antiretroviral therapy (ART) (Week 96) and every 8 weeks (Q8W) dosing was noninferior to Q4W (Week 152) in Phase 3/3b trials[1–3,6–8]
- Racial disparities in treatment outcomes are multifactorial and may be influenced by demographic, clinical, socioeconomic, and adherence factors;[9] these may be further compounded by the underrepresentation of non-White participants in clinical trials[10]
- This *post hoc* analysis summarizes pooled efficacy and safety outcomes stratified by race for participants in the FLAIR* and ATLAS-2M† global Phase 3/3b studies through Week 96

*NCT02938520. †NCT03299049.
ART; antiretroviral therapy; CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
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Methods

- Data from randomized participants who received CAB + RPV LA dosed Q4W in FLAIR, or dosed Q4W or Q8W in ATLAS-2M, were pooled and stratified by self-reported race (White, Black, Asian, or Other* races)
  - Participants in ATLAS-2M who transitioned from the ATLAS† CAB + RPV arm were excluded to ensure all participants included in the analysis had only 96 weeks of CAB + RPV follow-up

Endpoints assessed at Week 96 in this *post hoc* analysis:

- The proportion of participants with plasma HIV-1 RNA ≥50 copies/mL (FDA Snapshot)
- The proportion of participants with plasma HIV-1 RNA <50 copies/mL (FDA Snapshot)
- Incidence of confirmed virologic failure (CVF; two consecutive HIV-1 RNA measurements of ≥200 copies/mL)
- Safety and tolerability
- Treatment satisfaction (HIV Treatment Satisfaction Questionnaire status version [HIVTSQs]; FLAIR participants only)

*Other race participants: American Indian or Alaska Native, n=23; Native Hawaiian or other Pacific Islander, n=4; multiple, n=9. †NCT02951052.
CAB, cabotegravir; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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Baseline Characteristics

ITT-E population	CAB + RPV LA Q8W + Q4W pooled (n=937)			
	White* (n=711, 76%)	Black (n=149, 16%)	Asian† (n=41, 4%)	Other races‡ (n=36, 4%)
Median age (range), years	39 (19–71)	39 (20–83)	39 (21–68)	35.5 (22–59)
Female sex at birth, n (%)	137 (19)	66 (44)	4 (10)	4 (11)
Hispanic or Latinx, n (%)	91 (13)	7 (5)	0	25 (69)
Median body mass index (IQR), kg/m^2	24.8 (22.5–27.5)	27.5 (24.1–31.9)	22.7 (20.6–24.5)	25.1 (22.4–28.1)
≥30 kg/m^2, n (%)	95 (13)	49 (33)	1 (2)	6 (17)
Region, n (%)				
North America	193 (27)	76 (51)	11 (27)	9 (25)
European Union	380 (53)	24 (16)	4 (10)	16 (44)
Other§	138 (19)	49 (33)	26 (63)	11 (31)

- At baseline (Day 1), 937 participants received CAB + RPV LA (Q8W, n=327; Q4W, n=610)
- Overall, 76% (n=711) of participants were White; 13% (n=123) of participants were of Hispanic or Latinx ethnicity
- The median age (range) was 39 years (19–83), and 23% (n=211) were female (sex at birth)

*White participants: Arabic/North African heritage, n=11; White/Caucasian/European heritage, n=699; mixed White race, n=1. †Asian participants: Central/South Asian heritage, n=4; East Asian heritage, n=20; Japanese heritage, n=10; South East Asian heritage, n=7. ‡Other race participants: American Indian or Alaska Native, n=23; Native Hawaiian or other Pacific Islander, n=4; multiple, n=9. §Argentina, Australia, Japan, Mexico, Republic of Korea, Russian Federation, and South Africa.
CAB, cabotegravir; IQR, interquartile range; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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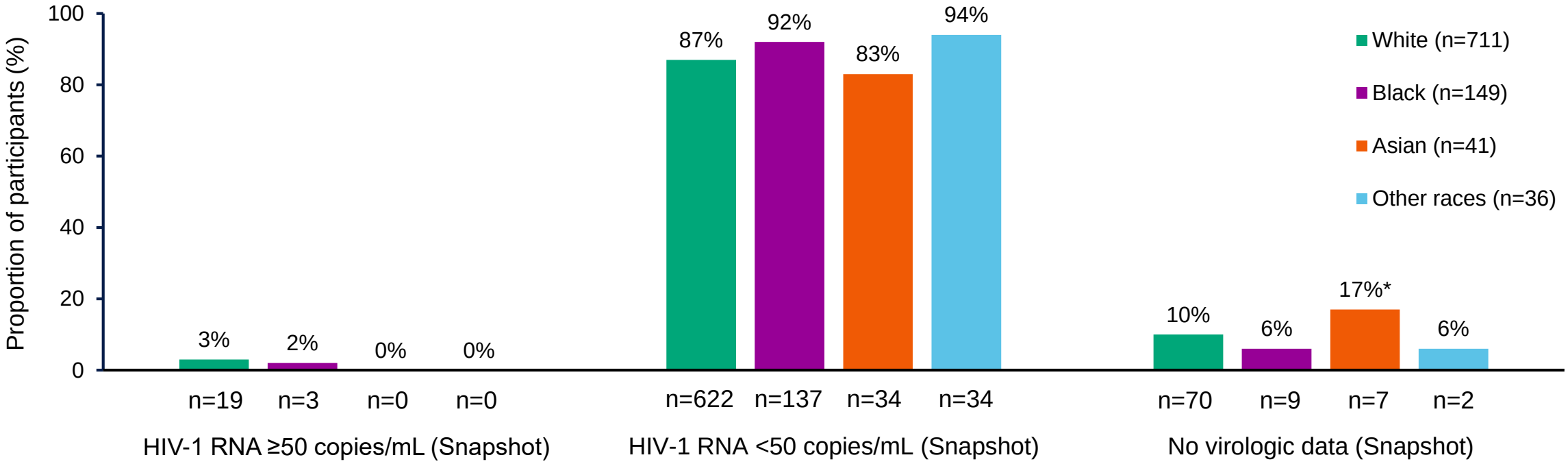
Virologic Response at Week 96 (Snapshot, ITT-E)



- At Week 96, rates of virologic non-response (HIV-1 RNA ≥50 copies/mL) and suppression (HIV-1 RNA <50 copies/mL) with CAB + RPV LA dosed Q8W or Q4W were similar across races

*The proportion of participants with no virologic data due to discontinuations 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).
CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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Snapshot Outcomes at Week 96

Parameter, n (%);	CAB + RPV LA Q8W + Q4W pooled (n=937)			
	White (n=711)	Black (n=149)	Asian (n=41)	Other races (n=36)
HIV-1 RNA <50 copies/mL (Snapshot)	622 (87)	137 (92)	34 (83)	34 (94)
HIV-1 RNA ≥50 copies/mL (Snapshot)	19 (3)	3 (2)	0	0
Data in window not below threshold	6 (<1)	0	0	0
Discontinued for lack of efficacy	11 (2)	3 (2)	0	0
Discontinued for other reason while not below threshold	2 (<1)	0	0	0
No virologic data (Snapshot)	70 (10)	9 (6)	7 (17)	2 (6)
Discontinued study due to AE*	30 (4)	3 (2)	3 (7)	2 (6)
Discontinued for other reason	37 (5)	6 (4)	4 (10)†	0
On study but missing data in window	3 (<1)	0	0	0

- Rates of virologic non-response and suppression ranged 0–3% and 83–94%, respectively, across races
- Of the 151 participants (16%) with BMI ≥30 kg/m^2, 87% maintained virologic suppression through Week 96‡

*There were no deaths. †Frequency of visits (n=1), intolerability of injections (n=1), participant relocated (n=1), concern for participant planning future pregnancy (n=1).
‡Through Week 48, 77% of injections were administered using a 1.4–1.6 inch needle for participants with a BMI ≥30 kg/m^2. 88% of participants with BMI <30 kg/m^2 maintained virologic suppression through Week 96.
AE, adverse event; BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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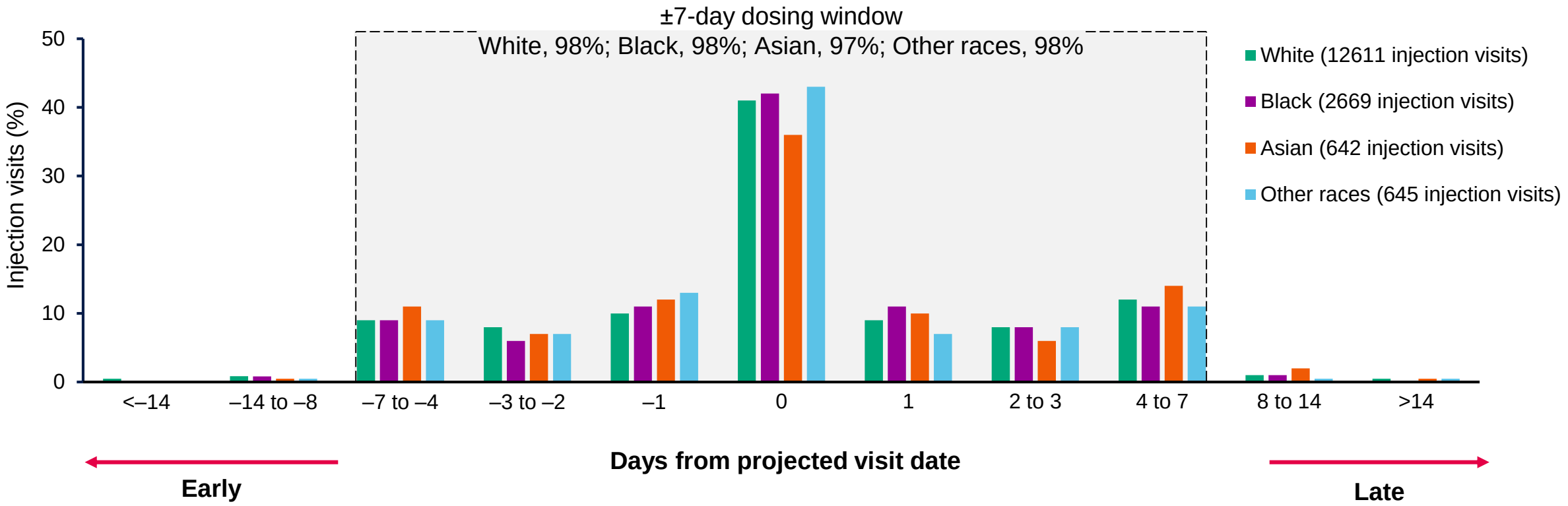
Adherence to Dosing Schedule Through Week 96



- Adherence was high and comparable by race, with 97–98% of injections administered within the ±7-day dosing window*
  - Overall, <1% (n=22/16,567) of injection visits were missed, all of which were covered by oral CAB + RPV therapy (82%, n=18/22) or oral ART (18%, n=4/22)†

*The most commonly used needle length was 1.5–2 inches. A needle gauge of 21–25 was used for CAB and a gauge of 21–23 was used for RPV.
†Missed injection visits covered by oral CAB + RPV: White, <1% (n=15/12,611); Black, <1% (n=2/2669); Asian, <1% (n=1/642). Missed injection visits covered by oral ART: White, <1% (n=4/12,611).
ART, antiretroviral therapy; CAB, cabotegravir; RPV, rilpivirine.

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Virologic Characteristics of CVF

Parameter, n	CAB + RPV LA Q8W + Q4W pooled (n=937)			
	White (n=711)	Black (n=149)	Asian (n=41)	Other races (n=36)
CVFs through Week 96	9	3	0	0
No associated baseline factors	3	0	–	–
One associated baseline factor	2	0	–	–
Archived RPV RAMs* alone	1	0	–	–
HIV-1 subtype A6/A1 alone	1	0	–	–
BMI ≥30 kg/m^2 alone	0	0	–	–
≥2 associated baseline factors†	4	3	–	–

- Overall, 12 (1%) participants met the CVF criterion through Week 96;‡ nine (1%) participants were White, and three (2%) were Black
- Overall, 7/12 (58%) of participants with CVF had ≥2 of the baseline factors associated with increased risk of CVF when found in combination (pre-existing RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m^2)[1]

*Participants were retrospectively assessed for archived resistance at baseline using next-generation sequencing of peripheral blood mononuclear cells.
†White: HIV-1 subtype A6/A1, and BMI ≥30 kg/m^2 (n=2); RPV RAM, HIV-1 subtype A6/A1, and BMI ≥30 kg/m^2 (n=2). Black: RPV RAM, and BMI ≥30 kg/m^2 (n=2); RPV RAM, HIV-1 subtype A6/A1, and BMI ≥30 kg/m^2 (n=1).
‡One additional White participant had CVF following oral CAB + RPV dosing interruption due to a false-positive pregnancy test.
BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.
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Safety Overview Through Week 96 (Excluding Injection Site Reactions [ISRs])

Parameter, n (%)	CAB + RPV LA Q8W + Q4W pooled (n=937)			
	White (n=711)	Black (n=149)	Asian (n=41)	Other races (n=36)
Any AE	632 (89)	135 (91)	38 (93)	35 (97)
Drug-related	229 (32)	23 (15)	18 (44)	15 (42)
Any Grade ≥3 AE	65 (9)	11 (7)	2 (5)	6 (17)
Drug-related	15 (2)	1 (<1)	0	1 (3)
AEs leading to withdrawal	29 (4)	2 (1)	3 (7)	3 (8)
Drug-related*	17 (2)	0	2 (5)	2 (6)
Any serious AE	46 (6)	7 (5)	5 (12)	3 (8)
Drug-related†	4 (<1)	0	0	1 (3)

- Excluding ISRs, drug-related Grade ≥3 AEs occurred in 2% (n=17/937) of participants, ranging 0–3% across races
- Drug-related serious AEs occurred in five (<1%) participants (White, <1% [n=4]; Other race, 3% [n=1])
- The most common drug-related AEs, excluding ISRs, were pyrexia (6%), headache (4%), and fatigue (3%), and differed in frequency by race‡

*__White__: depression (n=2), sweating and malaise (n=1), headache (n=1), osteonecrosis (n=1), pyrexia (n=1), discomfort, diarrhea, vomiting (n=1), myocardial infarction (n=1), dizziness, (n=1), hypersensitivity (n=1), nausea, vertigo (n=1), transaminases increased (n=1), depression, fatigue (n=1), asthenia (n=1), influenza (n=1), headache, hyperhidrosis, nausea, presyncope (n=1), disturbance in attention, sleep disorder (n=1); __Asian__: abnormal dreams, chills, disturbance in attention, fatigue, sweats, myalgia, pyrexia, sleep disorder (n=1), abnormal dreams, insomnia (n=1); __Other races__: fatigue, headache, rash maculopapular (n=1), drug hypersensitivity (n=1). †__White__: hypersensitivity and suspected (partial) intravenous administration of RPV (n=1), right knee monoarthritis (n=1), osteonecrosis (n=1), and myocardial infarction (n=1). The latter three were not considered drug related by sponsor. __Other races__: drug hypersensitivity (n=1). ‡__White__: pyrexia, 6% (n=44); headache, 3% (n=24); fatigue, 3% (n=22); __Black__: pyrexia, 2% (n=3); headache, 3% (n=4); fatigue, 3% (n=5); __Asian__: pyrexia, 12% (n=5); headache, 5% (n=2); fatigue, 7% (n=3); __Other races__: pyrexia, n=0; headache, 8% (n=3); fatigue, 6% (n=2). The number of Asian (n=41/937) and Other race (n=36/937) participants in the analysis was low.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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ISR Summary Through Week 96

Parameter	CAB + RPV LA Q8W + Q4W pooled (n=937)			
	White (n=711)	Black (n=149)	Asian (n=41)	Other races (n=36)
Participants who received ≥1 injection, n (%)	698 (98)	147 (99)	39 (95)	36 (100)
Number of injections, n	26,587	5630	1360	1362
ISR events, n*	6655	911	435	452
Injection site pain, n (% of injections)	5520 (21)	705 (13)	378 (28)	336 (25)
Injection site nodule, n (% of injections)	286 (1)	88 (2)	30 (2)	58 (4)
Grade 3, n (% of ISR events)†	81 (1)	9 (<1)	0	6 (1)
Median duration (IQR), days	3 (2–4)	4 (2–7)	2 (1–3)	3 (2–4)
Participants withdrawing due to injection-related reasons, n (% of participants with injections)	14 (2)	1 (<1)	4 (10)	1 (3)

- Most ISRs (99–100%) were Grade 1 or 2 in severity, with a median duration of 3 days, and there was a low rate of injection-related discontinuations
- Injection site pain (occurring with 20% of injections, n=6939/34,939) was the most common ISR event, reported at generally similar frequencies across races

*Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. †There were no Grade 4 or 5 ISR events.
CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

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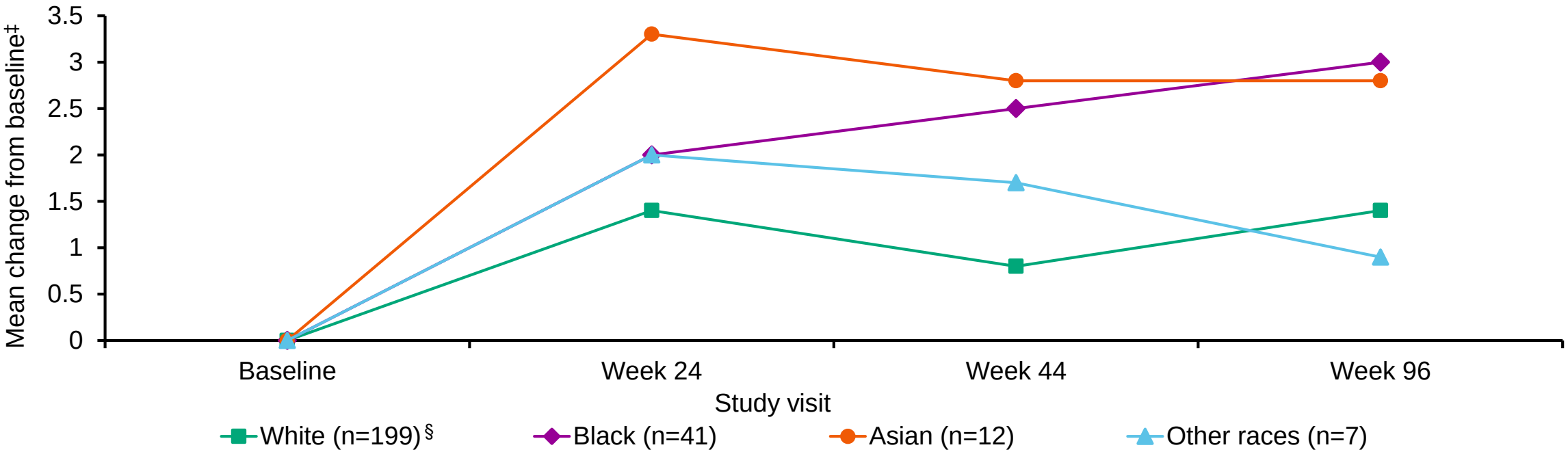
Treatment Satisfaction Through Week 96* (FLAIR Participants Only)†



- In participants receiving CAB + RPV LA dosed Q4W, similarly high HIVTSQs total mean scores were observed across races, with numerical improvements from baseline to Week 96 (White, +1.4; Black, +3.0; Asian, +2.8; Other races, +0.9) for all races
  - Maintenance baseline (Day 1) HIVTSQs total mean scores at baseline were: White, 59.3; Black, 60.7; Asian, 52.8; Other races, 61.1

*Last observation carried forward. †FLAIR participants were ART-naive at baseline and received the Q4W dosing regimen. ‡SD Week 24: White, 7.95; Black, 7.95; Asian, 9.14; Other races, 2.89. Week 44: White, 9.06; Black, 7.15; Asian, 7.71; Other races, 5.02. Week 96: White, 8.20; Black, 7.17; Asian, 13.21; Other races, 5.18. §Baseline, n=199; Week 24, n=197; Week 44, n=197; Week 96, n=197.
ART, antiretroviral therapy; CAB, cabotegravir; HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; LA, long-acting; Q4W, every 4 weeks; RPV, rilpivirine; SD, standard deviation.

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Conclusions

- CAB + RPV LA dosed monthly and Q2M demonstrated high efficacy across races, with 88% of participants maintaining HIV-1 virologic suppression at Week 96; 2% of participants had HIV-1 RNA ≥50 copies/mL
- The rate of CVF was low (1%), with no apparent differences by race through Week 96
- CAB + RPV LA was well tolerated, with pain being the most commonly reported ISR; ISRs were mostly Grade 1 or 2 and short-lived, with few participants withdrawing due to injection-related reasons
- Participant satisfaction with CAB + RPV LA was high at Week 96 for all races
- CAB + RPV LA dosed monthly and Q2M demonstrated comparable efficacy and safety outcomes across races through Week 96 and may be an effective treatment option for the maintenance of virologic suppression in people living with HIV-1

CAB, cabotegravir; CVF, confirmed virologic failure; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

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