ANTIVIRAL ACTIVITY AND SAFETY OF LONG-ACTING CABOTEGRAVIR PLUS LONG-ACTING RILPIVIRINE ADMINISTERED EVERY 2 MONTHS IN HIV-POSITIVE PARTICIPANTS: RESULTS FROM THE POLAR STUDY

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POLAR: Introduction

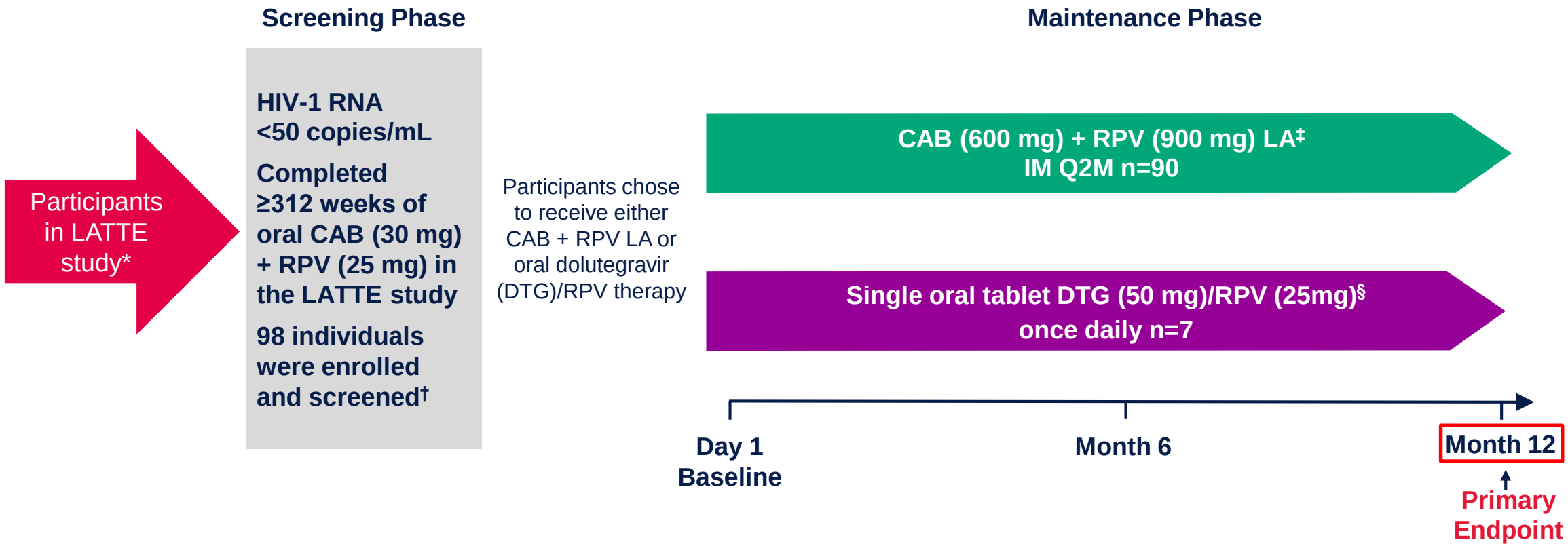
- Cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), an oral non-nucleoside reverse transcriptase inhibitor (NNRTI), are in development as long-acting (LA) agents for the maintenance of virologic suppression[1,2]
- CAB + RPV LA intramuscular (IM) injections dosed every 4 weeks (Q4W) demonstrated noninferior efficacy to daily oral comparator regimens in the Phase 3 FLAIR and ATLAS studies[1,2]
- CAB + RPV LA also showed noninferior efficacy when dosed every 8 weeks (Q8W) vs. Q4W in the Phase 3b ATLAS-2M study over a 48-week period[3]
- POLAR is a Phase 2b rollover study assessing the antiviral activity and safety of CAB + RPV LA given every 2 months (Q2M) in ART-experienced participants who received once-daily oral CAB + RPV treatment in the Phase 2b LATTE study.[4] The Month 12 results are presented here

ART, antiretroviral therapy.

1. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123.
2. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135.
3. Overton ET, et al. *Lancet.* Accepted 2020.
4. Margolis D, et al. *Lancet Infect Dis.* 2015;15(10):1145–1155.

POLAR: Study Design

Phase 2b, Open-Label, Multicenter, Non-Randomized Rollover Study



*Participants in LATTE received daily oral CAB (30 mg) + RPV (25 mg).
†One individual failed screening with the primary reason being "not meeting the inclusion or exclusion criteria."
‡Participants received CAB LA 600 mg + RPV LA 900 mg at Day 1 and Month 2, then Q2M thereafter. To be accessed commercially once CAB + RPV LA Q2M is approved. Any participant who received at least one dose of CAB LA and/or RPV LA and discontinued the CAB + RPV LA regimen for any reason entered a 52-week long-term follow-up phase and transitioned to an alternative highly active ART.
§To be accessed longer term via a commercial route. Participants will continue to receive DTG/RPV if located in a region where not commercially available.
ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; IM, intramuscular; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

POLAR: Month 12 Endpoints and Assessments

Primary endpoint

- Proportion of participants with HIV-1 RNA ≥50 copies/mL at Month 12 as per the FDA Snapshot algorithm

Secondary endpoints

- Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Month 12 as per the FDA Snapshot algorithm
- Incidence of protocol-defined confirmed virologic failure (CVF)
- Incidence and severity of adverse events (AEs) and laboratory abnormalities
- Proportion of participants who discontinue treatment due to AEs
- Incidence of treatment-emergent genotypic and phenotypic resistance
- Patient-reported outcomes (PROs) using preference questionnaires (exploratory endpoint)

No statistical tests of treatment comparisons were conducted within this study due to the limited population size.

CVF: two consecutive plasma HIV-1 RNA measurements of ≥200 copies/mL.
FDA, Food and Drug Administration.

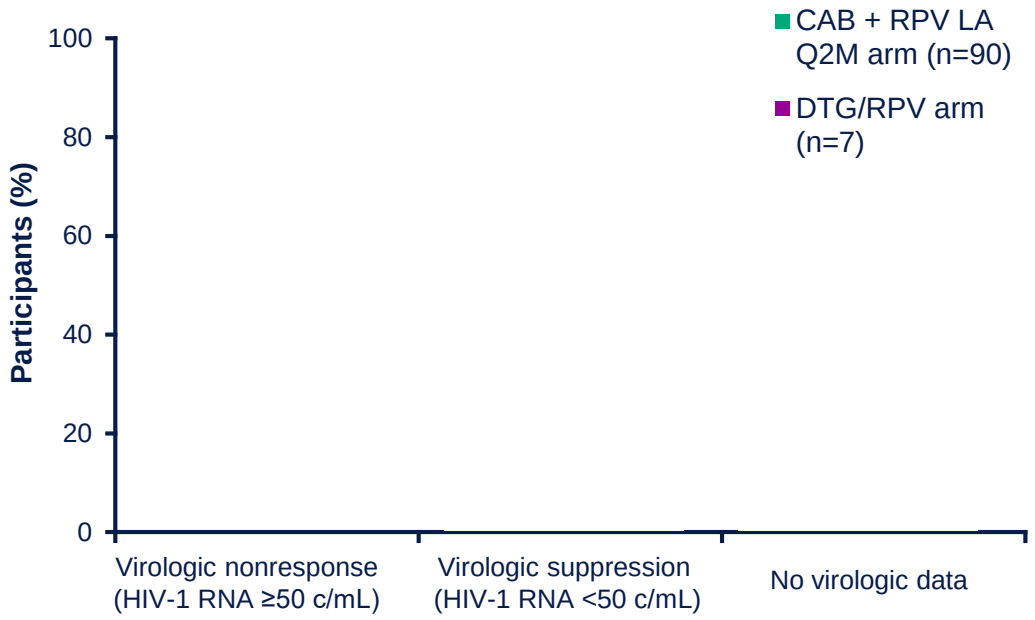
POLAR: Baseline Characteristics

Parameter	CAB + RPV LA Q2M arm n=90	DTG/RPV arm n=7	Total N=97
Age, median (range) years	41 (25–63)	53 (30–62)	41 (25–63)
Age ≥50 years, n (%)	16 (18)	4 (57)	20 (21)
Female (sex at birth), n (%)	2 (2)	0	2 (2)
Female (self-reported gender), n (%)	3 (3)	0	3 (3)
Race, n (%)			
White	63 (70)	4 (57)	67 (69)
Black or African American	21 (23)	3 (43)	24 (25)
Other	6 (7)	0	6 (6)
Body mass index, median (range) kg/m^2	27 (19–48)	27 (24–31)	27 (19–48)
CD4+ cell count, median (range) $cells/mm^3$	851 (376–1593)	779 (595–1050)	842 (376–1593)

- Of the 98 participants from the LATTE study who were screened for eligibility, 97 entered the Maintenance Phase (intention-to-treat exposed [ITT-E])
  - 1 participant failed screening
- Baseline characteristics were broadly similar between treatment groups, with high levels of baseline satisfaction observed

CAB, cabotegravir; DTG, dolutegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

High Levels of Snapshot Virologic Suppression at POLAR Month 12



Outcome, n (%)	CAB + RPV LA Q2M arm n=90	DTG/RPV arm n=7
HIV-1 RNA <50 copies/mL	88 (97.8)	7 (100)
HIV-1 RNA ≥50 copies/mL	0	0
Data in window not below threshold	0	0
Discontinued for lack of efficacy	0	0
Discontinued for other reason while not below threshold	0	0
Change in background therapy	0	0
No virologic data	2 (2.2)	0
Discontinued due to AE	1 (1.1)*	0
Discontinued due to death	0	0
Discontinued study for other reason	1 (1.1)†	0
On study but missing data in window	0	0

*Participant discontinued due to a drug-related AE of depression.
†Participant was lost to follow-up.

- Overall, 98% of participants in the CAB + RPV LA arm and 100% of participants in the DTG/RPV arm maintained virologic suppression at Month 12
- At Month 12, no participant had HIV-1 RNA ≥50 copies/mL per the FDA Snapshot algorithm in either treatment arm
- Through Month 12, no participants met the CVF criterion in either treatment arm

AE, adverse event; CAB, cabotegravir; CVF, confirmed virologic failure; DTG, dolutegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

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POLAR: Safety Overview

Parameter (including ISRs), n (%)	CAB + RPV LA Q2M arm n=90	DTG/RPV arm n=7
Any AE	86 (96)	3 (43)
Drug-related AEs	65 (72)	1 (14)
Any Grade ≥3 AE	9 (10)	0
AEs leading to withdrawal	1 (1)*	0
Drug-related AEs leading to withdrawal	1 (1)*	0
Any SAE	5 (6)†	0
Drug-related SAEs	1 (1) ‡	0

*Drug-related AE of depression.
†SAEs included cholecystitis acute (n=1), cholelithiasis (n=1), anal abscess (n=1), orchitis (n=1), urinary tract infection bacterial (n=1), proctitis (n=1), and injection site extravasation (n=1). Participants could have experienced more than one SAE.
‡Drug-related SAE of injection site extravasation.

- Through Month 12, 96% and 43% of participants in the CAB + RPV LA and DTG/RPV arms reported AEs, respectively
  - This difference was primarily due to the occurrence of injection site reactions (ISRs) in the CAB + RPV LA arm
- Only 1 participant withdrew due to an AE (CAB + RPV LA arm; drug-related AE of depression) and there was one drug-related serious AE (CAB + RPV LA arm; injection site extravasation)
- No clinically relevant patterns in clinical laboratory results over the 12-month period were observed

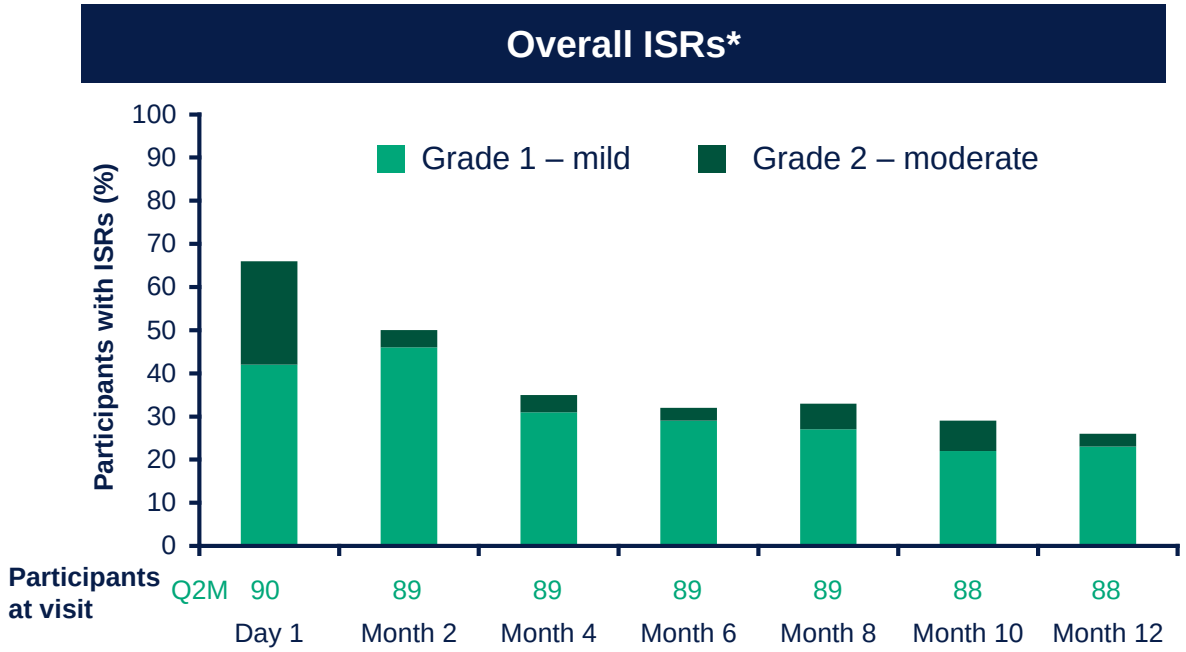
AE, adverse event; CAB, cabotegravir; DTG, dolutegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine; SAE, serious adverse event.

POLAR: Common Adverse Events (Excluding ISRs)

Common (≥5% in the CAB + RPV LA Q2M arm) AEs, n (%)	CAB + RPV LA Q2M arm n=90	DTG/RPV arm n=7
Nasopharyngitis	10 (11)	0
Upper respiratory tract infection	10 (11)	0
Diarrhea	9 (10)	0
Pyrexia	9 (10)	0
Headache	6 (7)	1 (14)
Fatigue	6 (7)	0
Syphilis	6 (7)	0
Cough	5 (6)	0
Hemorrhoids	5 (6)	0
Nausea	5 (6)	0
Common (≥3% in the CAB + RPV LA Q2M arm) drug-related AEs, n (%)		
Pyrexia	7 (8)	0
Fatigue	4 (4)	0
Pain	3 (3)	0

AE, adverse event; CAB, cabotegravir; DTG, dolutegravir; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

POLAR: Most Injection Site Reactions Were Mild and Decreased Over Time



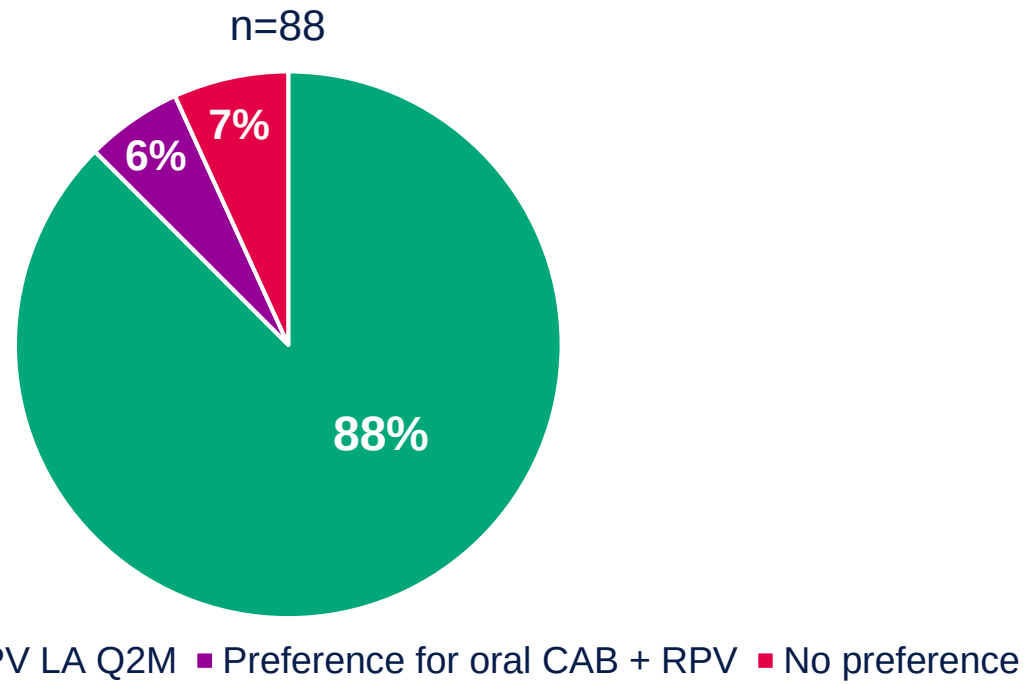
Parameter	CAB + RPV LA Q2M arm
Number or participants receiving injections	90
Number of injections	1534
ISRs events*, n (% of injections)	463
Pain	414 (27.0)
Discomfort	20 (1.3)
Swelling	11 (<1)
Nodule	6 (<1)
≥Grade 3 ISR events	0
Median duration of ISRs, days	3
Withdrawals due to ISR or injection intolerability, n (%)	0

*Only ISRs with an incidence of >5 events are listed.

- Cumulatively, 78% of participants in the CAB + RPV LA arm reported ISRs, for a total of 463 events
- ISR events were either mild (84%) or moderate (16%) in severity
- The majority of ISRs (92%) resolved within 7 days, with a median duration of 3 days
- No participants withdrew due to ISRs

*AE grade is the maximum grade reported by the participant at each visit.
CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

POLAR: CAB + RPV LA Participants Preferred LA Therapy to Their Previous Oral Regimen



- At Month 12, 88% of CAB + RPV LA participants who responded preferred CAB + RPV LA over oral CAB + RPV, the regimen they received in the LATTE study for ≥5 years
- The most commonly cited reasons for preference included increased convenience (69%) and the frequency of administration (57%)

CAB, cabotegravir; LA, long-acting; Q2M, every 2 months; RPV, rilpivirine.

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POLAR Month 12 Conclusions

- CAB + RPV LA, administered every 2 months, maintained high levels of virologic suppression, with no participant meeting the CVF criterion
- CAB + RPV LA had a favorable safety profile and was well tolerated. The frequency of ISRs reduced over time, with the majority classified as mild or moderate in severity, self-limited in duration, and not a cause of treatment discontinuation
- Preference for the injectable regimen was observed in this treatment-experienced cohort, who had previously received daily oral CAB + RPV for ≥5 years in the LATTE study
- Owing to the limited population size and unbalanced number of participants between arms, direct comparisons between CAB + RPV LA and DTG/RPV cannot be drawn
- Taken together, these results indicate that CAB + RPV LA given every 2 months is an efficacious and well-tolerated maintenance therapy for HIV-1 infection that may be preferable to daily oral therapy

CAB, cabotegravir; CVF, confirmed virologic failure; DTG, dolutegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

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