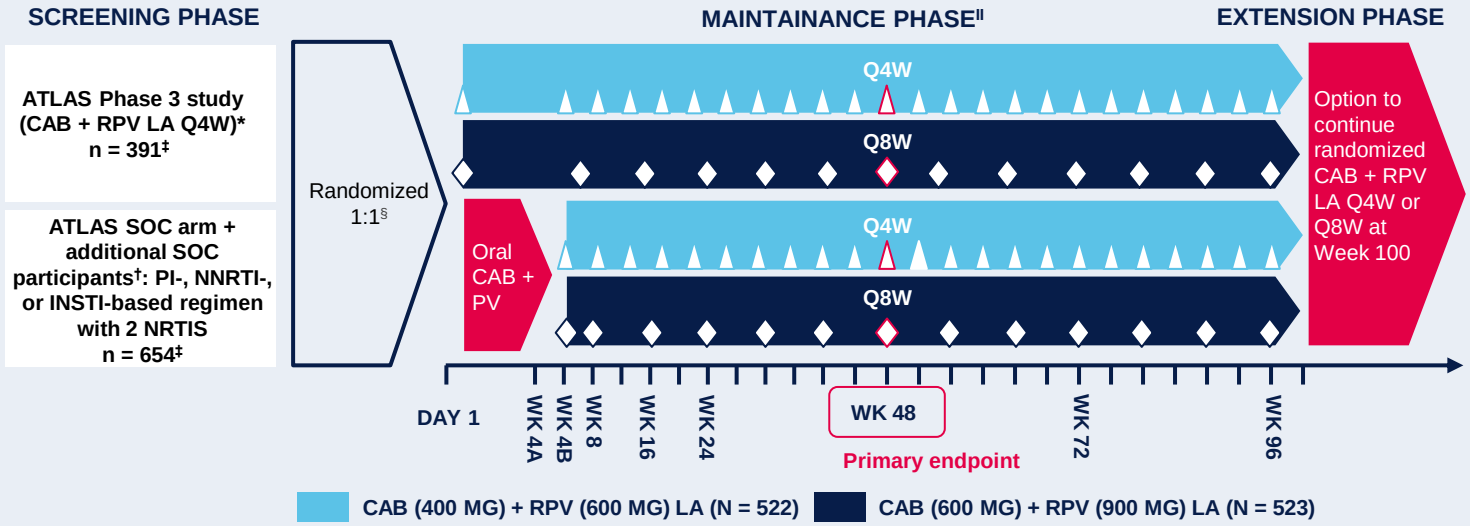
Cabenuva (CAB LA + RPV LA) Every 2 Months: ATLAS-2M Study

ATLAS-2M Study Design: Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study

Congress Presentation

Primary endpoint

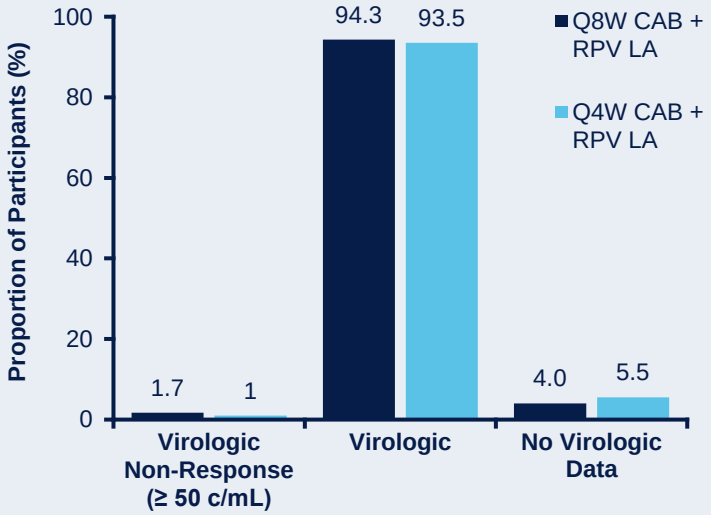
Proportion of participants with plasma HIV-1 RNA ≥ 50 c/mL at Week 48 (Snapshot, ITT-E); noninferiority margin of 4%.



*Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA < 50 c/mL at screening. †SOC participants not transitioning from the ATLAS study were to be on uninterrupted current regimen (either the initial or second combined ART regimen) for at least 6 months prior to screening. Documented evidence of at least two plasma HIV-1 RNA measurements < 50 c/mL in the 12 months prior to screening, one within the 6- to 12-month window and one within 6 months prior to screening, was required. Participants were excluded if they had a history of virologic failure; evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) from prior genotype assay results. ‡Intent-to-treat exposed population. §1149 participants were screened, and 1049 participants were randomized. 4 participants did not receive study drug and therefore were not part of the ITT-E population. ‖Participants who withdraw from the IM regimen must go into 52-week long-term follow-up if randomized regimen is not yet locally approved and commercially available. ¶Participants on oral lead-in treatment attended a Week 4 visit to assess tolerability. In participants in the Q4W arm who had an oral lead-in, the first LA dose was CAB 600 mg + RPV 900 mg.

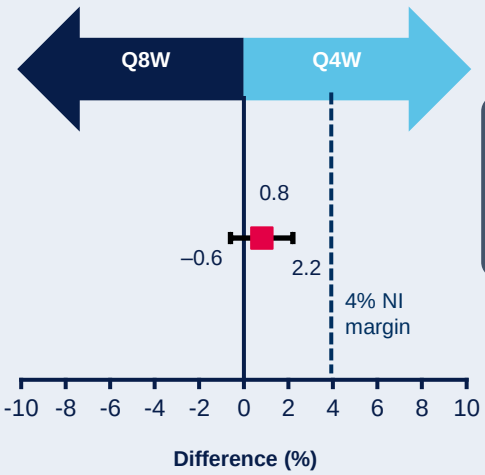
Results: Week 48

Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints



Participant numbers: n = 522 Q8; n = 523 Q4

Adjusted Treatment Difference at Week 48 (95% CI)*



Primary endpoint (≥ 50 c/mL): Q8W is noninferior to Q4W (Week 48)

*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, > 24 weeks).

Results: Week 48

Virologic Failures

Summary of Confirmed Virologic Failures

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs Observed at Failure	CVFs with IN RAMs*	IN RAMs Observed at Failure
Q8W	522	8 (1.5)	6/8	K101E, E138E/K, E138A, Y188L	5/8	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

Post hoc baseline PBMC HIV-1 DNA results for Q8W arm:

- 5/8 CVFs had pre-existing major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
- 1/8 CVFs had a pre-existing major IN RAM (G140G/R)
- 5/8 CVFs had L74I polymorphism (3 subtype A or A1, 1 subtype C, 1 complex subtype)

9/10 CVFs re-suppressed on fully active oral HAART (1/10 non-compliance on PI-based ART)

- All CVFs retained phenotypic sensitivity to dolutegravir

*For those with observed RAMs at failure: 6/6 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change > 2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change > 2.5); CVF definition: 2 consecutive plasma HIV-1 RNA levels ≥ 200 c/mL after prior suppression to < 200 c/mL. †Or mixture.

Safety and Tolerability

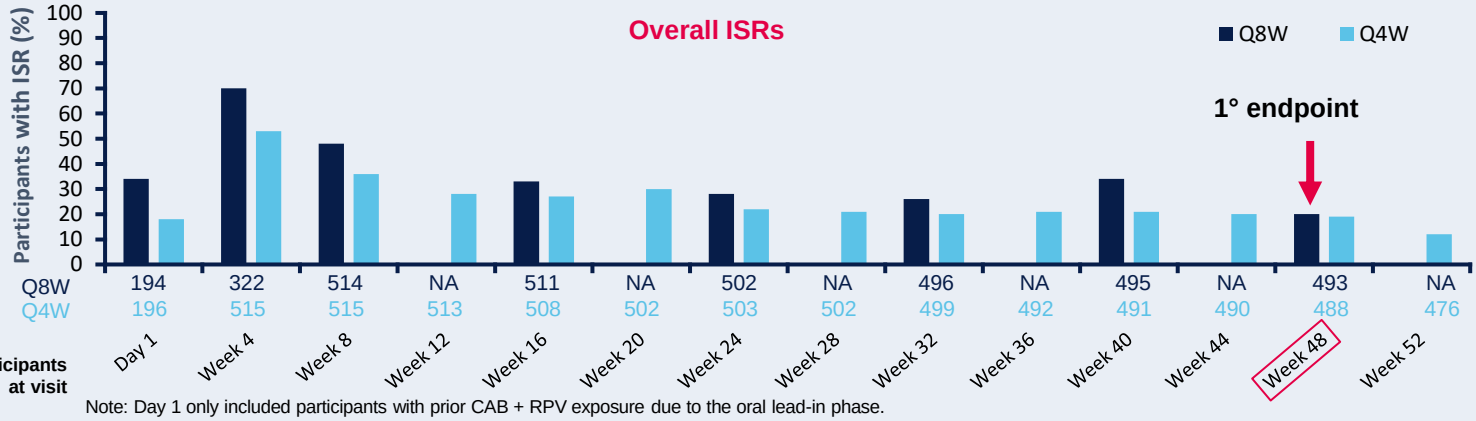
Similar Between Q8W and Q4W Dosing Arms: AEs Excluding ISRs

	Q8W (n = 522) n (%)	Q4W (n = 523) n (%)
Drug-related AEs	109 (21)	125 (24)
Drug-related Grade ≥ 3	4 (< 1)	5 (< 1)
Drug-related AEs leading to withdrawal	5 (< 1)	8 (2)
Drug-related SAEs*	2 (< 1)	1 (< 1)

AEs were similar between the Q8W and Q4W dosing arms; Overall, 96% of drug-related AEs were Grade 1–2; Drug-related AEs led to withdrawal in 5 participants in the Q8W arm and 8 in the Q4W arm

*Drug-related SAEs were presyncope and acute pancreatitis in the Q8W group and allergic reaction in the Q4W group.

Injection Site Reaction



Note: Day 1 only included participants with prior CAB + RPV exposure due to the oral lead-in phase.

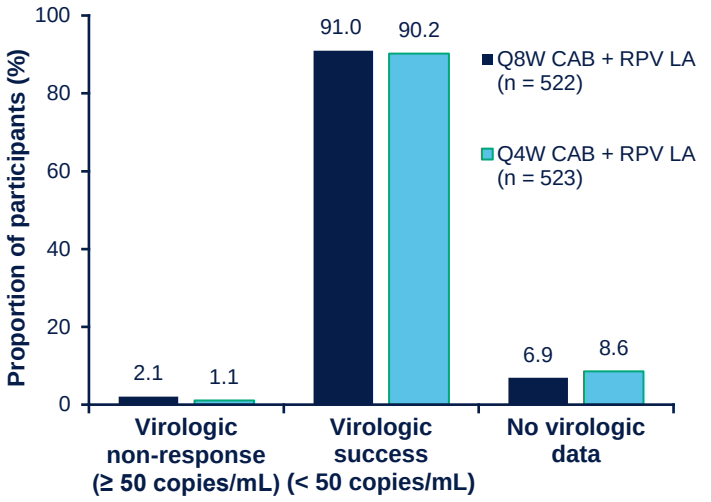
Outcome, n (%), ITT-E	Q8W (n = 522)	Q4W (n = 523)
Number of injections	8470	15,711
Number of ISR events (events/injections)*	2507 (30)	3152 (20)
Grade ≥ 3 – severe†	43 (< 1)	48 (< 1)
Injection site reactions‡		
Pain	2014 (24)	2567 (16)
Nodule	113 (1)	204 (1)
Discomfort	92 (1)	110 (1)
Withdrawals due to injection-related reasons, participant n (%)§	6 (1)	11 (2)

24,181 injections were administered in total; < 2% of participants discontinued due to injection-related reasons; The majority (98%, 5568/5659) of ISRs were Grade 1–2, with a median duration of 3 days in both arms

*All event-level ISR percentages are calculated from the total number of injections. Note: A single injection could result in more than one ISR. †There were no Grade 4 or Grade 5 ISRs. ‡ISRs occurring in > 1% of injections in either the Q4W or Q8W arms are shown. §Q8W: 5 participants had an ISR leading to withdrawal and 1 participant withdrew consent from the study due to injection intolerability; Q4W: 5 participants had an ISR leading to withdrawal and 6 participants withdrew consent from the study due to injection intolerability.

Results at Week 96 (Secondary Endpoint: proportion of patients with HIV-1 RNA ≥ 50 copies/mL)

Virologic Snapshot Outcomes at Week 96 for ITT-E[2]:



Confirmed Virologic Failures[2]

Summary of the 11 CVFs, 10 re-suppressed on alternative ART

Regimen	N	CVFs N (%)	CVFs with RPV RAMs*	RPV RAMs at Failure	CVFs with INSTI RAMs*	INSTI RAMs at Failure
Q8W	522	9 (1.7)	7/9	K101E, E138E/K, E138A, Y188L, Y181C	5/9	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

*For those with observed RAMs at failure: 7/7 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change > 2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change > 2.5) ; †Or mixture

– Between Weeks 48 and 96, one additional CVF occurred in the Q8W arm.

Safety[2]

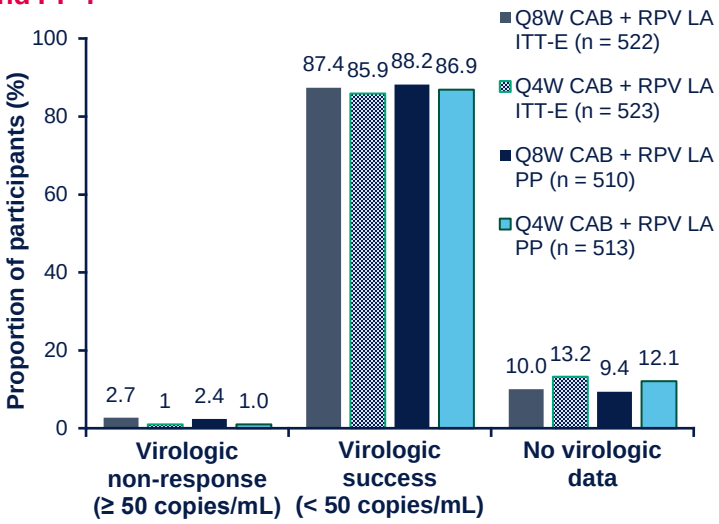
The occurrence of adverse events was generally similar between the treatment arms and consistent with what was reported at Week 48

ISRs were most common AEs reported with ≥ 1 occurring in **80%** of patients in Q8W **77%** of patients in Q4W

The most commonly reported non-ISR AEs were: **Pyrexia** **Fatigue**

Results at Week 152 (Secondary Endpoint: proportion of patients with HIV-1 RNA ≥ 50 copies/mL

Virologic Snapshot Outcomes at Week 152 for ITT-E and PP[3]:



Injection Site Reactions[3]

Through Week 152, ISRs were mild to moderate in severity (99%); there were no Grade 4/5 ISRs

Confirmed Virologic Failures[3]

Regimen	N	CVFs N (%)	CVFs with RPV RAMs*	RPV RAMs at Failure	CVFs with INSTI RAMs*	INSTI RAMs at Failure
Q8W	522	11 (2)	9/11	K101E, E138E/K, E138A, Y188L, Y181C*, M230M/L	7/11	Q148R,* N155H*
Q4W	523	2 (< 1)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

*or mixture

– An additional participant was identified as having non-protocol defined Virologic failure at Week 48 (Q8W). The participant had subtype A1, with RPV RAM E138K and IN mutation S230S/R observed at withdrawal; no RAMs to RPV or INIs were present at baseline; the participant resuppressed on an alternate regimen.

Safety[3]

	Q8W	Q4W
≥ 1 non-ISR adverse event through Week 152	90%	94%
Non-ISR drug-related adverse events	27%	32%
Drug-related AEs leading to withdrawal	1%	2%
Drug-related Grade 3 or higher AEs	2%	2%

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Abbreviations: AE = adverse event; ART = antiretroviral treatment; CAB = cabotegravir; CAB LA + RPV LA = cabotegravir+ rilpivirine; CI = confidence interval; CMH = Cochran–Mantel–Haenszel test; CVF = confirmed virologic failure; HAART = highly active antiretroviral therapy; INSTI = integrase strand transfer inhibitor; ISR = injection site reaction; ITT-E = Intent to treat-exposed; LA = long-acting; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PBMC = peripheral blood mononuclear cell; PI = protease inhibitor; PP= per protocol; RAM = resistance associated mutation; RPV = rilpivirine; SAE = serious adverse event; SOC = standard of care; Q8W = every-8-week; Q4W = every-4-week.

References: 1. Overton ET, et al. CROI 2020; Boston, MA. Presentation 3334; **2.** Jaeger H et al. *Lancet* 2021;8(11):E679-E689. DOI: https://www.doi.org/10.1016/S2352-3018(21)00185-5; **3.** Overton ET, et al. CROI, February 12-16, 2022, Virtual Event. Poster.