EPLBB05

Safety and Effectiveness From the CARISEL Study: Phase 3b Hybrid-III Implementation Study Integrating Cabotegravir + Rilpivirine Long-Acting Into European Clinical Settings

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Key Takeaways

- **We present key effectiveness and safety endpoints through Month 12 of the Phase 3b CARISEL implementation study, evaluating participants switching from daily oral therapy to cabotegravir + rilpivirine long-acting (CAB + RPV LA) dosed every 2 months (Q2M).**
- **Across diverse European clinical settings and participants, CAB + RPV LA dosed Q2M was highly effective and well tolerated, with 87% of participants maintaining HIV-1 virologic suppression and 0.23% meeting the confirmed virologic failure (CVF) criterion.**

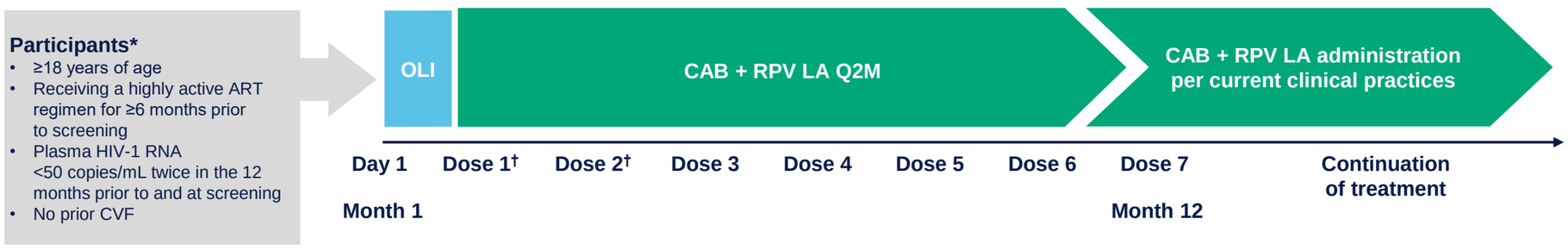
Background

- CAB + RPV LA dosed Q2M is a recommended regimen in European and US treatment guidelines for virologically suppressed people living with HIV-1 (PLWH) with no known CAB/RPV resistance.[1,2]
- CAB + RPV LA reduces dosing frequency compared with daily oral antiretroviral therapy (ART), and may help address concerns including fear of disclosure, anxiety around medication adherence, and daily reminders of HIV status.
- CAB and RPV Implementation Study in European Locations (CARISEL; NCT04399551) is a Phase 3b, multicenter, open-label, hybrid type III implementation–effectiveness trial evaluating participants switching from daily oral therapy to CAB + RPV LA dosed Q2M.
- Key effectiveness and safety endpoints through Month 12 are reported.

Methods

Figure 1. CARISEL Study Design

- This open-label study enrolled virologically suppressed PLWH to receive CAB + RPV LA dosed Q2M (**Figure 1**).
- Clinics with no prior experience with CAB + RPV LA were preferentially selected for study participation.
- Endpoints assessed:
  - The proportion of participants with plasma HIV-1 RNA ≥50 copies/mL and <50 copies/mL at Month 12 (FDA Snapshot algorithm, intention-to-treat exposed [ITT-E]).
  - The incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 copies/mL) and viral resistance through last participant last visit.
  - Safety and tolerability through last participant last visit.



*Female participants were eligible to participate if not pregnant or lactating and had non-reproductive potential or agreed to follow a highly effective method of avoiding pregnancy. †Dose 1 was received at Month 1, Dose 2 at Month 2, with the remaining doses Q2M thereafter.
ART, antiretroviral therapy; CAB, cabotegravir; LA, long-acting; OLI, oral lead-in; Q2M, every 2 months; RPV, rilpivirine.

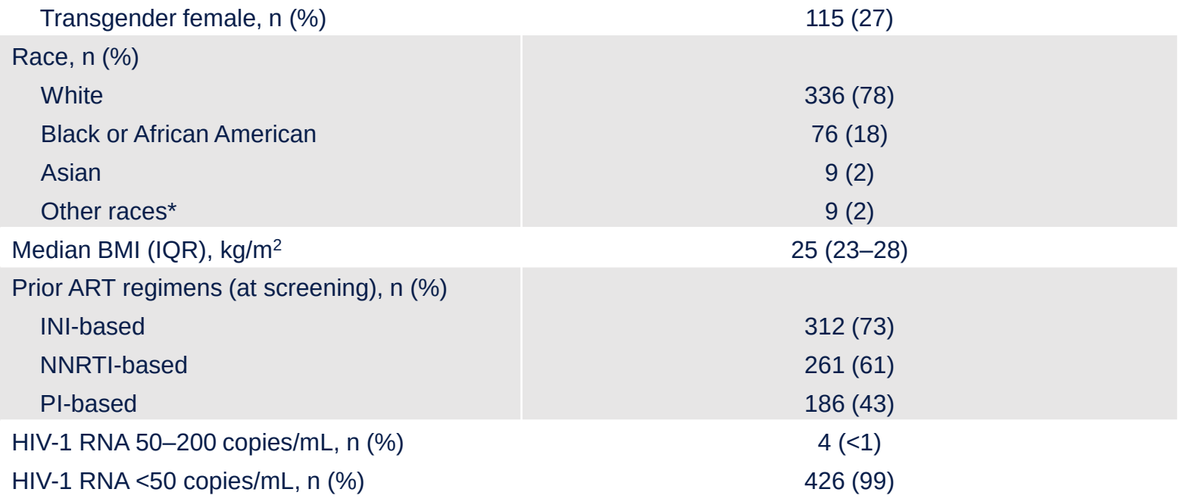
Table 1. Baseline Characteristics

Parameter	CAB + RPV LA (n=430)
Median age (IQR), years	44.0 (37–51)
Age ≥50 years, n (%)	129 (30)
Female (sex at birth), n (%)	109 (25)
Transgender female, n (%)	115 (27)
Race, n (%)	
White	336 (78)
Black or African American	76 (18)
Asian	9 (2)
Other races*	9 (2)
Median BMI (IQR), kg/m^2	25 (23–28)
Prior ART regimens (at screening), n (%)	
INI-based	312 (73)
NNRTI-based	261 (61)
PI-based	186 (43)
HIV-1 RNA 50–200 copies/mL, n (%)	4 (<1)
HIV-1 RNA <50 copies/mL, n (%)	426 (99)

*Other races: American Indian or Alaska Native, n=7; mixed race, n=2.
ART, antiretroviral therapy; BMI, body mass index; CAB, cabotegravir; INI, integrase inhibitor; IQR, interquartile range; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine.

- Baseline characteristics are presented in **Table 1**.
- 13 of 18 clinics (72%) had no experience with administering CAB + RPV LA at the start of the study.

Figure 2. Virologic Response at Month 12



CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

- At Month 12, 87% (n=373/430 [95% CI 83.2–89.8]) of participants maintained HIV-1 RNA <50 copies/mL (FDA Snapshot algorithm, ITT-E), with 0.7% (n=3/430 [95% CI 0.1–2.0]) having HIV-1 RNA ≥50 copies/mL (**Figure 2**).

Table 2. Snapshot Outcomes at Month 12

	CAB + RPV LA (n=430)
HIV-1 RNA ≥50 copies/mL, n (%)	3 (0.7)
Data in window not below threshold	0
Discontinued for lack of efficacy	1 (0.2)
Discontinued for other reason while not below threshold*	2 (0.5)
HIV-1 RNA <50 copies/mL, n (%)	373 (86.7)
No virologic data, n (%)	54 (12.6)
Discontinued study due to AE	40 (9.3)
Discontinued study for other reason†	7 (1.6)
On study but missing data in window	7 (1.6)

*Physician decision, n=2. †Protocol deviation, n=3; lost to follow-up, n=1; withdrawal by participant, n=3.
AE, adverse event; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

- At the Month 12 Snapshot, 13% of participants were classified as having no virologic data, most commonly due to withdrawals due to AEs (9% of participants) (**Table 2**).
  - 6/7 participants at one site had a missed viral load assessment at Month 12 and had HIV-1 RNA <50 copies/mL at Month 14. The seventh participant from another site had HIV-1 RNA <50 copies/mL at last visit (Month 8) and transitioned to commercial CAB + RPV LA, following a missed central laboratory viral load assessment at Month 12 and a local Month 12 viral load of <20 copies/mL.
- One participant (0.23%) met the CVF criterion with a viral load of 1861 copies/mL at discontinuation (Month 10) (**Table 3**).
  - In the CVF sample at Month 10, the RPV resistance-associated mutations (RAMs) E138A + M230L were detected; no INI RAMs were detected; E138A was present in baseline peripheral blood mononuclear cells (PBMCs).
- Another participant met the suspected virologic failure (SVF) criterion (HIV-1 RNA ≥200 copies/mL) at Month 4 and resuppressed upon retest, followed by a second SVF event at the last visit prior to withdrawal.
  - In the SVF sample at Month 4, the RPV RAM E138K and INI RAMs N155N/S were detected; no INI or RPV RAMs were present in baseline PBMCs.

Table 3. Virologic Characteristics of CVF and SVF

Sex at birth, baseline BMI (kg/m^2), country	HIV-1 subtype at baseline	Viral load at SVF/CVF (copies/mL)	RPV RAMs observed at baseline	INI RAMs observed at baseline	RPV RAMs observed at failure	INI RAMs observed at failure	Phenotypic resistance (fold-change) to RPV/CAB
Participant with CVF							
Female, 29, Germany	G	214/1861	E138A	None	E138A + M230L	None	22.0/0.9
Participant with SVF*							
Male, 30, Spain	B	585/N/A	None	None	E138K	N155N/S†	6.1/1.3

*Participant met the SVF criterion (HIV-1 RNA 585 copies/mL) at Month 4 but was not confirmed at the Month 4 retest. Following a second retest at Month 4, the participant met the SVF criterion (HIV-1 RNA 386 copies/mL at timing of resistance test) and withdrew from the study, as per the principal investigator's discretion, and switched ART to Symtuza. †N155S is an extremely rare non-polymorphic mutation that reduces raltegravir and elvitegravir susceptibility to a lesser degree than N155H.[3]
ART, antiretroviral therapy; BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; IC_{50}, half-maximal inhibitory concentration; INI, integrase inhibitor; N/A, not applicable; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure.

Table 4. Safety Overview (Excluding ISRs) Through Last Participant Last Visit*

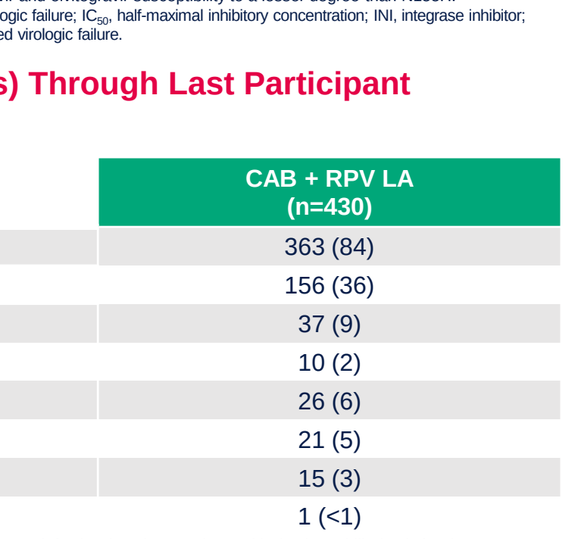
Parameter	CAB + RPV LA (n=430)
Any AE†	363 (84)
Any drug-related AE	156 (36)
Any Grade ≥3 AE	37 (9)
Drug-related‡	10 (2)
AEs leading to withdrawal	26 (6)
Drug-related§	21 (5)
Any serious AE	15 (3)
Drug-related‖	1 (<1)

*Month 14. †No Grade 5 AEs or deaths were reported; most common AEs were COVID-19 infection (16%); nasopharyngitis (6%); syphilis (4%). ‡Fatigue, n=1; malaise, n=1; headache, n=1; postural dizziness, n=1; nausea, n=1; depression, n=1; suicidal ideation, n=1; arthropathy, n=1; muscle spasms, n=1; musculoskeletal, n=1; increased blood creatinine, n=1; acute hepatitis, n=1; suicidal ideation, n=1. Participants may have reported more than one AE. §Weight gain, n=2; dizziness, n=1; myalgia, n=1; nausea, fever, and vomiting, n=1; non-cardiac chest pain, n=1; suicidal ideation, n=1; upper abdominal pain, abdominal distension, and diarrhea, n=1; abdominal distension and diarrhea, n=1; asthenia, insomnia, and irritability, n=1; decreased appetite, depressed mood, postural dizziness, headaches, malaise, and pain, n=1; depression, n=1; diarrhea, n=1; sciatica, n=1; asthenia and leg pain, n=1; anxiety, n=1; acute hepatitis, n=1; chills, fever, and night sweats, n=1; weight gain and lipodystrophy, n=1; insomnia, n=1; pain in right leg, chills, and fever, n=1. ‖Suicidal ideation, n=1.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

- Of participants who reported AEs (excluding ISRs; **Table 4**), most were Grade 1 or 2 (90%).

Figure 3. ISR Summary Through Last Participant Last Visit

Parameter	CAB + RPV LA (n=430)
Participants who received ≥1 injection	423
Number of injections	5844
Number of ISR events	1867
Pain, n (% of injections)*	1540 (26)
Discomfort, n (% of injections)*	94 (2)
Induration, n (% of injections)*	74 (1)
Grade 3, n (% of ISR events)†	32 (2)
Median duration, days	3
Participants withdrawing for injection-related reasons, n (% of participants with injections)	25 (6)



*The proportion of ISRs occurring in over 1% of participants are listed. †There were no Grade 4 or 5 ISRs. ‡AE grade is the maximum grade reported by the participant at each visit. §Please see IAS 2022 poster EPB181 "'Give It A Shot": Best Practices From HCPs For Administering Long-Acting Cabotegravir + Rilpivirine' for HCP perceptions on why ISRs decrease over time.
AE, adverse event; CAB, cabotegravir; HCP, healthcare professional; ISR, injection site reaction; LA, long-acting; M, month; RPV, rilpivirine.

- ISRs were reported in 86% of participants; 98% were mild or moderate in severity.
- The median ISR duration was 3 days, with 82% resolving within 7 days, and 25 out of 423 participants (who received an injection) withdrawing for injection-related reasons.
- The number of participants reporting ISRs at each visit decreased through Month 14 (**Figure 3**).

Conclusions

- CAB + RPV LA dosed Q2M was efficacious, with 87% of participants maintaining HIV-1 virologic suppression at Month 12; 0.7% of participants had HIV-1 RNA ≥50 copies/mL.
  - Most Snapshot failures were due to study discontinuation or missing data.
- In this large and diverse population receiving CAB + RPV LA dosed Q2M, the rate of CVF was low (n=1; 0.23%), supporting high efficacy of CAB + RPV LA dosed Q2M.
  - RPV RAMs were present at baseline (E138A) and failure (E138A + M230L); no INI RAMs were detected.
  - Another participant met the SVF criterion with no RAMs were observed at baseline, and RPV RAM E138K and INI RAMs N155N/S were detected at the first SVF.
- CAB + RPV LA was well tolerated, with ISRs being mostly Grade 1 or 2 (98%) and short-lived (median 3 days), with 6% of participants withdrawing due to injection-related reasons.
- Across diverse European clinical settings and participants, CAB + RPV LA dosed Q2M was well tolerated and highly effective in maintaining virologic HIV-1 suppression with a low rate of virologic failure.

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