EPB180

Long-Acting Cabotegravir + Rilpivirine in Older Adults: Pooled Phase 3 Week 96 Results

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Key Takeaways

- **We present longer-term efficacy, safety, adherence, and treatment satisfaction outcomes through Week 96 for the Phase 3/3b ATLAS-2M and FLAIR studies stratified by age group (<50 years [y] and ≥50 y).**
- **Efficacy and tolerability were similar across participants aged <50 y and ≥50 y, and support the use of cabotegravir + rilpivirine long-acting (CAB + RPV LA) dosed monthly or every 2 months as a complete regimen for the maintenance of HIV-1 virologic suppression in adults, irrespective of age.**

Background

- CAB + RPV is the first complete LA regimen recommended by treatment guidelines for the maintenance of HIV-1 virologic suppression.[1,2]
- In the Phase 3 development program, CAB + RPV LA dosed every 4 weeks (Q4W) was noninferior to daily oral therapy in the FLAIR and ATLAS studies,[3,4] and CAB + RPV LA dosed every 8 weeks (Q8W) was noninferior to Q4W dosing in the ATLAS-2M study.[5]
- With improvements in HIV management and the success of antiretroviral therapy, the proportion of people living with HIV aged ≥50 years (y) is increasing.[6]
- Here, we present longer-term efficacy and safety outcomes through Week 96 for ATLAS-2M and FLAIR stratified by age group.

Methods

- Data from the ATLAS-2M and FLAIR studies were pooled and stratified by age (<50 y and ≥50 y).
- 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 Evaluated Through Week 96 by Age Categories:

- The proportion of participants with plasma HIV-1 RNA <50 and ≥50 copies/mL.
- The incidence of confirmed virologic failure (CVF; two consecutive measurements of ≥200 copies/mL).
- Safety, including injection site reactions (ISRs) and adverse events (AEs).
- Adherence to dosing window.
- Treatment satisfaction (measured by HIV Treatment Satisfaction Questionnaire status version [HIVTSQs]; FLAIR only).

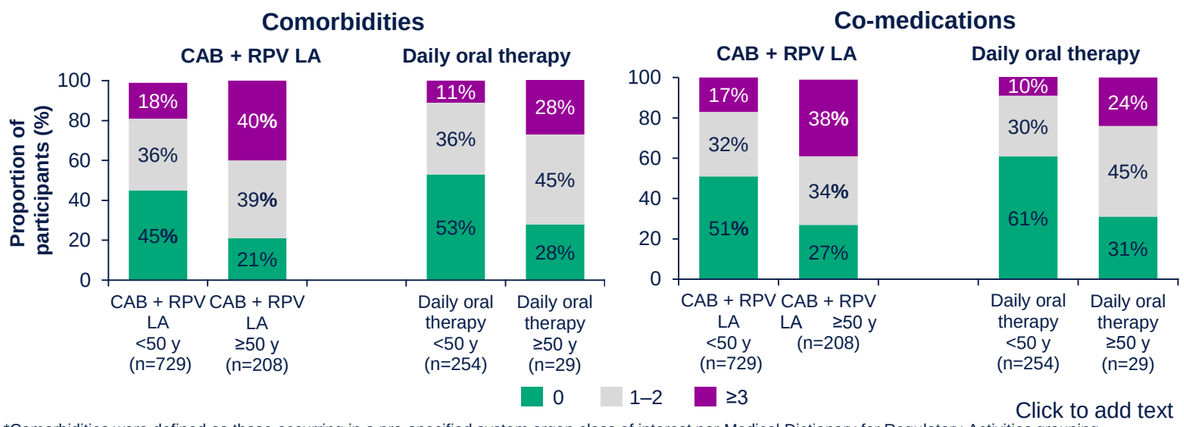
Table 1. Baseline Characteristics by Regimen and Age Group

Parameter	CAB + RPV LA Q8W n (%)		CAB + RPV LA Q4W n (%)		Daily oral therapy n (%)	
	<50 y (n=238)	≥50 y (n=89)	<50 y (n=491)	≥50 y (n=119)	<50 y (n=254)	≥50 y (n=29)
Age, median (range), years	37 (20–49)	56 (50–83)	35 (19–49)	55 (50–68)	33 (18–49)	55 (50–68)
Female (sex at birth)	49 (21)	24 (27)	101 (21)	37 (31)	52 (20)	12 (41)
Male (sex at birth)	189 (79)	65 (73)	390 (79)	82 (69)	202 (80)	17 (59)
Transgender women*	2 (<1)	0	4 (<1)	0	0	0
Body mass index ≥30 kg/m^2	43 (18)	16 (18)	70 (14)	22 (18)	31 (12)	6 (21)
Race						
White	170 (71)	69 (78)	377 (77)	95 (80)	178 (70)	25 (86)
Black or African American	42 (18)	15 (17)	75 (15)	17 (14)	53 (21)	3 (10)
Asian	13 (5)	4 (4)	20 (4)	4 (3)	15 (6)	0
Other	13 (5)	1 (1)	19 (4)	3 (3)	8 (3)	1 (3)

*There were no transgender men.
CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; y, years.

- In total, 983 participants aged <50 y and 237 aged ≥50 y were randomized to receive CAB + RPV LA Q8W or Q4W, or to continue daily oral therapy (**Table 1**).
- Participants ≥65 y accounted for only 1% (n=18/1220; LA, n=17; daily oral therapy, n=1) of the population.

Figure 1. Comorbidities* and Co-medications† in Participants at Baseline



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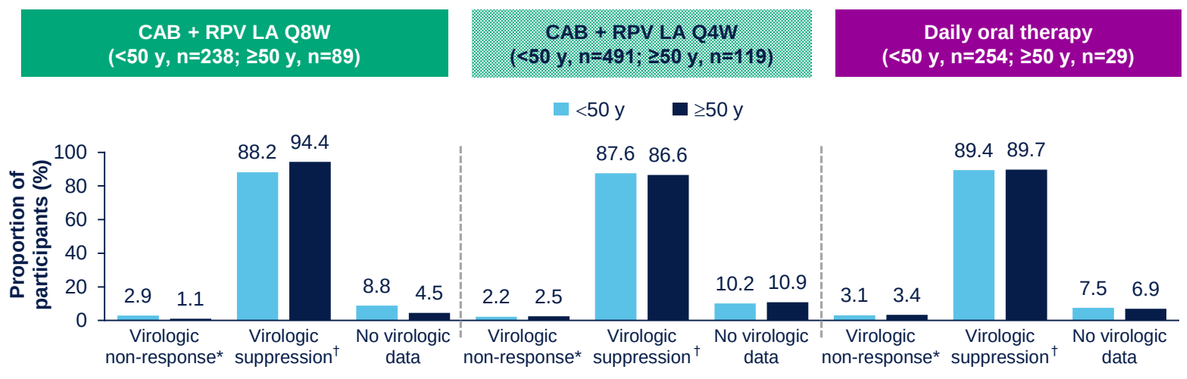
*Comorbidities were defined as those occurring in a pre-specified system organ class of interest per Medical Dictionary for Regulatory Activities grouping.
†Regular medications taken for ≥1 month continuously prior to the start of randomized treatment.
CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; y, years.

- The proportions of participants with comorbidities and co-medications are shown in **Figure 1**.
- The most common classes of comorbidities at baseline:
  - For participants <50 y were psychiatric disorder (LA, 21% [n=151]; daily oral therapy, 16% [n=40]), skin and subcutaneous disorder (LA, 16% [n=116]; daily oral therapy, 16% [n=41]), and gastrointestinal disorder (LA, 15% [n=106]; daily oral therapy, 13% [n=33]).
  - For participants ≥50 y were cardiovascular risk factor (LA, 43% [n=89]; daily oral therapy, 28% [n=8]), metabolism and nutrition disorder (LA, 31% [n=64]; daily oral therapy, 21% [n=6]), and musculoskeletal and connective tissue disorder (LA, 29% [n=60]; daily oral therapy, 28% [n=8]).
- The three most common co-medications by system for the LA arms:
  - For participants <50 y were alimentary tract and metabolism (25%, n=184), nervous system (19%, n=136), and genitourinary system and sex hormones (17%, n=123).
  - For participants ≥50 y were alimentary tract and metabolism (45%, n=93), cardiovascular system (41%, n=86), and nervous system (35%, n=72).

Figure 2. Virologic Outcomes at Week 96



*HIV-1 RNA ≥50 copies/mL per FDA Snapshot algorithm.. †HIV-1 RNA <50 copies/mL per FDA Snapshot algorithm.
CAB, cabotegravir; FDA, U.S. Food and Drug Administration; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; y, years.

- Virologic outcomes were similar across treatment arms and age groups; rates of virologic suppression were high (87–94%) and rates of non-response were low (1–3%), per the FDA Snapshot algorithm (**Figure 2**).
- CVF rates were similarly low across treatment arms and age groups.
  - Q8W: <50 y, 2.1% (n=5); ≥50 y, 1.1% (n=1); Q4W: <50 y, 0.8% (n=4); ≥50 y, 1.7% (n=2); daily oral therapy: <50 y, 1.6% (n=4); ≥50 y, 0%.

Table 2. AE Profiles (Excluding ISRs) Through Week 96

Parameter	CAB + RPV LA Q8W, n (%)		CAB + RPV LA Q4W, n (%)		Daily oral therapy, n (%)	
	<50 y (n=238)	≥50 y (n=89)	<50 y (n=491)	≥50 y (n=119)	<50 y (n=254)	≥50 y (n=29)
Any AE	199 (84)	78 (88)	450 (92)	113 (95)	217 (85)	25 (86)
Drug-related	65 (27)	19 (21)	166 (34)	35 (29)	29 (11)	4 (14)
AEs leading to withdrawal	9 (4)	2 (2)	20 (4)	6 (5)	4 (2)	0
Drug-related	5 (2)*	1 (1)†	11 (2)*	4 (3)†	3 (1)*	0
Any serious AE	13 (5)	8 (9)	29 (6)	11 (9)	18 (7)	4 (14)
Drug-related‡	1 (<1)	0	3 (<1)	1 (<1)	0	0

*Includes: Q8W, headache (n=2), hyperhidrosis, malaise, fatigue, maculopapular rash, osteonecrosis, and pyrexia; Q4W, fatigue (n=2), abnormal dreams (n=2), depression (n=2), discomfort, diarrhea, vomiting, myocardial infarction, dizziness, hypersensitivity, nausea, vertigo, increased transaminases, drug hypersensitivity, chills, disturbance in attention, hyperhidrosis, myalgia, pyrexia, sleep disorder, and insomnia; daily oral therapy, disturbance in attention, dysarthria, amnesia, renal failure, dizziness, fatigue, and nausea. All occurred in one participant each unless specified. More than one reason could have been reported per participant.
†Includes: Q8W, asthenia; Q4W, depression, influenza, headache, hyperhidrosis, nausea, presyncope, disturbance in attention, and sleep disorder. All occurred in one participant each. More than one reason could have been reported per participant.
‡Includes hypersensitivity and suspected (partial) intravenous administration of RPV; drug hypersensitivity; osteonecrosis; right knee monoarthritis; and myocardial infarction. The latter three were not considered drug related by sponsor. All occurred in one participant each.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; y, years.

- The frequency of drug-related AEs, serious AEs, and AEs leading to withdrawal were broadly comparable between age groups for both LA regimens (**Table 2**).

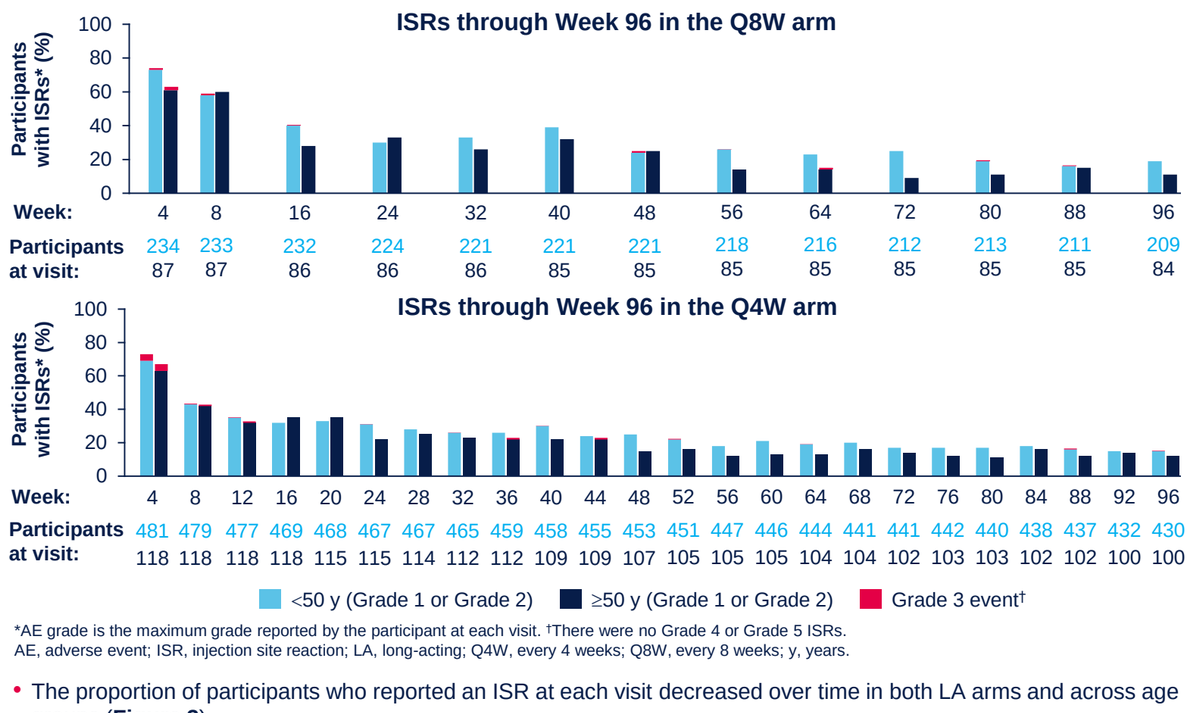
Table 3. ISR Summary Through Week 96

	CAB + RPV LA Q8W		CAB + RPV LA Q4W	
	<50 y (n=238)	≥50 y (n=89)	<50 y (n=491)	≥50 y (n=119)
Number of participants receiving injections, n (%)	234 (98)	87 (98)	481 (98)	118 (99)
Number of injections	5732	2222	21,784	5201
ISR events, n	1793	552	5145	963
Injection site pain, n (% of injections)*	1455 (25)	449 (20)	4291 (20)	744 (14)
Injection site nodule, n (% of injections)*	72 (1)	35 (2)	281 (1)	74 (1)
Injection site discomfort, n (% of injections)*	92 (2)	21 (<1)	69 (<1)	38 (<1)
Grade 3 ISR events, n (% of ISR events)†	30 (2)	4 (<1)	45 (<1)	17 (2)
Median (IQR) duration of ISRs, days	3 (2–4)	3 (2–5)	3 (2–4)	3 (2–5)
Participants withdrawing for injection-related reasons, n (%)	3 (1)	2 (2)	11 (2)	4 (3)

*Those occurring with ≥1% of injections in either treatment arm are shown. †There were no Grade 4 or 5 ISRs.
CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; y, years.

- Participants aged <50 y and ≥50 y experienced similar types of ISRs, with injection site pain being the most commonly reported (20% [n=6939/34,939] of all injections) (**Table 3**).
  - Of note, the ISR profile was similar in participants ≥65 y, with 68 ISRs reported across 552 injections, of which the most common was injection site pain, occurring with 11% of all injections (n=58/552).
- Overall, most ISRs were classified as Grade 1 (83%, n=7000/8453) or 2 (16%, n=1357/8453). The majority had a duration ≤7 days (median duration of 3 days) and few led to withdrawal.

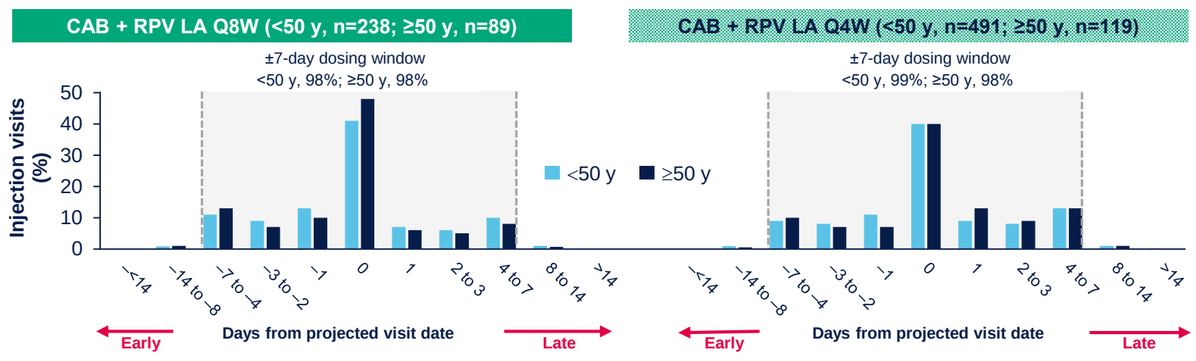
Figure 3. ISR Incidence Over Time Through Week 96



*AE grade is the maximum grade reported by the participant at each visit. †There were no Grade 4 or Grade 5 ISRs.
AE, adverse event; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; y, years.

- The proportion of participants who reported an ISR at each visit decreased over time in both LA arms and across age groups (**Figure 3**).

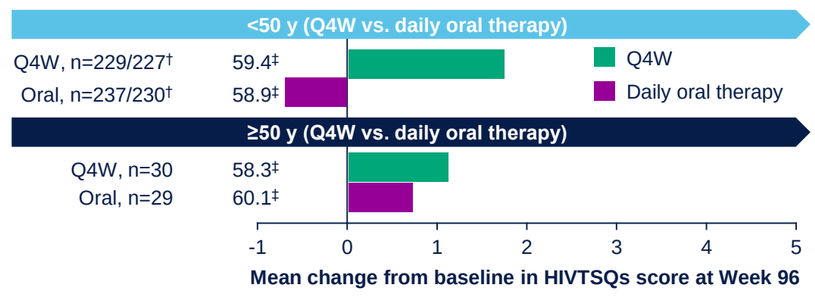
Figure 4. Adherence to Dosing Window Between Age Groups and Dosing Regimens



CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; y, years.

- Approximately 98% of injection visits occurred within the ±7-day dosing window, consistently across age and dosing groups (**Figure 4**). For participants ≥65 y, 96% (Q8W, n=138/144) and 99% (Q4W, n=114/115) of injection visits occurred within the ±7-day dosing window.

Figure 5. Treatment Satisfaction by Age Group (FLAIR only)*



*No statistical tests were carried out. †Baseline/Week 96. ‡Mean baseline HIVTSQs score.
HIVTSQs, HIV Treatment Satisfaction Questionnaire status version; LA, long-acting; Q4W, every 4 weeks; y, years.

- Irrespective of age group, mean improvement from baseline in HIVTSQs score was greater in participants receiving LA therapy in comparison to participants receiving daily oral therapy (**Figure 5**).

Pharmacokinetics

- **Q8W arm**: Median (5th and 95th percentile) plasma CAB and RPV trough concentrations were 1.73 (0.48, 3.83) µg/mL and 48.4 (20.9, 111.0) ng/mL at Week 8, 1.64 (0.71, 3.02) µg/mL and 64.2 (33.5, 128.0) ng/mL at Week 48, and 1.6 (0.79, 3.14) µg/mL and 87.6 (43.5, 160.0) ng/mL at Week 96, respectively.
- **Q4W arm**: Median (5th and 95th percentile) plasma CAB and RPV trough concentrations were 1.71 (0.49, 3.71) µg/mL and 42.9 (18.2, 98.4) ng/mL at Week 8, 2.94 (1.52, 5.42) µg/mL and 87.6 (41.3, 156.0) ng/mL at Week 48, and 2.82 (1.47, 5.10) µg/mL and 114.5 (65.5, 222.0) ng/mL at Week 96, respectively.
- CAB and RPV plasma concentrations over time were similar across both age groups.

Conclusions

- CAB + RPV LA demonstrated high efficacy across participants aged <50 y and ≥50 y, with 87–94% maintaining HIV-1 virologic suppression at Week 96.
  - CVF was infrequent (1–2%) and occurred at a similar rate across participants aged <50 y and ≥50 y.
- Safety and tolerability of CAB + RPV LA was similar in participants aged <50 y and ≥50 y through Week 96.
  - ISRs were mostly mild or moderate, short in duration, decreased in incidence over time, and led to few withdrawals.
- Most (98–99%) CAB + RPV LA injections were received within the ±7-day dosing window.
- These data support the use of CAB + RPV LA dosed monthly or every 2 months as a complete regimen for the maintenance of HIV-1 virologic suppression in adults, irrespective of age.

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