LONG-ACTING CABOTEGRAVIR+RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M WEEK 152 RESULTS

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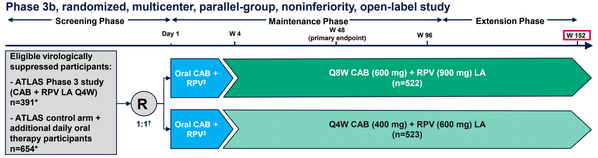
Introduction

- Long-acting cabotegravir + rilpivirine (CAB + RPV LA) administered monthly[1,2] or every 2 months[3] is the first and only complete LA regimen recommended by treatment guidelines[4–6] for the maintenance of HIV-1 virologic suppression.
- 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.
- Durable noninferior efficacy of CAB + RPV LA was demonstrated between monthly dosing and oral comparator ART, as well as between every 2 months and monthly dosing, at Weeks 48[1–3] and 96.[7–9]
- We report efficacy, safety, and satisfaction through 3 years of CAB + RPV LA monthly and every 2 months dosing from the Phase 3b ATLAS-2M study (NCT03299049).

Methods

Figure 1. ATLAS-2M Study Design



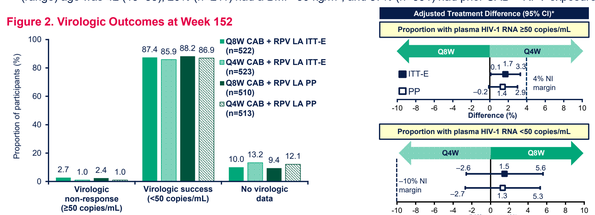
†ITT-E population. ‡Randomization was stratified by prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). §Excluding participants with prior CAB + RPV exposure in ATLAS (n=391). For further study design details, please see Overton ET, et al. *Lancet.* 2020;396(10267):1994–2005. CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; W, week.

- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (FDA Snapshot, ITT-E) (**Figure 1**).
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 copies/mL at Week 152 (FDA Snapshot, ITT-E).
  - Per-protocol analyses were carried out at specific time points, including Week 48, Week 96, and Week 152.
- Other endpoints assessed at Week 152 included the incidence of confirmed virologic failure (CVF; two consecutive plasma HIV-1 RNA levels ≥200 copies/mL), incidence of viral resistance in participants with CVF, safety and tolerability, and treatment satisfaction.

Results

- Baseline characteristics were similar between arms; 27% (n=280) of participants were female at birth, median (range) age was 42 (19–83), 20% (n=211) had a BMI ≥30 kg/m^2, and 37% (n=391) had prior CAB + RPV exposure.[3]

Figure 2. Virologic Outcomes at Week 152



*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; PP, per protocol; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- Noninferiority between Q8W and Q4W was confirmed for pre-specified analyses of HIV-1 RNA ≥50 and <50 copies/mL (**Figure 2**).
- Results for the pre-specified per-protocol population were consistent with those for the ITT-E population.

Long-acting CAB + RPV administered every 8 weeks demonstrated durable, noninferior efficacy and comparable safety outcomes compared with every 4 weeks dosing over 152 weeks of treatment.

Table 1. Snapshot Outcomes at Week 152 (ITT-E Population)

ITT-E Population, n (%)	Q8W (n=522)	Q4W (n=523)
HIV-1 RNA <50 copies/mL	456 (87)	449 (86)
HIV-1 RNA ≥50 copies/mL	14 (3)	5 (1)
Data in window not below threshold	1 (<1)	0 (0)
Discontinued for lack of efficacy	12 (2)	4 (1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)
No virologic data	52 (10)	69 (13)
Discontinued study due to AE or death*	23 (4)	24 (5)
Discontinued study for other reason†	28 (5)	44 (8)†
On study but missing data in window	1 (<1)‡	1 (<1)

*There were five deaths between the Week 96 and Week 152 analyses: suicide (n=1) and pancreatic cancer (n=1) in the Q8W arm; cardiac arrest (n=1), chronic obstructive pulmonary disease and chronic renal failure (n=1), and angina pectoris (n=1) in the Q4W arm. †Two participants discontinued due to COVID-19–related reasons. ‡COVID-19 related.
AE, adverse event; ITT-E, intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

- Efficacy results are shown in **Table 1**.

Table 2. Snapshot "Discontinued Study for Other Reason" Through Week 152 (ITT-E Population)

ITT-E Population, n (%)	Q8W (n=522)	Q4W (n=523)
Discontinued study for other reason	28 (5)	44 (8)
Withdrawal by participant	16 (2)*	33 (6)
Physician decision†	5 (1)	3 (<1)
Protocol deviation	2 (<1)	4 (<1)
Protocol-specified withdrawal criterion met‡	2 (<1)	3 (<1)
Lost to follow-up	2 (<1)	1 (1)
Lack of efficacy	1 (<1)	0 (0)

*Three participants completed the Maintenance Phase but decided not to continue to the Extension Phase, citing no specific reason for discontinuation beyond the completion of their study commitment. †Q8W, pulmonary tuberculosis (n=1), increased memory loss caused concerns about ability to consent (n=1), false-positive pregnancy test (n=1), participant was randomized in error (n=1), participant required long-term anticoagulant treatment (n=1); Q4W, other medical needs (n=1), participant relocated and communicated desire to withdraw to site staff (n=1), significant cardiovascular history (n=1). ‡The protocol-specified withdrawal criterion met for the five participants was pregnancy.
ITT-E, intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

- Withdrawal by participant was more common in the Q4W arm than the Q8W arm (**Table 2**).
  - The most common reasons for withdrawal by participant included frequency of visits (Q8W, n=4; Q4W, n=10), participant relocated (Q8W, n=1; Q4W, n=6), and intolerability of injections (Q8W, n=1; Q4W, n=8).
- Prohibited medication use (Q8W, n=0; Q4W, n=3) was the most common reason for protocol deviation.

Table 3. Participants With CVF Since the Week 96 Analysis

Participants With CVF Since Week 96					
#, arm	Sex at birth, BMI (kg/m^2), country	HIV-1 subtype at baseline	Viral load at failure (copies/mL)	RPV RAMs observed at failure	INI RAMs observed at failure
1, Q8W	Male, <30, Germany	B	24,221	E138A+M230M/L	Q148R
2, Q8W	Male, <30, Russia	A6*	59,467	E138A+Y181Y/C	Q148R

*This participant was originally classified as subtype A1 but, upon reanalysis, was later reclassified as subtype A6.
BMI, body mass index; CVF, confirmed virologic failure; INI, integrase inhibitor; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

- The characteristics of the two participants (Q8W arm) who met the CVF criterion between Week 96 and 152 (Week 112 and Week 120) are shown in **Table 3**.
  - Neither had RAMs at baseline; however, the participant with subtype A6 had L74I integrase (IN) polymorphism at baseline.
  - Both had treatment-emergent RAMs to CAB (Q148R) and RPV (E138A+Y181Y/C; E138A+M230M/L).
- In total, through Week 152, 13 participants had CVF (Q8W, n=11 [2%]; Q4W, n=2 [<1%]).
- Most CVFs occurred by Week 48 (77%, n=10/13), with 6/10 (60%) having ≥2 baseline factors (proviral RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m^2), which have been reported to be associated with increased risk of failure.[10]
- No participants with CVF through Week 152 had injection visits >7 days later than the scheduled visit date.
- Overall, 12/13 CVFs resuppressed on alternative regimens (one participant was non-adherent to protease inhibitor [PI]-based ART).
- An additional participant had a 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.

Table 4. Safety Summary (Excluding ISRs) Through Week 152

Parameter, n (%)	Q8W (n=522)	Q4W (n=523)
Any AE	469 (90)	490 (94)
Drug-related AEs	142 (27)	167 (32)
Any Grade ≥3 AE	66 (13)	63 (12)
Drug related*	10 (2)	10 (2)
Leading to withdrawal	17 (3)	20 (4)
Drug related	6 (1)	13 (2)
Any serious AE	48 (9)	44 (8)
Drug related	3 (<1)	3 (<1)

*One drug-related AE in each arm was Grade 4 (Q8W, acute pancreatitis [n=1]; Q4W, increased blood creatine phosphokinase [n=1]); none were Grade 5.
AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

- Safety profiles at Week 152 (**Table 4**) were consistent with the previous analyses, with no new significant safety information observed.
- Since Week 96, excluding ISRs, there were two participants with drug-related AEs leading to withdrawal (both Q4W, lipoatrophy and pyrexia) and no drug-related serious AEs.

Table 5. Common Adverse Events (Excluding ISRs) Through Week 152

Parameter, n (%)	Q8W (n=522)	Q4W (n=523)
AEs occurring in ≥10% of participants		
Nasopharyngitis	97 (19)	105 (20)
URTI	80 (15)	98 (19)
Headache	66 (13)	82 (16)
Back pain	64 (12)	77 (15)
Arthralgia	62 (12)	65 (12)
Diarrhea	56 (11)	66 (13)
Pyrexia	48 (9)	73 (14)
Drug-related AEs occurring in ≥3% of participants		
Pyrexia	23 (4)	33 (6)
Fatigue	11 (2)	23 (4)

AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks; URTI, upper respiratory tract infection.

- Common AEs (excluding ISRs) through Week 152 are shown in **Table 5**.

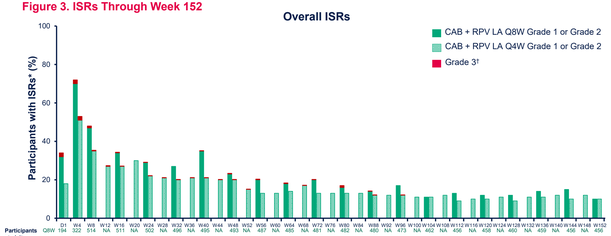
Table 6. ISR Summary Through Week 152

	Q8W (n=522)	Q4W (n=523)
Participants who received ≥1 injection, n (%)	516 (99)	517 (99)
Number of injections	20,563	39,478
ISR events, n*	4168	5494
Injection site pain, n (% of injections)†	3189 (16)	4180 (11)
Injection site nodule, n (% of injections)†	259 (1)	457 (1)
Grade 3, n (% of ISR events)‡	54 (1)	50 (1)
Median duration, days (IQR)	3 (2, 5)	3 (2, 5)
Participants withdrawing for injection-related reasons, n (% of participants with injections)	8 (2)	13 (3)

*Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. †Those occurring with ≥1% of injections in either treatment arm are shown. ‡There were no Grade 4 or Grade 5 ISRs. AE, adverse event; IQR, interquartile range; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks.

- ISRs were the most common AEs; most were mild to moderate in severity (99%, n=9555/9662), short-lived (median duration 3 days), with few participants discontinuing due to injection-related reasons (**Table 6**).
- Three participants withdrew due to injection-related reasons between Week 96 and Week 152 (Q8W, n=1; Q4W, n=2).

Figure 3. ISRs Through Week 152



*AE grade is the maximum grade reported by the participant at each visit. †There were no Grade 4 or 5 ISRs.
AE, adverse event; CAB, cabotegravir; D, day; ISR, injection site reaction; LA, long-acting; NA, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; W, week.

- The number of participants reporting ISRs at each visit decreased over the first 48 weeks and remained consistent thereafter (**Figure 3**).

Treatment Satisfaction

- In participants without prior CAB exposure, HIV treatment satisfaction questionnaire total mean scores significantly improved* (Q8W, 4.98; Q4W, 3.23) from baseline (Q8W, 57.73; Q4W, 56.72) to Week 152 for both treatment groups.
- The adjusted mean change* from baseline significantly favored Q8W dosing at all three timepoints (Week 24, 1.07 [p=0.036]; Week 48, 1.73 [p=0.004]; Week 152, 1.75 [p=0.004]).

*Adjusted for baseline score, sex at birth, age (<50, ≥50 years), race (White, non-White), and third agent class (INI, PI, non-nucleoside reverse transcriptase inhibitor).

Conclusions

- CAB + RPV LA Q8W continued to be noninferior to Q4W at Week 152, with both regimens maintaining high levels of virologic suppression (86–87%).
- Through Week 152, the overall rate of CVF was low (1%, n=13/1045), with two additional participants (Q8W arm) meeting the criterion after Week 96. One non-protocol-defined failure (<1%, n=1/1045) was identified at Week 48 and is reported herein.
  - Overall, 11/13 participants developed resistance to CAB and/or RPV; 12/13 resuppressed on an alternative treatment regimen (one participant was non-adherent to PI-based ART).
- CAB + RPV LA was well tolerated, with a comparable safety profile between arms.
  - No new safety signals were identified since the Week 48 analysis.
  - ISRs were mostly Grade 1–2 (99%), short-lived (median 3 days), with few discontinuations (2%) due to injection-related reasons.
- Treatment satisfaction increased significantly from baseline in participants without prior exposure and significantly favored Q8W at all timepoints through Week 152.
- These long-term data further support the efficacy, safety, and durability of CAB + RPV LA for the maintenance of HIV-1 virologic suppression.

Acknowledgments
The authors thank everyone who has contributed to the success of ATLAS-2M: all study participants and their families; the ATLAS-2M clinical investigators and their staff in Australia, Argentina, Canada, France, Germany, Italy, Mexico, Republic of Korea, Russian Federation, South Africa, Spain, Sweden, and the United States. ATLAS-2M was funded by ViiV Healthcare and Janssen Pharmaceutica.
Editorial assistance was provided by Poppie Cooper and Daniel Williams of SciMentum (Nucleus Global), with funding provided by ViiV Healthcare.

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