WEEK 96 EFFICACY AND SAFETY OF LONG-ACTING CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M


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ATLAS-2M Week 96: Introduction

• Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, have been approved in the US, Canada, and Europe as the first complete long-acting (LA) injectable regimen indicated for the maintenance of virologic suppression in people living with HIV-1\(^1\)–\(^3\)

• CAB + RPV LA administered monthly\(^4\),\(^5\) or at a longer every 2 months dosing interval\(^6\) may address challenges associated with daily oral ART, such as stigma, pill burden, drug/food interactions, and adherence

• Here, we report the Week 96 results of the ATLAS-2M study

ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

ATLAS-2M Week 96: Study Design

Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study

Screening Phase

Day 1

W 4

W 48

W 96

W 100

W 152

Maintenance Phase

Eligible participants:
- ATLAS Phase 3 study (CAB + RPV LA Q4W)
  n=391*
- ATLAS SoC arm + additional SoC participants
  n=654*

R

1:1†

Oral CAB + RPV‡

Q8W CAB (600 mg) + RPV (900 mg) LA
  (n=522)

Q4W CAB (400 mg) + RPV (600 mg) LA
  (n=523)

Participants had the option to continue randomized CAB + RPV LA therapy Q8W at Week 100

Participants had the option to continue randomized CAB + RPV LA therapy Q4W at Week 100

Extension Phase

Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study

• The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
• Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)
• Other endpoints assessed at Week 96 included the incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL), incidence of viral resistance in participants with CVF, and safety and tolerability

*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.

For further study design details, please see Overton et al, CROI 2020; Boston, MA. Presentation 3334.³
CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomized; RPV, rilpivirine; SoC, standard of care; W, week.


Conference on Retroviruses and Opportunistic Infections; March 6-10, 2021; Virtual

Jaeger et al. CROI 2021; Virtual. Science Spotlight
ATLAS-2M Week 96: Virologic Snapshot Outcomes for ITT-E: CAB + RPV LA Continued to Maintain High Levels of Viral Suppression

Adjusted Treatment Difference at Week 96 (95% CI)*

Proportion of participants with plasma HIV-1 RNA ≥50 c/mL

Proportion of participants with plasma HIV-1 RNA <50 c/mL

*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; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Jaeger et al. CROI 2021; Virtual. Science Spotlight
### ATLAS-2M Week 96: Snapshot Outcomes at Week 96 (ITT-E Population)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Q8W* (n=522)</th>
<th>Q4W* (n=523)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 c/mL</td>
<td>475 (91.0)</td>
<td>472 (90.2)</td>
</tr>
<tr>
<td>Adjusted† difference (95% CI)</td>
<td></td>
<td>0.8 (–2.8, 4.3)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥50 c/mL</td>
<td>11 (2.1)</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Adjusted† difference (95% CI)</td>
<td></td>
<td>1.0 (–0.6, 2.5)</td>
</tr>
<tr>
<td>Data in window not below threshold</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>8 (1.5)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Discontinued for other reason while not below threshold</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>No virologic data</strong></td>
<td>36 (6.9)</td>
<td>45 (8.6)</td>
</tr>
<tr>
<td>Discontinued study due to AE or death‡</td>
<td>17 (3.3)</td>
<td>17 (3.3)</td>
</tr>
<tr>
<td>Discontinued study for other reason</td>
<td>16 (3.1)</td>
<td>27 (5.2)</td>
</tr>
<tr>
<td>On study but missing data in window</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

*No discontinuations were attributed to COVID-19, though missing virologic data for four on-study participants were deemed to be COVID-19 related. COVID-19 introduced negligible impact on efficacy and no impact on the conclusions drawn at Week 96. n (%) unless otherwise stated.

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

‡There were two deaths in the Maintenance Phase; one due to sepsis reported in the Week 48 analysis (Q8W arm), and one due to suicide since the Week 48 analysis (Q4W arm).

AE: adverse event; CI: confidence interval; ITT-E: intention-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Jaeger et al. CROI 2021; Virtual. Science Spotlight
Overall Summary of CVFs through Week 96

<table>
<thead>
<tr>
<th></th>
<th>CVFs n (%)</th>
<th>CVFs with RPV RAMs*</th>
<th>RPV RAMs observed at failure</th>
<th>CVFs with IN RAMs*</th>
<th>IN RAMs observed at failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8W</td>
<td>9 (1.7)</td>
<td>7/9</td>
<td>K101E, E138E/K, E138A, Y188L, Y181C</td>
<td>5/9</td>
<td>Q148R,† N155H†</td>
</tr>
<tr>
<td>Q4W</td>
<td>2 (0.4)</td>
<td>1/2</td>
<td>K101E, M230L</td>
<td>2/2</td>
<td>E138E/K, Q148R, N155N/H</td>
</tr>
</tbody>
</table>

• One additional participant, who was in the Q8W arm, met the CVF criterion between Week 48 and 96 (Week 88):†
  • NNRTI RAM K103N and RPV RAM Y181C were detected at virologic failure in the plasma sample and retrospectively at baseline in the PBMC sample
  • No INSTI RAMs were present at virologic failure in the plasma sample or in the baseline PBMC sample; IN substitution L74L/I was present at baseline
  • 10/11 CVFs resuppressed on alternative regimens (one participant was non-adherent to PI-based ART)
  • All participants with CVF retained phenotypic susceptibility to dolutegravir

*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.
†The participant with CVF was a male from the US with a BMI <30 kg/m² and HIV-1 subtype B. The participant had a viral load of 1916 c/mL at SVF and 9063 c/mL at the confirmatory visit.
ART, antiretroviral therapy; BMI, body mass index; CVF, confirmed virologic failure; IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure.
ATLAS-2M Week 96: Adverse Event Profiles and Injection Site Reactions Were Similar Between Q8W and Q4W Dosing

<table>
<thead>
<tr>
<th></th>
<th>Q8W (n=522)</th>
<th>Q4W (n=523)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) [delta*]</td>
<td>n (%) [delta*]</td>
</tr>
<tr>
<td>Any AE</td>
<td>488 (93) [+15]</td>
<td>499 (95) [+17]</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>415 (80) [+15]</td>
<td>413 (79) [+14]</td>
</tr>
<tr>
<td>Excluding ISRs</td>
<td>122 (23) [+13]</td>
<td>146 (28) [+21]</td>
</tr>
<tr>
<td>Any Grade ≥3 AE</td>
<td>57 (11) [+16]</td>
<td>65 (12) [+16]</td>
</tr>
<tr>
<td>Drug-related (excluding ISRs)**</td>
<td>8 (2) [+4]</td>
<td>10 (2) [+5]</td>
</tr>
<tr>
<td>Leading to withdrawal</td>
<td>18 (3) [+6]</td>
<td>19 (4) [+6]</td>
</tr>
<tr>
<td>Drug-related (excluding ISRs)**</td>
<td>8 (2) [+3‡]</td>
<td>12 (2) [+4§]</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>33 (6) [+6]</td>
<td>28 (5) [+9]</td>
</tr>
<tr>
<td>Drug-related (excluding ISRs)**</td>
<td>3 (&lt;1) [+1]</td>
<td>3 (&lt;1) [+2]</td>
</tr>
</tbody>
</table>

- The AE profile remained consistent through the Week 48 and Week 96 analyses
- The type and frequency of AEs were similar between arms; the most common non-ISR drug-related AEs were pyrexia and fatigue
- Most ISRs were Grade 1–2 (99%, n=7453/7557), with <2% of participants withdrawing due to injection-related reasons; only one participant (Q8W arm) withdrew since the Week 48 analysis
- The number of participants experiencing an ISR at each visit decreased over the duration of the study‡‡

*Delta value represents new participants with AEs since the Week 48 analysis. †One drug-related AE in each arm was Grade 4; none were Grade 5. ‡Malaise and hyperhidrosis (n=1), headache (n=1), osteonecrosis (n=1). §Disturbance in attention and sleep disorder (n=1), nausea and vertigo (n=1), drug hypersensitivity (n=1), myocardial infarction (n=1). ‡‡There were no Grade 4 or Grade 5 ISRs. ††Week 48: Q8W, n=115/493 (23%); Q4W, n=100/488 (20%); Week 96: Q8W, n=74/473 (16%); Q4W, n=54/468 (12%).
ATLAS-2M Week 96: Conclusions

- Both dosing regimens of CAB + RPV LA maintained high levels of virologic suppression (Q8W 91%; Q4W 90%), with few participants having HIV-1 RNA ≥50 c/mL (Q8W, 2%; Q4W, 1%) at Week 96, demonstrating noninferiority of Q8W vs. Q4W dosing.

- The rate of CVF was low overall (n=11/1045 [1%]), with only one participant (Q8W arm) meeting the criterion in the second year of therapy.

- 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), and decreased in incidence over time.

- These longer-term efficacy, safety, and tolerability data support CAB + RPV LA dosed monthly or Q2M as a complete regimen for the maintenance of HIV-1 virologic suppression in adults.*

*Monthly dosing of CAB + RPV LA approved by the FDA (January 2021).

CAB, cabotegravir; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
The authors thank everyone who has contributed to the success of ATLAS-2M

- All study participants and their families
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