North American Phase 3/3b Experience With Long-Acting Cabotegravir and Rilpivirine: Efficacy, Safety, and Virologic Outcomes

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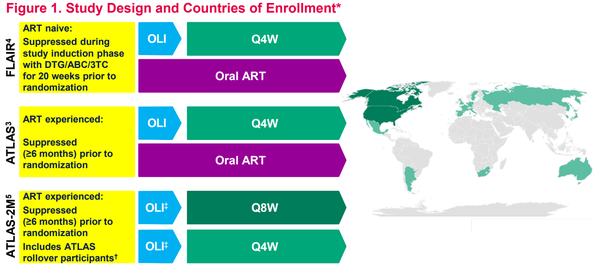
Introduction

- Cabotegravir (CAB) plus rilpivirine (RPV) is the first complete long-acting (LA) regimen recommended by treatment guidelines[1,2] for the maintenance of HIV-1 virologic suppression.
- Monthly or every 2 months dosing of CAB + RPV LA may address some of the challenges associated with daily oral antiretroviral therapy (ART), such as fear of inadvertent disclosure, anxiety related to staying adherent, and the daily reminder of HIV status.
- CAB + RPV LA dosed every 4 weeks (Q4W; ATLAS,[3] FLAIR,[4] ATLAS-2M[5]) or every 8 weeks (Q8W; ATLAS-2M[5]) has demonstrated efficacy in multinational Phase 3/3b trials (**Figure 1**).
- This *post hoc* descriptive analysis summarizes the efficacy, virologic outcomes, safety, and treatment preference for US and Canadian (US/CAN) participants across ATLAS, FLAIR, and ATLAS-2M through Week 48.
  - The presence of ≥2 baseline factors (archived RPV resistance-associated mutations [RAMs], HIV-1 subtype A6/A1, and/or body mass index [BMI] ≥30 kg/m^2) modestly increased risk of confirmed virologic failure (CVF) in a *post hoc* multivariable analysis.[6]

Figure 1. Study Design and Countries of Enrollment*

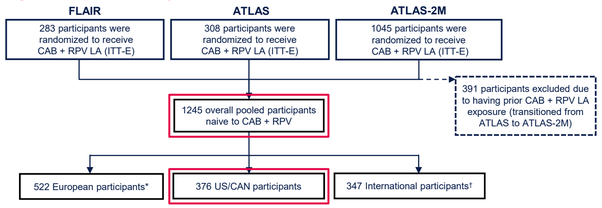


*Argentina, Australia, Canada, France, Germany, Italy, Japan, Mexico, the Netherlands, Republic of Korea, Russian Federation, South Africa, Spain, Sweden, United Kingdom, and United States. †Participants could enter ATLAS-2M from either arm of the ATLAS study. ‡Rollover participants with prior CAB + RPV exposure did not receive an OLI. ART, antiretroviral therapy; CAB, cabotegravir; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; OLI, oral lead-in; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Methods

- Data for US/CAN participants without prior CAB + RPV exposure (n=376) from the larger pooled ATLAS,[3] FLAIR,[4] and ATLAS-2M[5] Phase 3/3b studies (N=1245) were analyzed (**Figure 2**).

Figure 2. Population Analyzed



*France, Germany, Italy, Spain, Sweden, the Netherlands, and the United Kingdom.
†Argentina, Australia, Japan, Mexico, Republic of Korea, Russian Federation, and South Africa.
CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine; US/CAN, United States/Canada.

Endpoints Assessed at Week 48 in this *Post Hoc* Analysis

- The proportion of participants with plasma HIV-1 RNA ≥50 copies/mL.
- The proportion of participants with plasma HIV-1 RNA <50 copies/mL.
- The incidence of CVF (two consecutive HIV-1 RNA ≥200 copies/mL).
- The prevalence of baseline factors associated with CVF and their relation to virologic outcome.
- Safety and tolerability.
- Treatment preference.

Results

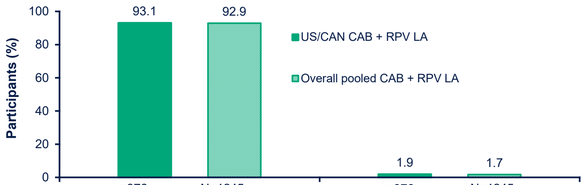
- Most US/CAN participants were white (67%), with a median age of 39 years (**Table 1**).
- Overall, 26% of US/CAN participants had BMI ≥30 kg/m^2, whereas the presence of HIV-1 subtype A6/A1 and archived RPV RAMs was uncommon.
  - HIV-1 subtype A6/A1 was notably more common in the overall pooled population due to the higher prevalence in Russia (**Table 1**).

Table 1. Baseline Characteristics (ITT-E Population)

ITT-E population	US/CAN CAB + RPV LA Q4W + Q8W (n=376)	Overall pooled CAB + RPV LA Q4W + Q8W (N=1245)
Age, median (range) years	39 (20–74)	39 (19–83)
Female (sex at birth), n (%)	56 (15)	310 (25)
Race, n (%)		
White	253 (67)	924 (74)
Black or African American	95 (25)	211 (17)
Asian	16 (4)	63 (5)
Other	12 (3)	47 (4)
Hispanic or Latinx ethnicity, n (%)	56 (15)	159 (13)
BMI, median (range) kg/m^2	26.7 (17.3–54.0)	25.1 (15.3–54.0)
Country of enrollment, n (%)		
Canada	81 (22)	81 (7)
United States	295 (78)	295 (24)
Baseline factors associated with increased risk of CVF, n (%)		
RPV RAM(s)	12 (3)	38 (3)
HIV-1 subtype A6/A1	4 (1)	127 (10)
BMI ≥30 kg/m^2	99 (26)	213 (17)

BMI, body mass index; CAB, cabotegravir; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine; US/CAN, United States/Canada.

Figure 3. Virologic Outcomes with CAB + RPV LA Q4W + Q8W at Week 48 (ITT-E Population)



CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; US/CAN, United States/Canada.

Table 2. Snapshot Outcomes at Week 48 (ITT-E Population)

(ITT-E population)	US/CAN CAB + RPV LA Q4W (n=265)	Overall pooled CAB + RPV LA Q4W (n=918)	US/CAN CAB + RPV LA Q8W (n=111)	Overall pooled CAB + RPV LA Q8W (n=327)
HIV-1 RNA <50 copies/mL, n (%)	246 (92.8)	850 (92.6)	104 (93.7)	306 (93.6)
HIV-1 RNA ≥50 copies/mL, n (%)	4 (1.5)	16 (1.7)	3 (2.7)	5 (1.5)
Data in window not below threshold	3 (1.1)	5 (0.5)	1 (0.9)	1 (0.3)
Discontinued for lack of efficacy	1 (0.4)	9 (1.0)	2 (1.8)	4 (1.2)
Discontinued for other reason while not below threshold	0	2 (0.2)	0	0
No virologic data in Week 48 window, n (%)	15 (5.7)	52 (5.7)	4 (3.6)	16 (4.9)
Discontinued due to AE or death	7 (2.6)	30 (3.3)	2 (1.8)	6 (1.8)
Discontinued for other reasons	8 (3.0)	22 (2.4)	2 (1.8)	10 (3.1)

AE, adverse event; CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; US/CAN, United States/Canada.

- The majority of US/CAN participants across the three studies maintained virologic suppression with CAB + RPV LA, similar to the overall pooled CAB + RPV LA population (**Figure 3/Table 2**).
- In the overall pooled oral ART comparator of participants from ATLAS and FLAIR, 94.4% (n=558/591) maintained virologic suppression, with 1.7% (n=10/591) having HIV-1 RNA ≥50 copies/mL.[7]

Table 3. Prevalence of Baseline Factors in Relation to Virologic Outcome (ITT-E Population) for US/CAN Participants

Baseline factors, n (%)	Virologic success, n (%)	CVF, n (%)
None of the three factors*	**214/229 (93.4)**	**1/229 (0.4)**
Any one of the three baseline factors*†	**83/89 (93.3)**	**0/89 (0)**
At least two of the three baseline factors*	**3/5 (60.0)**	**2/5 (40.0)**
RPV RAM(s) + HIV-1 subtype A6/A1	0/0 (0)	0/0 (0)
RPV RAM(s) + BMI ≥30 kg/m^2	2/3 (66.7)	1/3 (33.3)
HIV-1 subtype A6/A1 + BMI ≥30 kg/m^2	1/1 (100)	0/1 (0)
All three baseline factors	0/1 (0)	1/1 (100)
TOTAL (95% CI [exact method])	**350/376 (93.1) (90.0–95.4)**	**3/376 (0.8) (0.2–2.3)**

*53 participants with missing data were excluded; 50/53 maintained success, none had CVF. Baseline factors were archived RPV RAM(s), HIV-1 subtype A6/A1, and/or BMI ≥30 kg/m^2. †None of the 79 participants with BMI ≥30 kg/m^2 as the only factor had CVF.
BMI, body mass index; CI, confidence interval; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; RAM, resistance-associated mutation; RPV, rilpivirine; US/CAN, United States/Canada.

- Among the US/CAN participants with a single baseline factor, none met the CVF criterion; this included 79 participants with BMI ≥30 kg/m^2 as their only baseline factor (**Table 3**).
  - Subtype A6/A1 was uncommon in US/CAN participants, as shown in **Table 1**.
- All 3 participants with CVF had treatment-emergent RAMs to integrase strand transfer inhibitor (INSTI, n=3) or non-nucleoside reverse transcriptase inhibitor (n=1).
- All 3 participants were resuppressed on an alternate regimen (protease inhibitor based, n=2; INSTI based, n=1) during long-term follow-up.

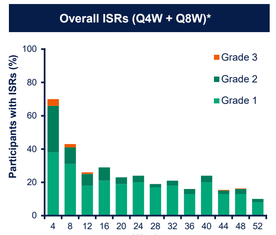
Table 4. Safety Overview Through Week 48 (Excluding Injection Site Reactions [ISRs])

Parameter, n (%)	US/CAN CAB + RPV LA Q4W + Q8W (n=376)	US/CAN oral ART (n=165)
Any AE	307 (82)	114 (69)
Any Grade ≥3 AE	19 (5)	13 (8)
Any drug-related AE	82 (22)	5 (3)
Any Grade ≥3 drug-related AE	2 (<1)	1 (<1)
AE leading to withdrawal	5 (1)	4 (2)
Drug related	5 (1)*	1 (<1)
Any SAE	9 (2)	10 (6)
Drug related	0	1 (<1)
Any fatal SAE	0	1 (<1)†

*Reasons included: headache, hyperhidrosis, nausea, presyncope (n=1); abnormal dreams, chills, disturbance in attention, fatigue, hyperhidrosis, myalgia, pyrexia, sleep disorder (n=1); depression, fatigue (n=1); abnormal dreams, insomnia (n=1); asthenia (n=1). †Methamphetamine overdose.
AE, adverse event; ART, antiretroviral therapy; CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SAE, serious adverse event; US/CAN, United States/Canada.

- No new safety signals were identified in the US/CAN participants (**Table 4**).
- The most common AEs in US/CAN participants were upper respiratory tract infection (22%, n=84), diarrhea (9%, n=35), and fatigue (9%, n=34).
- Drug-related AEs (excluding ISRs) were uncommon in US/CAN participants, with only fatigue (5%, n=20), nausea (4%, n=16), and headache (3%, n=13) occurring in ≥3% of participants.

Figure 4. ISR Summary in US/CAN Participants

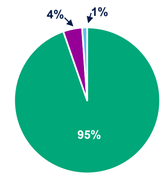


Parameter	US/CAN CAB + RPV LA Q4W + Q8W (n=376)
Number or participants receiving injections	371
Number of injections	8806
ISRs events†	2273
Pain, n (% of injections)	1833 (21)
Nodule, n (% of injections)	137 (2)
Discomfort, n (% of injections)	77 (<1)
Grade ≥3 ISR events	60
Median duration of ISRs, days	3
Withdrawals due to ISR or injection intolerability, n (%)	7 (2)

*Incidence is derived relative to the number of participants who received injections at each respective study visit. Week 4, n=371; Week 8, n=371; Week 12, n=257; Week 16, n=361; Week 20, n=255; Week 24, n=360; Week 28, n=254; Week 32, n=358; Week 36, n=250; Week 40, n=354; Week 44, n=249; Week 48, n=352; Week 52, n=199.
†Total and three most commonly occurring in US/CAN participants are shown.
CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; US/CAN, United States/Canada.

- The majority of ISRs were Grade 1 (74%, n=1684) or 2 (23%, n=529).
- The incidence of ISRs decreased over time (**Figure 4**), consistent with the overall pooled population.

Figure 5. Treatment Preference (ITT-E Population)*



*22/376 participants did not provide a response. The question asked in ATLAS and FLAIR was *"For the past 44 weeks you have received long-acting injectable HIV medication every month. Today we would like you to compare your experience on the long acting injections with the oral medication you received prior to entering the study (ATLAS) or during the induction phase of the study (FLAIR). Which therapy do you prefer?"* The questions asked in ATLAS-2M was *"Based on your experience, which HIV treatment do you prefer?"*
ART, antiretroviral therapy; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

- Most responding participants (n=335/354, 95%) preferred LA over oral dosing (n=15/354, 4%) (**Figure 5**).

Conclusions

- In US/CAN Phase 3/3b trial participants, CAB + RPV LA was highly effective, well tolerated, and preferred over daily oral ART, with outcomes consistent with the overall pooled population.
- 3 US/CAN participants met the CVF criterion (~1%), consistent with the rate seen in the overall study population.
  - No participant with only a single baseline factor previously associated with increased odds of failure (including BMI ≥30 kg/m^2) met the CVF criterion.
- A6/A1 subtype was rare in US/CAN participants, consistent with regional prevalence/surveillance data.
- 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.

Acknowledgments

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