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

Jean-Michel Molina[1], M. Luisa Montes[2], Stefan Esser[3], Nathalie De Castro[1], Parul Patel[4], Samia Dakhia[5], Joseph W. Polli[4], Louise Garside[6], Ronald D'Amico[4], Christine Talarico[4], Veerle Van Eygen[7], Kati Vandermeulen[7], William R. Spreen[4], Michael Aboud[5], Matthew Bosse[8]

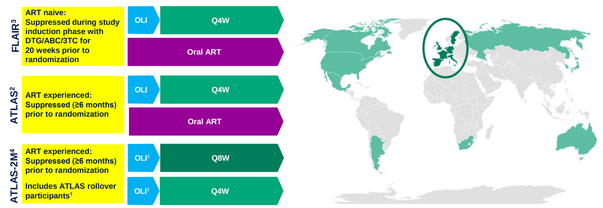
[1]University of Paris Diderot, Saint-Louis Hospital, Paris, France; [2]La Paz University Hospital, Madrid, Spain; [3]University Hospital Duisburg-Essen, Germany; [4]ViiV Healthcare, Research Triangle Park, NC, United States; [5]ViiV Healthcare, Brentford, United Kingdom; [6]GlaxoSmithKline, London, United Kingdom; [7]Janssen Research & Development, Beerse, Belgium; [8]ViiV Healthcare, San Diego, CA, United States

Poster PE2/67

Introduction

- Cabotegravir (CAB) plus rilpivirine (RPV) is the first complete long-acting (LA) regimen for the maintenance of HIV-1 virologic suppression and is approved in Europe.[1]
- 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) in ATLAS[2] and FLAIR,[3] or Q4W/every 8 weeks (Q8W) in ATLAS-2M,[4] has demonstrated high virologic suppression in participants across all three multinational Phase 3 studies at Week 48 (**Figure 1**).
- This *post hoc* descriptive analysis summarizes efficacy, virologic outcomes, safety, and treatment preference for European (France, Germany, Italy, Spain, Sweden, the Netherlands, and the United Kingdom) Phase 3 trial participants across ATLAS, FLAIR, and ATLAS-2M through Week 48.

Figure 1. Phase 3 Study Designs Through Week 48 and Participating Countries*

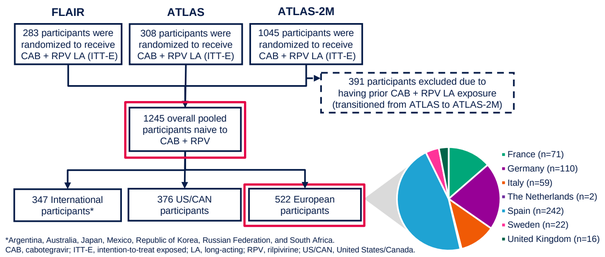


*Argentina, Australia, Canada, France, Germany, Italy, Japan, Mexico, the Netherlands, Republic of Korea, Russian Federation, South Africa, Spain, Sweden, United Kingdom, and United States. †Participants could enter ATLAS-2M from either arm of the ATLAS study. ‡Rollover participants with prior CAB + 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 European participants without prior CAB + RPV exposure (n=522) from the larger pooled ATLAS, FLAIR, and ATLAS-2M Phase 3/3b studies (N=1245) were analyzed (**Figure 2**).

Figure 2. Study Population



*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 (archived RPV RAMs, HIV-1 subtype A6/A1, and/or BMI ≥30 kg/m^2) associated with CVF and their relation to virologic outcome.[5]
- Safety and tolerability.
- Treatment preference.

Results

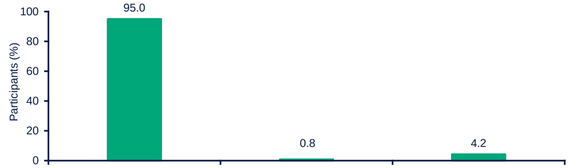
Table 1. Baseline Characteristics

ITT-E population	European CAB + RPV LA Q4W + Q8W (n=522)
Age, median (range) years	40 (19–83)
Female (sex at birth), n (%)	111 (21)
Race, n (%)	
White	465 (89)
Black or African American	32 (6)
Other	25 (5)
Hispanic or Latinx ethnicity, n (%)	52 (10)
BMI, median (range) kg/m^2	24.0 (16.7–44.9)
Baseline factors associated with increased risk of CVF*, n (%)	
Archived RPV RAMs†	9 (2)
HIV-1 subtype A6/A1	16 (4)
BMI ≥30 kg/m^2	51 (10)

*Two consecutive HIV-1 RNA ≥200 copies/mL.
†Obtained retrospectively via proviral DNA testing (these data were not available for participants at screening).
BMI, body mass index; CVF, confirmed virologic failure; CAB, cabotegravir; ITT-E, intention-to-treat exposed; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

- Baseline characteristics for European participants are shown in **Table 1**.
- European participants had a median (range) age of 40 (19–83) years, were mostly White, 21% were female, with a ≤10% prevalence of baseline factors associated with CVF.

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.

Table 2. Snapshot Outcomes at Week 48

(ITT-E population)	European CAB + RPV LA Q4W (n=387)	European CAB + RPV LA Q8W (n=135)
HIV-1 RNA <50 copies/mL, n (%)	365 (94.3)	131 (97.0)
HIV-1 RNA ≥50 copies/mL, n (%)	4 (1.0)	0
Data in window not below threshold	0	0
Discontinued for lack of efficacy	3 (0.8)	0
Discontinued for other reason while not below threshold	1 (0.3)	0
No virologic data in Week 48 window, n (%)	18 (4.7)	4 (3.0)
Discontinued due to AE or death	11 (2.8)	2 (1.5)
Discontinued for other reasons	7 (1.7)	2 (1.5)

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

- CAB + RPV LA maintained high levels of viral suppression across both dosing regimens in European participants with HIV-1 at Week 48 (**Figure 3/Table 2**).
- In the overall pooled population, 92.9% (n=1156/1245) maintained suppression and 1.7% (n=21/1245) had virologic non-response.
- In the oral ART comparator arms in ATLAS and FLAIR, 94.2% (n=226/240) of European participants maintained virologic suppression; 1.7% (n=4/240) had virologic non-response.

Table 3. Summary of Participants with CVF

Regimen /country	Sex at birth/ BL BMI (kg/m^2)	Study/ week of SVF*	Subtype	Viral load SVF*/CVF† (c/mL)	RAMs observed at BL‡		RAMs observed at failure	
					NNRTI	INSTI	NNRTI	INSTI
Q4W/ France	Female/ ≥30 kg/m^2	ATLAS/ Week 12	AG	695/ 258	V108V/I and E138K	None	V108I and E138K	None
Q8W/ Spain	Male/ <30 kg/m^2	ATLAS-2M Week 16	B	737,830/ 259	None	None	None	None
Q4W/ France	Male/ <30 kg/m^2	ATLAS-2M Week 16	B	121,233/ 173,421	None	None	None	N155N/H

*First visit at which HIV-1 RNA level was ≥200 copies/mL. †Two consecutive HIV-1 RNA ≥200 copies/mL. ‡Obtained retrospectively via proviral DNA testing (these data were not available for participants at screening). All three participants had HIV-1 RNA <50 copies/mL at all visits prior to SVF.
BL, baseline; BMI, body mass index; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; SVF, suspected virologic failure.

- In European participants, <1% met the CVF criterion through 48 weeks; all occurred within the first 24 weeks of the studies (**Table 3**).
- All three participants resuppressed on an alternative regimen (protease inhibitor–based [ritonavir/darunavir + abacavir/lamivudine] n=2; INSTI-based [dolutegravir/abacavir/lamivudine], n=1) during long-term follow-up.
- Of the three participants with CVF, one had ≥2 baseline factors associated with CVF (archived RPV RAMs and BMI ≥30 kg/m^2) and two had no baseline factors.

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

Parameter, n (%)	European CAB + RPV LA Q4W + Q8W (n=522)	European oral ART* (n=240)
Any AE	456 (87)	192 (80)
Any Grade ≥3 AE†	35 (7)	10 (4)
Any drug-related AE	158 (30)	18 (8)
Any Grade ≥3 drug-related AE	8 (2)	0
AE leading to withdrawal	16 (3)	5 (2)
Drug related	8 (2)‡	3 (1)
Any SAE	24 (5)	10 (4)
Drug related	2 (<1)§	0

*Comparator oral ART arms in ATLAS and FLAIR.
†No fatalities occurred.
‡Reasons included: discomfort, diarrhea, vomiting (n=1); headache (n=1); asthenia, myalgia (n=1); anxiety (n=1); influenza (n=1); dizziness (n=1); RPV post-injection reaction reported as hypersensitivity (n=1); pyrexia (n=1).
§Reasons included: arthritis (n=1); RPV post-injection reaction reported as hypersensitivity (n=1).
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.

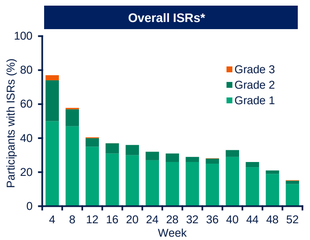
- CAB + RPV LA was well tolerated in European participants (**Table 4**) and safety outcomes were consistent with the European product labeling.
- Common adverse events (AEs) and drug-related AEs are shown in **Table 5**.

Table 5. Common AEs and Drug-Related AEs (Excluding ISRs)

Parameter, n (%)	European CAB + RPV LA Q4W + Q8W (n=522)
AEs occurring in ≥5% of participants	
Nasopharyngitis	161 (31)
Headache	64 (12)
Pyrexia	60 (11)
Diarrhea	54 (10)
Back pain	52 (10)
Influenza	37 (7)
Gastroenteritis	37 (7)
Pharyngitis	29 (6)
Drug-related AEs occurring in ≥3% of participants	
Pyrexia	40 (8)
Headache	20 (4)

AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure 4. ISRs Were Mostly Mild in Severity

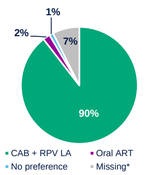


Parameter	European CAB + RPV LA Q4W + Q8W (n=522)
Number of participants receiving injections	516
Number of injections	12,882
ISR events†	3918
Pain, n (% of injections)	3362 (26)
Nodule, n (% of injections)	179 (1)
Induration, n (% of injections)	74 (<1)
Grade ≥3 ISR events	42
Median duration of ISRs, days	3
Withdrawals due to ISR or injection intolerability, n (%)	11 (2)

*Incidence is derived relative to the number of participants who received injections at each respective study visit.
†Total and three most commonly occurring in European participants are shown.
CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- The majority of ISRs were Grade 1 (83%, n=3268) or 2 (15%, n=608) and short-lived.
- The incidence of ISRs decreased over time, consistent with the overall pooled population (**Figure 4**).

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



*39/522 participants did not provide a response.
ART, antiretroviral therapy; CAB, cabotegravir; LA, long-acting; RPV, rilpivirine.

- 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 question asked in ATLAS-2M was *"Based on your experience, which HIV treatment do you prefer?"*
- Most (90%, n=468/522) participants preferred LA vs. oral therapy (2%, n=9/522) (**Figure 5**).
  - Of those who responded, 97% (n=468/483) of responding participants preferred LA vs. oral therapy (2%, n=9/483).

Conclusions

- The data for these European participants across the Phase 3/3b trials are consistent with the overall pooled data.
  - CAB + RPV LA maintained viral suppression in 95% of European participants maintaining suppression.
  - CAB + RPV LA was well tolerated, with ISRs being mostly mild, decreasing in incidence over time, and few leading to withdrawal (~2%).
  - 90% of participants preferred CAB + RPV LA over daily oral therapy.
- CVF was infrequent, occurring in <1% of European participants.
- The presence of ≥2 of the three baseline factors associated with CVF (archived RPV RAMs, HIV-1 subtype A6/A1, and/or BMI ≥30 kg/m^2) was rare, occurring in 0.4% of European participants.
- These data support the continued 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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Presenting author: Jean-Michel Molina, jean-michel.molina@aphp.fr