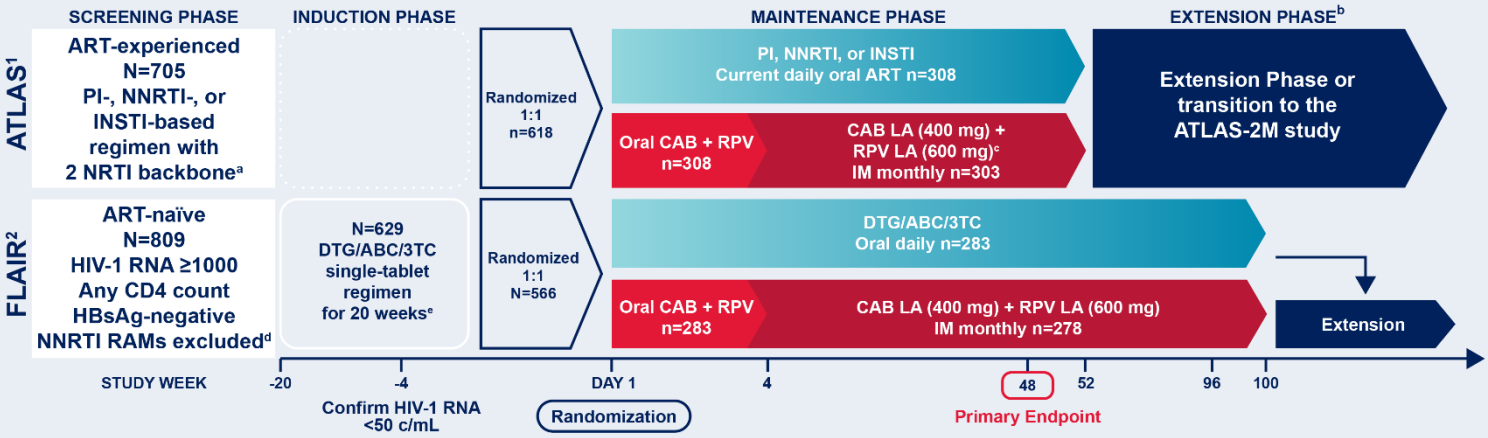
Efficacy and Safety of *CABENUVA* [Long-Acting Cabotegravir and Rilpivirine (CAB + RPV LA)] in Treatment-Experienced, Virologically Suppressed Patients with HIV-1

ATLAS and FLAIR Study Design: Randomized, Multicenter, International, Open-Label, Noninferiority Studies in Virologically Suppressed Patients

Study Design



[a]Uninterrupted ART 6 months and VL < 50 c/mL at Screening, 2× VL < 50 c/mL ≤ 12 months; [b]Optional switch to CAB LA + RPV LA at Week 52 for those on CAR; [c]Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4b. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; [d]NNRTI RAMs but not K103N were exclusionary; [e]DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive.

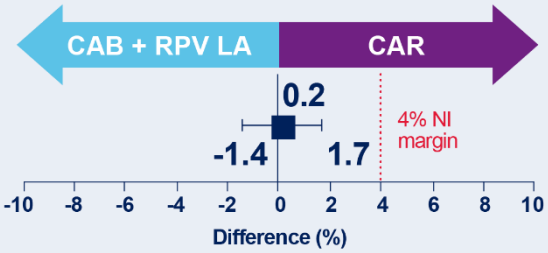
RESULTS: WEEK 48 (ATLAS and FLAIR)

Pooled baseline characteristics were similar with a median age of 38, mostly white male participants (73%), and approximately 30% female subjects.

In both phase 3 trials, 1182 patients were randomized to either CAB + RPV LA (N = 591) or continuing their CAR (N = 591). CAB + RPV LA was found to be non-inferior to CAR in each study individually and the pooled analysis.[1-4]

- 93.1% of patients in the CAB + RPV LA arm achieved viral load < 50 copies/mL vs 94.4% in the CAR arm
- 1.9% of patients in the CAB + RPV LA arm had a viral load ≥ to 50 copies/mL vs 1.7% in the CAR arm

Virologic Response[a] by FDA Snapshot Algorithm from the Pooled Analysis of ATLAS and FLAIR at Week 48[3]

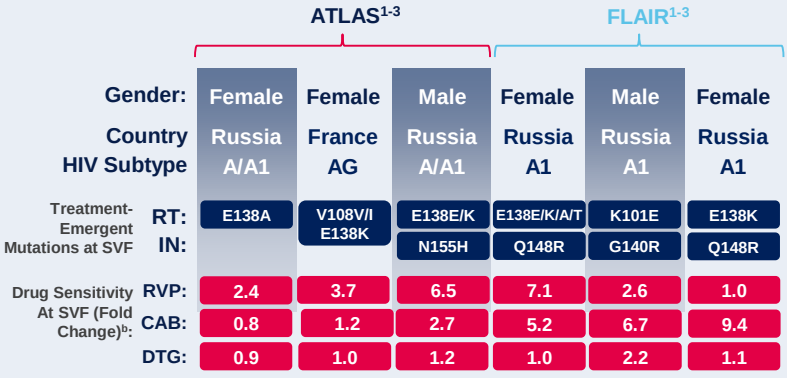


Primary Endpoint: LA noninferior to CAR (HIV-1 RNA ≥ 50 c/mL) at Week 48

[a]Adjusted for sex and baseline third agent.

Confirmed Virologic Failures

CVFs and treatment-emergent mutations were geographically focused and limited to HIV subtype A/A1/AG[3]



Safety:[3,5] Drug-related adverse events were experienced by 83% of patients who received CAB + RPV LA versus 6% of patients who were in the CAR arm. A majority of these were ISRs.

Serious adverse events related to study treatment were reported in < 1% of patients in either arm. Adverse events leading to withdrawal were reported in 4% of patients in the CAB + RPV LA arm and 2% of patients in the CAR arm.

ISRs were reported in 83% of patients receiving CAB + RPV LA and the incidence decreased over the course of the studies.

- Most ISRs were Grades 1 or 2 in severity. 4% of ISR events were Grade 3. No Grade 4 or 5 ISR events were reported. No ISR events were considered serious and 1% led to discontinuation.
- The median (range) duration of ISRs was 3 (1 - 341) days.

N = 6
CVFs[a] among CAB + RPV LA experienced patients
1%

N = 4
Patients with treatment-emergent mutations at SVF[a]
< 1%

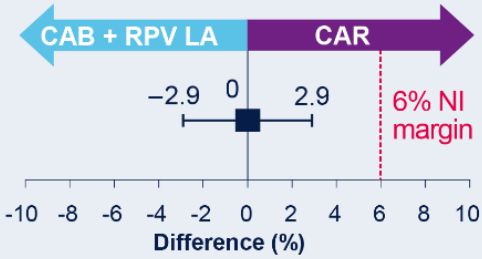
Of the 6 CVFs in the CAB + RPV LA arms in ATLAS and FLAIR, 5 went on to re-suppress on a subsequent regimen chosen by the investigator.[6,7] Four of the 5 regimens were protease inhibitors [lopinavir/ritonavir n = 2), darunavir with ritonavir (n = 1), and atazanavir (n = 1)] plus 2 nucleoside reverse transcriptase inhibitors. The fifth patient received dolutegravir, abacavir, and lamivudine.

The patient who did not re-suppress was placed on lopinavir/ritonavir plus lamivudine and zidovudine.[7]

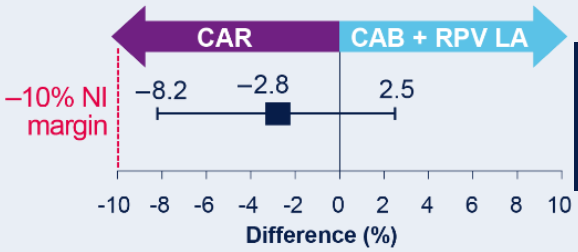
[a]CVF is defined as 2 consecutive plasma HIV-1 RNA ≥ 200 c/mL after prior suppression to < 200 copies/mL; [b]Monogram biological cutoffs are: CAB = 2.5, RPV = 2.0. Clinical cutoff: dolutegravir (4.0). Fold change = IC_{50} patients/IC_{50} reference.

RESULTS: WEEK 96 (FLAIR only)[8]

Virologic Outcomes, Adjusted Treatment Difference (95% CI)*



LA is noninferior to CAR (≥ 50 c/mL) at Week 96



LA is noninferior to CAR (< 50 c/mL) at Week 96

*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

Confirmed Virologic Failures*

There was a total of 4 CVFs in both arms at Week 96; however, there were no new virologic failures in the LA arm from Week 48 through Week 96

Variable	CAB + RPV LA n=283, n (%)	CAR n=283, n (%)
CVF between Week 48 and Week 96	**0**	**1 (<1)†**
Total CVF through Week 96	4 (1.4)‡	4 (1.4)
Total treatment-emergent resistance	3 (1.1)§	0

*Where CVF is defined as rebound as indicated by 2 consecutive plasma HIV-1 RNA levels ≥ 200 c/mL after prior suppression to < 200 c/mL. †DTG/ABC/3TC CVF occurred at Week 64 with no resistance mutations; ‡1 participant in FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected virologic failure that was confirmed; §Subtype A1 assignment based on Monogram Algorithm which does not include reference sequences for A6, a predominant subtype in Russia. Further in-house analysis suggests that the subtype for all 3 is A6.

Safety Overview (Excluding ISRs)

91/95 (96%) of CAB + RPV LA participants had non-ISR drug-related AEs at maximum Grade 1 or 2. One drug-related SAE occurred in the LA arm (right knee monoarthritis). Between the nominal Week 48 and Week 96 data cut-off points, 4 participants discontinued due to AEs (excluding ISRs), none of which were drug-related: 2 depression, 1 hepatitis A, 1 hepatitis C

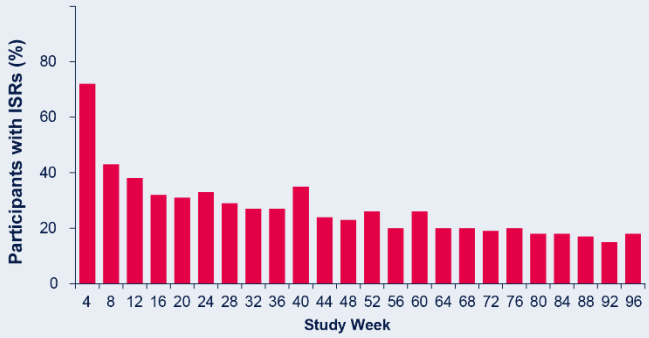
	Cumulative Week 48 Data Analysis		Cumulative Week 96 Data Analysis		New participants with AEs between Week 48 and Week 96 Data Analysis†	
	CAB + RPV LA n=283, n (%)	CAR n=283, n (%)	CAB + RPV LA n=283, n (%)	CAR n=283, n (%)	CAB + RPV LA n=283, n	CAR n=283, n
Any AE (number of participants)						
Any AE	246 (87)	225 (80)	264 (93)	242 (86)	18	18
Any Grade 3 to 4 AEs	22 (8)	11 (4)	29 (10)	16 (6)	8	5
AEs leading to withdrawal	8 (3)	4 (1)	12 (4)	4 (1)	4	0
Drug-related AEs	79 (28)	28 (10)	95 (34)	33 (12)	16	6
Drug-related Grade 3 to 4 AEs	4 (1)	0	4 (1)	0	0	0
Any SAE	18 (6)	12 (4)	24 (8)	22 (8)	6	10
Drug-related SAEs	1 (<1)	0	1 (<1)	0	0	0
Deaths	0	0	0	0	0	0

†Participants with first reported AE of the type specified occurring after the Week 48 data analysis reporting date.

Injection Site Reactions Through Week 96

The majority (3082/3100, 99%) of ISRs were Grade 1–2 and most (89%) resolved within ≤ 7 days (median duration, 3 days)

ISR Incidence by Week



Outcome , n (%)	CAB + RPV LA n=283
Number of injections	12,552
ISR events, n (% of total injections)	3100 (24.7)
Grade 1 – mild	2730 (21.7)
Grade 2 – moderate	352 (2.8)
Grade 3 – severe	18 (<1)
ISR events (most frequent), n (% of total injections)	
Pain	2613 (20.8)
Nodule	132 (1.1)
Induration	119 (<1)
Warmth	59 (<1)
Pruritus	56 (<1)
Swelling	45 (<1)
Participant withdrawals due to ISR-related reasons, n (%)	6 (2.1)
• ISRs leading to withdrawal	3 (1.1)
• Withdrew consent due to intolerability of injections	3 (1.1)

Between Week 48 and 96, 2 participants withdrew due to ISR-related reasons, 1 for an ISR and 1 for intolerability of injections.

RESULTS: WEEK 124 (FLAIR only)[9]

Virologic Response by FDA Snapshot Algorithm (ITT-E)

	CAB + RPV LA (N = 283)
HIV-1 RNA < 50 copies/mL	227 (80.2)
HIV-1 RNA ≥ 50 copies/mL	14 (4.9)
Data in window not below threshold	5 (1.8)
Discontinued for lack of efficacy	8 (2.8)
Discontinued for other reason while not below threshold	1 (0.4)
No virologic data in Week 124 window	42 (14.8)
Discontinued study due to AE*	15 (5.3)
Discontinued study for other reasons†	26 (9.2)
On study but missing data in window	1 (0.4)
CVF (two consecutive plasma HIV-1 RNA ≥ 200 copies/mL)	4 (1.8)

*three additional patients since the 96 week analysis (paracetamol overdose, acute hepatitis A, depression); †ten additional patients since the 96 week analysis: withdrawal by subject, n = 8 (frequency of injections [n = 1], subject relocation [n = 2], frequency of visits [n = 3], physician decision [n = 2, pregnancy].

RESULTS: WEEK 124 (FLAIR only)[9]

Confirmed Virologic Failures

A total of four subjects had CVF through the 124 week analysis; one additional patient was identified with CVF since the 96 week analysis

CVF Patient Characteristics (Week 108):

Sex at birth	Male
Body Mass Index	24.7 kg/m^2
HIV-1 subtype	A6
Baseline RAMs	None*
Viral load at SVF/CVF	887/1112 copies/mL
Treatment emergent NNRTI RAMs	V106V/A, V108V/I, E138G, M230L†
Treatment emergent INSTI RAMs	N155H, R263K‡
Week 8 CAB/RPV troughs	1.05 µg/mL/24.6 µg/mL§
Week 108 CAB/RPV troughs	1.73 µg/mL/79.5 µg/mL¶
Resuppression	< 50 c/mL at LTFU Month 3 on EFV/TDF/FTC

*L74I was present at baseline; †at SVF the virus had reduced susceptibility to RPV (27-fold change); ‡at SVF, the virus had reduced susceptibility to CAB (9-fold change); §for comparison, Week 8 CAB and RPV geometric mean (5th, 95th percentile) for the FLAIR population was 1.56 µg/mL (0.551, 3.61) and 41.2 ng/mL (17.9, 92.7), respectively; ¶lower CAB and RPV concentrations earlier in treatment may have contributed to CVF with development of resistance to both drugs.

Safety

Most drug-related AEs (excluding ISRs) were Grade 1 or 2 (n = 97/102 [95%]). One drug-related Grade 3/4 AE occurred since the Week 96 analysis (paracetamol overdose, Grade 3)

Adverse Events (Excluding ISRs) Through Week 124 in FLAIR

	CAB + RPV LA (Cumulative Through Week 124) (n = 283), n (%)	Additional subjects since the Week 96 analysis n (%)
Any AE	271 (96)	7 (2)
Grade 3 to 4 AEs	38 (13)	9 (3)
Drug-related AEs	102 (36)	7 (2)*
Drug-related Grade 3-4 AEs	5 (2)	1 (< 1)
AEs leading to withdrawal	15 (5)	1 (< 1)†
Any SAE	33 (12)	2 (1)
Drug-related SAEs	1 (< 1)‡	0
Fatal SAEs	0	0
Drug-related AEs (≥ 3%)§		
Pyrexia	18 (6)	1 (< 1)
Headache	15 (5)	0
Fatigue	10 (4)	3 (1)

*Seven subjects reported 22 events since the 96 week analysis (pyrexia n = 1, fatigue n = 3, chills n = 2, influenza-type illness n = 1, parasthesia n = 1, autonomic nervous system imbalance n = 1, hypoesthesia n = 1, lethargy n = 1, restless leg syndrome n = 1, nausea n = 1, blood creatinine phosphokinase increased n = 1, myalgia n = 1, back pain n = 1, erythema n = 1, syphilis n = 1, dyspnea n = 1, cough n = 1, flushing n = 1, overdose n = 1; †paracetamol overdose n = 1; ‡Drug-related SAE was right knee monoarthritis reported in Week 48 analysis; §Drug-related AEs are based on investigator assessment

Injection Site Reactions

ISRs were the most common AE; most were Grade 1 (n = 3315; 89%) or Grade 2 (n = 399; 11%). Of 17,392 injections through 124 weeks, there were 3732 ISRs. One additional patient discontinued due to ISRs since the 96 week analysis

Data on the use of cabotegravir (CAB) plus rilpivirine (RPV) in treatment-naïve patients with HIV are not available at this time.

Important safety information is found in the attached Prescribing Information.

For more information

Medical Information Response

Prescribing Information

Some information contained in this response may not be included in the approved Prescribing information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling. Please note that reports of adverse events in the published literature often lack causality assessments and may contain incomplete information; therefore, conclusions about causality generally cannot be drawn. In order for ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877–844–8872. Please consult the attached Prescribing Information. This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

Abbreviations: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ART= antiretroviral therapy; CAB = cabotegravir; CAR = current antiretroviral; CI = confidence interval; CVF = confirmed virologic failure; CAB + RPV LA = long-acting cabotegravir and rilpivirine; DTG = dolutegravir; EFV/TDF/FTC = efavirenz/tenofovir/emtricitabine; FLAIR = First Long-Acting HIV Injectable Regimen; HLA = human leukocyte antigen; HBsAg = hepatitis B surface antigen; IM = intramuscular; INSTI = integrase strand transfer inhibitor; ITT-E = intent-to-treat- exposed; ISR = injection site reaction; LA = long-acting; LTFU = long-term follow up; NI = non-inferiority; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAM = resistance-associated mutation; RPV = rilpivirine; SAE = serious adverse event; SVF = suspected virologic failure; VL = viral load.

References: 1. Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475; **2.** Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947; **3.** Overton ET, et al. 10th International AIDS Society Conference on HIV Science 2019M; Mexico City, Mexico. Poster MOPEB257; **4.** ViiV Healthcare, Module 5.3.5.3, Integrated Summary of Efficacy for cabotegravir, version 2.0, March 19, 2019; **5**. ViiV Healthcare, Module 5.3.5.3, Integrated Summary of Safety for cabotegravir, version 2.0, March 29, 2019; **6**.Data on File. Study 201585 (NCT02951052). ViiV Healthcare Study Register. Study entry at https://www.viiv-studyregister.com/19594. **7**.Data on File. Study 201584 (NCT02938520). ViiV Healthcare Study Register. Study entry at https://www.viiv-studyregister/19593. **8**.Orkin C, et al. Lancet HIV 2021;8:e185-96. **9**. Orkin C, et al. Lancet HIV 2021;8:e668-78.