Monthly Long-Acting Cabotegravir and Rilpivirine is Noninferior to Oral ART as Maintenance Therapy for HIV-1 Infection: Week 48 Pooled Analysis From the Phase 3 ATLAS and FLAIR Studies

MOPEB257

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Background

- Despite the success of daily oral therapy, considerable interest exists in long-acting (LA) treatment options for HIV-1 infection.
- Cabotegravir (CAB) is an HIV-1 integrase strand transfer inhibitor.[1,2]
  - Oral 30 mg tablet: half-life ($t_{½}$) ≈ 40 hours.
  - LA intramuscular (IM) injection, 200 mg/mL: $t_{½}$ ≈ 40 days.
- Rilpivirine (RPV) is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).[1,2]
  - Oral 25 mg tablet: $t_{½}$ ≈ 50 hours.
  - LA IM injection, 300 mg/mL: $t_{½}$ ≈ 90 days.
- ATLAS[1] (NCT02951052) and FLAIR[2] (NCT02938520) are two randomized, open-label, international Phase 3 studies which evaluate switching to monthly IM injections.

Objective and Endpoints

Objective

- Establish noninferior antiviral activity of monthly IM CAB + RPV LA vs continuing current antiretroviral regimen (CAR) in treatment-experienced (ATLAS) and previously treatment-naïve (FLAIR) participants.

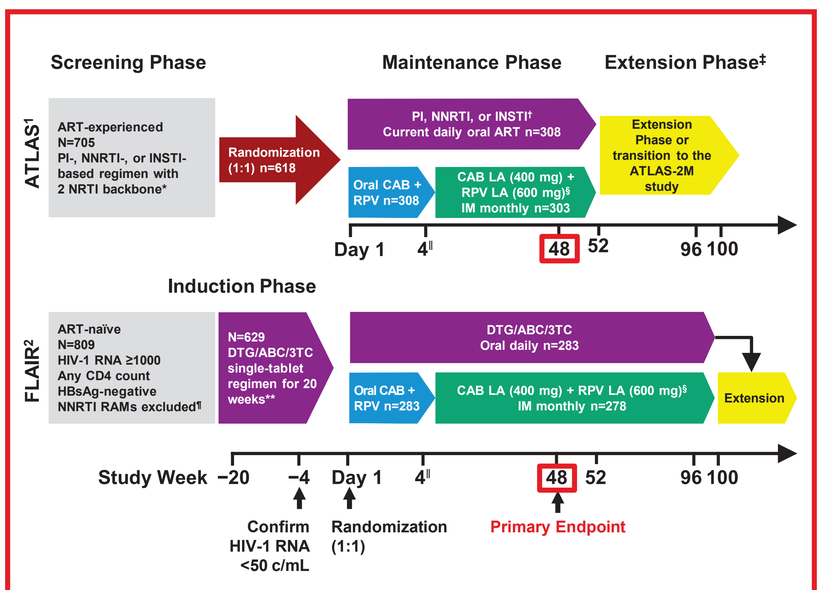
Primary Endpoint

- Proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 using the U.S. Food and Drug Administration (FDA) Snapshot algorithm (4% noninferiority margin on difference between groups).

Selected Secondary and Exploratory Endpoints

- HIV-1 RNA <50 c/mL at Week 48 (Snapshot).
- Safety and tolerability.
- Treatment satisfaction and preference.
- Resistance analysis of confirmed virologic failure (CVF).

Figure 1. ATLAS and FLAIR Study Design



*Uninterrupted ART ≥ 6 months and VL <50 c/mL at Screening, 2× VL <50 c/mL ≤12 months; †INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study; ‡Optional switch to CAB + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB + RPV LA must complete 52 weeks of follow-up; ¶Participants received initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; ¶NNRTI RAMs, but not K103N, were exclusionary; **DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive.

Results

Table 1. Baseline Characteristics: ITT-E Population

	CAB + RPV LA N=591	CAR N=591
Median age, years (range)	38 (19–74)	38 (18–82)
Age ≥50 years, n (%)	99 (17)	125 (21)
Female, n (%)	162 (27)	168 (28)
Race, n (%)		
White	430 (73)	408 (69)
Black or African American	109 (18)	133 (23)
Other	52 (9)	50 (8)
Median BMI (range), kg/m²	24.9 (15.3–50.9)	24.8 (12.6–57.7)
Median CD4+ cell count (IQR), cells/mm³	645 (487–824)	641 (480–821)
HIV-1–HCV co-infection, n (%)	42 (7)	40 (7)

*Baseline for FLAIR was Day 1 (Maintenance Phase).

Figure 2. Summary of ITT-E Participants by Region and Country

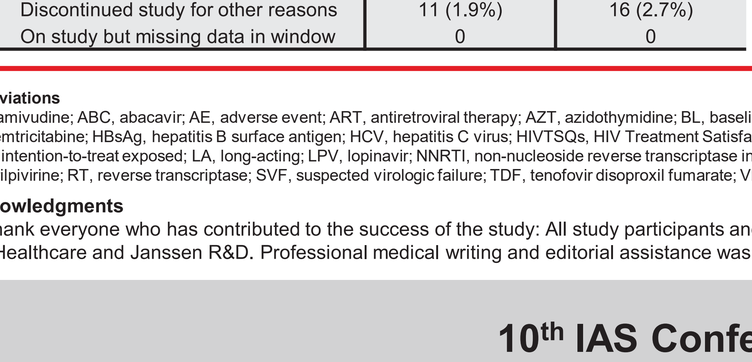
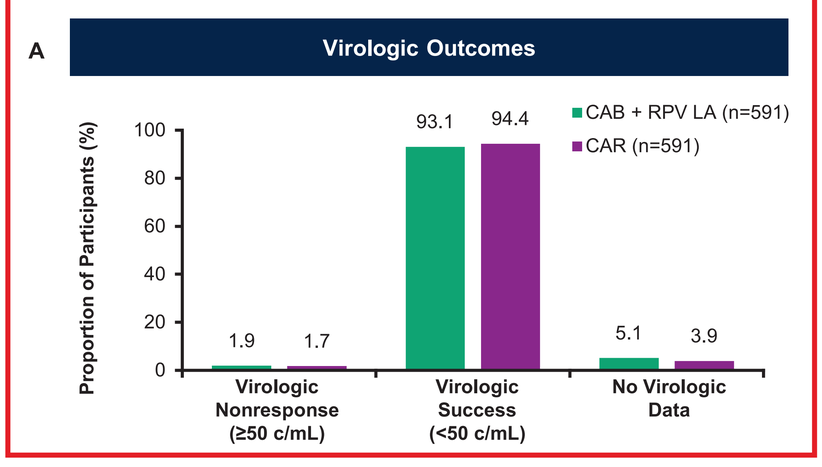


Table 2. Pooled Snapshot Outcomes at Week 48 (ITT-E)

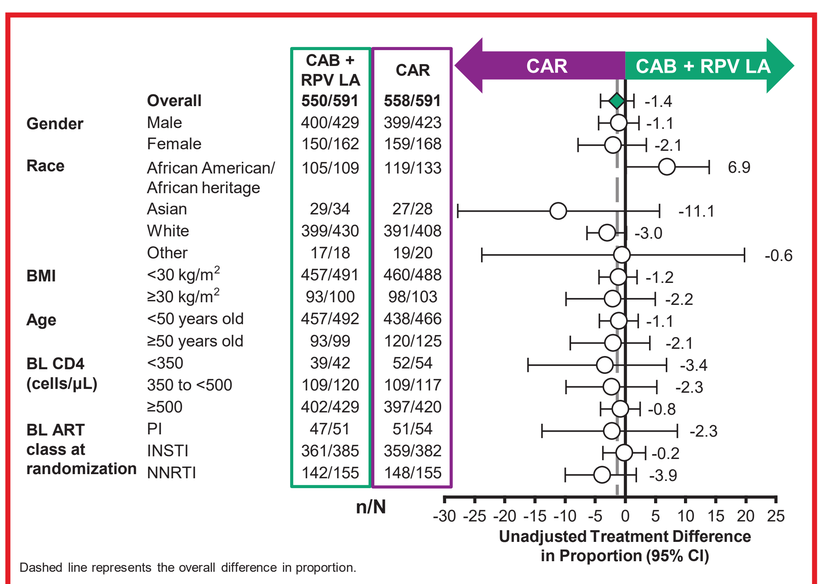
	CAB + RPV LA N=591	CAR N=591
HIV-1 RNA <50 c/mL	550 (93.1%)	558 (94.4%)
HIV-1 RNA ≥50 c/mL	11 (1.9%)	10 (1.7%)
Data in window not below threshold	3 (0.5%)	3 (0.5%)
Discontinued for lack of efficacy	7 (1.2%)	5 (0.8%)
Discontinued for other reason while not below threshold	1 (0.2%)	2 (0.3%)
Change in background therapy	0	0
No virologic data	30 (5.1%)	23 (3.9%)
Discontinued study due to AE	19 (3.2%)	7 (1.2%)
Discontinued study due to death	0	1 (0.2%)
Discontinued study for other reasons	11 (1.9%)	16 (2.7%)
On study but missing data in window	0	0

Figure 3. Virologic Snapshot Outcomes at Week 48 for ITT-E Noninferiority Achieved for Primary and Secondary Endpoints



*Adjusted for sex and baseline third agent class.

Figure 4. Treatment Difference in Proportion (95% CI) Snapshot HIV-1 RNA <50 c/mL at Week 48 by Subgroup



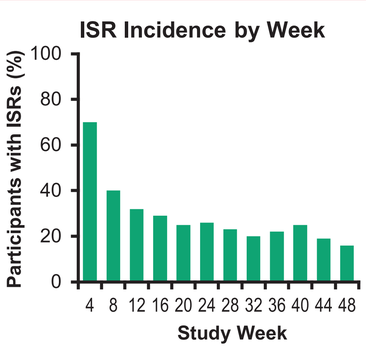
Dashed line represents the overall difference in proportion.

Table 3. Safety Overview, Excluding ISRs, Through Week 48 in Maintenance Phase

	CAB + RPV LA N=591	CAR N=591
Any AE	506 (86%)	444 (75%)
Any Grade 3/4/5 AE*	44 (7%)	35 (6%)
Any drug-related AE	165 (28%)	35 (6%)
Any Grade 3/4/5 drug-related AE*	8 (1%)	1 (<1%)
Any AEs leading to withdrawal	17 (3%)	9 (2%)
Any serious AE	24 (4%)	25 (4%)
Serious AEs related to study treatment†	1 (<1%)	1 (<1%)
Common AEs (≥5%)		
Nasopharyngitis	108 (18%)	90 (15%)
Headache	73 (12%)	38 (6%)
Upper respiratory tract infection	70 (12%)	53 (9%)
Diarrhea	54 (9%)	40 (7%)
Back pain	43 (7%)	23 (4%)
Influenza	42 (7%)	34 (6%)
Pyrexia	43 (7%)	13 (2%)
AEs of special interest		
Anxiety	27 (5%)	20 (3%)
Depression	16 (3%)	14 (2%)
Suicidal ideation/behavior	4 (<1%)	5 (<1%)

*There was only one (<1%) participant with Grade 5 AE in the CAR arm; †Serious AEs related to study treatment: LA arm – arthritis; CAR arm – suicidal ideation.

Figure 5. Pooled Injection Site Reactions



Event	CAB + RPV LA N=591
Participants receiving injections, n	581
Injections given, n	14682
ISR events, n (%)	3663 (24.9)
Pain	3087 (21.0)
Nodule	140 (1.0)
Induration	136 (0.9)
Swelling	86 (0.6)
Grade 3 ISR pain	32 (0.2)
Median duration of ISRs, days	3
Participants with ISR leading to withdrawal, n (%)	6 (1)

Bars represent incidence of onset ISRs relative to the most recent IM injection visit.

- The majority (99%, 3628/3663) of ISRs were Grade 1–2 and most (88%) resolved within ≤7 days

Table 4. ATLAS and FLAIR Confirmed Virologic Failures*: CAB + RPV LA Arm

Study	Sex, Country, HIV-1 Subtype	Previous CAR	Baseline RAMs† RT	Baseline RAMs† INSTI	Viral Load at SVF / CVF (c/mL)	SVF Timepoint RAMs RT	SVF Timepoint RAMs INSTI‡	Drug Sensitivity at SVF (Fold Change)§
ATLAS	F, Russia, A/A1	3TC, AZT, LPV/r	E138E/A	None	79,166 / 25,745	E138A	None	**RPV (2.4)** CAB (0.8) DTG (0.9)
ATLAS	F, France, AG	3TC, AZT, NVP to 3TC, ABC, NVP	V108V/I E138K	None	695 / 258	V108I E138K	None	**RPV (3.7)** CAB (1.2) DTG (1.0)
ATLAS	M, Russia, A/A1	FTC, RAL, TDF to ABC, EFV, 3TC	None	None	544 / 1841	E138E/K	N155H	**RPV (6.5) CAB (2.7)** DTG (1.2)
FLAIR¶	F, Russia, A1	–	None	None	373 / 456	E138E/A/K/T	Q148R	**RPV (7.1) CAB (5.2)** DTG (1.0)
FLAIR¶	M, Russia, A1	–	None	None	287 / 299	K101E	G140R	**RPV (2.6) CAB (6.7)** DTG (2.2)
FLAIR¶	F, Russia, A1	–	None	None	488 / 440	E138K	Q148R	RPV (1.0) **CAB (9.4)** DTG (1.1)

**In the CAR arm, there were seven CVFs. In ATLAS, there were 4 CVFs in the CAR arm, where RT mutations M184I, M184V+G190S, and M230M/I were detected in HIV-1 RNA samples from one participant each, and one had no mutations. In FLAIR, there were 3/4 CVFs in the CAR arm without treatment-emergent resistance mutations or phenotypic changes.*

†Baseline RAMs were determined using DNA for ATLAS and RNA for FLAIR; ‡L74I was present at baseline in 5/6 subjects and is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity; §Monogram biological cutoffs are: RPV=2.0, CAB=2.5, and the Monogram clinical cutoff for DTG=4.0; ¶FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected VF that was confirmed.

Table 5. Summary of the Prevalence of L74I at Baseline* by Subtype in FLAIR Participants

Subtype	CAB + RPV LA L74I† Within Subtype, n/N (%)‡	CAR L74I† Within Subtype, n/N (%)‡
Total L74I Present / Total tested	54/243 (22)	47/240 (20)
A	32/38 (84)	28/32 (88)
A1	5/8 (63)	3/4 (75)
AE	0/0	0/3
AG	3/10 (30)	3/13 (23)
B	12/165 (7)	11/161 (7)
C	0/2	0/4
Undetermined	0/5	0/5
Other	2/15 (13)	2/18 (11)

*Baseline values taken at Week –20 in participants that were randomized; †L74I is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity; ‡Results pending for 40 and 43 samples, respectively.

- 101/483 subjects tested had the L74I substitution, with the majority of subjects with L74I (64/101, 63.4%) coming from the Russian Federation. In contrast, 5/84 (6.0%) subjects from the United States had the L74I substitution.
- L74I was most commonly observed in Subtype A (60/70; 85.7%) (**Table 5**).
- Subtype B (326/483, 67.5%) was the most prevalent subtype observed in the FLAIR subjects.

Table 6. Effect of L74I on Virologic Suppression at Week 48 in FLAIR Participants

L74I Polymorphism at Induction BL	Treatment	Number of HIV-1 RNA <50 c/mL / Total Assessed (%)	Difference in Proportion* (95% CI)
Yes	CAB + RPV LA	50/54 (93)	–1.0 (–12.7, 11.0)
	CAR	44/47 (94)	
No	CAB + RPV LA	177/189 (94)	0.4 (–4.9, 5.6)
	CAR	180/193 (93)	

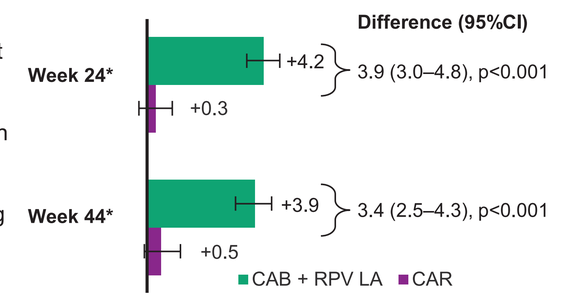
*Difference (unadjusted): Proportion on CAB + RPV LA – Proportion on CAR.

- The presence of L74I IN polymorphism had no impact on overall treatment outcomes:
  - HIV-1 RNA <50 by Snapshot (**Table 6**).
  - HIV-1 RNA ≥50 by Snapshot (CAB + RPV LA 3/54 [5.6%]; CAR 1/47 [2.1%], treatment difference of 3.4 [95% CI –6.8, 13.5]).

Figure 6. Participant Satisfaction (HIVTSQs) and Preference for Injectable Therapy

HIVTSQs Total Score* — Improvement

The pooled data reported a significant increase among study participants in treatment satisfaction of injectable therapy compared with participants receiving oral therapy at Weeks 24 and 44



Patient Preference Survey (LA Arm)

Single-item question on participants' preference at Week 48

- ITT-E population: 88% (523/591) preferred LA; 2% (9/591) preferred daily oral therapy
  - **Responding participants: 98% (523/532) preferred the LA regimen over previous oral therapy**

*Adjusted mean change from baseline; adjusted for baseline score, sex, age, and race. Error bars show 95% CI. n=557 for CAB + RPV LA at Week 24 and Week 44; n=543 for CAR at Week 24 and n=552 at Week 44.

Conclusions

- Monthly injections of CAB + RPV LA were noninferior to daily oral CAR for key virologic endpoints at Week 48.
  - Primary and secondary outcomes in ATLAS[1] and FLAIR[2] analyzed separately were similar to the results in the pooled analysis.
- Low CVF (1.2%) was seen across both treatment arms.
- Injection site reactions in the LA arm were common but mainly Grade 1 or 2, with few associated discontinuations.
- L74I polymorphism alone had no impact on overall efficacy among FLAIR participants; further research on the interplay between L74I and HIV sub-type is ongoing.
- High treatment satisfaction reported among those receiving CAB + RPV LA.
- Overall, ATLAS and FLAIR show that CAB + RPV LA offers individuals with HIV-1 infection a well-tolerated, novel, long-acting two-drug regimen without an increased risk of virologic failure.

Abbreviations

3TC, lamivudine; ABC, abacavir; AE, adverse event; ART, antiretroviral therapy; AZT, azidothymidine; BL, baseline; BMI, body mass index; CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; CVF, confirmed virologic failure; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIVTSQs, HIV Treatment Satisfaction Questionnaire (Status); HLA, human leukocyte antigen; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; ISR, injection site reaction; ITT-E, intention-to-treat exposed; LA, long-acting; LPV, lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; RAM, resistance-associated mutation; RPV, rilpivirine; RT, reverse transcriptase; SVF, suspected virologic failure; TDF, tenofovir disoproxil fumarate; VL, viral load.

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