LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR HIV TREATMENT: FLAIR WEEK 96 RESULTS

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Background

- Despite the success of daily oral ART, challenges still exist in some patients around stigma, pill burden, drug/food interactions, and adherence. Therefore there is considerable interest in developing long-acting (LA) therapeutics for HIV-1 infection.
- Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, are currently under development as a LA, injectable, two-drug regimen for the maintenance of virologic suppression in individuals living with HIV-1.
- Previously, the LATTE-2 study demonstrated that CAB + RPV LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for >3 years.[1]
- The FLAIR Phase 3 randomized controlled trial (NCT02938520) has shown that monthly intramuscular (IM) CAB + RPV LA is noninferior to daily oral three-drug ART (dolutegravir/abacavir/lamivudine; DTG/ABC/3TC) in the maintenance of virologic suppression at Week 48.[2,3]
- Here, we report the Week 96 results from FLAIR.

Endpoints

Objective

- Establish noninferior antiviral activity of monthly IM CAB + RPV LA vs continuing current antiretroviral regimen in previously treatment-naive participants.

Primary endpoint

- Proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 using the U.S. Food and Drug Administration (FDA) Snapshot algorithm (6% noninferiority margin on difference between groups).

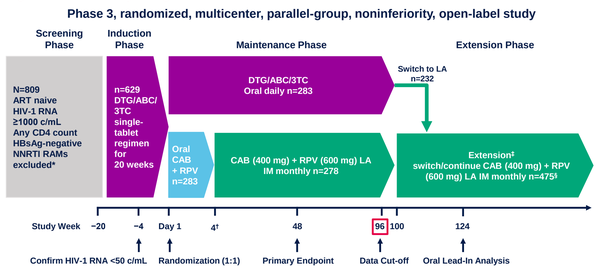
Selected endpoints assessed at Week 96

- Proportion with HIV-1 RNA ≥50 c/mL at Week 96 (Snapshot, intention-to-treat exposed [ITT-E]).
- Proportion with HIV-1 RNA <50 c/mL at Week 96 (Snapshot, ITT-E).
- Incidence of confirmed virologic failure (CVF; 2 consecutive HIV-1 RNA ≥200 c/mL).
- Treatment-emergent genotypic resistance.
- Incidence and severity of adverse events (AEs).
- Number of discontinuations for AEs.
- Participant satisfaction and quality of life.

Study Design

- ART-naive participants received induction therapy with DTG/ABC/3TC. After 16 weeks, participants with HIV-1 RNA <50 c/mL were eligible to enter the maintenance phase and, after completing 20 weeks of induction therapy, were randomized (1:1) to either switch to LA or continue oral DTG/ABC/3TC (**Figure 1**).
- If the participant had toxicity or intolerability in association with DTG/ABC/3TC, one switch to an approved alternative background NRTI was permitted. Participants who were positive for HLA-B*5701 received DTG plus two alternative non-ABC NRTIs instead of DTG/ABC/3TC (n=30).
- Those randomized to the LA arm received an oral lead-in of CAB 30 mg + RPV 25 mg once daily for 4 weeks as a tolerability check.
- Participants who received at least one dose of CAB + RPV LA who subsequently withdrew from FLAIR entered long-term follow-up for 52 weeks.

Figure 1. FLAIR Study Design



*NNRTI RAMs but not K103N were exclusionary or any known resistance to INIs.
†Participants received initial loading doses of CAB 600 mg and RPV 900 mg LA at Week 4. Beginning at Week 8, participants received CAB 400 mg + RPV 600 mg LA injections every 4 weeks.
‡The extension phase will continue until CAB + RPV LA is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either CAB or RPV is terminated.
§Estimate based on Maintenance Phase Conclusion Form – data on file.

Results

Table 1. Baseline* Characteristics: ITT-E Population

Parameter	CAB + RPV LA n=283, n (%)†	DTG/ABC/3TC n=283, n (%)†	Total n=566, n (%)†
Median age (range) – years	34 (19–68)	34 (18–68)	34 (18–68)
Age ≥50 years	33 (12)	29 (10)	62 (11)
Female‡	63 (22)	64 (23)	127 (22)
Transgender§ (male to female)	2 (<1)	0	2 (<1)
Race			
White	216 (76)	203 (72)	419 (74)
Black or African American	47 (17)	56 (20)	103 (18)
Other	20 (7)	24 (8)	44 (8)
Median body mass index (range) – kg/m^2	24 (17–45)	24 (16–47)	24 (16–47)
HIV-1 RNA, copies/mL			
<100,000	227 (80)	227 (80)	454 (80)
≥100,000	56 (20)	56 (20)	112 (20)
Median baseline CD4+ cell count (IQR) – cells/mm^3	437 (314, 609)	452 (321, 604)	444 (320, 604)
<200 cells/mm^3	16 (6)	23 (8)	39 (7)
Median Day 1 CD4+ cell count (IQR) – cells/mm^3	624 (473, 839)	625 (472, 799)	625 (473, 818)
HIV-1–HCV co-infection	19 (7)	9 (3)	28 (5)

*Baseline is Week −20 unless stated otherwise. †n (%) unless stated otherwise. ‡Sex at birth. §Self-reported gender.

- Baseline characteristics were similar between treatment groups (**Table 1**).

Figure 2A. FLAIR Week 48 Virologic Response

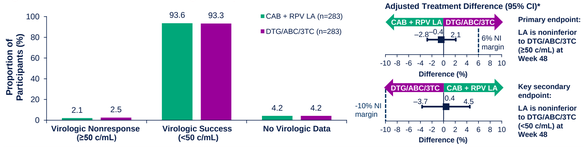
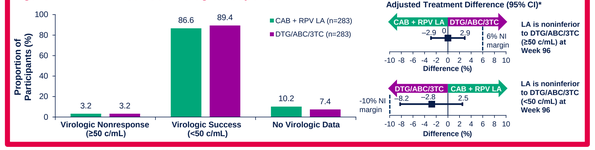


Figure 2B. FLAIR Week 96 Virologic Response



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

- At Week 96, 9 (3.2%) participants in each arm had HIV-1 RNA ≥50 c/mL, confirming the noninferiority established at Week 48 (**Figure 2A** and **2B**).

Table 2. Snapshot Outcomes at FLAIR Week 96 (ITT-E)

	CAB + RPV LA n=283, n (%)	DTG/ABC/3TC n=283, n (%)
HIV-1 RNA <50 c/mL*	**245 (86.6)**	**253 (89.4)**
HIV-1 RNA ≥50 c/mL*	**9 (3.2)**	**9 (3.2)**
Data in window not below threshold	3 (1.1)	2 (0.7)
Discontinued for lack of efficacy	6 (2.1)	5 (1.8)
Discontinued for other reason while not below threshold	0	2 (0.7)†
No virologic data in Week 96 window	**29 (10.2)**	**21 (7.4)**
Discontinued due to AE‡	12 (4.2)	4 (1.4)
Discontinued for other reasons	16 (5.7)§	17 (6.0)¶
On study but missing data in window	1 (0.4)	0

*Per FDA Snapshot algorithm.
†1 relocation, 1 lost to follow-up.
‡No deaths occurred during the maintenance phase.
§In the LA arm, 16 participants discontinued due to reasons other than AEs: 3 relocations, 2 intent to become pregnant, 2 tolerability of injections, 2 lost to follow-up, 1 need to initiate prohibited medication, 1 incarceration, 1 pregnancy, 1 frequency of visits, 1 burden of travel, 1 change of job, 1 unreliable with visits.
¶In the DTG/ABC/3TC arm, 17 participants discontinued due to reasons other than AEs: 4 frequency of visits, 3 non-compliance with study treatment and protocol procedures, 1 relocation, 1 participant decision to stop treatment, 1 late to attend visits, 1 lost to follow-up, 1 pregnancy, 1 burden of travel, 1 unspecified reason, 1 prohibited medication use, 1 substance abuse, 1 met protocol stopping criteria.

- ‡LA arm: injection site pain (2), acute hepatitis B (2), discomfort/injection site pain/diarrhea/vomiting, hepatitis A/secondary syphilis, hepatitis A, hepatitis C, acute hepatitis C, transaminases increased, depression and adenocarcinoma of the colon.
- ‡DTG/ABC/3TC arm: suicide attempt, disturbance in attention/dysarthria/amnesia, dizziness/fatigue/nausea, and renal failure.

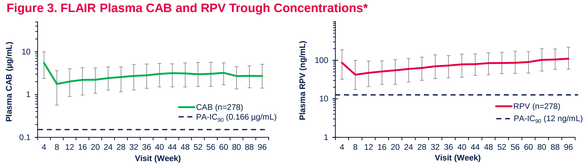
Table 3. Confirmed Virologic Failures*

Variable	CAB + RPV LA n=283, n (%)	DTG/ABC/3TC 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.

There were no virologic failures in the LA arm from Week 48 to Week 96 (Table 3)

Figure 3. FLAIR Plasma CAB and RPV Trough Concentrations*



*Median (5th, 95th percentile) concentration–time data for CAB (left) and RPV (right) following monthly LA administration.

- Throughout the maintenance phase, plasma concentrations after IM CAB + RPV LA were comparable with those during efficacious oral regimens (**Figure 3**).
- Achievement of steady state for CAB was confirmed at Week 44 and was not reassessed using data through Week 96.
- RPV had not achieved steady state by Week 44 and was not reassessed for data through Week 96. However, RPV pre-dose concentrations appeared to plateau between Week 60 and Week 96.

Table 4. Safety Overview (Excluding ISRs)

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

*Week 48 is a nominal cut-off point and contains data collected for participants with dosing beyond Week 48 (approximately 25% with dosing >64 weeks).
†Participants with first reported AE of the type specified occurring after the Week 48 data analysis reporting date.
‡Includes 1 participant at Week 48 data analysis who is not present at Week 96 data analysis.
§Includes 1 participant with adverse event reported as being Grade 4 at Week 48 data analysis but was corrected to Grade 2 at Week 96 data analysis.
¶2 pyrexia, 2 fatigue, 1 headache/nausea, 1 presyncope, 1 depressed mood, 1 pyrexia/chills, 1 chronic sinusitis/chronic tonsilitis, 1 back pain/nasopharyngitis, 1 musculoskeletal pain, 1 dizziness, 1 anxiety, 1 influenza-like illness, 1 asthenia/depressed mood, 1 dizziness.
#1 diarrhea/abdominal pain/nasopharyngitis/eye pain, 1 insomnia, 1 abnormal dreams, 1 poor quality sleep, 1 nausea, 1 hypercholesterolemia/vitamin D decreased.

- Overall, 91/95 (96%) drug-related AEs in the LA arm (excluding ISRs [injection site reactions]) were of maximum Grade 1 or 2 (**Table 4**).
- One drug-related SAE occurred in the LA arm (right knee monoarthritis). None occurred in the DTG/ABC/3TC arm.
- Between the nominal Week 48 and Week 96 data cut-off points, 4 participants discontinued due to AEs (excluding ISRs) in the LA arm: 2 depression (drug-related), 1 hepatitis A, 1 hepatitis C.

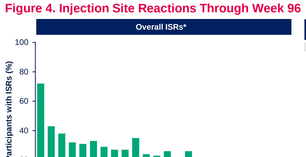
Table 5. Adverse Events Through Week 96 (Excluding ISRs)

	CAB + RPV LA n=283, n (%)	DTG/ABC/3TC n=283, n (%)
Any AE (≥10% in LA arm)		
Any event	264 (93)	242 (86)
Nasopharyngitis	78 (28)	63 (22)
Headache	50 (18)	33 (12)
Upper respiratory tract infection	47 (17)	41 (14)
Diarrhea	43 (15)	38 (13)
Influenza	37 (13)	29 (10)
Back pain	34 (12)	18 (6)
Pyrexia	30 (11)	7 (2)
Drug-related AEs (≥3% in LA arm)		
Any event	95 (34)	33 (12)
Pyrexia*	17 (6)	0
Headache	15 (5)	4 (1)
Asthenia	8 (3)	0
Body temperature increased*	8 (3)	0

*Pyrexia and body temperature increased AE terms as reported by the investigator.

- The most common drug-related AE (excluding ISRs) in the LA arm was pyrexia, occurring in 6% of participants (**Table 5**).

Figure 4. Injection Site Reactions Through Week 96



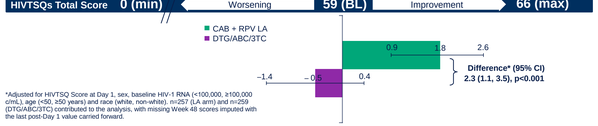
Outcome , n (%)	CAB + RPV LA n=283
Number of injections	12,552
ISR events, n (% of total injections)	3100 (24.7)
Grade 1 – mild	2730 (21.7)
Grade 2 – moderate	352 (2.8)
Grade 3 – severe	18 (<1)
ISR events (most frequent), n (% of total injections)	
Pain	2613 (20.8)
Nodule	132 (1.1)
Induration	119 (<1)
Warmth	59 (<1)
Pruritus	56 (<1)
Swelling	45 (<1)
Median duration of ISRs, days	3
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)

*Incidence is derived relative to the number of participants who received injections at each respective study visit.

- The majority (3082/3100, 99%) of ISRs were Grade 1–2 and most (89%) resolved within ≤7 days (median duration, 3 days) (**Figure 4**).
- Between Week 48 and Week 96, 2 participants withdrew due to ISR-related reasons, 1 for an ISR and 1 for intolerability of injections.

Figure 5. Participant Satisfaction

Adjusted Mean (95% CI) Change from Baseline (BL) in HIV Treatment Satisfaction (HIVTSQs) Total Score



*Adjusted for HIVTSQ Score at Day 1, sex, baseline HIV-1 RNA (<100,000, ≥100,000 c/mL), age (<50, ≥50 years) and race (white, non-white). n=257 (LA arm) and n=259 (DTG/ABC/3TC) contributed to the analysis, with missing Week 48 scores imputed with the last post-Day 1 value carried forward.

- Participants on CAB + RPV LA demonstrated a statistically significant improvement from baseline in treatment satisfaction compared with DTG/ABC/3TC at Week 96 (**Figure 5**).

Conclusions

- Monthly CAB + RPV LA was noninferior to continued oral DTG/ABC/3TC at Week 96 for maintaining suppression of HIV-1 and was consistent with results at Week 48.
- No CVFs occurred in the CAB + RPV LA arm between Week 48 and Week 96.
- CAB + RPV LA was tolerated well and had few new AEs beyond Week 48.
  - Two participants withdrew due to ISR-related events between Week 48 and Week 96, and the frequency of ISRs decreased over the study period.
- Overall treatment satisfaction was higher with CAB + RPV LA vs oral DTG/ABC/3TC as measured by HIVTSQ.
- These results build on the positive data collected at Week 48 and support the therapeutic potential of monthly CAB + RPV LA.

References: 1. Margolis D, et al. *HIV Glasgow* 2018 (Poster 118). **2.** Orkin C, et al. *N Engl J Med.* DOI: 10.1056/NEJMoa1909512 (in press). **3.** Orkin C, et al. CROI 2019 (Abstract 140).

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