Safety and Efficacy of Long-Acting Cabotegravir and Rilpivirine With and Without the Oral Lead-In

Summary

FLAIR[1]

- In FLAIR, after Week 96, patients originally randomized to abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) were eligible to transition to long-acting cabotegravir and rilpivirine (*Cabenuva*, CAB + RPV LA) with or without an OLI period beginning at Week 100 (extension phase).
- Virologic outcomes at Week 124 (after 24 weeks of CAB + RPV LA) during the extension phase of FLAIR were similar between patients who received the oral lead-in (OLI) and those who did not.
    - 1 patient in the direct-to-injection (DTI) arm met the criteria for confirmed virologic failure (CVF) on Week 12 of CAB + RPV LA. No integrase resistance-associated mutations (RAMs) were detected at failure.
- No clinically meaningful differences in median CAB and RPV concentrations were observed between the treatment arms.
- The rates of adverse events between the two treatment arms were similar.

SOLAR[2]

- In SOLAR, patients either continued oral bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) or switched to CAB + RPV LA, where investigators and patients were given the option to forgo the oral lead-in (OLI) and move directly to injection (DTI).
    - Non-inferiority was established between CAB + RPV LA and B/FTC/TAF, with no differences between the OLI and DTI groups in efficacy or safety outcomes. One participant in the OLI group and 2 participants in the DTI group had CVF.

FRENCH COHORT STUDY[3]

- In a French cohort study (n=58), low cabotegravir trough concentrations were reported at Months 1 and 3. Low trough concentrations were associated with not administering an oral lead-in before instituting CAB + RPV LA injections.
- Important Safety Information can be found in the Prescribing Information and also at Our HIV Medicines.

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BACKGROUND

Because of the long-acting nature of CAB + RPV LA all phase 2 and 3 trials required an ~4-week OLI period with oral cabotegravir and oral rilpivirine to assess tolerability before a patient could be switched to the long-acting formulation(s).[4-8]

No major safety signals have been identified during the OLI period. This provided the rationale to investigate CAB + RPV LA administered directly without an OLI (DTI).[1]

FLAIR

FLAIR is an ongoing phase 3 trial originally designed to assess the efficacy and safety of CAB + RPV LA versus ABC/DTG/3TC in virologically suppressed patients with HIV-1.[1] Please click here for more details about the study design of FLAIR.

After Week 96, patients originally randomized to ABC/DTG/3TC were eligible to transition to CAB + RPV LA with or without an OLI period beginning at Week 100 (extension phase).[1]

The objectives of this analysis were to evaluate the antiviral and immunologic effects, pharmacokinetics, safety and tolerability, and viral resistance of CAB + RPV LA among patients switching from ABC/DTG/3TC.[1]

Results

A total of 232 patients (OLI arm, n=121; DTI am, n=111) out of the original 283 chose to transition to CAB + RPV LA during the extension phase.[1]

As with the original analysis of data from FLAIR, patients were predominately white and male.[1] Approximately 19% of patients overall were Black or African American and 22% were female at birth.

Virologic outcomes at Week 124 (after 24 weeks of CAB + RPV LA) can be found below in Table 1 and Figure 1.[1]

One patient in the DTI arm met the criteria for CVF (2 consecutive HIV-1 RNA ≥200 copies/mL) on week 12 of CAB + RPV LA.[1] No integrase or non-nucleoside reverse transcriptase inhibitor (NNRTI) RAMs were detected at baseline and no integrase RAMs were detected at the timepoint of the suspected virologic failure.

Table 1. Virologic Outcomes (FDA Snapshot) from FLAIR at Week 124[1]

	OLI Arm (n=121)	DTI Arm (n=111)
HIV-1 RNA ≥50 copies/mL	1 (0.8)	1 (0.9)
Data in window not below threshold	1 (0.8)*	0
D/C due to lack of efficacy	0	1 (0.9)†
D/C for other reason while not below threshold	0	0
Change in background therapy	0	0
HIV-1 RNA <50 copies/mL	113 (93.4)	110 (99.1)
No virologic data	7 (5.8)	0
D/C due to AE	2 (1.7)‡	0
D/C due to death	0	0
D/C study for other reason	5 (4.1)§	0
On study but missing data in window	0	0

*Participant had HIV-1 RNA of 57 copies/mL at Week 124.

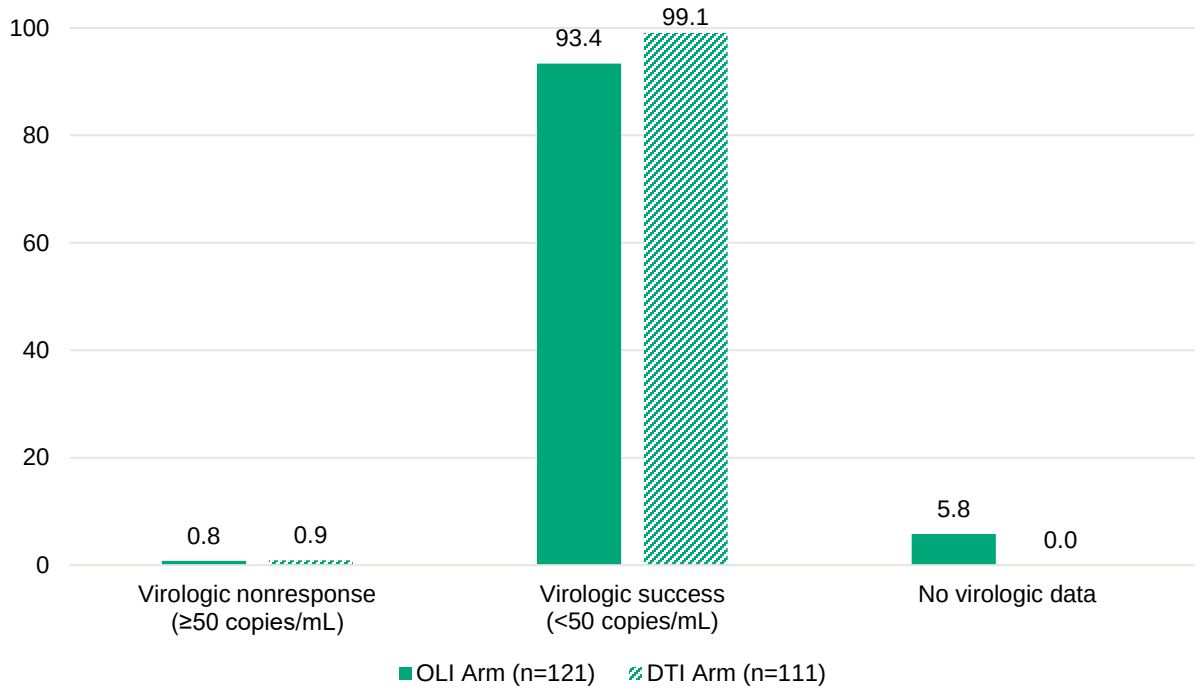
†Participant met the CVF criterion at Week 112.

‡Two participants discontinued due to AEs of injection site pain and weight gain.

§Five participants discontinued due to other reasons, which included burden of travel, prohibited medication use, participant relocation, burden of procedures/intolerability of injections and pregnancy

OLI = oral lead-in; DTI = direct-to-injection; D/C = discontinued; AE = adverse event

Figure 1. Virologic Outcomes (FDA Snapshot) from FLAIR at Week 124[1]



Assay for CAB and RPV concentrations was conducted 1 and 4 weeks after the loading dose injections were administered.[1] No clinically meaningful differences in median CAB and RPV concentrations were observed between the treatment arms.

A summary of adverse events reported in FLAIR through Week 124 can be found in Table 3.[1] The most common adverse events reported in both arms (excluding ISRs) were pyrexia and dizziness.

There were no liver stopping events, confirmed hypersensitivity reactions, or other dermatological manifestations in either treatment arm.[1]

Table 2. Summary of Adverse Events (Excluding ISRs) in FLAIR through Week 124[1]

Paramter, n (%)	OLI Arm (n=121)	DTI Arm (n=111)
Any AE	85 (70)	88 (79)
Any Grade 3 to 4 AE	5 (4)	4 (4)
Drug-related AE	23 (19)	22 (20)
Drug-related Grade 3 to 4 AE	0	1 (<1)*
AEs leading to withdrawal	1 (<1)†	1 (<1)*
Any SAE	5 (4)	4 (4)
Drug-related SAE	0	1 (<1)*
Fatal SAE	0	0

*Grade 4 drug-related SAE leading to withdrawal in the DTI arm was Hodgkin's disease mixed cellularity.

†One participant discontinued from the OLI arm due to AE of weight gain (8 kg).

OLI = oral lead-in; DTI = direct-to-injection; AE = adverse event; SAE = serious adverse event

The reporting of ISRs was similar to what has been reported for FLAIR previously and for other phase 2 and 3 trials more broadly.[1] A total of 4442 injections were administered leading to 914 (21%) ISR events.

ISRs were numerically less common in the OLI arm (16%) than the DTI arm (25%). The most common event reported was pain. There were 2 withdrawals due to ISRs (both in OLI arm). Most ISRs were mild to moderate in severity and decreased over the course of the study.

SOLAR

A Phase 3b, randomized, multicenter, active-controlled, parallel-group, non-inferiority study (SOLAR) evaluated switching from bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) to CAB + RPV LA, where investigators and patients were given the option to forgo the oral lead-in and move directly to injection (DTI).[2,9] For additional information on the SOLAR study, please click here.

At Month 12, 447 patients were randomized to switch to CAB + RPV LA (OLI, n=173; DTI, n=274) and 223 patients were randomized to continue daily oral B/FTC/TAF. See Table 3.

Table 3. Select Baseline Characteristics from SOLAR (mITT-E)[10]

Characteristic	CAB + RPV LA Q2M			B/FTC/TAF (N=223)	Total (N=670)
	OLI (n=173)	DTI (n=274)	Q2M Total (N=447)		
Median age, years (range)	36 (20-74)	38 (18-70)	37 (18-74)	37 (18-66)	37 (18-74)
Age group (years), n (%)					
<35	77 (45)	115 (42)	192 (43)	98(44)	290 (43)
35 to < 50	60 (35)	109 (40)	169 (38)	83 (37)	252 (38)
≥ 50	36 (21)	50 (18)	86 (19)	42 (19)	128 (19)
Sex at birth, n (%)					
Female	25 (14)	52 (19)	77 (17)	41 (18)	118 (18)
Race, n (%)					
Asian[a]	7 (4)	16 (6)	23 (5)	11 (5)	34 (5)
Black	39 (23)	56 (20)	95 (21)	49 (22)	144 (21)
White[b]	113 (65)	194 (71)	307 (69)	156 (70)	463 (69)
Median weight (kg) at baseline, range	81.50 (48.5-199.7)	80.50 (48.1-153.4)	81.10 (48.1-199.7)	79.00 (43.3-169.0)	80.55 (43.3-199.7)
Median BMI (kg/m2) at baseline, range	26.07 (18.12-65.21)	25.96 (16.63-50.67)	26.01 (16.63-65.21)	25.43 (16.48-68.35)	25.86 (16.48-68.35)

a=Asian heritage includes central/south Asian, East Asian, Japanese and Southeast Asian; b=White heritage includes Arabic/North African, white/Caucasian/European heritage, mixed white race

B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BMI = body mass index; CAB + RPV LA = long-acting cabotegravir + rilpivirine; DTI = direct to injection; Q2M = every-2-month; OLI = oral lead-in

Efficacy[2,10]

At Month 12, non-inferior efficacy of CAB + RPV LA vs B/FTC/TAF was demonstrated for the proportion with HIV-1 RNA ≥ 50 c/mL. The upper bound of 95% confidence interval (CI) for the adjusted treatment difference between CAB + RPV LA Q2M and B/FTC/TAF was less than the pre-defined non-inferiority margin of 4%.[10] See Table 4.

Table 4. Summary of Study Outcomes at Month 12 (Maintenance Phase) - FDA Snapshot Analysis (mITT-E Population)[10]

Outcome	CAB + RPV LA Q2M			B/FTC/TAF (n=223) n (%)
	OLI (n=173) n (%)	DTI (n=274) n (%)	Q2M Total (n=447) n (%)	
HIV-1 RNA ≥ 50 copies/mL	**2 (1)**	**3 (1)**	**5 (1)**	**1 (< 1)**

Adjusted treatment difference [% (95% CI)]			0.7 (-0.7, 2.0)	
Data in window not below threshold	1 (<1)	2 (<1)	3 (<1)	1 (<1)
Discontinued for lack of efficacy	1 (<1)	0	1 (<1)	0
Discontinued for other reason while not below threshold	0	1 (<1)	1 (<1)	0
No virologic data	20 (12)	19 (7)	39 (9)	15 (7)
Discontinued study due to AE or death [a]	10 (6)	3 (1)	13 (3)	1 (< 1)
Discontinued study for other reasons	9 (5)	15 (5)	24 (5)	13 (6)
On study but missing data in window	1 (<1)	1 (<1)	2 (<1)	1 (< 1)

a=one death was reported during the Maintenance Phase; this participant in the B/FTC/TAF group has a fatal event of brain injury and encephalopathy

B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CAB + RPV LA = long-acting cabotegravir and rilpivirine; DTI = direct-to-injection; mITT-E = modified intent-to-treat exposed; OLI = oral lead-in; Q2M = every 2 months

Confirmed Virologic Failure

In the mITT-E population, 2 participants treated with CAB + RPV LA (one in OLI group, one in DTI group) had CVF through Month 12. Additionally, 1 participant from the ITT-E population (DTI group) had CVF.[10]

Safety

Drug-related AEs were reported at a higher frequency with CAB + RPV LA during the Maintenance Phase, largely attributed to the incidence of ISRs. See Table 5 below for an overall summary of adverse events through Month 12.

Table 5. Month 12 Analysis of Adverse Events – Maintenance Phase (Safety Population)[10]

Preferred Term	CAB + RPV LA Q2M			B/FTC/TAF (n=227) n (%)
	OLI (n=166) n (%)	DTI (n=279) n (%)	Q2M Total (n=445) n (%)	
Any AE	155 (89)	250 (90)	405 (89)	172 (76)
Any drug-related AE	128 (73)	199 (71)	327 (72)	2 (<1)
Drug-related AE, excluding ISRs	45 (26)	45 (16)	90 (20)	2 (<1)
Drug-related Grade 2-5 AE	67 (38)	75 (27)	142 (31)	1 (<1)
Drug-related Grade 2-5 AE, excluding ISRs	23 (13)	11 (4)	34 (7)	1 (<1)
Drug-related SAEs[a]	3 (2)	1 (<1)	4 (<1)	0

a=The drug-related SAEs in the CAB + RPV OLI group were ALT increased, acute myocardial infarction, and injection site pain; the drug-related SAE in the CAB + RPV DTI group was ALT increased.
AE = adverse event; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CAB + RPV LA = long acting cabotegravir + rilpivirine; DTI = direct to injection; ISR = injection site reaction; OLI = oral lead-in; Q2M = every 2 months; SAE = serious adverse event

In the CAB + RPV Q2M group, the most frequently reported non-ISR drug-related AEs were pyrexia (13 [3%] participants), fatigue (10 [2%] participants), diarrhea (9 [2%] participants), headache (11 [2%] participants), nausea (6 [1%] participants), chills (6 [1%] participants), and dizziness (5 [1%] participants); all other non-ISR drug-related AEs had a frequency of ≤1%. Incidences were similar between OLI and DTI groups. Nine subjects (3 in the OLI group and 6 in the DTI group) withdrew during the maintenance phase due to drug-related non-ISR events through Month 12.[10]

Injection Site Reactions[10]

Most ISRs were Grades 1 or 2 (98%) and short-lived (median 3 days). [2,10] See Table 6.

Table 6. Injection Site Reactions Summary (Event-Level) at Month 12[2,10]

Parameter	Randomized to CAB + RPV LA Q2M		
	OLI (N=166)[a] n (%)	DTI (N=279)[a] n (%)	Q2M Total (N=445)[a] n (%)
Number of injections, n	2228	3724	5952
ISR events, n[b]	734	1181	1915
Pain, n (% of injections)	507 (23)	887 (24)	1394 (23)
Discomfort, n (% of injections)	56 (3)	65 (2)	121 (2)
Nodule, n (% of injections)	28 (1)	56 (2)	84 (1)
Grade 3, n (% of ISR events)[c]	19 (3)	10 (<1)	29 (2)
Median Duration (IQR), days	3 (2, 5)	3 (2, 5)	3 (2, 5)
Participant withdrawal due to ISR-related reason, n (% of participants with injections)[d]	3 (2)	8 (3)	11 (2)

a=represents the number of participants who received an injection; b=a single injection could result in one more ISR. Grading was missed in 1 ISR in the CAB + RPV LA DTI group; c=there were no Grade 4 or Grade 5 ISRs. d=Includes participants who discontinued due to ISR AEs, and an additional participant who withdrew from the study citing injection intolerability. This also includes one participant who was excluded from the primary analysis (mITT-E) population.
CAB = cabotegravir; DTI = direct to injection; IQR = interquartile range; ISR = injection site reaction; LA = long-acting; mITT-E = modified intention-to-treat exposed; OLI = oral lead-in; Q2M = every 2 months

An online survey was conducted among 111 health care providers in 13 countries during the SOLAR trial that assessed reasons for utilizing an oral lead-in prior to LA injections versus those who started with injections without an oral lead-in. Results indicated increased future intentions to start with injections over an oral lead-in among providers who were initiating participants on CAB + RPV LA.[11]

FRENCH COHORT DATA

A prospective cohort study was conducted between March 1, 2022 – January 31, 2023 to assess safety and efficacy of switching to CAB + RPV LA in two French University Hospitals.[3] The oral lead-in was instituted at only one of the hospital sites. A total of 58 patients were included in the study; 16 (28%) received the oral lead-in with cabotegravir + rilpivirine. Patients were followed for a median time of 8 months (IQR 7-10 months). Trough concentrations were measured using liquid chromatography with mass tandem spectrometry, which differed from the assay methods utilized in FLAIR (results presented above).

Low cabotegravir concentrations were observed in 60% of patients at Month 1 and 77% of patients at Month 3. In patients without an oral lead-in, month 3 median trough levels were <4xPAIC90. One patient had virologic failure without resistant mutations. High BMI and the absence of an oral lead-in were associated with low CAB trough concentrations. No risk factors were identified for low RPV trough levels at Month 1 and Month 3.[3]

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