WEEK 124 OF THE RANDOMIZED, OPEN-LABEL, PHASE 3 FLAIR STUDY EVALUATING LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR TREATMENT IN ADULTS WITH HIV-1 INFECTION

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FLAIR Week 124: Disclosures

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- Professor Chloe Orkin reports personal fees for travel to conferences, lectureship fees, contributions to advisory boards, and development of slide decks from ViiV Healthcare, Gilead Sciences, MSD, and Janssen, and received grants from ViiV Healthcare, Gilead Sciences, MSD, and Janssen

FLAIR Week 124: Introduction

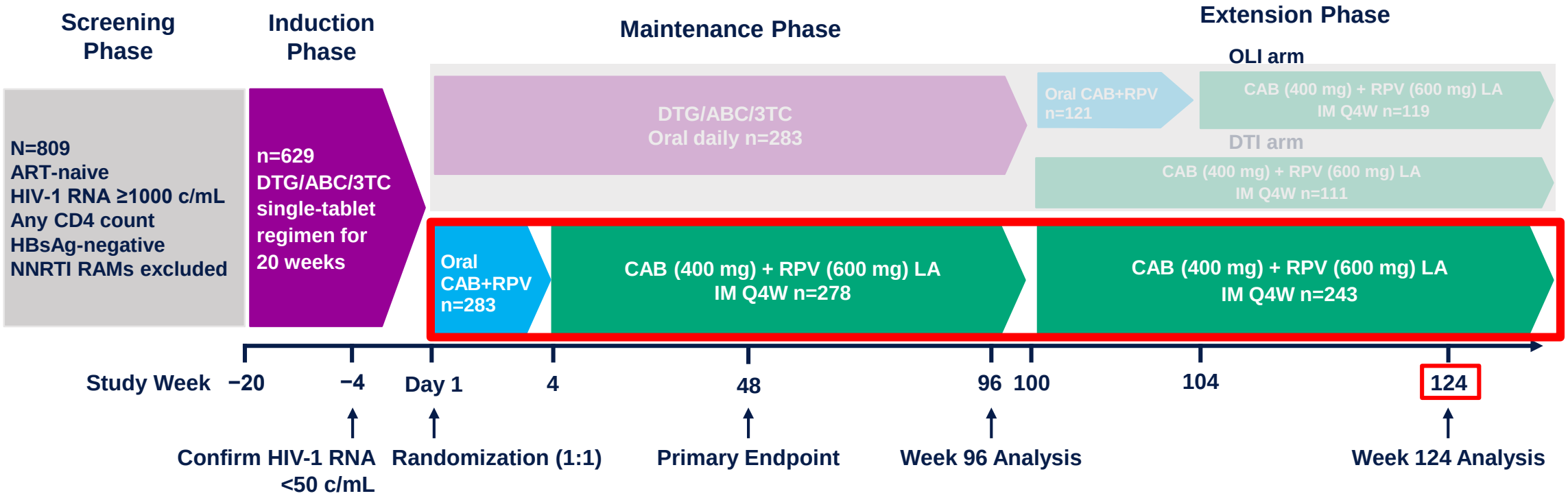
- Cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) is the first complete injectable regimen approved and recommended by treatment guidelines[1,2] for the maintenance of virologic suppression in people living with HIV-1[3–6]
- Monthly[7–9] or every 2 months dosing[10] of CAB + RPV LA may address some of the challenges associated with daily oral ART, such as stigma, pill burden/fatigue, drug–food interactions, and adherence
- FLAIR (NCT02938520), a Phase 3, randomized, multicenter, open-label study, demonstrated noninferiority of switching virologically suppressed participants from daily oral dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) to monthly IM CAB + RPV LA over 96 weeks
  - Results for participants switching from DTG/ABC/3TC to CAB + RPV LA (with or without an oral lead-in) were previously presented[11]
- Efficacy and safety results for participants initially randomized to CAB + RPV LA through Week 124 are presented herein

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral therapy; DTG, dolutegravir; IM, intramuscular; LA, long-acting; RPV, rilpivirine.

1. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/15/virologic-failure. Accessed March 25, 2021. 2. Saag MS, et al. *JAMA*. 2020;324(16):1651–1669. 3. ViiV Healthcare. Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) Prescribing Information. US, January 2021. 4. ViiV Healthcare. Vocabria Summary of Product Characteristics. EU, December 2020. 5. ViiV Healthcare. Vocabria (cabotegravir tablets) and Cabenuva (cabotegravir and rilpivirine extended release injectable suspensions) Product Monograph. Canada, March 2020. 6. CABENUVA. Available at: https://viivhealthcare.com/en-au/our-medicines/cabenuva/. Accessed April 9, 2021. 7. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123. 8. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135. 9. Orkin, et al. *Lancet HIV*. 2021;8(4):e185–e196. 10. Overton ET, et al. *Lancet*. 2020;396(10267):1994–2005.
11. D'Amico R, et al. Glasgow HIV 2020;O414.

FLAIR Week 124: Study Design and Endpoints

Phase 3, Randomized, Multicenter, Parallel-Group, Noninferiority, Open-Label Study*

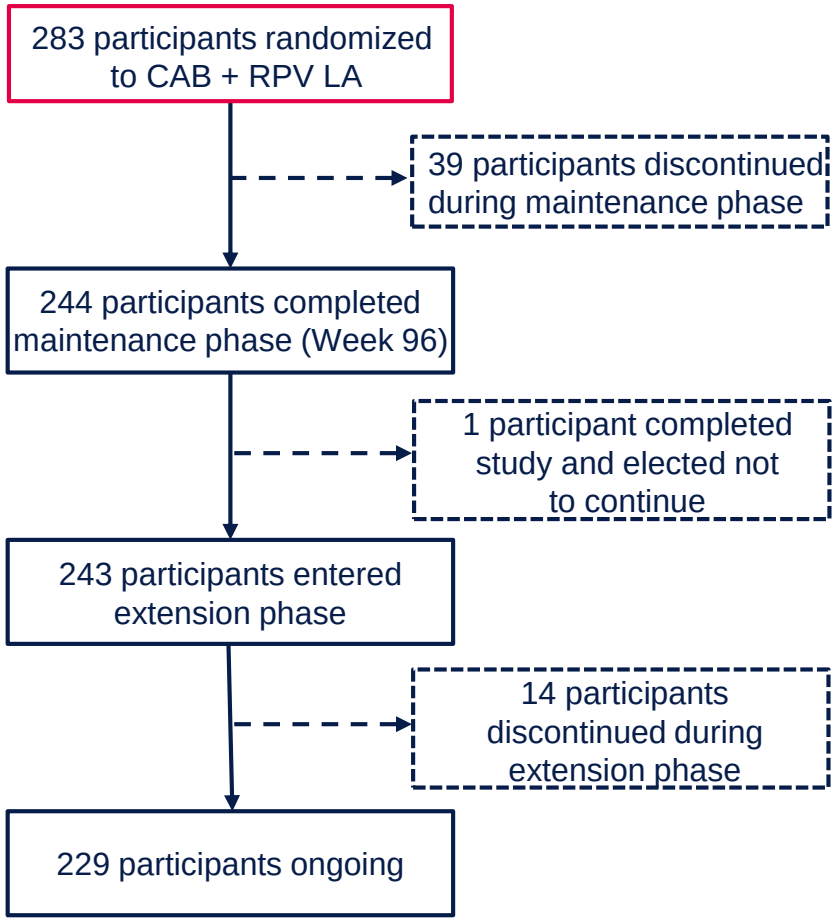


- Endpoints at Week 124 included the proportion of participants with HIV-1 RNA ≥50 and <50 copies/mL (FDA Snapshot), confirmed virologic failure (CVF; two consecutive viral loads ≥200 copies/mL), and safety and tolerability

*The study design figure has been adapted from Orkin C, et al. *N Engl J Med* 2020;381:1124–1135 and Orkin, et al. *Lancet HIV* 2021;8(4):e185–e196.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CVF, confirmed virologic failure; DTI, direct-to-injection; DTG, dolutegravir; FDA, Food and Drug Administration; HBsAg, hepatitis B surface antigen; IM, intramuscular; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; OLI, oral lead-in; Q4W, every 4 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

FLAIR Week 124: Baseline Characteristics and Participant Disposition*

ITT-E population	Randomized CAB + RPV LA n=283†
Age, median (IQR) years	34 (29–42)
Female (sex at birth), n (%)	63 (22)
Female (self-reported gender), n (%)	65 (23)
Race, n (%)	
White	216 (76)
Black or African American	47 (17)
Other	20 (7)
Hispanic or Latinx ethnicity (%)	28 (10)
Body mass index, median (IQR) kg/m^2	24 (22–27)
CD4+ cell count, median (IQR) cells/mm^3	624 (473–839)

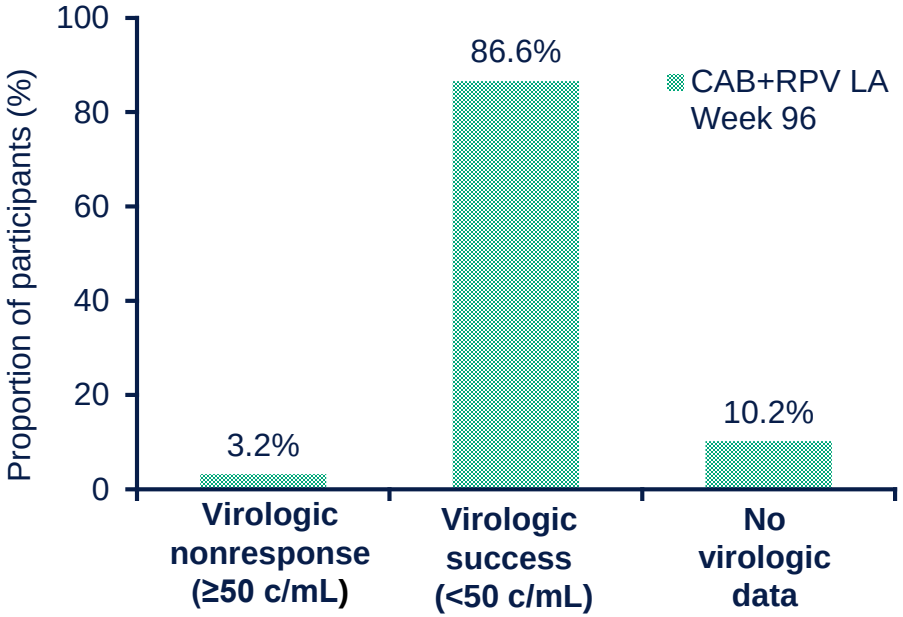


*The baseline characteristics table and participant disposition figure have been adapted from Orkin C, et al. *N Engl J Med* 2020;381:1124–1135 and Orkin, et al. *Lancet HIV* 2021;8(4):e185–e196. †Data collected at maintenance baseline (Day 1).
CAB, cabotegravir; IQR, interquartile range; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

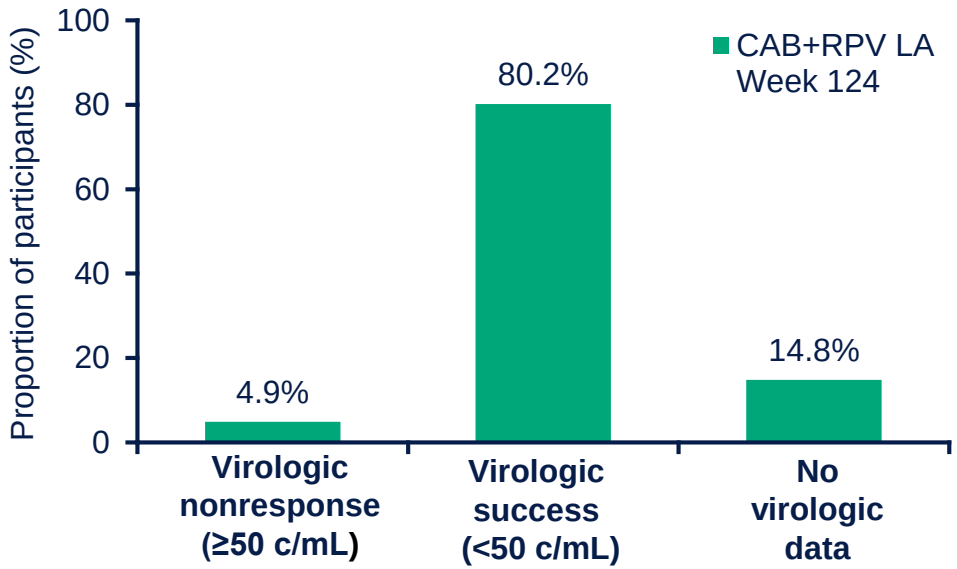
Orkin C et al. IAS 2021; Virtual. Presentation OAB0302.

FLAIR Week 124: Virologic Snapshot Outcomes (ITT-E Population) CAB + RPV LA Continued to Maintain High Levels of Viral Suppression

Virologic Outcomes at Week 96*



Virologic Outcomes at Week 124†



- Five (1.8%) additional participants had HIV-1 RNA ≥50 copies/mL since the Week 96 analysis
- One additional participant had CVF since the Week 96 analysis
- Of those with no virologic data at Week 124 (14.8%, n=42/283), most were due to discontinuations due to AEs or other non-virologic reasons

*Week 96 data have been presented previously.[1] †There is no CAR arm at Week 124.
AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral therapy; CVF, confirmed virologic failure; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.
1. Orkin, et al. *Lancet HIV*. 2021;8(4):e185–e196.

Orkin C et al. IAS 2021; Virtual. Presentation OAB0302.

FLAIR Week 124: Virologic Snapshot Outcomes (ITT-E Population) One Participant Met the CVF Criterion Since Week 96

	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	**42 (14.8)**
Discontinued due to AE*	15 (5.3)
Discontinued study for other reason†	26 (9.2)
On study but missing data in window	1 (0.4)
CVF (two consecutive plasma HIV-1 RNA ≥200 copies/mL) at Week 124‡	5 (1.8)
Additional since Week 96 analysis	1 (<1)

CVF participant 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, and M230L¶
Treatment-emergent INSTI RAMs	N155H and R263K‖
Week 8 CAB/RPV troughs	1.05 µg/mL/24.6 ng/mL**
Week 108 CAB/RPV troughs	1.73 µg/mL/79.5 ng/mL††
Resuppression	<50 copies/mL at LTFU Month 3 on EFV/TDF/FTC

*Three additional participants since the Week 96 analysis[1] (paracetamol overdose, acute hepatitis A, depression). †Ten additional participants since the Week 96 analysis: withdrawal by subject, n=8 (frequency of injections [n=1], subject relocation [n=2], frequency of visits [n=3], other [n=7]) and physician decision, n=2 (pregnancy). ‡One participant temporarily discontinued CAB + RPV due to a false-positive pregnancy test and had CVF prior to receiving an LA injection. §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.

CAB, cabotegravir; CAR, current antiretroviral therapy; CVF, confirmed virologic failure; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; ITT-E, intention-to-treat exposed; LA, long-acting; LTFU, long-term follow-up; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; SVF, suspected virologic failure; TDF, tenofovir disoproxil fumarate.

1. Orkin, et al. *Lancet HIV*. 2021;8(4):e185–e196.

FLAIR Week 124: Safety Overview (Excluding ISRs)

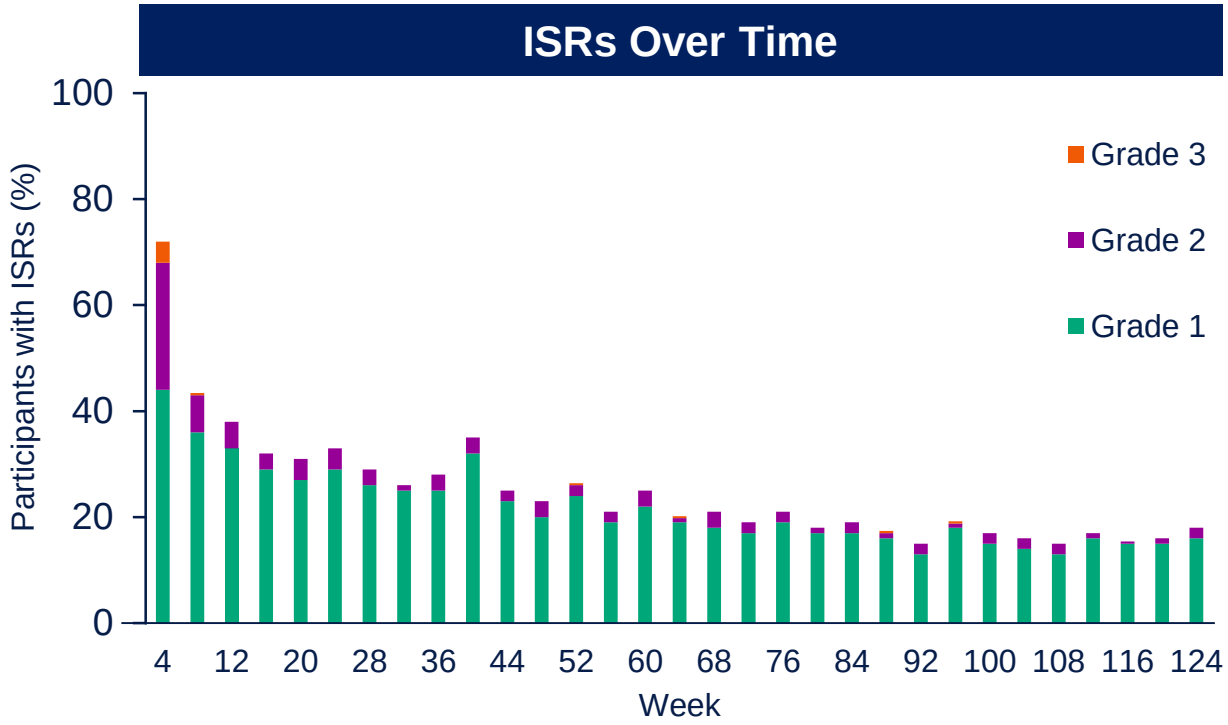
	CAB + RPV LA (Cumulative through Week 124) (n=283), n (%)	Additional participants since Week 96 data analysis n (%)
Any AE	271 (96)	7 (2)
Grade 3 to 4 AEs	38 (13)	9 (3)
Drug-related AEs	102 (36)	7 (2)*
Drug-related Grade 3 to 4 AEs	5 (2)	1 (<1)
AEs leading to withdrawal	15 (5)	1 (<1)†
Any SAE	33 (12)	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)

- Most drug-related AEs (excluding ISRs) were Grade 1 or Grade 2 (n=97/102 [95%]); only one drug-related Grade 3/4 AE occurred since the Week 96 analysis (paracetamol overdose, Grade 3)
- There were no confirmed drug-related hypersensitivity reactions from baseline through 124 weeks and there was one additional case of liver stopping criteria being met since the Week 96 analysis¶

*Seven participants reported 22 events since the Week 96 analysis (pyrexia n=1, fatigue n=3, chills n=2, influenza-like illness n=1, paresthesia n=1, autonomic nervous system imbalance n=1, hypoesthesia n=1, lethargy n=1, restless leg syndrome n=1, nausea n=1, blood creatine 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. ‡Drug-related SAE was right knee monoarthritis reported in the Week 48 analysis. §Drug-related AEs are based on investigator assessment. ¶Secondary syphilis; not drug related. AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine; SAE, serious adverse event.

Orkin C et al. IAS 2021; Virtual. Presentation OAB0302.

FLAIR Week 124: ISR Summary



Outcome, n (%)	CAB + RPV LA n=283
Number of injections	17,392
ISR events	3732
Pain, n (% of total injections)*	3131 (18)
Nodule, n (% of total injections)*	162 (<1)
Indurations, n (% of total injections)*	158 (<1)
Median duration of ISRs, days	3
Participants who withdrew due to ISR-related reasons, n (% of participants)†	7 (2)

- ISRs were the most common AE; most events were Grade 1 (89%, n=3315) or Grade 2 (11%, n=399)‡
- One additional participant discontinued due to ISRs since the Week 96 analysis

*Three most common ISRs. †Participants who withdrew due to ISR-related reasons included participants with injection intolerability (n=4) and those who had ISRs leading to withdrawal (n=3). ‡There were no Grade 4 or 5 events.
AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.

Orkin C et al. IAS 2021; Virtual. Presentation OAB0302.

FLAIR Week 124: Conclusions

- At Week 124, 80.2% of participants maintained virologic suppression on monthly CAB + RPV LA
- The majority of participants who did not maintain suppression did so due to non-virologic reasons
- The safety and tolerability profile was consistent with the prior Week 48 and Week 96 analyses
  - ISRs were mostly mild/moderate in severity, self-limited, and decreased over time
  - There was 1 additional participant with CVF since Week 96, totaling 5 participants over 124 weeks
  - AEs leading to withdrawal occurred infrequently and no drug-related SAEs were recorded beyond Week 96
- These results demonstrate the durability of CAB + RPV LA dosed monthly as a well-tolerated, effective maintenance therapy for people living with HIV-1

AE, adverse event; CAB, cabotegravir; CVF, confirmed virologic failure; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine; SAE, serious adverse event.

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FLAIR Week 124: Acknowledgments

- We thank everyone who has contributed to the success of the study: all study participants and their families; the FLAIR clinical investigators and their staff; and the ViiV Healthcare, GlaxoSmithKline, and Janssen study team members

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