SAFETY AND EFFICACY OF CABOTEGRAVIR + RILPIVIRINE LONG-ACTING WITH AND WITHOUT ORAL LEAD-IN: FLAIR WEEK 124 RESULTS

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FLAIR OLI: Introduction

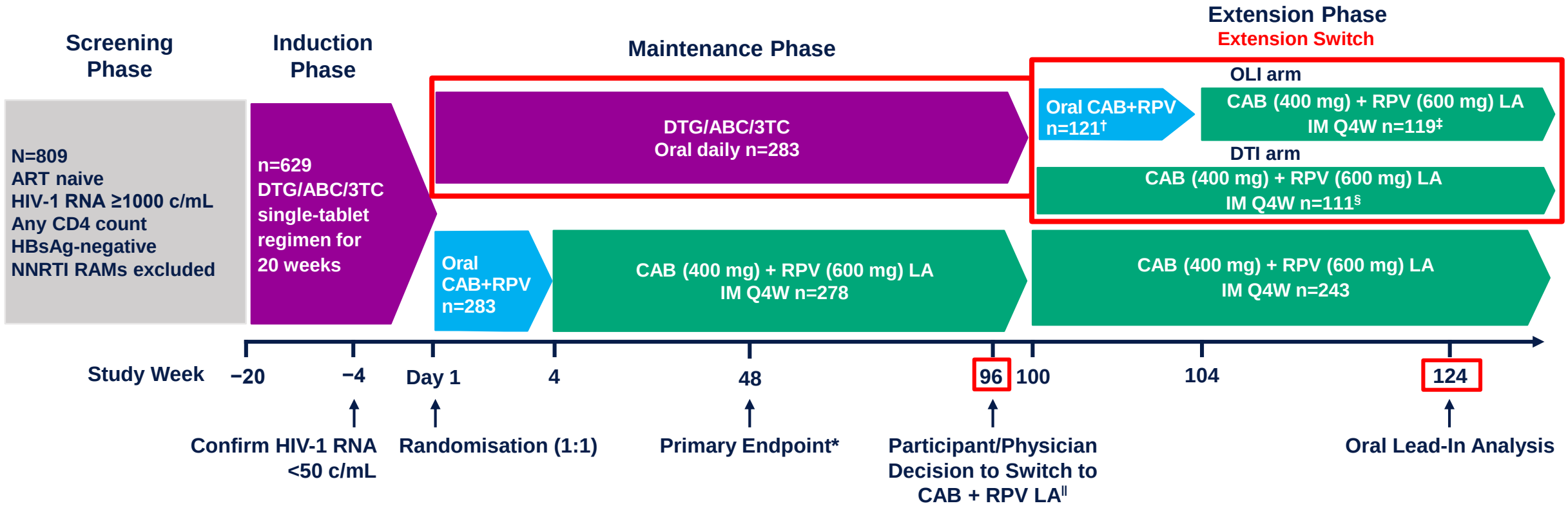
- The Phase III FLAIR study demonstrated noninferior efficacy of switching to CAB + RPV LA every 4 weeks (Q4W) compared with continuing daily oral dolutegravir/abacavir/lamivudine (DTG/ABC/3TC [CAR])* through ~2 years[1,2]
- A 4-week oral lead-in (OLI) period to assess safety and tolerability prior to intramuscular (IM) CAB + RPV LA administration has been used in Phase II and Phase III studies[1–5]
- No major safety signals were identified during the OLI period across the Phase II and III programme, providing the rationale to investigate CAB + RPV LA administered directly without an OLI (direct to inject [DTI])[1–5]
- The efficacy, safety and pharmacokinetics of CAB + RPV LA, given with or without an OLI, in CAR arm participants who elected to receive LA therapy in the Extension Phase of FLAIR (Extension Switch) are presented

*If any participant had toxicity or intolerability in association with DTG/ABC/3TC, one switch to an approved alternative background nucleoside reverse transcriptase inhibitor (NRTI) was permitted. Participants who were positive for HLA-B*5701 received DTG plus two alternative non-ABC NRTIs instead of DTG/ABC/3TC.

1. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135.
2. Orkin C, et al. CROI 2020; Boston, Massachusetts; March 8–11, 2020; Poster 0482.
3. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123.
4. Margolis D, et al. *Lancet*. 2017;390(10101):1499–1510.
5. Overton ET, et al. *Lancet*. Accepted 2020.

FLAIR OLI: Study Design

Phase III, Randomised, Multicentre, Parallel-Group, Noninferiority, Open-Label Study



*Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48 as per the Food and Drug Administration (FDA) Snapshot algorithm.
†Two discontinuations during OLI: 1 participant relocation, 1 pregnancy.
‡For participants in the OLI arm, daily oral CAB (30 mg) + RPV (25 mg) was initiated at Week 100 and continued for ≥4 weeks. Participants received their last dose of oral CAB + RPV and their first loading injections of CAB (600 mg) + RPV (900 mg) LA at Week 104. This was followed by CAB 400 mg + RPV 600 mg LA Q4W.
§For participants in the DTI arm, the last dose of CAR and first loading injections of CAB (600 mg) + RPV (900 mg) LA were administered at Week 100. This was followed by CAB 400 mg + RPV 600 mg LA Q4W.
‖Participants, in consultation with their physician, elected to receive CAB + RPV LA either with an OLI or DTI at Week 96. The new treatment regimen began at Week 100.
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CAR, current antiretroviral therapy; DTI, direct to inject; DTG, dolutegravir; 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 OLI: Objective and Endpoints at Week 124

Objective

- To evaluate the antiviral and immunologic effects, pharmacokinetics, safety and tolerability and viral resistance of CAB + RPV LA at Week 124 for participants switching from CAR in the Extension Phase, with and without OLI*

Endpoints assessed at Week 124 for the Extension Switch population

- Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 124 per the FDA Snapshot algorithm
- Proportion of participants with HIV-1 RNA <50 copies/mL at Week 124 per the FDA Snapshot algorithm
- Incidence of protocol-defined confirmed virologic failure (CVF)†
- Incidence and severity of adverse events (AEs) and laboratory abnormalities
- Proportion of participants who discontinue treatment due to AEs
- Pharmacokinetics of CAB + RPV LA in the context of no OLI

*The study protocol was amended to give participants in the comparator arm the option to transition to CAB + RPV LA either directly or with an OLI. Consequently, no formal statistical comparisons between arms were performed.

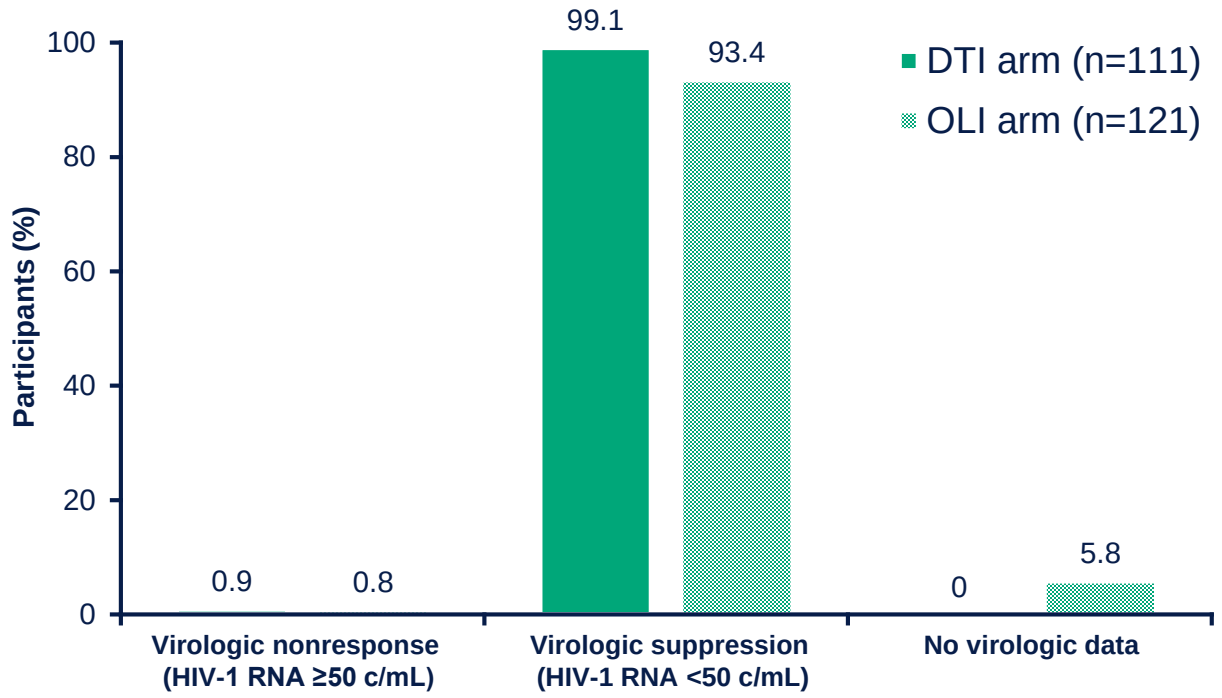
†Two consecutive plasma HIV-1 RNA measurements of ≥200 copies/mL.
CAB, cabotegravir; CAR, current antiretroviral therapy; LA, long-acting; OLI, oral lead-in; RPV, rilpivirine.

FLAIR OLI: Baseline Characteristics (Extension Switch)

Parameter	DTI arm n=111	OLI arm n=121
Age, median (range) years	38 (21–70)	39 (21–65)
Age ≥50 years, n (%)	16 (14)	17 (14)
Age <35 years, n (%)	49 (44)	43 (36)
Female (sex at birth), n (%)	24 (22)	27 (22)
Female (self-reported gender), n (%)	24 (22)	27 (22)
Race, n (%)		
White	77 (69)	94 (78)
Black or African American	23 (21)	21 (17)
Other	11 (10)	6 (5)
Body mass index, median (range) kg/m^2	26 (18–52)	25 (17–41)
CD4+ cell count, median (interquartile range) cells/mm^3	752 (590–988)	718 (595–852)

DTI, direct to inject; OLI, oral lead-in.

FLAIR OLI: Snapshot Virologic Outcomes at Week 124 (Extension Switch)



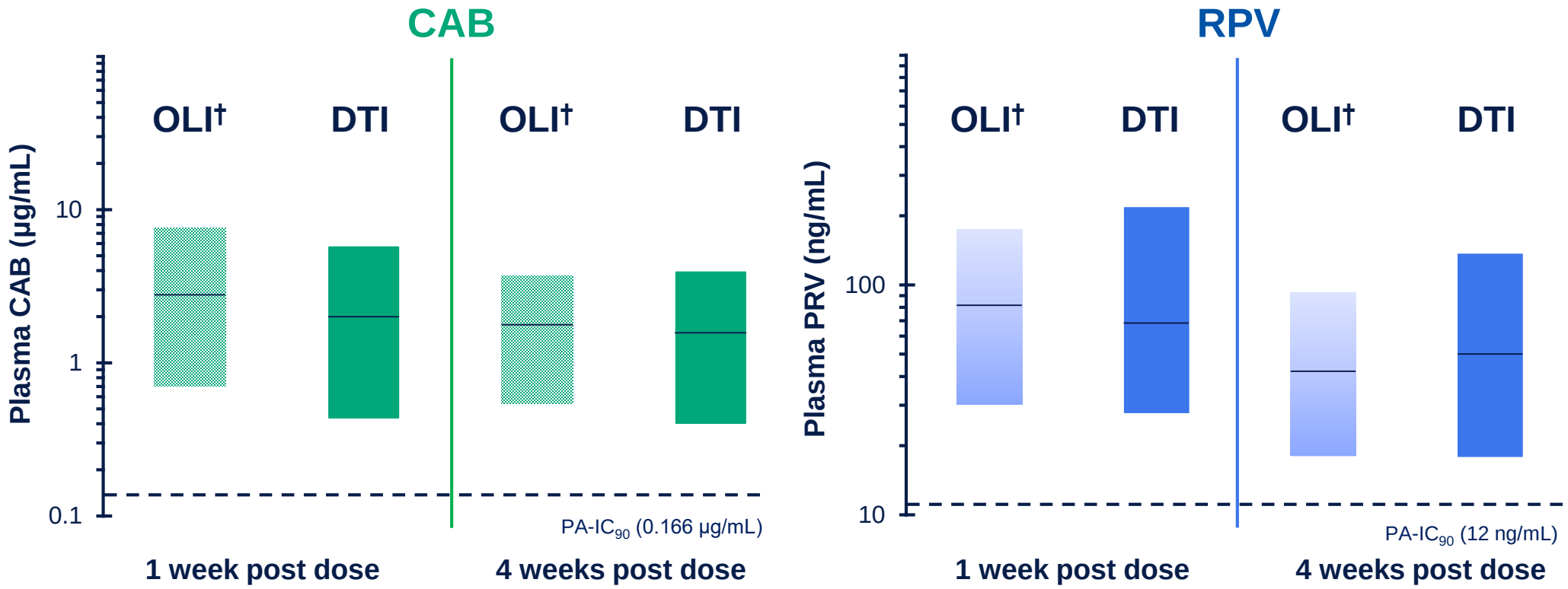
Outcome, n (%)	DTI arm n=111	OLI arm n=121
HIV-1 RNA <50 copies/mL	110 (99.1)	113 (93.4)
HIV-1 RNA ≥50 copies/mL	1 (0.9)	1 (0.8)
Data in window not below threshold	0	1 (0.8)*
Discontinued for lack of efficacy	1 (0.9)†	0
Discontinued for other reason while not below threshold	0	0
Change in background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

- Only 1 participant (0.4%) met the CVF criterion in the Extension Switch population
  - The participant was in the DTI arm and met the CVF criterion on the 12th week of LA therapy. No INSTI or NNRTI resistance-associated mutations were detected at baseline and no INSTI resistance-associated mutations were detected at the timepoint of suspected virologic failure (NNRTI mutations could not be generated)

AE, adverse event; CVF, confirmed virologic failure; DTI, direct to inject; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; OLI, oral lead-in.

FLAIR OLI: Pharmacokinetics*
No Impact on Early CAB + RPV LA Concentrations in Absence of OLI



*5th percentile, median and 95th percentile values 1 week and 4 weeks after LA administration (OLI, LA arm: Week 5, n=262[CAB]/263[RPV]; Week 8, n=250[CAB]/251[RPV]; no OLI, DTI arm: Week 101, n=104; Week 104, n=79).
†Historical data: participants who were randomised to CAB + RPV LA in the Maintenance Phase.

- CAB and RPV concentrations were assessed 1 week and 4 weeks post loading dose injections
- No clinically meaningful differences in median CAB and RPV concentrations were observed between the DTI vs. OLI participants

CAB, cabotegravir; DTI, direct to inject; LA, long-acting; OLI, oral lead-in; PA-IC_{90}, protein-adjusted concentration required for 90% inhibition; RPV, rilpivirine.

FLAIR OLI: Extension Phase Safety Overview (Excluding ISRs, Extension Switch)

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

- 4% (9/232) of participants in the Extension Switch population (DTI + OLI) experienced a Grade 3 or Grade 4 non–injection site reaction (ISR) AE

AE, adverse event; DTI, direct to inject; ISR, injection site reaction; OLI, oral lead-in; SAE, serious adverse event.

FLAIR OLI: Extension Phase Common AEs and Drug-Related AEs (Excluding ISRs, Extension Switch)

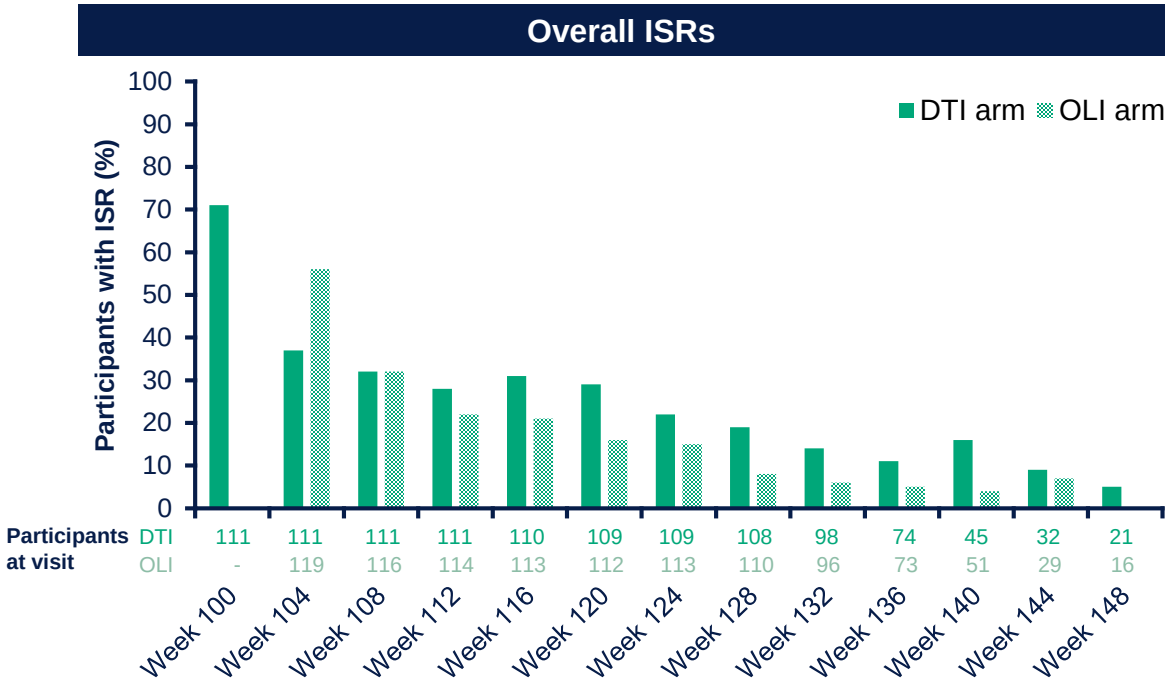
Common (≥5% in either arm) AEs, n (%)	DTI arm n=111	OLI arm n=121
Nasopharyngitis	20 (18)	13 (11)
Upper respiratory tract infection	10 (9)	7 (6)
Pyrexia	9 (8)	4 (3)
Diarrhoea	2 (2)	10 (8)
Dizziness	8 (7)	4 (3)
Gastroenteritis	7 (6)	3 (2)
Headache	7 (6)	3 (2)
Common (≥3% in either arm) drug-related AEs, n (%)		
Pyrexia	6 (5)	2 (2)
Dizziness	3 (3)	2 (2)

- **There were no liver monitoring/stopping events, confirmed hypersensitivity reactions or other significant dermatological manifestations observed in either treatment arm**
- The incidence of Grade 3 or 4 emergent chemistry toxicities (13 vs. 5)* and rash (4 vs. 2; all Grade 1 or 2)† was higher in the DTI arm than the OLI arm

*DTI arm: Grade 3 AST, CPK, GFR, lipase and phosphate toxicities and Grade 4 CPK and lipase toxicities; OLI arm: Grade 3 CPK and lipase toxicities and Grade 4 CPK toxicities.
†One AE of rash pruritic (Grade 1), reported during the OLI period in the OLI arm, was considered related to study drugs.

AE, adverse event; AST, aspartate aminotransferase; CPK, creatine phosphokinase; DTI, direct to inject; GFR, glomerular filtration rate; ISR, injection site reaction; OLI, oral lead-in.

FLAIR OLI: Extension Phase ISRs (Extension Switch)



Parameter	DTI arm n=111	OLI arm n=121
Number of injections	2314	2128
Number of ISR events	576	338
Grade 1 – mild, n (% of total injections)	478 (20.7)	271 (12.7)
Grade 2 – moderate, n (% of total injections)	97 (4.2)	62 (2.9)
Grade 3 – severe, n (% of total injections)	1 (<1)	5 (<1)
Median duration of ISR events, days	3	3
ISR events leading to withdrawal, n (% of ISRs)	0	2 (<1)

- 4442 injections were administered in total
  - Only 1 participant discontinued due to two Grade 3 ISRs (one for each injection at the same visit)
- The majority (>99%, 908/914) of ISRs were Grade 1 (82%, 749/914) or Grade 2 (17%, 159/914), and their incidence decreased over the study period
  - 89% of these events were injection site pain

DTI, direct to inject; ISR, injection site reaction; OLI, oral lead-in.

FLAIR OLI: Conclusions

- CAB + RPV LA, given with or without an OLI, was found to be a well-tolerated, safe and effective maintenance regimen up to Week 124
  - The proportion of participants with CVF in the Extension Switch population was low, with one participant in the DTI group (0.4%) meeting the CVF criterion
- Switching directly to CAB + RPV LA was comparable in terms of safety and tolerability to treatment with OLI
- ISRs were mostly mild, consistent with previous findings[1–4]
- No meaningful impact of OLI on early CAB and RPV pharmacokinetics was observed

1. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135.
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