Patient-Reported Outcomes on Long-Acting Cabotegravir + Rilpivirine as Maintenance Therapy: FLAIR 48-Week Results

MOPEB258

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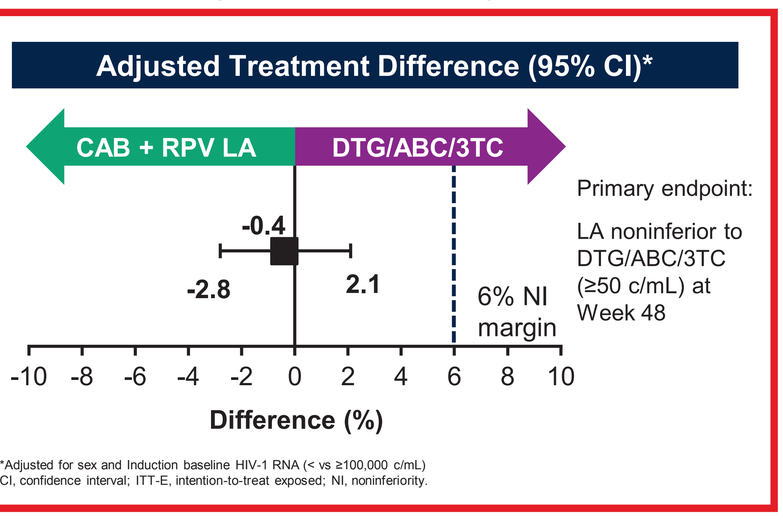
Background

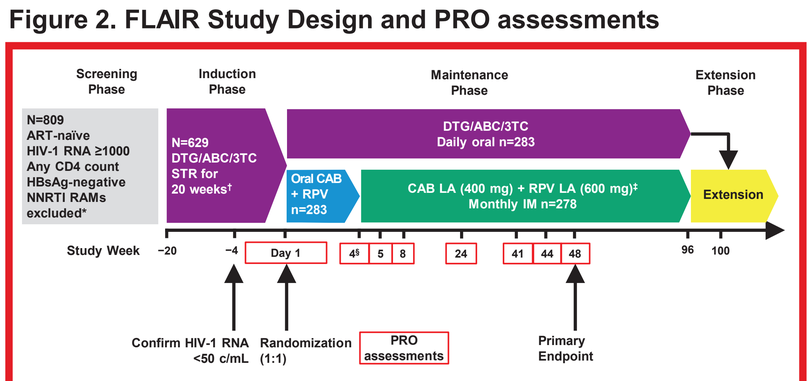
- Long-acting (LA) injectable formulations of antiretroviral therapy (ART) provide an alternative to current daily oral dosing regimens, enhancing convenience while reducing dosing frequency and facilitating adherence.
- LA intramuscular (IM) injectable suspensions of cabotegravir (CAB) and rilpivirine (RPV) are currently in Phase 3 development for the treatment of virologically suppressed people living with HIV (PLHIV).
  - CAB LA IM injectable: 200 mg/mL; half-life ($t_{1/2}$) ≈ 40 days.
  - RPV LA IM injectable: 300 mg/mL; $t_{1/2}$ ≈ 90 days.
- In the Phase 3 FLAIR study (NCT02938520), ART-naïve participants with HIV-1 infection were virologically suppressed to <50 c/mL with 20 weeks of oral dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), then randomly assigned to continue oral therapy or switch to monthly IM injections of CAB LA and RPV LA.[1]
  - In the primary efficacy analysis at Week 48, monthly CAB + RPV LA was noninferior (6% margin) to continued oral DTG/ABC/3TC for maintaining HIV-1 suppression; 2.1% (6/283) of LA participants and 2.5% (7/283) of DTG/ABC/3TC participants had HIV-1 RNA ≥50 c/mL by the FDA Snapshot algorithm.
  - Injection site reactions (ISRs) were common but mainly Grade 1 or 2, with few associated discontinuations.
- Patient-reported outcome (PRO) measures, which are complementary to clinical endpoints and serve to reflect participants' views, have been included in the Phase 3 program of CAB + RPV LA to understand patient preferences and experiences with the LA formulation.
- Here we present the results of PRO endpoints included in the FLAIR study up to Week 48.

Figure 1. FLAIR Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary Endpoint



*Adjusted for sex and Induction baseline HIV-1 RNA (< vs ≥100,000 c/mL)
CI, confidence interval; ITT-E, intention-to-treat exposed; NI, noninferiority.

Figure 2. FLAIR Study Design and PRO assessments



*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; ‡Participants who withdraw/complete CAB + RPV LA enter 52-week long-term follow-up; §Participants received initial loading doses of CAB 600 mg and RPV LA 900 mg at Week 4. Beginning Week 8, participants received CAB LA 400 mg + RPV LA 600 mg injections every 4 weeks.
HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; STR, single-table regimen.

FLAIR Baseline Characteristics in the ITT-E Populations are Similar Between Treatment Groups

- Baseline and demographic characteristics were similar between treatment groups (**Table 1**).
- Eligible participants (aged ≥18 years old) were ART-naïve men and women living with HIV-1 infection.
- >20% female participants were recruited, exceeding the initial goal for female recruitment.

Table 1. FLAIR Induction Baseline Characteristics: ITT-E Population

Parameter	CAB + RPV LA N=283	DTG/ABC/3TC N=283	Total N=566
Median age (range), years	34 (19–68)	34 (18–68)	34 (18–68)
Age ≥50 years, n (%)	33 (12)	29 (10)	62 (11)
Female, n (%)	63 (22)	64 (23)	127 (22)
Race, n (%)			
White	216 (76)	201 (71)	417 (74)
Black or African American	47 (17)	56 (20)	103 (18)
Other or missing	20 (7)	26 (9)	46 (8)
Median BMI* (range), kg/m^2	24 (17–45)	24 (13–47)	24 (13–47)
HIV-1 RNA*, c/mL, n (%)			
<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, n (%)	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, n (%)	19 (7)	9 (3)	28 (5)

*Baseline results were taken at Induction, Week −20.
BMI, body mass index; HCV, hepatitis C virus; IQR, interquartile range

Methods and Study Design

- Literature reviews and qualitative interviews in LATTE-2 study informed the concepts of interest in the Phase 3 development program. Additional literature searches were conducted to identify PRO instruments fit for purpose to measure the selected endpoints.
- Secondary endpoints included treatment satisfaction and acceptance, tolerability of ISRs during and following injections and health status from maintenance baseline (MB) up to Week 48.
  - Preference for LA injectable treatment vs daily oral treatment was included as exploratory endpoint at Week 48.
- A list of the selected PRO instruments is shown in **Table 2**.

Table 2. FLAIR Patient-Reported Outcome Measures

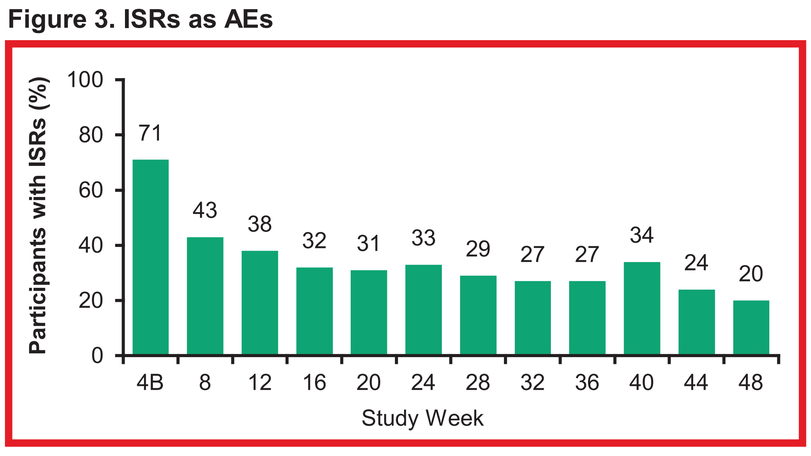
PRO	Description	Endpoint
Short Form Health Survey (SF-12)	12 items produce 2 component scores: the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score (12 items)	Change from MB in physical & mental health status at Weeks 24, 48
Chronic Treatment Acceptance Questionnaire (ACCEPT)	3 items produce the General Acceptance score, asking participants to weight the advantages and disadvantages associated with their treatment	Change from MB in general acceptance of HIV treatment at Weeks 8, 24, 48
Perception of Injection Questionnaire (PIN)	21 items total: produce 4 dimensions: "Bother from ISRs", "Leg movement", "Sleep" and "Acceptance of ISRs" and 5 individually reported items. Modified from a Vaccinees' Perception of Injection (VAPI) questionnaire	Acceptability of injections and ISRs over time from Week 5 to Week 41 and 48
HIV Treatment Satisfaction Questionnaire status and change versions (HIVTSQs,c)	12 items total: produce treatment satisfaction total score (11 items) and 1 standalone item on pain/ discomfort. Adapted from the 10-item HIVTSQ and validated in LATTE-2 study.	Change from MB in treatment satisfaction at Weeks 24, 44 ("status" version) and at Week 48 ("change" version)
HIV/AIDS Targeted Quality of Life* (HAT-QoL)	14 items assessing 3 out of 9 dimensions of HAT-QoL. These dimensions are "life satisfaction", "disclosure worries", and "HIV medication" concerns	Change from MB in life satisfaction, disclosure worries, and HIV medication concerns at Weeks 24, 48
Numeric Rating Scale* on pain during and following injections	1 item assessing maximum level of pain on the day of the injection as well as maximum level of pain 1 week following injections on a numeric rating scale ranging from 0 "no pain" to 10 "extreme pain"	Tolerability of injections over time from Week 4 to Week 40 (injection day) and Week 5 to 41 (1 week following injection)
Preference for HIV Treatment	1 item assessing patients' preference for CAB + RPV compared with the daily oral ART medication they were receiving prior to study entry	Preference of CAB + RPV LA compared with previous daily oral treatment at Week 48

*These PRO measures were utilized in the FLAIR study but are not discussed in this presentation.

Results

- During Maintenance Phase, ISRs were frequently reported as adverse events (AEs) in participants receiving CAB + RPV LA, but rates decreased over time (**Figure 3**).
  - 71% of participants reported ISRs at the initial injection visit (Week 4b) reducing to 20% at Week 48.

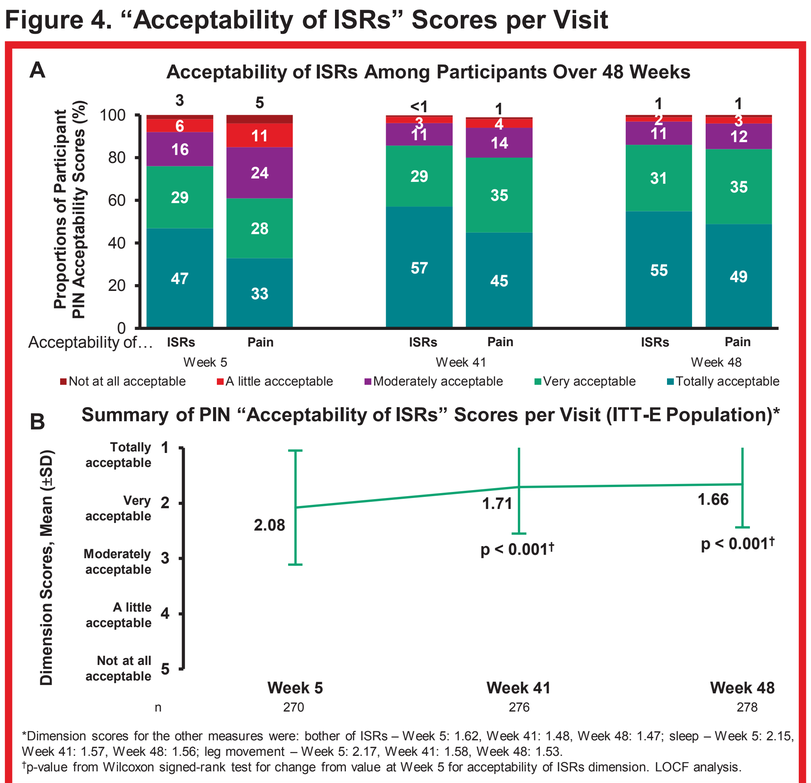
Figure 3. ISRs as AEs



Increased Acceptability of Pain and ISRs Over Time

- Most participants rated the pain and ISRs 1 week following their first injections with CAB + RPV LA as "totally acceptable" or "very acceptable" (Week 5) according to PIN questionnaire (**Figure 4A**).
- A statistically significant improvement from Week 5 to Weeks 41 and 48 in the mean score of the "Acceptability of ISRs" dimension of the PIN Questionnaire was reported (**Figure 4B**), consistent with the reduction in the reporting of ISRs as AEs (**Figure 3**).
- For the remaining three dimensions ("Bother of ISRs", impact on "Leg movement", and impact on "Sleep"), consistent results were observed between Week 5 and 48 following the trend of "Acceptability of ISRs" dimension.
  - To avoid multiplicity, statistical tests of significance were not pre-planned.

Figure 4. "Acceptability of ISRs" Scores per Visit



*Dimension scores for the other measures were: bother of ISRs – Week 5: 1.62, Week 41: 1.48, Week 48: 1.47; sleep – Week 5: 2.15, Week 41: 1.57, Week 48: 1.56; leg movement – Week 5: 2.17, Week 41: 1.58, Week 48: 1.53.
†p-value from Wilcoxon signed-rank test for change from value at Week 5 for acceptability of ISRs dimension. LOCF analysis.

Similar and High Level of Acceptance For Long Acting Therapy And Daily Oral Therapy

- Mean "General acceptance" scores of the ACCEPT questionnaire were high and similar for both treatment groups at MB.
- Both groups reported a numerical improvement from MB in "General Acceptance" scores across all measured visits (**Figure 5**).
- A small but not statistically significant difference in favor of the CAB + RPV LA arm was observed for Weeks 8, 24 and 48, indicating that LA therapy has the same level of acceptance as daily oral therapy

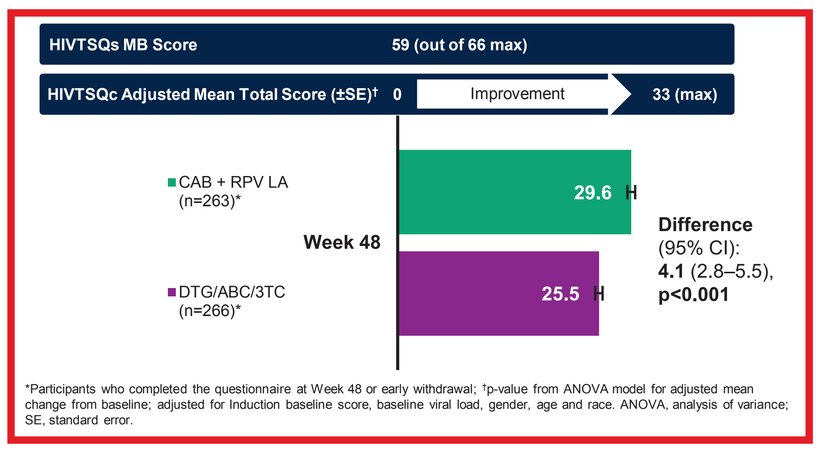
Figure 5. General Treatment Acceptance (ACCEPT) Scores by Visit*

*Scores taken from LOCF during Maintenance Phase.

Greater Participant Treatment Satisfaction for Long Acting Therapy Compared to Daily Oral Therapy

- Mean HIVTSQ status version (HIVTSQs) scores at MB were high, with values of 59.3 and 59.1 out of maximum 66 for the CAB + RPV LA and the DTG/ABC/3TC treatment arms, respectively, and remained high over 44 weeks indicating ceiling effects with the HIVTSQs.
- HIVTSQ change version (HIVTSQc) was administered at Week 48 only, to assess change in treatment satisfaction from Induction Phase for participants receiving CAB + RPV LA or DTG/ABC/3TC, to address ceiling effects as per guidance[2,3] (**Figure 6**).
- At Week 48, participants on the CAB + RPV LA treatment arm reported a significantly greater improvement in treatment satisfaction from Induction Phase compared with those on DTG/ABC/3TC as per HIVSTQc.

Figure 6. HIVTSQc Total Scores at Week 48

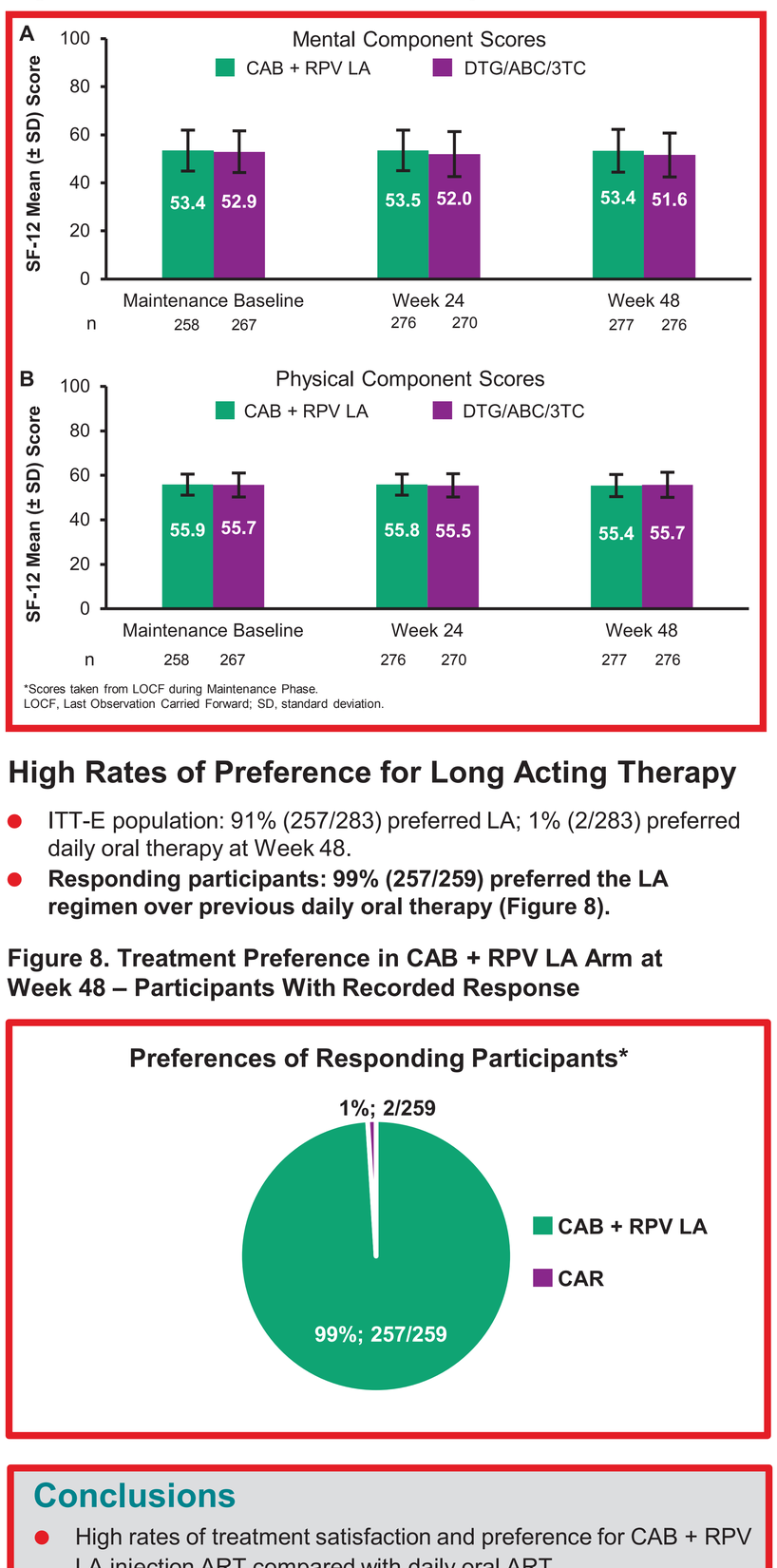


*Participants who completed the questionnaire at Week 48 or early withdrawal; †p-value from ANOVA model for adjusted mean change from baseline; adjusted for Induction baseline score, baseline viral load, gender, age and race. ANOVA, analysis of variance; SE, standard error.

No Significant Changes Were Observed in the SF-12 PCS and MCS

- No significant difference in change from MB in SF-12 physical component and mental component score was observed between treatment groups at any measured visit (**Figure 7**).

Figure 7. SF-12 MCS and PCS Scores by Visit*



*Scores taken from LOCF during Maintenance Phase.
LOCF, Last Observation Carried Forward; SD, standard deviation.

High Rates of Preference for Long Acting Therapy

- ITT-E population: 91% (257/283) preferred LA; 1% (2/283) preferred daily oral therapy at Week 48.
- **Responding participants: 99% (257/259) preferred the LA regimen over previous daily oral therapy (Figure 8).**

Figure 8. Treatment Preference in CAB + RPV LA Arm at Week 48 – Participants With Recorded Response

Conclusions

- High rates of treatment satisfaction and preference for CAB + RPV LA injection ART compared with daily oral ART.
- For most participants receiving CAB + RPV LA, tolerability of ISRs following first injection was high and improved over time, consistent with reduced number of ISRs as AEs.
- FLAIR PRO results are reassuring and indicate that LA injectable treatment meets participants' expectations despite its potential challenges (e.g. ISRs or visits to a healthcare professional).
- Positive PRO findings support the therapeutic value and acceptability of monthly injectable LA therapy, providing an additional treatment choice for PLHIV.

Acknowledgments

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