Safety Profile of Cabotegravir + Rilpivirine During Oral Lead-In and Through Long-Acting Therapy: Pooled Analysis of the Phase 3 FLAIR, ATLAS, and ATLAS-2M Studies

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Introduction

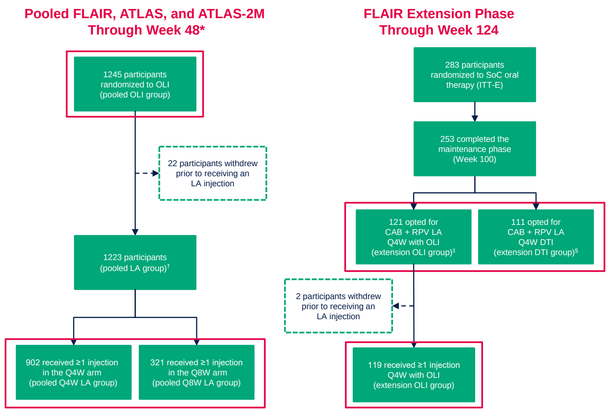
- Cabotegravir (CAB) + rilpivirine (RPV) is the first complete long-acting (LA) regimen recommended by treatment guidelines[1,2] for the maintenance of HIV-1 virologic suppression.
- CAB + RPV LA currently requires an oral lead-in (OLI) as a tolerability check, consisting of oral CAB + RPV taken daily for approximately 1 month (at least 28 days) prior to the first injection.[3,4]
- The purpose of the OLI[5–9] was to assess individual safety and tolerability prior to receiving an LA depot injection, while the CAB-specific safety profile was being characterized.
  - Oral RPV has a well-established and favorable safety profile and was initially approved in 2011.
- No safety signals were identified during the OLI in the development program, providing the rationale to investigate direct administration of CAB + RPV LA, without an OLI, in the FLAIR study extension phase to simplify initiation of the regimen.[5–11]
- The FLAIR 124-week extension phase compared OLI versus transitioning patients directly to injections of CAB + RPV LA; no meaningful differences in virologic suppression, tolerability, and pharmacokinetics were seen over 24 weeks.[10,11]
- This *post hoc* analysis reports safety data for CAB + RPV during the OLI and LA periods for:
  - Participants pooled across the Phase 3/3b program through 48 weeks.
  - Participants initiating OLI or directly transitioning to LA injections from comparator antiretroviral therapy through the FLAIR extension phase (Week 100–Week 124).

Methods

- Safety outcomes were summarized separately from the CAB + RPV OLI and LA periods from:
  - Pooled FLAIR, ATLAS, and ATLAS-2M Phase 3/3b study participants without prior CAB + RPV exposure who utilized OLI prior to transitioning to LA injections.
  - FLAIR extension phase (Week 100–Week 124) participants initially randomized to the oral comparator arm, who could opt to switch to CAB + RPV LA, either directly or first using an OLI.

Results

Figure 1. Study Populations



*ATLAS and FLAIR investigated Q4W dosing; ATLAS-2M investigated Q4W and Q8W dosing. †44 weeks of CAB + RPV LA. ‡20 weeks of CAB + RPV LA. §24 weeks of CAB + RPV LA.
CAB, cabotegravir; DTI, direct to injection; ITT-E, intention-to-treat exposed; LA, long-acting; OLI, oral lead-in; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SoC, standard of care.

- Overall, 1245 participants were included in the pooled OLI population, with 22 (1.8%) participants discontinuing during the OLI, resulting in 1223 transitioning to LA therapy (**Figure 1**).
  - In total, 902 and 321 participants received CAB + RPV LA every 4 weeks (Q4W) and every 8 weeks (Q8W) for 44 weeks, respectively, following an OLI.
  - In the FLAIR extension-switch population, 232 participants opted to receive CAB + RPV LA Q4W, either directly (n=111) or following an OLI (n=121), for 24 and 20 weeks, respectively.
- The median (interquartile range) duration of exposure to CAB + RPV OLI was:
  - 5.4 (5.1–6.1) weeks during the maintenance phase for the pooled OLI population.
  - 5.3 (5.1–5.9) weeks during the FLAIR extension phase (extension OLI group only).

Table 1. OLI Safety Summary in Pooled Phase 3 Studies

Parameter, n (%)	Pooled OLI population (N=1245)
Any AE	396 (32)
Any Grade 3 to 5 AE	15 (1)
Drug-related Grade 3 to 5 AEs	5 (<1)
Drug-related AEs	102 (8)
AEs leading to withdrawal	10 (<1)
Drug-related AEs leading to withdrawal	6 (<1)
Any SAE	9 (<1)*

*Includes enterocolitis (n=1), acute hepatitis A (n=1), pyrexia (n=1), missed abortion (n=1), intervertebral disc protrusion (n=1), spontaneous abortion (n=1), recurrent sinusitis (n=1), pneumonia (n=1), and sialadenitis (n=1). There were no drug-related SAEs.
AE, adverse event; OLI, oral lead-in; SAE, serious adverse event.

- Most adverse events (AEs) during the OLI were Grade 1 or Grade 2 (96%, n=381/396) with <1% leading to withdrawal (**Table 1**).
- The only AEs occurring in ≥2% of participants were headache (3%, n=34/1245), nasopharyngitis (2%, n=28/1245), and diarrhea (2%, n=26/1245); no drug-related AEs occurred in ≥2% of participants.
- Few serious AEs (SAEs) were observed during the OLI and none were reported as drug related.
- No delayed-type drug hypersensitivity reactions (HSR) were reported.
- One participant with a possible drug-induced liver event* was identified during the OLI that prohibited transition to LA therapy.

*This participant had an asymptomatic increase in liver biochemistry (alanine aminotransferase and aspartate transaminase 4- and 3-times the upper limit of normal, respectively) after receiving CAB + RPV OLI for 28 days. Alanine aminotransferase and aspartate transaminase returned to normal after discontinuation. This participant did not meet liver-stopping criteria; however, a temporal association with alanine aminotransferase elevation and study drug was noted, and therefore the case was referred to the Hepatic Adjudication Committee as a case of potential interest. The Hepatic Adjudication Committee determined that this was a possible case of drug-induced liver injury (DILI) related to CAB + RPV.

Table 2. Drug-Related AEs Resulting in Withdrawal During OLI: Pooled Phase 3/3b Studies

Adverse event, n (%)	Pooled OLI population (N=1245)
Participants with drug-related AEs leading to withdrawal*	**6 (<1)**
Asthenia	2 (<1)†‡
Transaminases increased	1 (<1)§
Myalgia	1 (<1)†
Headache	1 (<1)§
Depression/suicidal	1 (<1)‡
Depression	1 (<1)§
Fatigue	1 (<1)§

*More than one reason could be reported for withdrawal. †Grade 1. ‡Grade 2. §Grade 3. AE, adverse event; OLI, oral lead-in.

- Few participants withdrew due to drug-related AEs during OLI (**Table 2**).

Table 3. CAB + RPV LA Safety Summary (Excluding Injection Site Reactions [ISRs]): Pooled Phase 3/3b Studies

Parameter, n (%)	Pooled LA population during 44 weeks* of CAB + RPV LA Q4W + Q8W (n=1223)
Any AE	997 (82)
Any Grade 3 to 5 AE	64 (5)
Drug-related Grade 3 to 5 AEs	10 (<1)
Drug-related AEs	278 (23)
AEs leading to withdrawal	23 (2)
Drug-related AEs leading to withdrawal	11 (<1)†
Any SAE	41 (3)
Drug-related SAEs	2 (<1)‡

*Excludes the 4-week OLI period. †Includes general discomfort (Grade 2, n=1), diarrhea (Grade 2, n=1; Grade 3, n=1), vomiting (Grade 2, n=1), headache (Grade 1, n=1; Grade 2, n=1; Grade 3, n=1), nausea (Grade 2, n=1; Grade 3, n=1), anxiety (Grade 2, n=1), fatigue (Grade 2, n=2), rash maculo-popular (Grade 2, n=1), pyrexia (Grade 2, n=1; Grade 3, n=1), influenza (Grade 2, n=1), hyperhidrosis (Grade 2, n=2), presyncope (Grade 2, n=1), dizziness (Grade 2, n=1), RPV post-injection reaction reported as hypersensitivity (Grade 3, n=1), abnormal dreams (Grade 1, n=1; Grade 2, n=1), chills (Grade 2, n=1), disturbance in attention (Grade 2, n=1), myalgia (Grade 2, n=1). More than one reason could be reported for withdrawal. ‡Includes right knee monoarthritis (Grade 3, n=1), and RPV post-injection reaction reported as hypersensitivity (Grade 3, n=1 [as reported in the previous footnote]). AE, adverse event; CAB, cabotegravir; LA, long-acting; OLI, oral lead-in; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SAE, serious adverse event.

- Most drug-related AEs were mild/moderate in severity (95% Grade 1 or 2), with few leading to withdrawal.
  - There was no pattern of events leading to treatment discontinuation observed with CAB + RPV LA.
- No cases of delayed-type hypersensitivity were identified with CAB + RPV LA (**Table 3**).
- The type and frequency of AEs reported in participants receiving CAB + RPV LA Q4W or Q8W were similar.

Table 4. CAB + RPV LA Common AEs (Excluding ISRs): Pooled Phase 3/3b Studies

Parameter, n (%)	Pooled LA population during 44 weeks* of CAB + RPV LA Q4W + Q8W (n=1223)
AEs occurring in ≥5% of participants	
Nasopharyngitis	183 (15)
URTI	139 (11)
Pyrexia	92 (8)
Headache	90 (7)
Diarrhea	75 (6)
Back pain	63 (5)
Drug-related AEs occurring in ≥3% of participants	
Pyrexia	58 (5)

*Excludes the 4-week OLI period. CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; OLI, oral lead-in; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; URTI, upper respiratory tract infection.

- Common AEs during the LA period of CAB + RPV LA are shown in **Table 4**.

Table 5. CAB + RPV LA Safety Summary (Excluding ISRs): FLAIR Extension

Parameter, n (%)	DTI group during 24 weeks of CAB + RPV LA Q4W (n=111)	OLI group* during 20 weeks† of CAB + RPV LA Q4W (n=119)
Any AE	88 (79)	83 (70)
Any Grade 3 to 5 AE	4 (4)	4 (3)
Drug-related Grade 3 to 5 AEs	1 (<1)	0
Drug-related AEs	22 (20)	21 (18)
AEs leading to withdrawal	1 (<1)‡	1 (<1)§
Drug-related AEs leading to withdrawal	1 (<1)‡	1 <1)§
Any SAE	4 (4)	5 (4)
Drug-related SAEs	1 (<1)‡	0

*Safety during the FLAIR extension OLI period was similar to the pooled Phase 3/3b OLI period. During the FLAIR OLI period at the start of the maintenance phase, three participants withdrew due to AEs: acute hepatitis C (n=1), acute hepatitis A (n=1), and transaminases increase (n=1). No AEs, drug-related AEs, or SAEs led to discontinuation during the FLAIR extension OLI period prior to LA administration. †Excludes the 4-week OLI period. ‡Hodgkin's disease mixed cellularity (the study sponsor did not consider this SAE to be related to study medication). §Weight increase. AE, adverse event; CAB, cabotegravir; DTI, direct to injection; LA, long-acting; OLI, oral lead-in; Q4W, every 4 weeks; RPV, rilpivirine; SAE, serious adverse event.

- The safety profile of CAB + RPV LA was comparable between participants choosing to initiate treatment with or without an OLI, with no new safety concerns identified when initiating injections directly (**Table 5**).
- Grade 3 and 4 AEs, SAEs, and AEs leading to withdrawal occurred at a similar incidence in both arms.
- No cases of DILI, confirmed HSRs, or other significant dermatological manifestations observed in either group.

Table 6. Common CAB + RPV LA AEs (Excluding ISRs): FLAIR Extension

Parameter, n (%)	DTI group during 24 weeks of CAB + RPV LA Q4W (n=111)	OLI group during 20 weeks* of CAB + RPV LA Q4W (n=119)
AEs occurring in ≥5% of participants		
Nasopharyngitis	20 (18)	11 (9)
URTI	10 (9)	6 (5)
Pyrexia	9 (8)	4 (3)
Dizziness	8 (7)	4 (3)
Diarrhea	2 (2)	8 (7)
Headache	7 (6)	3 (3)
Gastroenteritis	7 (6)	3 (3)
Drug-related AEs occurring in ≥3% of participants		
Pyrexia	6 (5)	2 (2)

*Excludes the 4-week OLI period. CAB, cabotegravir; DTI, direct to injection; LA, long-acting; OLI, oral lead-in; Q4W, every 4 weeks; RPV, rilpivirine; URTI, upper respiratory tract infection.

- Common AEs (excluding ISRs) during the LA period of CAB + RPV therapy in the FLAIR extension are shown in **Table 6**.
- Overall patterns of common non-ISR AE occurrences observed were comparable across those who initiated injections directly or with an OLI.

Conclusions

- CAB + RPV was well tolerated in those initiating the regimen with an OLI then transitioning to LA, during both the OLI and LA periods.
- A 4-week OLI of CAB + RPV was well tolerated in >1200 participants across the Phase 3/3b program.
  - Headache (3%), nasopharyngitis (2%), and diarrhea (2%) were the most common AEs during the OLI period in the pooled OLI population, with few withdrawals.
  - There were no delayed-type HSRs or drug-related SAEs during the OLI periods.
  - There was one possible drug-induced liver event identified during 4 weeks of OLI that prohibited transition to LA therapy.
- During the LA period through Week 48, no specific safety concerns were identified in the pooled Phase 3/3b CAB + RPV LA participants that could have been mitigated by OLI.
- The safety profile of CAB + RPV LA dosing was similar regardless of whether participants opted to receive OLI or initiated injections directly in the FLAIR extension, and was consistent with what was seen in pooled Phase 3/3b studies.
  - Initiating CAB + RPV LA directly is also being used in the ongoing SOLAR study (NCT04542070).
- The totality of the safety data obtained during OLI, during the CAB + RPV LA treatment phase, and for the subset of participants initiating injections without an OLI during the FLAIR extension phase supports the initiation of CAB + RPV LA directly as a potential strategy to simplify initiation of the regimen.

Acknowledgments

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References

1. U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2021. Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/15/virologic-failure. Accessed September 2021.
2. Saag MS, et al. *JAMA*. 2020;324(16):1651–1669.
3. ViiV Healthcare. Vocabria Summary of Product Characteristics. EU, December 2020.
4. ViiV Healthcare. Cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (Cabenuva) Prescribing Information. US, January 2021.
5. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112–1123.
6. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124–1135.
7. Orkin C, et al. *Lancet HIV*. 2021;8(4):e185–e196.
8. Overton ET, et al. *Lancet*. 2020;396(10267):1994–2005.
9. Margolis D, et al. *Lancet*. 2017;390(10101):1499–15107.
10. Orkin C, et al. *Lancet HIV*. Accepted 2021.
11. Orkin C, et al. HIV Drug Therapy Glasgow; Glasgow, United Kingdom; October 5–8, 2020; oral, abstract 0414.

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