SAFETY, EFFICACY, AND DURABILITY OF LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE AS MAINTENANCE THERAPY FOR HIV-1 INFECTION: LATTE-2 WEEK 256 RESULTS

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Introduction

- Whilst advances in antiretroviral therapy (ART) have made HIV-1 infection a chronic condition for most, inherent challenges associated with the need for daily oral therapy remain, such as stigma, drug/food interactions, pill burden, and adherence
- Long-acting (LA) ART options may help address these challenges; thus, there is considerable interest in the development of LA therapeutic alternatives to daily oral ART
- Cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), an approved oral non-nucleoside reverse transcriptase inhibitor (NNRTI), are two agents for which an LA injectable formulation has been developed and approved for use in Canada[1-3]
- LATTE-2 (NCT02120352) is a Phase 2b randomized clinical trial that demonstrated CAB + RPV LA dosed either every 4 (Q4W) or every 8 weeks (Q8W) is comparable with daily oral three-drug therapy for the primary efficacy endpoint of HIV-1 RNA <50 copies/mL as per the US Food and Drug Administration (FDA) Snapshot algorithm at Week 32, as well as at the subsequent Week 48, 96, and 160 analyses[4,5]
  - CAB + RPV LA was also found to be a well-accepted and tolerated treatment through 160 weeks
- Here we present data from the Week 256 analysis evaluating the long-term efficacy, safety, and tolerability of Q4W and Q8W CAB + RPV LA intramuscular (IM) dosing over an ~5-year period

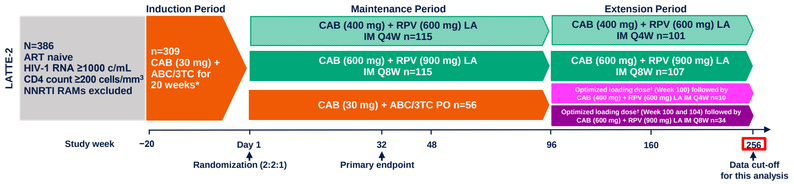
Methods

- LATTE-2 is a Phase 2b, multicenter, parallel-arm, open-label study in ART-naive adults living with HIV-1
- After a 20-week Induction Period on once-daily oral CAB (30 mg) plus abacavir/lamivudine (600/300 mg), participants with plasma HIV-1 RNA <50 copies/mL were randomized 2:2:1 to either IM CAB + RPV LA Q8W, CAB + RPV LA Q4W, or to continue their oral regimen (PO) in the Maintenance Period (Figure 1)
- After Week 96, participants randomized to LA treatment continued their Maintenance Period regimen into the Extension Period. Participants randomized to PO in the Maintenance Period who completed 96 weeks had the option to switch to their choice of either CAB + RPV LA Q8W or Q4W in the Extension Period

Assessments at Week 256

- The Week 256 analysis of the Maintenance Period and Extension Period included the proportion of participants with virologic success (HIV-1 RNA <50 copies/mL; FDA Snapshot analysis), protocol-defined virologic failure (PDVF; 2 consecutive plasma HIV-1 RNA measurements of ≥200 copies/mL), and safety (safety maintenance population)

Figure 1. Study Design

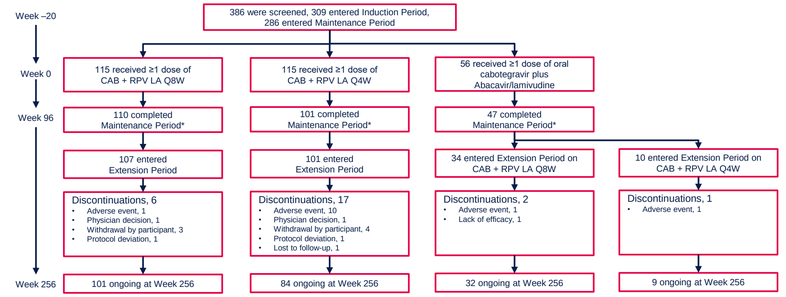


*RPV 25 mg was added at Week −4 for the remainder of the Induction Period. †Optimized loading dose: CAB (600 mg) + RPV (900 mg) LA IM. ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; PO, oral regimen; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once-daily; RAM, resistance-associated mutation; RPV, rilpivirine.

Results

- 386 participants were screened; 309 entered the Induction Period, and 286 were randomized into the Maintenance Period (Maintenance-exposed population) (Figure 2)
  - Baseline characteristics were similar and have been reported previously[4]
    - Overall, 18% of participants had HIV-1 RNA ≥100,000 copies/mL at baseline

Figure 2. Study Disposition



*Details for discontinuations in the Maintenance Period have been presented previously.[4] CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Snapshot Study Outcomes at Week 256

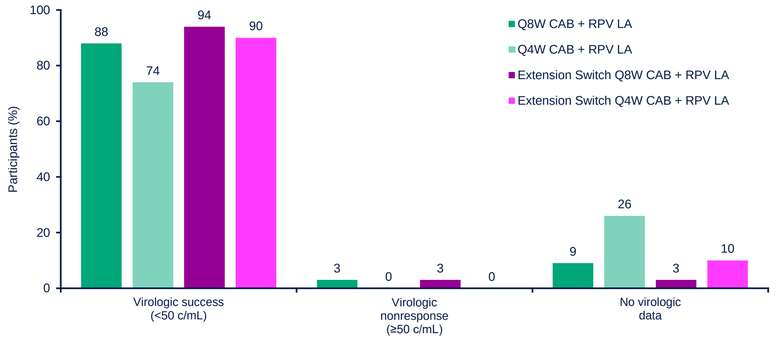
- At Week 256, 88% and 74% of participants randomized to Q8W and Q4W, respectively, maintained virologic suppression (HIV-1 RNA <50 copies/mL), as did 93% of participants who switched from PO and had 160 weeks of LA therapy (Figure 3/Table 1)
  - The higher percentage of participants with no virologic data in the Q4W IM arm (26%) compared with the Q8W IM arm (9%) was driven by non-virologic reasons

Table 1. Week 256 Snapshot Outcomes

Week 256 Snapshot study outcomes,* n (%)	Randomized to Q8W (n=115)	Randomized to Q4W (n=115)	Extension Switch Q8W IM†‡ (n=34)	Extension Switch Q4W IM†§ (n=10)
HIV-1 RNA <50 copies/mL	101 (88)	85 (74)	32 (94)	9 (90)
HIV-1 RNA ≥50 copies/mL	4 (3)	0	1 (3)	0
Discontinued due to lack of efficacy	1 (<1)	0	1 (3)	0
Discontinued due to other reasons while not below threshold	3 (3)‖	0	–	–
No virologic data at Week 256 window	10 (9)	30 (26)	1 (3)	1 (10)
Discontinued due to AE or death¶	2 (2)**	18 (16)††	1 (3)‡‡	1 (10)¶¶
Discontinued for other reasons	8 (7)	11 (10)	–	–
Missing data during window but on study	0	1 (<1)	–	–

*Week 256 represents 276 weeks on study (20-week induction with oral CAB 30 mg + ABC/3TC followed by 256-week maintenance therapy). †Participants completing the 96-week maintenance with oral CAB 30 mg + ABC/3TC could continue in extension by switching to IM dosing regimen of their choice (Q8W or Q4W). ‡PO for 96 weeks then CAB LA 600 mg + RPV LA 900 mg IM Q8W for 160 weeks in extension. §PO for 96 weeks then CAB LA 400 mg + RPV LA 600 mg IM Q4W for 160 weeks in extension. ‖Includes withdrawn consent due to intolerability of injections (n=1). ¶3 deaths occurred (all Q4W arm): toxicity to various agents (not study drug related), epilepsy (not study drug related), and myocardial infarction (drug related). One participant could have more than one reason leading to withdrawal. **Injection site pain, injection site pruritus, chills, hepatitis C, and pain. ††Injection site pain, fatigue, injection site nodule, coronary artery disease, myocardial infarction, sinus tachycardia, hepatitis C, respiratory tract infection, epilepsy, hypoesthesia, motor neuron disease, adjustment disorder with depressed mood, drug abuse, psychotic disorder, suicide attempt, lymphadenopathy, splenic vein thrombosis, mesenteric vein thrombosis, muscular weakness, rhabdomyolysis, deep vein thrombosis, portal vein thrombosis, eosinophilic granulomatosis with polyangiitis, toxicity to various agents, electrocardiogram QT prolonged, metabolic acidosis, acute kidney injury, rash. ‡‡Back pain, erythema, conjunctive hyperemia, urticaria popular. §§Injection site pain. ABC/3TC, abacavir/lamivudine; AE, adverse event; CAB, cabotegravir; IM, intramuscular LA, long-acting; PO, oral regimen; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Figure 3. Week 256 Snapshot Outcomes



CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Participants With PDVF Through Week 256

- No participants met PDVF after Week 48
  - Three participants met PDVF through 48 weeks (Q8W: n=2; PO: n=1). Resistance data for these participants have been previously reported[4]

Safety

- A summary of adverse events (AEs) is shown in Table 2
- In the randomized Q8W and Q4W arms (Maintenance Period and Extension Period) excluding injection site reactions (ISRs), nasopharyngitis (45%; n=103/230), diarrhea (28%; n=65/230), and headache (24%; n=55/230) were the most common AEs
  - Excluding ISRs, the most common drug-related AEs were pyrexia (7%; n=17/230), back pain, and fatigue (both 3%; n=7/230)
- In the participants who switched from PO (Extension Period), the most common AEs were nasopharyngitis (25%; n=11/44), influenza (23%; n=10/44), and back pain (18%; n=8/44)
  - Excluding ISRs, no drug-related AE occurred in more than one participant who switched from PO
- No new AEs of clinical concern were reported except for one participant randomized to Q4W who experienced a serious AE at Week 256 (abdominal pain, chest pain, dyspnea, and flushing) considered to be the result of a post-injection reaction to RPV

Table 2. Adverse Events Through Week 256

	Randomized Q8W IM (n=115)	Randomized Q4W IM (n=115)	Extension Switch Q8W IM (n=34)	Extension Switch Q4W IM (n=10)
Grade ≥3 AEs, n (%)	39 (34)	38 (33)	7 (21)	3 (30)
Excluding ISRs	31 (27)	35 (30)	4 (12)	2 (20)
Drug related excluding ISRs	4 (3)	7 (6)	0	0
Serious AEs, n (%)	25 (22)	27 (23)	6 (18)	1 (10)
Excluding ISRs	25 (22)	27 (23)	6 (18)	1 (10)
Drug related*	2 (2)	5 (4)	0	0
Death	0	3 (3)†	0	0
AEs leading to withdrawal, n (%)‡	3 (3)§	20 (17)‖	1 (3)¶	1 (10)**
Excluding ISRs	1 (1)	18 (16)	1 (3)	0
Drug related	2 (2)	8 (7)	1 (3)	1 (10)

*Chest pain, abdominal pain, delusion, depression, dyspnea, flushing, myocardial infarction. †Toxicity to various agents (not study drug related), epilepsy (not study drug related), and myocardial infarction (drug related). ‡Drug-related AEs (excluding ISRs) leading to withdrawal are bolded in the reasons footnoted. One participant could have more than one reason for withdrawal. §Injection site pain, injection site pruritus, **chills**, injection site induration, injection site swelling, **pain**, hepatitis C. ‖Injection site pain, **chest pain**, fatigue, injection site nodule, coronary artery disease, **myocardial infarction**, **sinus tachycardia**, hepatitis C, respiratory tract infection, epilepsy, hypoesthesia, motor neuron disease, **adjustment disorder with depressed mood**, drug abuse, **psychotic disorder**, suicide attempt, lymphadenopathy, splenic vein thrombosis, **abdominal pain**, mesenteric vein thrombosis, muscular weakness, rhabdomyolysis, deep vein thrombosis, **flushing**, portal vein thrombosis, eosinophilic granulomatosis with polyangiitis, toxicity to various agents, **electrocardiogram QT prolonged**, metabolic acidosis, squamous cell carcinoma of lung, acute kidney injury, **dyspnea**, **rash**. ¶**Back pain**, **erythema**, **conjunctive hyperemia**, **urticaria popular**. **Injection site pain. AE, adverse event; IM, intramuscular; Q4W, every 4 weeks; Q8W, every 8 weeks.

ISRs

- ISRs were common, with 8686 occurring over 23,498 administered injections (Table 3); however, ISRs reduced in incidence over time through 96 weeks and remained consistent from Week 96 to 256
- Most ISRs were Grade 1 or 2 (99%), with a median duration of 3 days in participants randomized to CAB + RPV LA, and 2 days in those who switched from PO

Table 3. Event-Level ISR Summary Through Week 256

Outcome, n (%), ITT-ME	Randomized Q8W IM (n=115)	Randomized Q4W IM (n=115)	Extension Switch Q8W IM (n=34)	Extension Switch Q4W IM (n=10)
Number of injections	7673	13,506	1503	816
Number of ISR events	3373	4702	429	182
Grade ≥3 – severe*	24 (<1)	22 (<1)	7 (2)	3 (2)
ISRs (most common)				
Pain	2265	2936	368	166
Nodule	238	557	26	13
Pruritis	230	222	8	0
Swelling	200	248	9	2
Withdrawals due to injection-related reasons†	4 (3)‡	3 (3)§	0	1 (10)‖

*Percentage based on number of ISR events. There were no Grade 4 or Grade 5 ISRs. †One participant could have more than one reason for withdrawal. ‡Injection site pain (n=2), injection intolerability (n=2), injection site induration (n=1), injection site pruritis (n=1), and injection site swelling (n=1). §Injection site pain (n=1), injection site nodule (n=1), and injection intolerability (n=1). ‖Injection site pain. IM, intramuscular; ISR, injection site reaction; ITT-ME, intention-to-treat maintenance exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Conclusions

- CAB + RPV LA, dosed both Q4W and Q8W, demonstrated durable antiviral activity through ~5 years of treatment in virologically suppressed participants randomized to LA therapy
  - At Week 256, 81% of participants randomized to LA therapy at Day 1 and 93% of participants who switched from PO at Week 100 maintained virologic suppression (HIV-1 RNA <50 copies/mL)
  - No participants had PDVF after Week 48 in any treatment arm, demonstrating the durability of CAB + RPV LA as a maintenance therapy
- CAB + RPV LA continues to be well tolerated through 5 years of treatment for both dosing regimens
- ISRs, whilst frequent, were mostly mild or moderate in severity and resolved within a median of 2-3 days
- CAB + RPV LA is therefore a potential therapeutic alternative to daily PO that may help address challenges such as stigma, drug/food interactions, pill burden, and adherence

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