Safety, Efficacy and Durability of Long-acting Cabotegravir (CAB) and Rilpivirine (RPV) as Two-Drug IM Maintenance Therapy for HIV-1 Infection: LATTE-2 Week 160 Results

P118

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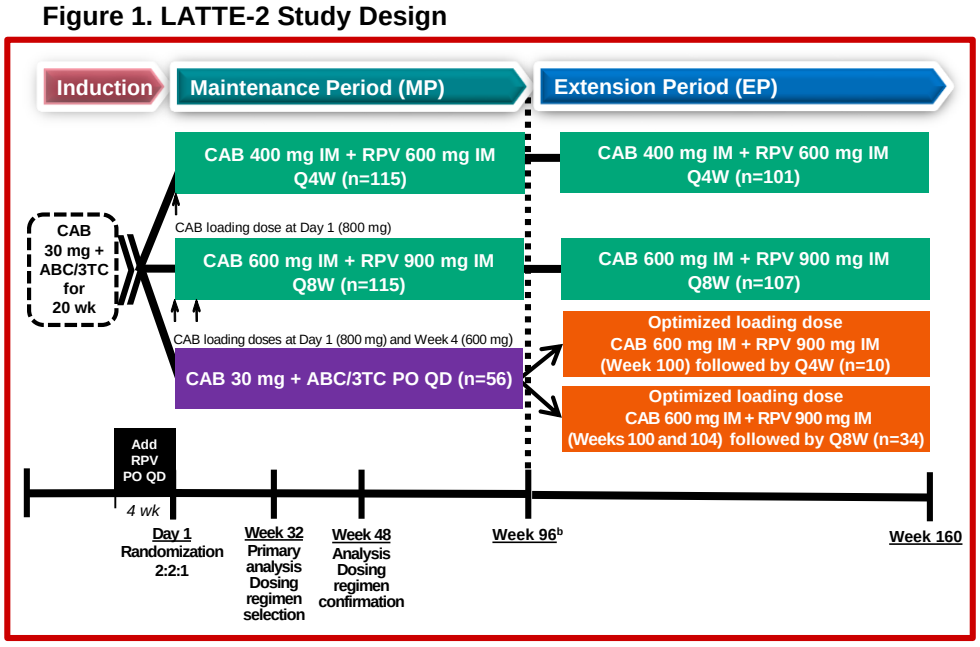
Introduction

- Long-acting (LA) injectable suspensions of cabotegravir (CAB) and rilpivirine (RPV) are in phase III development
- LATTE-2 Week 48/96 data supported the decision to evaluate the Q4W and Q8W CAB LA + RPV LA IM regimen in ongoing phase III studies[1]
- The Week 160 analysis evaluated the long-term efficacy, safety, and tolerability of both IM dosing regimens

Methods

- Phase IIb, multicenter, parallel-group, open-label study in ART-naive HIV-infected adults

Figure 1. LATTE-2 Study Design



- Patients randomized to Q8W/Q4W IM continued MP IM dosing regimen in the EP. Patients who successfully completed 96 weeks of oral CAB in the MP had the option of continuing study participation in the EP by switching to an optimized IM dosing regimen of their choice
- The data cut for analysis is associated with date of last patient's Week 160 visit and includes data past Week 160 for patients who completed this visit earlier
- Evaluations included virologic success <50 c/mL (FDA snapshot analysis), protocol-defined virologic failure (PDVF), and safety at the prespecified Week 160 exploratory endpoint (ITT-maintenance exposed [ME])

Results

- 309 patients were enrolled (ITT-exposed): 91% male, 20% non-white, and 19% >100,000 c/mL HIV-1 RNA. 286 patients were randomized into the MP; 258 completed MP with 252 entering EP

Table 1. Snapshot Outcomes at Week 160

Outcome at W160[a]	Q8W IM n (%)	Q4W IM n (%)	Optimized Q8W IM n (%)	Optimized Q4W IM n (%)
Snapshot (ITT-ME)	N=115	N=115	N=34	N=10
HIV-1 RNA <50 c/mL	**104 (90)**	**95 (83)**	**33 (97)**	**10 (100)**
HIV-1 RNA ≥50 c/mL	**5 (4)**	**0**	**1 (3)**	**0**
Data in window not <50 c/mL	1 (<1)[b]	0	0	0
DC for lack of efficacy	1 (<1)	0	1 (3)	0
DC for other reason while not <50 c/mL	3 (3)[c]	0	0	0
No virologic data in window	**6 (5)**	**20 (17)**	**0**	**0**
W/D due to AE or death	1 (<1)	12 (10)[d]	0	0
W/D due to other reasons	5 (4)[e]	8 (7)[f]	0	0

[a]Data presented for the randomized Q8W/Q4W IM arms are inclusive of MP and EP. Data presented for the optimized Q8W/Q4W IM arms are inclusive of on-treatment events occurring from the first date of first injection in the EP, W100. [b]77 c/mL. [c]>50 c/mL at W96 and did not qualify for EP. [d]Added in EP: CAD; MI (death); motor neuron disease. [e]Relocation; entered LTFU; burden of travel; lost to FU. [f]Added in EP: PD; lost to FU; WD by patient.

Protocol-Defined Virologic Failure

- Through 160 weeks, there were 2 PDVFs, both Q8W. No additional PDVFs occurred after Week 48 in any arm. Resistance data were previously reported[1]

Adverse Events

- Through Week 160, the most commonly reported non–injection-site reaction (ISR) adverse events (AEs) for the randomized Q8W/Q4W IM arms included nasopharyngitis (38%; 87/230), diarrhea (22%; 50/230), and headache (22%; 50/230)
  - The most commonly reported non-ISR, drug-related (per investigator) AEs for the randomized Q8W/Q4W IM arms included pyrexia (5%; 12/230), headache (3%; 7/230), and fatigue (3%; 6/230)
- The most commonly reported non-ISR AEs for the optimized Q8W/Q4W IM arms included nasopharyngitis (14%; 6/44), back pain (11%; 5/44), and influenza (11%; 5/44)
  - The most commonly reported non-ISR, drug-related (per investigator) AEs for the optimized Q8W/Q4W IM arms were asthenia, fatigue and palpitations, each at 2% (1/44)

Table 2. Adverse Events Through Week 160

Week 160 Safety[a]	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	Optimized Q8W IM N=34 n (%)	Optimized Q4W IM N=10 n (%)
Grade 3/4 AEs, excluding ISRs	24 (21)	29 (25)	0	1 (10)
Drug-related grade 3/4 AEs, excluding ISRs	2 (2)	6 (5)	0	0
Serious AEs	17 (15)	21 (18)	2 (6)	0
Drug-related SAEs	0	1 (<1)[b]	0	0
Fatal SAEs	0	2 (2)[b]	0	0
AEs leading to withdrawal[c]	3 (3)	12 (10)	0	1 (10)
Grade 3/4 hematology labs	4 (3)	2 (2)	0	0
Grade 3/4 chemistry labs	28 (24)	38 (33)	3 (9)	1 (10)
Select grade 3-4 laboratory abnormalities				
Creatine kinase (CK)	11 (10)	13 (11)	1 (3)	0
Alanine aminotransferase (ALT)	6 (5)	5 (4)	0	0
Lipase	8 (7)	7 (6)	1 (3)	1 (10)
Total neutrophils	3 (3)	2 (2)	0	0

[a]Data presented for the randomized Q8W/Q4W IM arms are inclusive of MP and EP. Data presented for the optimized Q8W/Q4W IM arms are inclusive of on-treatment events occurring from the first date of first injection in the EP, W100. [b]MI (possibly drug-related, fatal), epilepsy (fatal). [c]Added in EP: Q8W: Hep C; Q4W: CAD, MI, motor neuron disease, hypoaesthesia/muscular weakness/fatigue; Optimized Q4W: injection site pain.

- Through 160 weeks, in the randomized Q8W/Q4W IM arms, 99% of ISR events were mild (85%) or moderate (14%), and 87% resolved within 7 days
  - 2/230 (<1%) had an ISR that led to discontinuation (both Q8W subjects) through Week 160. No randomized IM patient had an ISR that led to discontinuation after Week 48
- In the optimized Q8W/Q4W IM arms, 98% of ISR events were mild (81%) or moderate (17%), and 91% resolved within 7 days
  - 1/44 (2%) had an ISR that led to discontinuation (Q4W)

Conclusions

- CAB LA + RPV LA, dosed every 8 or 4 weeks, successfully maintained HIV-1 viral load <50 c/mL. The Week 160 data demonstrate long-term durability and tolerability of both dosing options
- 2 patients on LA dosing met PDVF criteria, no subjects after Week 48 across all arms
- Good injection tolerability was demonstrated over time
  - Majority of ISRs were grade 1/2 pain with a median duration of 3 days
  - ~1% of patients had an ISR that led to discontinuation through 3 years of dosing
- Q8W and Q4W dosing are both under evaluation in ongoing phase III studies

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Reference: 1. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet.* 2017;390(10101):1499-1510.