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Cabotegravir and Rilpivirine As Two-Drug Oral Maintenance Therapy: LATTE Week 96 Results

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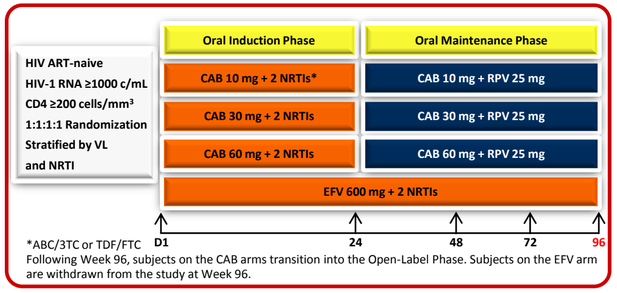
Introduction

- Cabotegravir (CAB; GSK1265744) is an HIV integrase inhibitor (INI) under development as a tablet for oral lead-in and as a long-acting injectable.
- LAI116482 (LATTE) is an ongoing phase IIb multicenter, partially-blind, dose-ranging study in ART-naive HIV-1 infected adults designed to select an oral CAB dose as part of a two-drug antiretroviral (ART) maintenance regimen with oral rilpivirine (RPV).
- The Week 48 primary endpoint (% HIV-1 RNA <50 c/mL, Snapshot) data was presented at the 21st CROI.[1]
- Data from LATTE will inform future studies in which the long-acting (LA) injectable formulations of both CAB and RPV make up a two-drug maintenance regimen for HIV treatment.

Methods

- A sample size of 50 subjects per arm was chosen to ensure a high probability that a dosage arm with an inadequate response was not selected for further study, while allowing for the formal consideration of other factors in dose selection should efficacy be similar across dosage arms.
- Secondary endpoint: % HIV-1 RNA <50 c/mL at 96 weeks (FDA "Snapshot")
- Intent-to-treat exposed (ITT-E) – received at least one dose of Investigational Product (IP)
- Intent-to-treat maintenance exposed (ITT-ME) – received at least one maintenance dose
- Eligibility for the Maintenance Phase was determined by the Week 20 HIV-1 RNA (<50 c/mL). Subjects randomized to EFV did not have to meet this eligibility criteria.
- Protocol-defined virologic failure (PDVF) HIV-1 RNA measures:
  - Non-response: <1 $\log_{10}$ c/mL decrease by Week 4, unless <400 c/mL; OR ≥200 c/mL on or after Week 16
  - Rebound: ≥200 c/mL after confirmed <200 c/mL; OR >0.5 $\log_{10}$ c/mL above nadir (the lowest prior value ≥200 c/mL). Both non-response and rebound required consecutive confirmatory results.
- PDVF rate was monitored in real time during the Maintenance Phase to assess virologic response in the two-drug arms and prompt an internal safety committee review if a threshold rate was exceeded. This threshold was not met at any point in the study.

Figure 1. LATTE Study Design



*ABC/3TC or TDF/FTC

Following Week 96, subjects on the CAB arms transition into the Open-Label Phase. Subjects on the EFV arm are withdrawn from the study at Week 96.

Results

- 243 patients were randomized and treated (ITT-E): 96% male, 38% non-white, 14% >100,000 c/mL HIV-1 RNA, 61% TDF/FTC.

Table 1. Baseline Characteristics

		CAB 10 mg n=60	CAB 30 mg n=60	CAB 60 mg n=61	EFV 600 mg n=62
Age	Median (y)	32.0	32.5	36.0	32.5
Gender	Male	95%	97%	93%	98%
Race	White	62%	65%	59%	63%
	African American/African	35%	28%	30%	32%
Ethnicity	Hispanic/Latino	15%	27%	23%	19%
Baseline HIV-1 RNA	Median ($\log_{10}$ c/mL)	4.281	4.178	4.349	4.343
	Median (c/mL)	19,099	15,066	22,336	22,029
	≥100,000 c/mL	13%	12%	20%	13%
Baseline CD4+	Median (cells/mm³)	415.0	404.0	420.0	416.5
	<200 cells/mm³	3%	7%	3%	2%
Hepatitis coinfection	HCV Ab +	0%	8%	7%	2%
Investigator-selected dual NRTIs at Day 1	TDF/FTC	62%	62%	61%	61%
	ABC/3TC	38%	38%	39%	39%

Table 2. Subject Disposition – ITT-E

	CAB 10 mg n=60	CAB 30 mg n=60	CAB 60 mg n=61	CAB total n=181	EFV 600 mg n=62
Subjects withdrawn through W96	**14 (23%)**	**12 (20%)**	**9 (15%)**	**35 (19%)**	**21 (34%)**
Adverse event*	1 (2%)	1 (2%)	4 (7%)	6 (3%)	9 (15%)
Lack of efficacy	5 (8%)	2 (3%)	2 (3%)	9 (5%)	5 (8%)
Insufficient viral load response†	3 (5%)	0	1 (2%)	4 (2%)	1 (2%)
PDVF	2 (3%)	2 (3%)	1 (2%)	5 (3%)	4 (6%)
Protocol deviation	2 (3%)	1 (2%)	1 (2%)	4 (2%)	0
Lost to follow-up	3 (5%)	2 (3%)	1 (2%)	6 (3%)	5 (8%)
Investigator discretion	0	2 (3%)	0	2 (1%)	1 (2%)
Withdrew consent	3 (5%)	4 (7%)	1 (2%)	8 (4%)	1 (2%)
Subjects withdrawn at W24-W96	**6 (10%)**	**5 (8%)**	**3 (5%)**	**14 (8%)**	**5 (8%)**

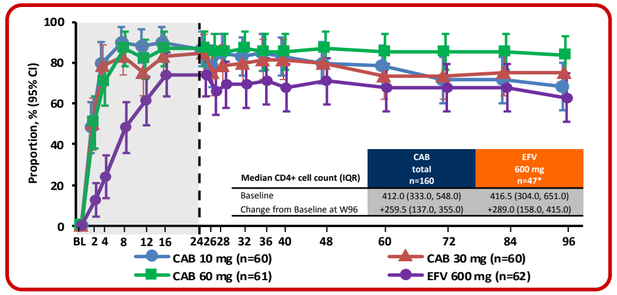
*Most occurred during the Induction Phase.
†Week 20 HIV-1 RNA values: CAB 10 mg, 51, 107, 189 c/mL; CAB 60 mg, 108 c/mL; EFV 600 mg, 146 c/mL.
CAB 10 mg (n=1) and EFV (n=2) met the definition for PDVF (not primary reason for WD).

Table 3. Week 96 Treatment Outcomes

Outcome at Week 96**	CAB 10 mg	CAB 30 mg	CAB 60 mg	CAB total	EFV 600 mg
% <50 c/mL at W96 Snapshot **(ITT-E)**	41/60 (68%)	45/60 (75%)	51/61 (84%)	137/181 (76%)	39/62 (63%)
Protocol-defined virologic failure	3 (5%)	2 (3%)	1 (2%)	6 (3%)	6 (10%)
Failure - adverse event	1 (2%)	1 (2%)	4 (7%)	6 (3%)	9 (15%)
Failure - HIV-1 RNA ≥50 c/mL[¥]	5 (8%)	1 (2%)	2 (3%)	8 (4%)	2 (3%)
Failure - other* reasons while ≥50 c/mL	2 (3%)	2 (3%)	1 (2%)	5 (3%)	3 (5%)
Failure - other* reasons while <50 c/mL	8 (13%)	9 (15%)	2 (3%)	19 (10%)	3 (5%)
% <50 c/mL at W96 Snapshot **(ITT-ME)**	41/52 (79%)	45/53 (85%)	51/55 (93%)	137/160 (86%)	39/47* (83%)
Protocol-defined virologic failure	2 (4%)	1 (2%)	0	3 (2%)	2 (4%)
Failure - adverse event	1 (2%)	0	1 (2%)	2 (1%)	2 (4%)
Failure - HIV-1 RNA ≥50 c/mL[¥]	4 (8%)	1 (2%)	1 (2%)	6 (4%)	2 (4%)
Failure - other* reasons while ≥50 c/mL	1 (2%)	1 (2%)	1 (2%)	3 (2%)	0
Failure - other* reasons while <50 c/mL	3 (6%)	5 (9%)	1 (2%)	9 (6%)	2 (4%)

**W96 represents a 24-week Induction Phase followed by a 72-week Maintenance Phase.
¥HIV-1 RNA ≥50 c/mL reasons include HIV-1 RNA ≥50 c/mL at Week 96 or discontinued while not suppressed (≥50 c/mL) for lack of efficacy.
*Other reasons include missing data, protocol deviation, non-compliance, lost to follow-up, withdrawn consent, investigator discretion, ART change and ineligible for Maintenance Phase.
*EFV patients with a W24 visit (n=47).
Subcategories are a slight variation on FDA Snapshot Study Outcomes categories.

Figure 2. Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)



Protocol-Defined Virologic Failure

Induction Phase:

- Seven subjects total: CAB 10 mg, n=1 Week 8; 30 mg, n=1 Week 4; 60 mg, n=1 Week 8; EFV 600 mg, n=4 Weeks 4 (n=2), 8 and 16
- No treatment-emergent genotypic or phenotypic resistance

Maintenance Phase:

- Five subjects total:
  - CAB 10 mg, n=2 Weeks 48 and 72; CAB 30 mg, n=1 Week 36; EFV 600 mg, n=2 Weeks 36 and 60

Treatment-Emergent Resistance:

- CAB 10 mg – NNRTI (E138Q) and IN (Q148R) in one subject with PDVF at Week 48. CAB FC = 3; RPV FC = 2. CAB and RPV exposures <50% of predicted concentrations at PK assessments.[2]
- CAB 10 mg – NNRTI K101K/E and E138E/A in one subject with PDVF at Week 72 with RPV FC = 4.6. No treatment-emergent integrase resistance.
- One additional subject on CAB 10 mg + RPV with suspected virologic failure (without confirmatory lab draw; lost to follow-up) developed treatment-emergent NNRTI K101K/E and E138E/K at Week 48. RPV FC = 2.18.

Table 4. Adverse Events

	CAB 10 mg n=60	CAB 30 mg n=60	CAB 60 mg n=61	EFV 600 mg n=62
Grade 2-4 drug-related events (>3% any arm)	**5 (8%)**	**8 (13%)**	**13 (21%)**	**12 (19%)**
Insomnia	1 (2%)	2 (3%)	0	4 (6%)
Depression	0	0	2 (3%)	0
Nausea	0	2 (3%)	3 (5%)	1 (2%)
Fatigue	0	2 (3%)	1 (2%)	1 (2%)
Headache	1 (2%)	1 (2%)	3 (5%)	0
Rash macular	0	0	0	3 (5%)
Grade 2-4 drug-related events (W24+)†	**1 (2%)**	**2 (3%)**	**3 (5%)**	**2 (3%)**
Serious AEs	**7 (12%)**	**5 (8%)**	**7 (11%)**	**4 (6%)***
Serious AEs (W24+)	**5 (8%)**	**5 (8%)**	**5 (8%)**	**2 (3%)**
AEs leading to withdrawal (>1 subject)	**1 (2%)**	**2 (3%)**	**4 (7%)**	**9 (15%)**
Dizziness	0	0	0	2 (3%)
ALT increased	0	0	2 (3%)**	0
Grade 1-4 ALT abnormalities	**8 (13%)**	**12 (20%)**	**17 (28%)**	**13 (21%)**
Select Grade 3-4 laboratory abnormalities				
Creatine phosphokinase (CPK)	7 (12%)	7 (12%)	5 (8%)	9 (15%)
Alanine aminotransferase (ALT)	0	1 (2%)	2 (3%)**	1 (2%)
Lipase	3 (5%)	2 (3%)	6 (10%)	1 (2%)
Total bilirubin	0	0	0	0
Total neutrophils	1 (2%)	1 (2%)	2 (3%)	2 (3%)
Creatinine	0	0	0	0

†All Grade 2.
*One drug-related SAE: suicide attempt (EFV).
**Two subjects with steatohepatitis developed asymptomatic Grade 4 ALT elevations (meeting protocol-defined liver stopping criteria) with normal bilirubin levels, at Week 4 and Week 8, which resolved off investigational product.

Conclusions

- Following induction therapy, oral CAB + RPV maintained virologic suppression at a rate similar to EFV + NRTIs through 96 weeks.
  - Primary endpoint: 76% of CAB + RPV and 63% of EFV + NRTIs subjects had HIV-1 RNA <50 c/mL.
  - Secondary endpoint (ITT-ME): 86% of CAB + RPV and 83% of EFV + NRTIs subjects had HIV-1 RNA <50 c/mL.
  - Numerically lower response rate of CAB 10 mg and 30 mg, relative to 60-mg arm is largely due to non-virologic discontinuations, with a low PDVF rate across all arms.
- CAB + RPV was well tolerated, with few drug-related AEs leading to withdrawal.
- CAB 30-mg once-daily dose was selected for further oral development.
- These regimen POC results support evaluation of long-acting injectable regimens of CAB LA + RPV LA as maintenance therapy.

Acknowledgments

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