# Long-term Safety and Efficacy of CAB and RPV as 2-Drug Oral Maintenance Therapy

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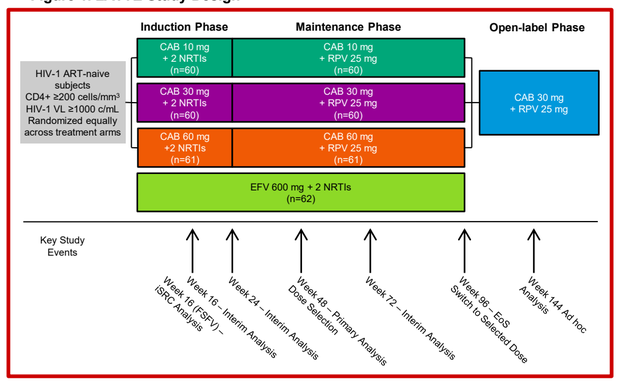
## Background

- Cabotegravir (CAB) is an HIV integrase inhibitor (INI) under development as a tablet for oral lead-in and as a long-acting (LA) injectable nanosuspension
- 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 therapy (ART) maintenance regimen with oral rilpivirine (RPV)
- The Week 96 secondary endpoint (% HIV-1 RNA <50 c/mL, snapshot) data were presented at the 22nd CROI[1]
- Data from LATTE will inform future studies in which the LA formulations of both CAB and RPV are used for the treatment of HIV-1 infection

## Study Design and Methods

**Figure 1. LATTE Study Design**




- A sample size of 50 patients (Pts) per arm was chosen to ensure a high probability that a dosage arm with 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
- 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
- Randomization was stratified by screening viral load and choice of background NRTIs
- Eligibility for the Open-label (OL) phase was determined by the Week 96 HIV-1 RNA (<50 c/mL)
  - Following Week 96, all Pts who qualified for the OL phase were transitioned to the sponsor-selected dose of CAB 30 mg + RPV 25 mg. Efavirenz (EFV) arm Pts completed the study
- 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 and OL phases 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

## Results

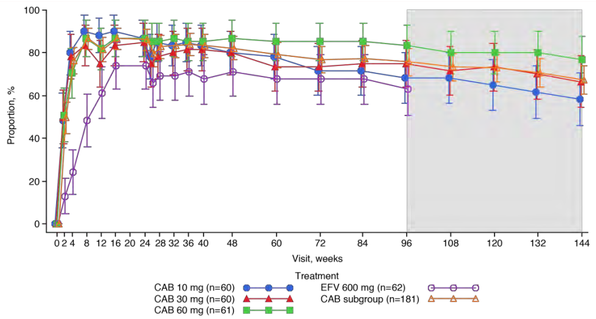
- 243 Pts were randomized and initiated treatment (ITT-E): 96% male, 38% non-white, 14% >100,000 c/mL HIV-1 RNA, 61% TDF/FTC. Of those randomized to CAB (n=181), 160 Pts began the maintenance regimen (Week 24). 146 Pts completed Week 96, of which 142 Pts entered the OL phase. After the last Pt completed Week 96, the study was unblinded, and 136 Pts transitioned to the sponsor-selected regimen of CAB 30 mg + RPV 25 mg (transition took place between Weeks 96 and 120). 129 Pts remained on study at the time of the Week 144 analysis
  - Pts are shown by their original randomization regimen

**Table 1. Subject Accountability: ITT-E Population, Week 96 to Week 144**

| | CAB 10 mg N=60 n (%) | CAB 30 mg N=60 n (%) | CAB 60 mg N=61 n (%) | CAB Subtotal N=181 n (%) |
|---|---|---|---|---|
| **Completed study at W96[a]** | 0 | 3 (5) | 1 (2) | 4 (2) |
| **Entered OL phase** | **46 (77)** | **45 (75)** | **51 (84)** | **142 (78)** |
| W/D prior to receiving OL drug[b] | 3 (5) | 1 (2) | 2 (3) | 6 (3) |
| Received OL drug | 43 (72) | 44 (73) | 49 (80) | 136 (75) |
| W/D after receiving OL drug | 6(10) | 1(2) | 0 | 7(4) |
| **Reason for W/D in OL phase** | **9 (15)** | **2 (3)** | **2 (3)** | **13 (7)** |
| Adverse event | 1 (2) | 1 (2) | 0 | 2 (1) |
| Lack of efficacy (PDVF) | 3 (5)[c] | 1 (2) | 0 | 4 (2) |
| Lost to follow-up | 4 (7) | 0 | 1 (2) | 5 (3) |
| Withdrew consent | 1 (2) | 0 | 1 (2) | 2 (1) |

Pts can only have one primary reason for withdrawal. [a]Successfully completed 96 weeks of treatment; chose not to enter the OL phase of study. [b]Six Pts continued beyond W96 into the OL phase but withdrew (W/D) prior to actually switching to the sponsor-selected regimen. The switch did not occur until all Pts completed W96. [c]One Pt listed as W/D due to lack of efficacy (PDVF) did not confirm virologic failure while on treatment.

**Figure 2. Proportion of Subjects With Plasma HIV-1 RNA <50 c/mL by Visit: Snapshot (MSDF) Analysis**




Note: At W96, EFV Pts completed study participation. Pts in the CAB arms who qualified for and chose to enter the OL phase were all switched to CAB 30 mg + RPV 25 mg (shaded area).

**Table 2. Week 144 Treatment Outcomes**

| Outcome at W144[a] | CAB 10 mg n (%) | CAB 30 mg n (%) | CAB 60 mg n (%) | CAB Subtotal n (%) |
|---|---|---|---|---|
| **Snapshot (ITT-E)** | N=60 | N=60 | N=61 | N=181 |
| HIV-1 RNA <50 c/mL | 35 (58) | 40 (67) | 47 (77) | 122 (67) |
| HIV-1 RNA ≥50 c/mL[b] | 8 (13) | 8 (13) | 2 (3) | 18 (10) |
| Prior change in ART | 0 | 3 (5) | 0 | 3 (2) |
| No virologic data in window | 17 (28) | 12 (20) | 12 (20) | 41 (23) |
| W/D due to AE or death | 2 (3) | 2 (3) | 4 (7) | 8 (4) |
| W/D due to other reasons | 14 (23) | 8 (13) | 5 (8) | 27 (15) |
| On study but missing data in window | 1 (2) | 2 (3) | 3 (5) | 6 (3) |
| **PDVF (ITT-E)** | 5 (8) | 3 (5) | 1 (2) | 9 (5) |
| **Snapshot (ITT-ME)** | N=52 | N=53 | N=55 | N=160 |
| HIV-1 RNA <50 c/mL | 35 (67) | 40 (75) | 47 (85) | 122 (76) |
| HIV-1 RNA ≥50 c/mL[b] | 6 (12) | 6 (11) | 1 (2) | 13 (8) |
| Prior change in ART | 0 | 2 (4) | 0 | 2 (1) |
| No virologic data in window | 11 (21) | 7 (13) | 7 (13) | 25 (16) |
| W/D due to AE or death | 2 (4) | 1 (2) | 1 (2) | 4 (3) |
| W/D due to other reasons | 8 (15) | 4 (8) | 3 (5) | 15 (9) |
| On study but missing data in window | 1 (2) | 2 (4) | 3 (5) | 6 (4) |
| **PDVF (ITT-ME)** | 4 (8) | 2 (4) | 0 | 6 (4) |

[a]Outcomes are presented by original randomization regimen. All Pts who qualified for, and chose to enter, the OL phase were treated with the sponsor selected regimen between W96 and W144. [b]HIV-1 RNA ≥50 c/mL reasons include HIV-1 RNA ≥50 c/mL at W144, discontinued while not suppressed (≥50 c/mL) or for lack of efficacy, or prior ART changes even if protocol approved.

## Protocol-Defined Virologic Failure

- There were 9 PDVFs on CAB, with 3 occurring between Week 96 and Week 144 (OL phase)
  - The 6 PDVFs that occurred in the Induction and Maintenance phases were characterized and presented at the 22nd CROI[1]
  - The 3 PDVFs that occurred in the OL phase are listed below (Pts are shown by their original randomization regimen. The CAB 10 mg Pts listed in this section switched to the sponsor-selected regimen at their Week 108 visit)
    - CAB 10 mg (n=2): one Pt had a V151V/I mutation (not a primary INI resistance mutation) with a 1.05 FC to CAB and 1.74 FC to RAL. Suspected virologic failure (SVF) was 385 c/mL HIV-1 RNA at Week 108 and confirmed virologic failure (CVF) was 772 c/mL HIV-1 RNA. Another Pt had treatment-emergent NNRTI mutations K101E and M230M/L with a 12 FC to RPV. SVF was 836 c/mL HIV-1 RNA at Week 132 and CVF was 1727 c/mL HIV-1 RNA
    - CAB 30 mg (n=1): this Pt did not have any treatment-emergent mutations. SVF was 908 c/mL HIV-1 RNA at Week 132 and CVF was 211 c/mL HIV-1 RNA
    - One Pt (CAB 10 mg) did not confirm virologic failure while on treatment and was not counted as a PDVF, but virology was performed with the following results: treatment-emergent NNRTI mutations E138K and V108V/I with SVF of 281 c/mL HIV-1 RNA at Week 108 and CVF of 140 c/mL HIV-1 RNA with a 5.73 FC to RPV

**Table 3. Adverse Events Through Week 144**

| Maintenance safety population[a] | CAB 10 mg N=52 n (%) | CAB 30 mg N=53 n (%) | CAB 60 mg N=55 n (%) | CAB Subtotal N=160 n (%) |
|---|---|---|---|---|
| **Grade 2-4 drug-related events (>3% in any arm)[b]** | 1 (2) | 3 (6) | 3 (5) | 7 (4) |
| Depression | 0 | 0 | 2 (4) | 2 (1) |
| **Serious AEs[c]** | 5 (10) | 5 (9) | 5 (9) | 15 (9) |
| **AEs leading to withdrawal (≥1 Pt)** | 1 (2) | 2 (4) | 1 (2) | 4 (3) |
| Anxiety disorder | 0 | 0 | 1 (2) | 1 (<1) |
| Abnormal ECG | 1 (2) | 0 | 0 | 1 (<1) |
| Acute hepatitis C[d] | 0 | 1 (2) | 0 | 1 (<1) |
| Burkitt's lymphoma | 0 | 1 (2) | 0 | 1 (<1) |
| **Grade 1-4 ALT abnormalities[e]** | 7 (13) | 12 (23) | 8 (15) | 27 (17) |
| **Select Grade 3-4 laboratory abnormalities** | | | | |
| Creatine kinase (CK) | 5 (10) | 4 (8) | 3 (5) | 12 (8) |
| Alanine aminotransferase (ALT) | 0 | 1 (2) | 0 | 1 (<1) |
| Lipase[f] | 2 (4) | 1 (2) | 3 (5) | 6 (4) |
| Total neutrophils[g] | 2 (4) | 1 (2) | 1 (2) | 4 (3) |

[a]The Maintenance Safety Population consists of all randomized Pts who were exposed to IP during the Maintenance and OL phases of the study. [b]All Grade 2; blood bilirubin increase (CAB 30 mg; n=1; not shown in table) was the only drug-related G2-4 AE added in OL phase (W96 through W144). [c]No SAEs were treatment related. [d]Acute Hep C was diagnosed in OL phase. [e]Less than 1% were ≥Grade 3; CAB 30 mg (n=2) and CAB 60 mg (n=1) were the only Grade 1-4 ALT abnormalities added in the OL phase. [f]CAB 10 mg (n=1) and CAB 60 mg (n=1); the only Grade 3-4 lipase abnormalities added in OL phase. [g]CAB 10 mg (n=1) was the only Grade 3-4 neutrophils abnormality added in OL phase.

## Conclusions

- Oral CAB + RPV continues to provide durable virologic suppression through 144 weeks of treatment
  - Pts who entered the OL phase and switched to CAB 30 mg oral continued to remain virologically suppressed, with few non-virologic discontinuations or virologic failures
  - These data support the selection of CAB 30 mg + RPV 25 mg for future use to support LA therapy (ie, as an oral lead-in and/or oral bridging supply)
- Overall, CAB + RPV was well tolerated, with few AEs leading to withdrawal
- These results continue to support evaluation of all-injectable regimens of CAB LA + RPV LA as maintenance therapy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**Reference**


Margolis DA, Brinson CC, Graham HR, et al. Cabotegravir and rilpivirine as two-drug oral maintenance therapy: LATTE week 96 results. Abstract 554LB. Published at: 22nd Conference on Retroviruses and Opportunistic Infections; February 23-26, 2015; Seattle, WA.