Long-Term Efficacy, Safety and Durability of CAB and RPV as Two-Drug Oral Maintenance Therapy – LATTE Week 312 Results

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- The LATTE study was funded by ViiV Healthcare and Janssen Pharmaceuticals
- David Margolis, MD, MPH
  - Director of HIV Drug Development, ViiV Healthcare
  - David Margolis is employed by ViiV Healthcare and owns company stocks from GlaxoSmithKline

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LATTE Background and Objectives

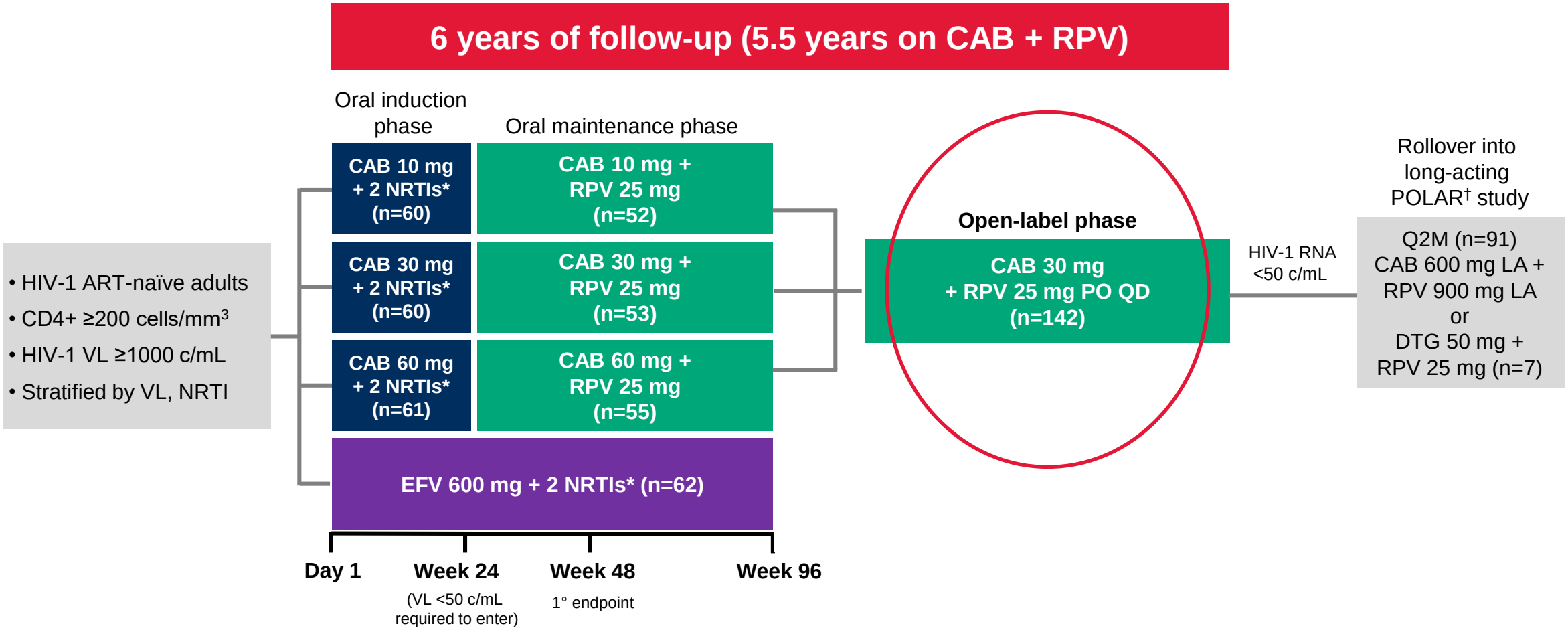
- CAB is an HIV-1 INSTI under development as both oral and long-acting injectable formulations
- RPV is an HIV-1 NNRTI approved as an oral formulation; it is currently under development as a long-acting injectable formulation
- The LATTE study was designed to select a daily oral dose of CAB, followed by evaluation of the 2DR CAB + RPV as a maintenance therapy in virologically suppressed adults with HIV-1
  - Results enabled evaluation of long-acting formulations of CAB + RPV in the LATTE-2 study
- The primary endpoint of the LATTE study was the % of participants with <50 c/mL of HIV-1 RNA (FDA Snapshot) at Week 48[1]
  - 82% of participants treated with CAB + RPV vs. 71% of those treated with EFV + 2 NRTIs had <50 c/mL of HIV-1 RNA[1]
- Durable virologic suppression with CAB + RPV has been reported through Weeks 96[2] and 144[3]
- Presented here are the Week 312 (6-year) end-of-study results

2DR, two-drug regimen; CAB, cabotegravir; EFV, efavirenz; INSTI, integrase strand transfer inhibitor; LATTE, Long-Acting antireTroviral Treatment Enabling (NCT01641809); LATTE-2 (NCT02120352); NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RPV, rilpivirine.

1. Margolis DA, et al. CROI 2014; Abstract 91LB; 2. Margolis DA, et al. *Lancet Infect Dis* 2015;15:1145–55; 3. Margolis D, et al. CROI 2017; Poster 442. Margolis DA, et al. IDWeek 2019™; Washington DC, USA. Oral 2840.

LATTE Study Design

Phase 2b, randomized, multicenter (USA and Canada), partially blinded, dose-ranging study



3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LA, long acting; NRTI, nucleoside reverse transcriptase inhibitor; PO, orally; QD, once daily; Q2M, every 2 months; RPV, rilpivirine; TDF, tenofovir; VL, viral load. *ABC/3TC or TDF/FTC; †NCT03639311.

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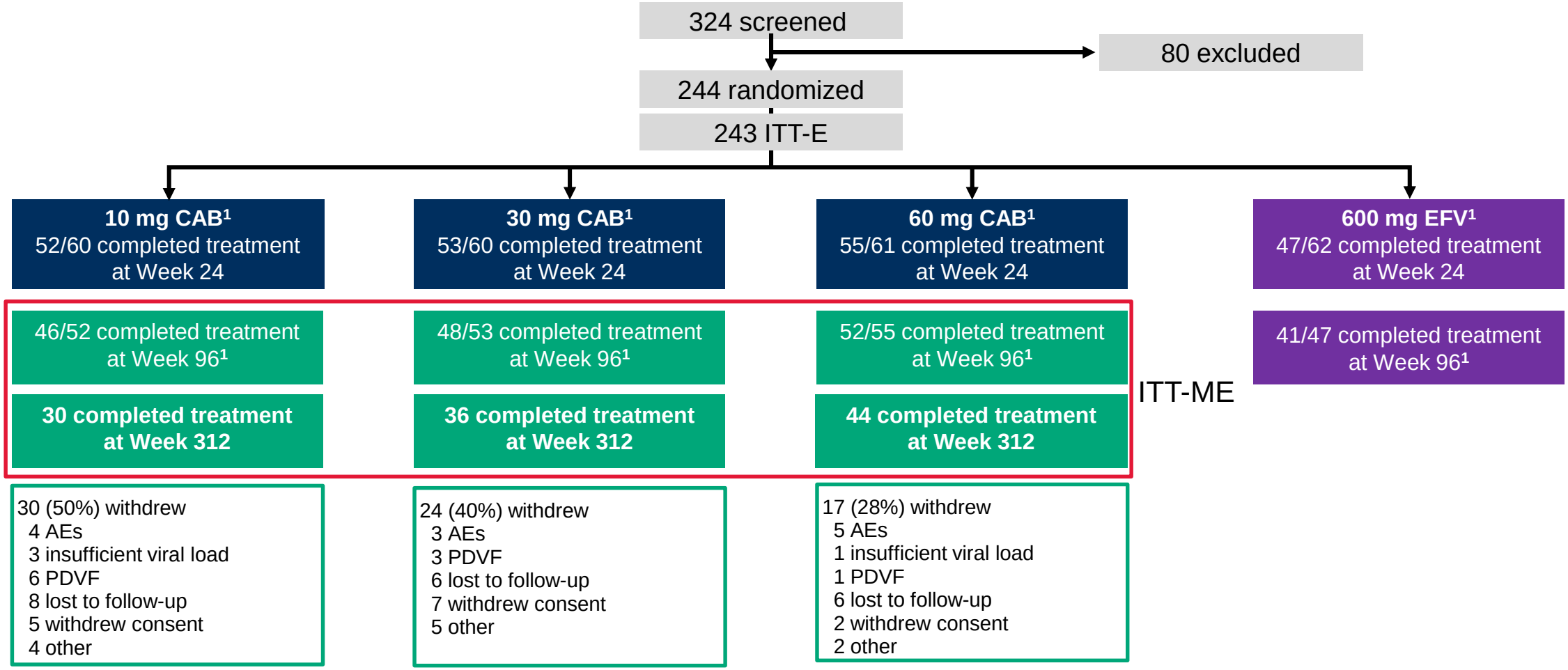
LATTE Subject Disposition Through Week 312



AE, adverse event; CAB, cabotegravir; EFV, efavirenz; ITT-E, intent-to-treat exposed (received at least one dose of Investigational Product); ITT-ME, intent-to-treat maintenance exposed (received at least one maintenance dose); PDVF, protocol-defined virologic failure;

1. Margolis DA, et al. *Lancet Infect Dis* 2015;15:1145–55.
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LATTE ITT-ME Baseline* Characteristics

Parameter	10 mg CAB (n=52)	30 mg CAB (n=53)	60 mg CAB (n=55)	600 mg EFV (n=47)
Age, median (range) years	32.0 (19–54)	33.0 (20–57)	34.0 (19–56)	33.0 (19–70)
Male, n (%)	50 (96)	52 (98)	52 (95)	46 (98)
Race, n (%) White African American or African heritage Other	 33 (63) 19 (37) 0	 36 (68) 14 (26) 3 (6)	 32 (58) 16 (29) 7 (13)	 33 (70) 12 (26) 2 (4)
Baseline HIV-1 RNA, c/mL Median (IQR), log_{10} ≥100,000 n, (%)	 4.29 (4.01–4.72) 6 (12)	 4.16 (3.84–4.69) 6 (11)	 4.36 (3.95–4.79) 10 (18)	 4.44 (3.76–4.80) 8 (17)
Baseline CD4 cell count, median (IQR) cell/μL	442 (351–541)	406 (324–549)	420 (342–529)	424 (288–651)
Hepatitis C co-infection, n (%)†	0	5 (8)	3 (5)	1 (2)

CAB, cabotegravir; EFV, efavirenz; IQR, interquartile range; ITT-E, intent-to-treat exposed (received at least one dose of Investigational Product); ITT-ME, intent-to-treat maintenance exposed (received at least one maintenance dose).
*Baseline = Day 1 prior to induction; †ITT-E population (10 mg CAB, n=60; 30 mg CAB, n=60; 60 mg CAB, n=61; EFV, n=62).

Adapted from: Margolis DA, et al. *Lancet Infect Dis* 2015;15:1145–55.
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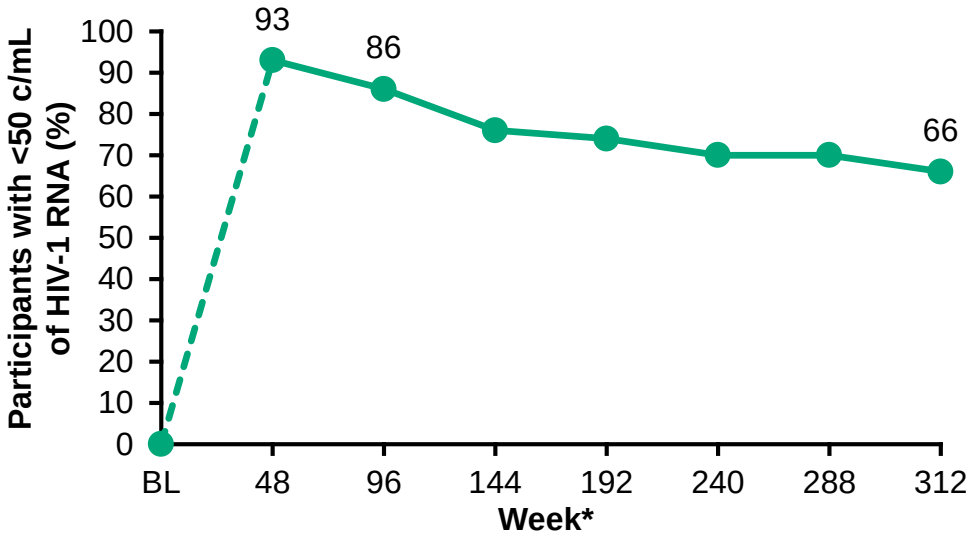
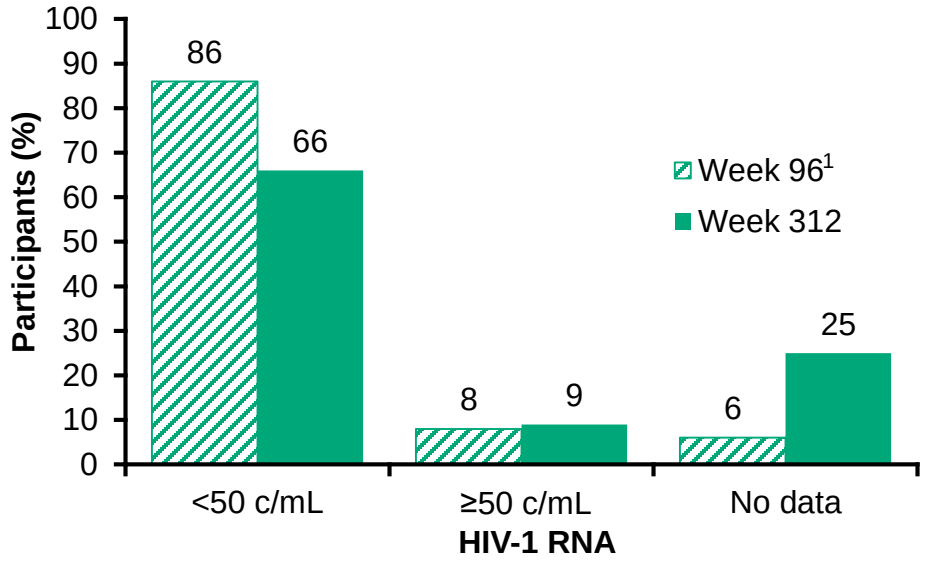
LATTE HIV-1 RNA <50 c/mL Through Week 312 Snapshot Analysis, ITT-ME





AE, adverse event; ART, antiretroviral therapy; BL, baseline; CAB, cabotegravir; ITT-ME, intent-to-treat maintenance exposed (received at least one maintenance dose). *Week 48 and 96 data include participants receiving any CAB dose (10 mg, 30 mg, or 60 mg); †3/6 were virologic failures at Week 96 and Week 312, but in a different category; ‡For the 24 additional subjects who discontinued at Week 312, reasons for discontinuation were as follows: lack of efficacy (n=2), withdrawal of consent (n=5), investigator discretion (n=2), protocol deviation (n=2), lost to follow-up (n=11), no reason provided (n=2).

Week 96 and Week 312 outcomes, n (%)	CAB + RPV Total Week 96[1] (N=160)	CAB = RPV Total Week 312 (N=160)
Virologic success (HIV-1 RNA <50 c/mL)	137 (86)	105 (66)
Virologic failure (HIV-1 RNA ≥50 c/mL)	13 (8)	15 (9)
Data in window not below threshold	6 (4)†	1 (<1)
Discontinued for lack of efficacy	1 (<1)	4 (3)
Discontinued for other reason while not below threshold	4 (3)	8 (5)
Prior change in ART	2 (1)	2 (1)
No virologic data	10 (6)	40 (25)
Discontinued due to AE or death	2 (1)	8 (5)
Discontinued for other reasons	7 (4)	31 (19)‡
Missing data during window but on study	1 (<1)	1 (<1)

1. Margolis DA, et al. *Lancet Infect Dis* 2015;15:1145–55.

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LATTE Protocol-Defined Virologic Failure and Resistance Summary

- 5.5 years on CAB + RPV, 8/160 (5%) participants met PDVF criteria
  - 6 individuals through W144 (W36, W48, W72, W108, W132)
    - 1/6 with treatment-emergent IN mutations (Q148R) – participant with extreme calorie restricted diet at PDVF
    - 3/6 with treatment emergent NNRTI mutations (E138Q; K101K/E, E138E/A; K101E, M230M/L)
    - All Subtype B, 4/6 on 10 mg, 2/6 on 30 mg
    - 2 additional participants had SVF with RPV resistance at Weeks 48 and 108; 1 was lost to follow-up and 1 did not have failure confirmed
  - 2 individuals W144 – W312

PDVFs W144 – W312				
Participants with treatment-emergent INSTI resistance	**Participants with treatment-emergent NNRTI resistance**	**SVF timepoint**	**Viral load at SVF/CVF (c/mL)**	**Notes**
E138K§, G140A‡, Q148R§ (FC 116)	K101E§ (FC 21)	Week 132 (DNC)§ Week 144 (DNC)§ Week 168 (DNC) Week 180‡§	243 / 1748	Viral suppression through W108 followed by extended period of intermittent/low-level viremia
G140S, Q148R (FC 9.84)	K101K/E, E138E/K (FC 1.77)	Week 216 (DNC) Week 264	656 / 304	Single episode of VL >50 c/mL (W216), prior to CVF

CAB, cabotegravir; CVF, confirmed virologic failure; DNC, did not confirm; FC, fold change; IN, integrase; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PDVF, protocol-defined virologic failure; RPV, rilpivirine; SVF, suspected virologic failure; VL, viral load; W, Week.
‡G140A only detected at Week 180; §E138K, Q148R and K101E detected at all timepoints.

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LATTE Week 96 Safety Summary (Maintenance Safety Population)

Parameter, n (%)	CAB + RPV Total Week 96 (N=160)
Grade 2–4 drug-related events	**6 (4)**
Serious AEs	**15 (9)**
Drug related	**0**
AEs leading to withdrawal	**3 (2)**
Electrocardiogram abnormal	1 (<1)
Liver function test increased	0
Weight decreased	0
Acute hepatitis C	0
Burkitt's lymphoma	1 (<1)
Anxiety disorder	1 (<1)
Depression	0
Suicidal ideation	0
Irritable bowl syndrome	0
Chest discomfort	0
Grade 3–4 treatment-emergent laboratory abnormalities* (>5%)	**46 (29)**
Creatine kinase	18 (11)
Lipase	10 (6)

Median (range) weight change from baseline in participants receiving CAB†: + 3.0 kg (-17.7, +26.7)
Median (range) weight change from baseline in participants receiving EFV‡: -1.10 kg (-16.4, +13.9)

AE, adverse event; CAB, cabotegravir; EFV, efavirenz; LDL, low-density lipoprotein.
*Occurring in ≥4 subjects; †Safety population (CAB, N=181), median (range) weight of participants receiving CAB: 78 kg (50, 152) at baseline; ‡Safety population (EFV, N=62), median (range) weight of participants receiving EFV was 75 (54, -137) at baseline.

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LATTE Week 312 Safety Summary (Maintenance Safety Population)

Parameter, n (%)	CAB + RPV Total Week 96 (N=160)	CAB + RPV Total Week 312 (N=160)
Grade 2–4 drug-related events	**6 (4)**	**10 (6)**
Serious AEs	**15 (9)**	**32 (20)**
Drug related	**0**	**2 (1)**
AEs leading to withdrawal	**3 (2)**	**8 (5)**
Electrocardiogram abnormal	1 (<1)	1 (<1)
Liver function test increased	0	1 (<1)
Weight decreased	0	1 (<1)
Acute hepatitis C	0	1 (<1)
Burkitt's lymphoma	1 (<1)	1 (<1)
Anxiety disorder	1 (<1)	1 (<1)
Depression	0	1 (<1)
Suicidal ideation	0	1 (<1)
Irritable bowl syndrome	0	1 (<1)
Chest discomfort	0	1 (<1)
Grade 3–4 treatment-emergent laboratory abnormalities* (>5%)	**46 (29)**	**69 (43)**
Creatine kinase	18 (11)	26 (16)
Lipase	10 (6)	16 (10)
Phosphate	6 (4)	8 (5)
LDL cholesterol calculation	4 (3)	13 (8)

Median (range) weight change from baseline in participants receiving CAB† : + 3.0 kg (-17.7, +26.7) + 6.5 kg (-14.7, +32.2)

AE, adverse event; CAB, cabotegravir.
*Occurring in ≥4 subjects; †Safety Population (CAB, N=181), median (range) weight of participants receiving CAB was 78 kg (50, 152) at baseline.

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LATTE Conclusions

- Oral CAB + RPV 2DR provided durable virologic suppression throughout 5.5 years in the LATTE study
- Oral CAB + RPV was generally well tolerated, with few AEs leading to discontinuation
  - There were minimal additional serious drug-related AEs and discontinuations after Week 96
- Few PDVFs were reported in participants treated with oral CAB + RPV
  - Through 144 weeks, 6 PDVFs (3 occurring before Week 96) were reported; the majority (4/6) occurred in the 10 mg dosing arm; 1/6 with INI resistance and 3/6 with NNRTI resistance
  - Two additional failures (>Week 144) developed INI and NNRTI resistance
- These results support the longer-term safety and efficacy of oral CAB + RPV dosing
- The evaluation of oral CAB + RPV in the LATTE study paved the way for long-acting studies, with different dosing, compliance and pharmacokinetic considerations
  - Long-acting CAB + RPV is being investigated in the ongoing LATTE-2, ATLAS, ATLAS-2M, FLAIR, and POLAR studies

2DR, 2-drug regimen; AE, adverse event; CAB, cabotegravir; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PDVF, protocol-defined virologic failure; RPV, rilpivirine.

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