Distribution in Cerebrospinal Fluid (CSF) of Cabotegravir (CAB) and Rilpivirine (RPV) After Intramuscular Administration of Long-Acting (LA) Injectable Suspensions in HIV-1-Infected Patients

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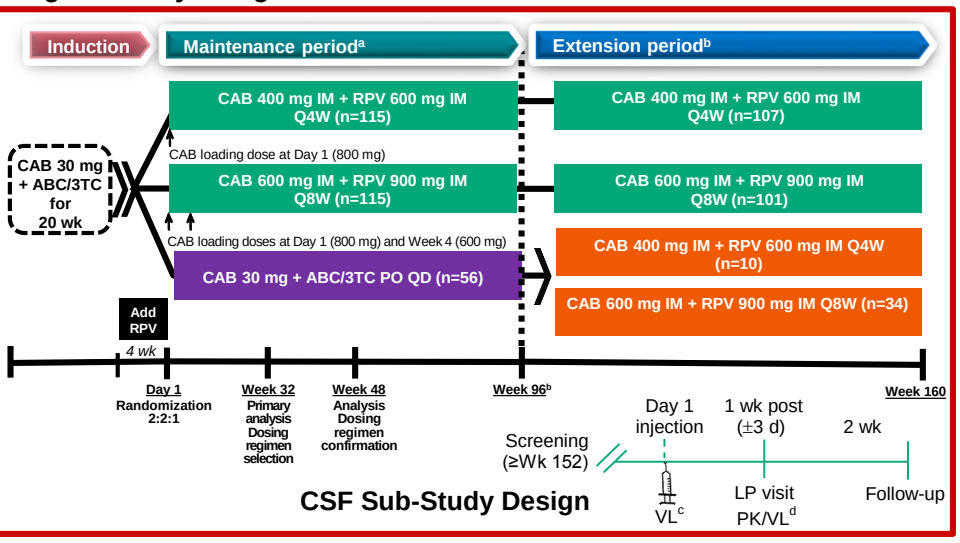
Introduction

- Cabotegravir (CAB), an integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), are long-acting (LA) injectables in phase III development under evaluation for the maintenance of HIV virologic suppression in antiretroviral (ARV)-naive participants after induction with triple therapy and in virally suppressed treatment-experienced participants
- CAB LA + RPV LA administered intramuscularly (IM) every 4 weeks (Q4W) or every 8 weeks (Q8W) may offer a better tolerability profile, improved adherence, and treatment satisfaction relative to daily oral antiretroviral therapy (ART)
- The blood–brain barrier can limit penetration of ARV agents
- The objective of this study was to assess CAB and RPV distribution into the central nervous system and HIV-1 RNA levels in this "sanctuary" site

Methods

- Previously ART-naive, HIV-infected adults on either IM regimen in the extension phase of the LATTE-2 study were eligible to participate in the cerebrospinal fluid (CSF) sub-study

Figure. Study Design



ABC, abacavir; CAB, cabotegravir; CSF, cerebrospinal fluid; IM, intramuscularly; 3TC, lamivudine; LP, lumbar puncture; PK, pharmacokinetics; PO, oral; QD, once a day; Q4W, every 4 wk; Q8W, every 8 wk; RPV, rilpivirine; VL, viral load. [a]Participants who withdrew after ≥1 IM dose of maintenance or extension phases entered the long-term follow-up period. [b]Participants could elect to enter the Q4W and Q8W long-acting extension phase beyond Week 96. [c]Plasma HIV-1 RNA. [d]CSF/plasma PK and HIV-1 RNA 1 wk post-dose.

- Paired plasma and CSF samples were collected 7 days (±3 days) after an injection for total and unbound plasma CAB concentration; total plasma RPV concentration; and total CSF CAB and RPV concentrations
- Paired plasma and CSF samples for HIV-1 RNA were analyzed using Abbott (<50 c/mL; plasma) and SuperLow (<2 c/mL: plasma and CSF) assays

Results

Table 1. CSF Sub-Study Population Demographics

Demographics	Q8W IM (N=15)	Q4W IM (N=3)	Total (N=18)
Age, mean (SD), y	37.2 (11.12)	44.0 (13.08)	38.3 (11.35)
Male gender, n (%)	12 (80)	3 (100)	15 (83)
BMI, mean (SD), kg/m^2	26.7 (5.28)	26.0 (1.51)	26.5 (4.83)
Weight, kg, mean (SD)	82.2 (15.27)	87.0 (18.81)	83.0 (15.40)
Race/Ethnicity, n (%)			
Not Hispanic/Latino	11 (73)	3 (100)	14 (78)
Asian	1 (7)	1 (33)	2 (11)
Black/African American	5 (33)	0	5 (28)
White	9 (60)	2 (67)	11 (61)
Plasma HIV-1 RNA, n (%) <50 c/mL	15 (100)	3 (100)	18 (100)
Mean CD4 cell count, mean (SD), cells/mm^3	827 (280)	685 (164)	803 (266)

BMI, body mass index; CSF, cerebrospinal fluid; IM, intramuscularly; Q4W, every 4 wk; Q8W, every 8 wk; SD, standard deviation.

Table 2. Plasma and CSF PK Results

	CAB (µg/mL) Median (min, max)		RPV (ng/mL) Median (min, max)	
PK	Q8W (n=15)	Q4W (n=3)	Q8W (n=15)	Q4W (n=3)
Total plasma	**3.92** (1.30, 6.41)	**3.02** (2.37, 5.10)	**192** (91.7, 378)	**134** (83.0, 187)
Unbound plasma	**0.0047** (0.0007, 0.0220)	**0.0019** (0.0014, 0.0698)	NP	NP
Unbound fraction in plasma, %	**0.103** (0.056, 0.912)	**0.075** (0.062, 1.45)	NP	NP
Total CSF	**0.0106** (0.0053, 0.0245)[a]	**0.0127** (0.0082, 0.0159)	**1.84** (NQ, 2.90)[a,b]	**1.67** (1.40, 2.47)
CSF/Total plasma, %	**0.304** (0.218, 0.449)[a]	**0.344** (0.312, 0.421)	**1.07** (NQ, 1.52)[a,b]	**1.32** (1.25, 1.69)

CAB, cabotegravir; CSF, cerebrospinal fluid; PK, pharmacokinetics; Q4W, every 4 wk; Q8W, every 8 wk; NP, not performed; NQ, not quantifiable; RPV, rilpivirine. [a]N=13; failed to collect CSF for 2 participants. [b]1 participant had RPV CSF total as NQ (<1 ng/mL) and was imputed with a value of 0.

- Median total CSF/total plasma concentration ratio was 0.30% to 0.34% for CAB and 1.0% to 1.32% for RPV
- All CSF concentrations exceeded the upper limit of the in vitro 50% inhibitory concentration (IC_{50}) for wild-type HIV (CAB, 0.0003 µg/mL; RPV, 0.081 ng/mL)
  - 1 participant's CSF RPV concentration was not quantifiable (<1 ng/mL); plasma RPV was 117 ng/mL (HIV-1 RNA was <2 c/mL in CSF and 5 c/mL in plasma)
- CAB CSF concentrations were significantly and positively correlated with total plasma CAB concentrations (r=0.899; *P*<0.001), whereas no significant correlation was seen between RPV CSF concentrations and total plasma RPV (r=0.432; *P*=0.14)

Table 3. Plasma and CSF HIV-1 RNA Results

	Abbott real-time assay HIV-1 RNA <50 c/mL n/N (%)		SuperLow assay HIV-1 RNA <2 c/mL n/N (%)	
Antiviral activity	Q8W (N=15)	Q4W (N=3)	Q8W (N=15)	Q4W (N=3)
Plasma HIV-1 RNA on Day 8	15/15 (100)	3/3 (100)	9/15[a] (60)	3/3 (100)
CSF HIV-1 RNA on Day 8	13/13[a] (100)	3/3 (100)	12/13[b] (92)	3/3 (100)

CSF, cerebrospinal fluid; Q4W, every 4 wk; Q8W, every 8 wk. [a]Actual Day 8 plasma HIV-1 RNA levels for 6 participants who were not <2 c/mL were 3, 5, 5, 10, 15, and 42 c/mL. [b]N=13; failed to collect CSF for 2 participants.

Antiviral Activity (1 week post-injection):

- All participants had HIV-1 RNA <50 c/mL in both plasma and CSF
- All except 1 participant (Q8W) had CSF viral load <2 c/mL
  - CSF HIV-1 RNA was 2 c/mL and plasma HIV-1 RNA was <2 c/mL in this participant
- 6 participants (46%) in the Q8W IM group and 3 participants (100%) in the Q4W IM group had both plasma and CSF HIV-1 RNA <2 c/mL

Safety

- 19 adverse events (AEs; 1 during screening and 18 during treatment) were reported in 8 participants during the sub-study; fewer AEs were associated with injection-site reactions (ISRs) compared with the parent LATTE-2 study, with types of AEs reported consistent with previous reports from the parent study
- 2 participants reported an AE of post–lumbar puncture syndrome (grade 2/3 intensity)
  - Headache and back pain were the most common AEs and resolved within 2 days
  - 4 participants reported 10 ISR AEs
- There were no severe AEs, AEs leading to discontinuation, or deaths during the sub-study

Discussion

- Total CAB CSF concentrations exceeded unbound plasma CAB concentrations, and median CSF/total plasma ratios of 0.30% to 0.34% were similar for Q4W and Q8W
- In a previous study, total CSF concentration of dolutegravir, a related analogue to CAB, was similar to unbound plasma concentrations with median CSF/total plasma ratios of 0.52% (range, 0.12-0.66) at Week 2 and 0.41% (range, 0.30-2.04) at Week 16[1]
- The median CSF/plasma ratio of RPV observed in this study (Q8W: 1.07%; Q4W: 1.32%) was comparable with the mean CSF/plasma ratio of 1.4% reported in a previous study with oral RPV (25 mg once daily) administered for 60 days[2]

Conclusions

- CAB and RPV CSF concentrations exceeded in vitro IC_{50} values for wild-type HIV-1, suggesting that CAB and RPV achieve therapeutic concentrations in the CSF at steady state following LA administration
- A dual CAB LA + RPV LA IM regimen administered Q8W or Q4W distributed into the central nervous system resulted in 92% to 100% of participants achieving CSF HIV-1 RNA levels <2 c/mL
- CAB LA + RPV LA was well tolerated in both IM dosing regimens, with no discontinuations due to AEs during the sub-study

Acknowledgment: This study was funded by ViiV Healthcare and Janssen. We acknowledge the study researchers, site staff, and participants in this study. We appreciate support from Joseph Piscitelli, PharmD candidate, UNC School of Pharmacy, intern, for poster creation. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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