Poster #

# Population Pharmacokinetic (PPK) Modeling and Simulation of Long-Acting (LA) Cabotegravir (CAB) to Inform Strategies Following Dosing Interruptions in HIV-1 Infected Subjects

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## Introduction

- CAB is an integrase strand transfer inhibitor under investigation as an injectable LA formulation for the treatment and prevention of HIV, and as a tablet formulation as an oral lead-in and bridging treatment for dose interruptions [1,2].
- The monthly injection regimen of CAB LA and rilpivirine (RPV) LA was non-inferior to standard oral therapy in maintaining HIV-1 suppression in Phase 3 studies [1,2].
- Generally, a one-week delay of dosing was permitted in Phase 3 studies based on the study protocols. However, longer delay may result in exposure that is lower than expected, and may be managed by taking daily oral tablet during the period of delay (oral bridging).
- PPK modeling and simulation was used to evaluate the acceptability of delays in dosing ranging from 1 to 12 weeks at various injection visits and to inform strategies for managing treatment interruptions in coordination with results of dosing delay simulations for RPV LA.

## Methods

### CAB PPK model

- A two-compartment model with first-order oral and intramuscular (IM) absorption and first-order elimination adequately described the data from 23,926 concentration records in 1647 subjects following oral and LA administration [3].
- Covariates retained in the model included gender, BMI, needle length, and split injection on absorption rate constant following LA administration (KA LA) and current smoker status and body weight on CL and volume. No CAB dose adjustment is necessary for the covariates evaluated.

### Plasma CAB Concentration Targets for Treatment Simulations

- Efficacy
  - The 5th percentile of the individual predicted concentration (IPRED) of trough following the loading dose in Phase 3 studies [1,2] from the final model output (0.65 µg/mL) was used as a benchmark to assess the impact of aberrations in dosing against the standard regimen
  - The protein-adjusted IC90 (PA-IC90, 0.166µg/mL) was also considered when assessing the acceptability of a dosing delay.
- Safety:
  - Long-term safety threshold was assigned of 13.1 µg/mL, the median steady-state Cmax following the highest oral dose of CAB 60 mg QD administered for 96 weeks in Study LAI116482 (LATTE) [4].

### Simulations

- 1- to 12 delays in dosing of the 2nd, 3rd, and 4th injection were simulated (Table 1). Q4W dosing was resumed after each delay.
- Oral bridging started at the time of the missed injection for a duration of 1-2 months when CAB LA dosing was resumed (Table 2). The 4th IM dose was assumed to be missed. Dosing resumed the Q4W pattern.
- A blended population of males (80%) and females (20%) was assumed to represent the expected population. Each scenario included 5000 virtual subjects to ensure 1000 female virtual subjects. Individual PK parameters were calculated by the population parameter estimates, subject-specific NONMEM inter-individual errors (ETAs) sampled from the distributions that are decided by the estimated variance-covariate matrix of between-subject variability and by subject-specific covariates.

**Table 1. Scenarios of Delayed Dosing for CAB Monthly Treatment Regimen (CAB LA 600mg (3mL) Initial Injection Followed by 400mg (2mL) with RPV LA Q4W)**

| Sim # | Late Dose | W D | Time Relative to 1st LA Dose (Time Zero) in Weeks | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 22 | 24 |
| 1 | None | 0 | 3 | 2 | | | | 2 | | | | 2 | | | | 2 | | | | 2 | | |
| 2 | Delay the 2nd IM Dose | 1 | 3 | | 2 | | | | 2 | | | | 2 | | | | 2 | | | | | |
| 3 | | 2 | 3 | | | 2 | | | | 2 | | | | 2 | | | | 2 | | | 2 | |
| 4 | | 3 | 3 | | | | 2 | | | | 2 | | | | 2 | | | | 2 | | | |
| 5 | | 4 | 3 | | | | | 2 | | | | 2 | | | | 2 | | | | 2 | | 2 |
| 6 | | 4 | 3 | | | | | 3 | | | | 2 | | | | 2 | | | | 2 | | 2 |
| 7 | | 6 | 3 | | | | | | | 2 | | | | 2 | | | | 2 | | | 2 | |
| 8 | | 8 | 3 | | | | | | | | | 2 | | | | 2 | | | | 2 | | 2 |
| 9 | | 8 | 3 | | | | | | | | | 3 | | | | 2 | | | | 2 | | 2 |
| 10 | | 12 | 3 | | | | | | | | | | | | | 2 | | | | 2 | | 2 |
| 11 | | 12 | 3 | | | | | | | | | | | | | 3 | | | | 2 | | 2 |
| 12 | Delay the 3rd IM Dose | 1 | 3 | 2 | | | | | 2 | | | | 2 | | | | 2 | | | | | |
| 13 | | 2 | 3 | 2 | | | | | | 2 | | | | 2 | | | | 2 | | | 2 | |
| 14 | | 3 | 3 | 2 | | | | | | | 2 | | | | 2 | | | | 2 | | | |
| 15 | | 4 | 3 | 2 | | | | | | | | 2 | | | | 2 | | | | 2 | | 2 |
| 16 | | 4 | 3 | 2 | | | | | | | | 3 | | | | 2 | | | | 2 | | 2 |
| 17 | | 6 | 3 | 2 | | | | | | | | | | 2 | | | | 2 | | | 2 | |
| 18 | | 8 | 3 | 2 | | | | | | | | | | | | 2 | | | | 2 | | 2 |
| 19 | | 8 | 3 | 2 | | | | | | | | | | | | 3 | | | | 2 | | 2 |
| 20 | | 12 | 3 | 2 | | | | | | | | | | | | | | | | 2 | | 2 |
| 21 | | 12 | 3 | 2 | | | | | | | | | | | | | | | | 3 | | 2 |
| 22 | Delay the 4th IM Dose | 1 | 3 | 2 | | | | 2 | | | | | 2 | | | | 2 | | | | | |
| 23 | | 2 | 3 | 2 | | | | 2 | | | | | | 2 | | | | 2 | | | 2 | |
| 24 | | 3 | 3 | 2 | | | | 2 | | | | | | | 2 | | | | 2 | | | |
| 25 | | 4 | 3 | 2 | | | | 2 | | | | | | | | 2 | | | | 2 | | 2 |
| 26 | | 4 | 3 | 2 | | | | 2 | | | | | | | | 3 | | | | 2 | | 2 |
| 27 | | 6 | 3 | 2 | | | | 2 | | | | | | | | | | 2 | | | 2 | |
| 28 | | 8 | 3 | 2 | | | | 2 | | | | | | | | | | | | 2 | | 2 |
| 29 | | 8 | 3 | 2 | | | | 2 | | | | | | | | | | | | 3 | | 2 |
| 30 | | 12 | 3 | 2 | | | | 2 | | | | | | | | | | | | | | 2 |
| 31 | | 12 | 3 | 2 | | | | 2 | | | | | | | | | | | | | | 3 |

Sim: simulation. WD: weeks delayed. Red: 600 mg (3 mL). Blue: 400 mg (2 mL). Gray shading: reinitiation with loading dose after delay. Not all visits are shown between Week 20 and 24.

**Table 2. Scenarios of Oral Bridging for CAB Q4W Treatment Regimen**

| Sim # | OB | Time Relative to 1st LA Dose (Time Zero) in Weeks | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 4 | 8 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| 32 | 4 | 3 | 2 | 2 | | | | | 2 | | | | 2 |
| 33 | 6 | 3 | 2 | 2 | | | | | | | 2 | | |
| 34 | 8 | 3 | 2 | 2 | | | | | | | | | 2 |
| 35 | 8 | 3 | 2 | 2 | | | | | | | | | 3 |

OB: duration of oral bridging in weeks.
Sim: simulation.
Red: 600 mg (3 mL).
Blue: 400 mg (2 mL).
Gold: oral bridging daily.

## Results

**Figure 1. Simulated Concentration-versus-Time Profiles for a) no delay (Sim# 1), b) Injection 2 delayed by 1 week (Sim# 2), c) Injection 3 delayed by 4 weeks with 2mL or 3mL reinitiation (Sim# 15, Sim# 16), d) Injection 4 delayed by 4 weeks with 2mL or 3mL reinitiation (Sim# 25, Sim# 26), e) 4-week delay at Injection 4 with and without oral bridge (Sim# 25, Sim# 32) and f) 8-week delay at Injection 4 with and without oral bridge (Sim# 29, Sim# 35). See Sim# in Table 1 and 2.**

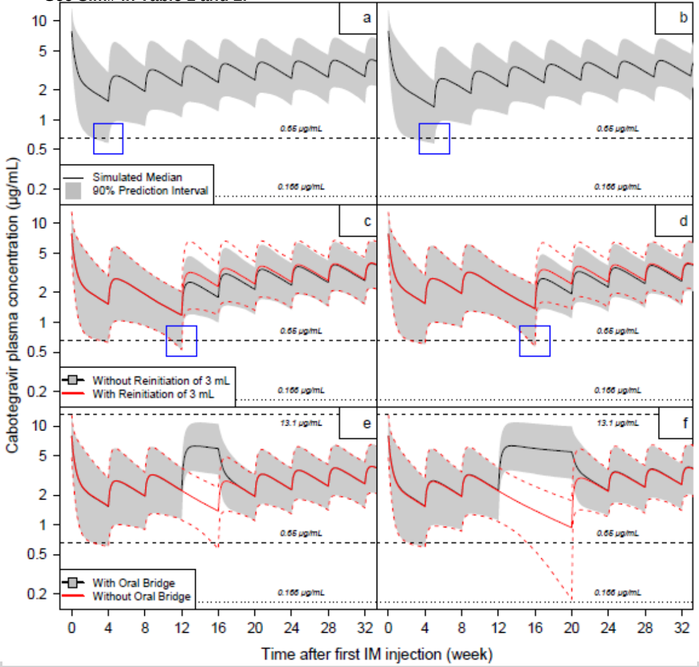


**Table 3. Proportion of Subjects (%) with Plasma CAB Trough Concentration >0.65 µg/mL (target 95%)**

| DI | Weeks Delayed | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 12 |
| 2nd | 93 | 92 | 90 | 88 | 81 | 61 | 38 | 10 |
| 3rd | 98 | 98 | 97 | 94 | 91 | 79 | 65 | 35 |
| 4th | 99 | 99 | 98 | 96 | 93 | 85 | 73 | 48 |

DI: delayed injection. Blue: tolerable delays. Gold: Recommend reload

- Tolerance:
  - Delay of ≤1 week of the 2nd LA dose (Figure 1b, Table 3)
  - More forgiveness in 3rd or later LA doses (Figure 1c and 1d)
- Reinitiating with a loading dose may further reduce the risk of underexposure for longer delays.
- Oral bridging of 1 to 2 months (Figures 1e and 1f) is predicted to result in adequate/safe exposures.
- Recommendations based on delays or interruptions of the 4th injection apply to those occurring later.

## Conclusions

- Dosing delays should be avoided
- Delays of ≤1 week provide similar exposures to the standard regimen.
- Oral bridging is predicted to provide therapeutic and safe exposures for planned interruptions in IM dosing.
- Considering clinical practicality and simplicity, recommendations for resumption of CAB LA along with RPV LA following an unplanned or planned (oral bridging) interruption of any dose in CAB LA treatments are the same:
  - resuming CAB LA dosing of 400 mg (2 mL) for interruptions of <1 month (<2 months between injections)
  - reinitiating CAB LA with a loading dose of 600 mg (3 mL) and subsequent monthly injections of 400 mg (2 mL) for interruptions of ≥1 month (≥2 months between injections).

**References**

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