PEMOB029

Selection of Cabotegravir Dosing Regimens For HIV Treatment and Pre-Exposure Prophylaxis (PrEP) in Adolescents by Leveraging Adult Data

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Key Takeaways

- **Population pharmacokinetic (PPK) modeling was used to support data extrapolation from adults to adolescents to bridge cabotegravir (CAB) oral and long-acting (LA) dosing regimens for both treatment and prevention of HIV.**
- **The adult PPK model adequately predicted CAB oral and every 4 week (Q4W) exposure in the eight adolescents in the MOCHA study.**
- **The consistency of adolescent and adult pharmacokinetics (PK) supports the use of adult CAB oral and Q4W and every 8 week (Q8W) LA dosing regimens in adolescents ≥12 years and ≥35 kg.**

Background

- CAB + rilpivirine is the first complete LA injectable regimen, administered Q4W or Q8W, approved for maintaining virological suppression in adults and adolescents living with HIV-1 (≥35 kg) in the United States.[1,2]
- CAB monotherapy for HIV pre-exposure prophylaxis (PrEP) administered every 2 months was recently approved for use in adults and adolescents (≥35 kg) in the US.[3]
- Poor adherence to daily oral regimens is common among adolescents,[4] and CAB LA may be suited to address contributing factors.
- CAB oral and LA PK were initially characterized in virologically suppressed adolescents (≥35 kg) receiving stable background combination antiretroviral therapy (Cohort 1C) in the ongoing IMPAACT 2017 (MOCHA) study (NCT03497676).[5]
- PPK modeling was used to support data extrapolation from adults to adolescents to bridge CAB oral and LA dosing regimens for both treatment and prevention of HIV-1.

Methods

- Interim PK data from Cohort 1C of the MOCHA study (eight adolescents) was compared with adult PK to establish similarities between the PK profiles and determine the feasibility of extrapolation.
- To simulate CAB PK in adolescents, a virtual population of 24,000 adolescents (aged 12–<18 years) with a male-to-female ratio of 1 was simulated using Simcyp™, from which 22,876 virtual adolescents were selected with a bodyweight of ≥35 kg.
- Adolescent CAB PK profiles following oral, Q4W, and Q8W dosing regimens were simulated in this virtual population (n=22,876) using a previously developed adult PPK model and compared with adult PK targets.
- CAB PK profiles are similar in participants with and without HIV infection based on the previous adult PPK analysis,[6]* and therefore the results of this analysis are applicable to treatment and PrEP of HIV.

*Based on 1647 adults who received CAB oral and LA dosing regimens, including Q4W and Q8W.

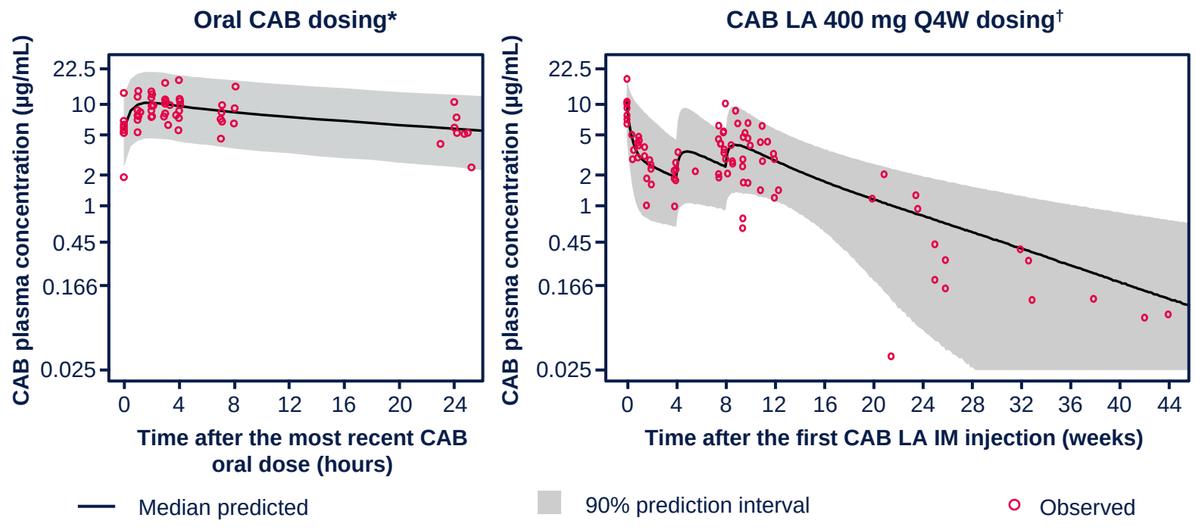
Table 1. Baseline Characteristics (MOCHA)

Parameter	Adolescents in the MOCHA study Cohort 1C (n=8)
Median age (range), years	14.5 (12–17)
Female (sex at birth), n (%)	2 (25)
Median weight (range), kg	57 (43–74)
Median BMI (range), kg/m^2	19.6 (16.4–27.2)

BMI, body mass index.

- Overall, eight adolescents (**Table 1**) living with HIV-1 from MOCHA contributed 153 CAB plasma concentrations following daily oral CAB 30 mg dosing and three intramuscular (IM) injections of CAB LA 4 weeks apart (600 mg for injection 1; 400 mg for the subsequent two injections).
- Baseline characteristics for the virtual adolescent population were broadly similar to the MOCHA study participants contributing PK data, except for the proportion of female (sex at birth) participants, which was higher in the virtual population (51%).

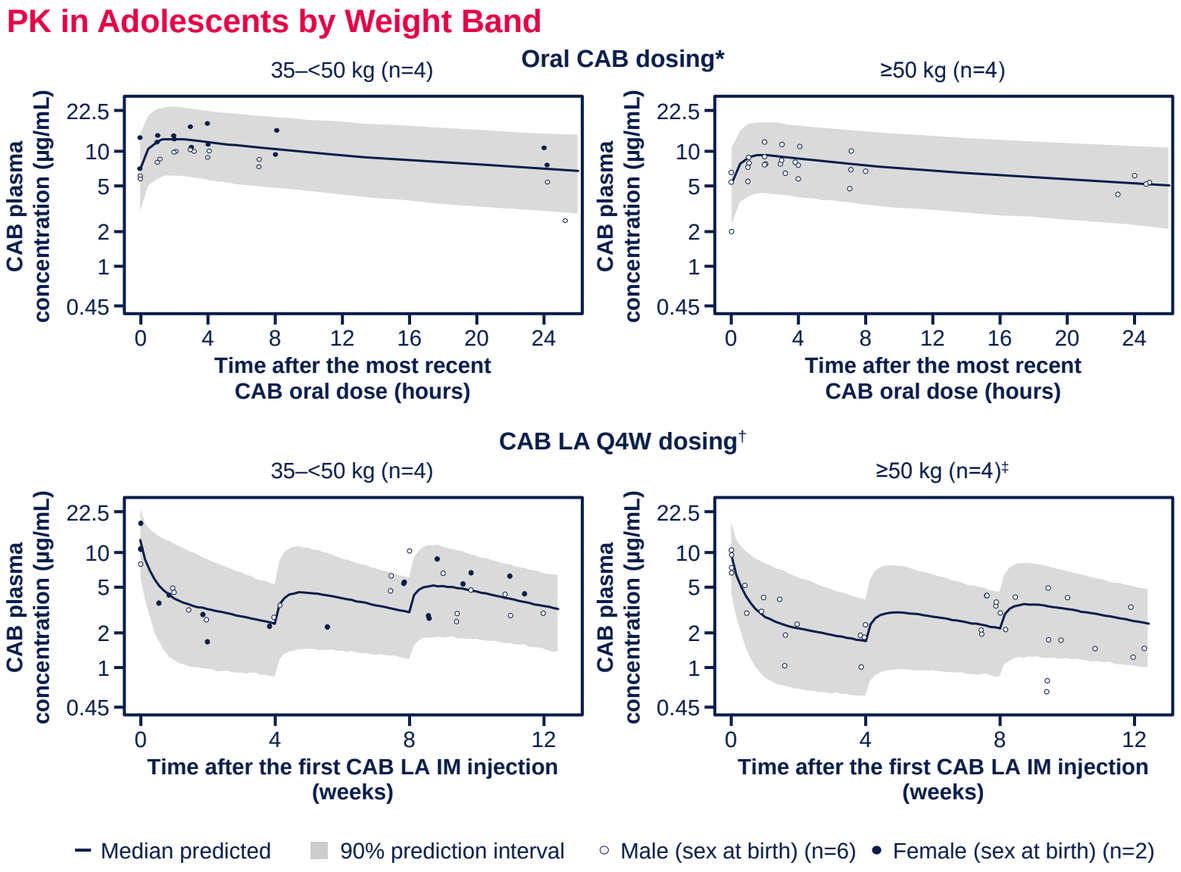
Figure 1. Comparison Between Observed and Simulated PK in Adolescents Following CAB Oral and LA Dosing



*Evaluated at steady state (14 days after first CAB 30 mg daily dose). †Three single IM injections of CAB LA 4 weeks apart (600 mg for the first injection and 400 mg for each of the two subsequent injections) following 30 mg daily oral lead-in for 4–6 weeks.
CAB, cabotegravir; IM, intramuscular; LA, long-acting; Q4W, every 4 weeks.

- The adult PPK model adequately predicted CAB daily oral and Q4W exposure in the eight adolescents in Cohort 1C of the MOCHA study (**Figure 1**).

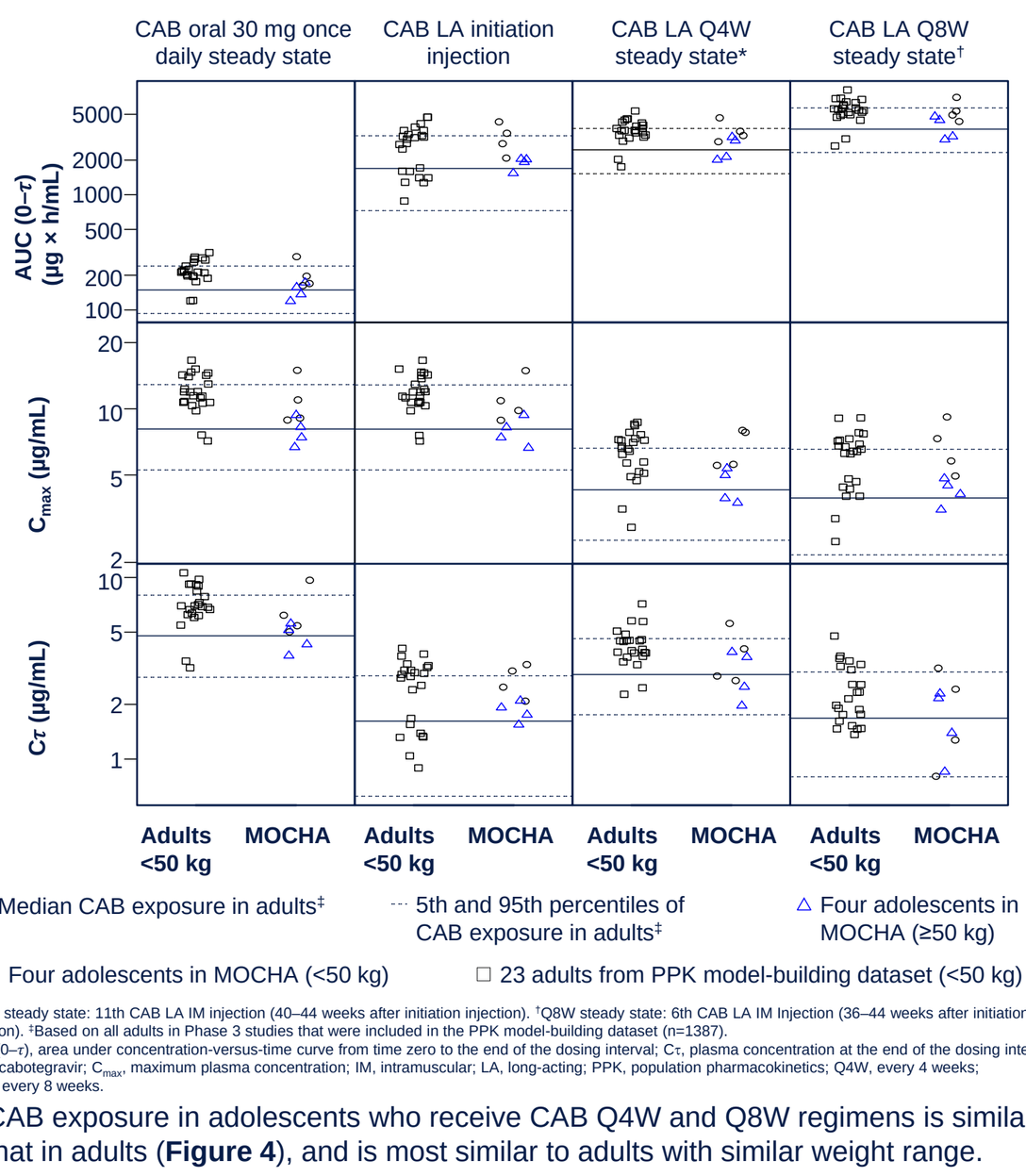
Figure 2. Comparison Between Observed and Simulated CAB Oral and LA PK in Adolescents by Weight Band



*Evaluated at steady state (14 days after first CAB 30 mg daily dose). †Truncated at 12 weeks after first injection for better data visualization. ‡Two CAB concentrations from one ≥50 kg participant were below the 90% prediction interval between 8 and 12 weeks, likely because this participant missed the second injection at Week 4 and delayed the third injection at Week 8.
CAB, cabotegravir; IM, intramuscular; LA, long-acting; PK, pharmacokinetics; Q4W, every 4 weeks.

- The adult PPK model adequately predicted CAB daily oral and Q4W exposure for the eight adolescents in Cohort 1C of the MOCHA study for both bodyweight ranges (35–<50 kg and ≥50 kg), and for both sexes (**Figure 2**).

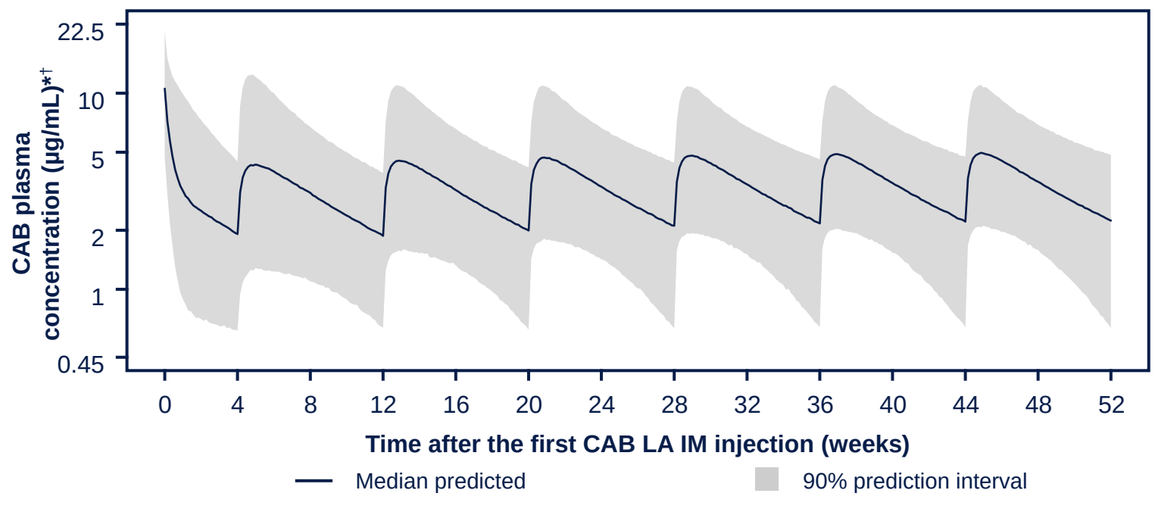
Figure 3. Comparison of CAB *Post-hoc* Exposure Between Adolescents in Cohort 1C of the MOCHA Study and Adults



*Q4W steady state: 11th CAB LA IM injection (40–44 weeks after initiation injection). †Q8W steady state: 6th CAB LA IM Injection (36–44 weeks after initiation injection). ‡Based on all adults in Phase 3 studies that were included in the PPK model-building dataset (n=1387).
AUC (0–τ), area under concentration-versus-time curve from time zero to the end of the dosing interval; Cτ, plasma concentration at the end of the dosing interval; CAB, cabotegravir; C_{max}, maximum plasma concentration; IM, intramuscular; LA, long-acting; PPK, population pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks.

- CAB exposure in adolescents who receive CAB Q4W and Q8W regimens is similar to that in adults (**Figure 4**), and is most similar to adults with similar weight range.
- The use of adult CAB oral and LA dosing regimens results in adequate PK for HIV treatment and PrEP in adolescents.

Figure 4. Simulated CAB Concentration-Versus-Time Profile Following Q8W Dosing in Adolescents ≥35 kg



*0.45 µg/mL=5th percentile of the observed CAB trough concentration following the initiation injection in adults in the Phase 3 Studies FLAIR (NCT02938520) and ATLAS (NCT02951052) studies. †22.5 µg/mL=geometric mean of CAB C_{max} observed at the supratherapeutic dose of oral CAB 150 mg (three doses in total, twice daily) in the adults in the thorough QT/QTc study, which is not associated with any toxicity but is the highest exposure observed in clinical studies.
CAB, cabotegravir; C_{max}, maximum plasma concentration; IM, intramuscular; LA, long-acting; Q8W, every 8 weeks.

- The predicted CAB concentrations remain above PK treatment benchmarks observed in adults and below safety thresholds (**Figure 4**).

Conclusions

- The observed adolescent PK data in the MOCHA study were similar to adult PK data.
- The adult PPK model was able to reliably describe CAB PK of the eight adolescents in the MOCHA study, demonstrated good performance for predicting CAB PK in adolescents, and allowed for dose extrapolation in adolescents for HIV treatment and PrEP.
- CAB Q4W and Q8W regimens were predicted to provide adequate CAB exposure in adolescents aged 12 to <18 years with a bodyweight of ≥35 kg.
- The consistency of adolescent and adult PK supports the use of adult CAB oral and Q4W and Q8W LA dosing regimens in adolescents ≥12 years and ≥35 kg.

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