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Physiologically based pharmacokinetic (PBPK) modelling of cabotegravir (CAB) to support design of microarray patches (MAPs) for the treatment of HIV positive children

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Objectives

- What doses of cabotegravir (CAB) should be administered via MAPs to achieve therapeutic target concentrations in plasma for HIV positive pediatrics from neonates to adolescents?
- What patch sizes are needed to administer the estimated doses, and are the patch sizes feasible for monthly dosing?

Background

Administration of anti-retroviral (ARV) drugs via MAPs has the potential to increase compliance and acceptability of HIV treatment for children. MAPs are easy to apply to the skin and can be administered by less skilled healthcare personnel or even caregivers as compared to intramuscular injections. MAPs may also be more acceptable than oral dosing, especially in young children. By adjusting the size based on weight, MAPs can be tunable for growing children and deposit a depot of medication to limit the frequency of administration.

CAB is an ARV drug, administered orally or intra-muscularly, and is inactivated in the body by UGT1A1 and UGT1A9[1,2].

PBPK modelling allows the integration of age-dependent anatomy, physiology, and enzyme ontogeny together with MAP release kinetics and CAB disposition.

Methods

A stepwise approach was used to develop CAB PBPK model using PK-Sim® (v9)[3] (Figure 1). Physicochemical properties, in vitro data and clinical observations were used to inform the CAB PBPK model in terms of absorption, distribution, and elimination. The elimination of CAB was attributed to UGT1A1 and UGT1A9 metabolism. Ontogeny and expression of UGT1A1 and UGT1A9 were obtained from the RT-PCR database available in PK-Sim®.

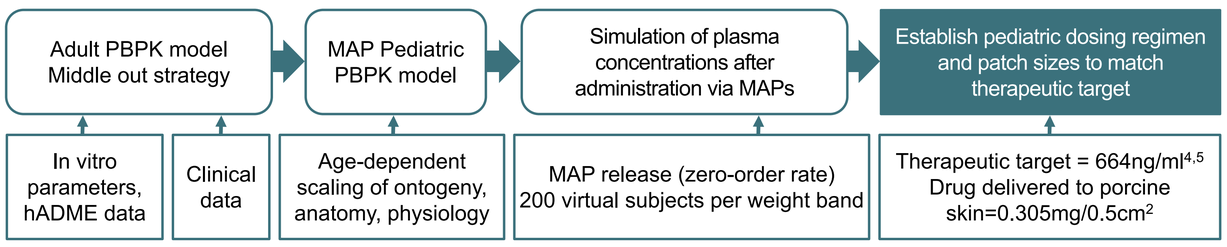

Figure 1. *Schematic overview of cabotegravir PBPK model development and application including source of information for respective sub-activity.*

Simulations with virtual populations were performed for all external datasets used for model development and qualification. Model performance was evaluated by comparing simulated with observed PK profiles and parameters.

The final CAB PBPK model was applied to simulate plasma concentrations in pediatric populations, from neonates to adolescents, after administration of CAB MAPs. Systemic drug input, i.e. drug release from MAPs and absorption from administration site, was described with zero-order kinetics. MAPs dosing regimens was established for a dosing interval of 1 month to achieve therapeutic target concentrations for 90% of the pediatric population in each weight band. The patch sizes and loaded doses were calculated based on the estimated effective dose needed to achieve therapeutic target, and the drug delivered into porcine skin from prototype MAPs and the drug loaded into MAPs. A maximum patch size of 20cm^2 was considered in the analysis.

References

1. European Medicines Agency, 2021, Vocabria:EPAR – Product information.
2. US Food and Drug Administration, 2019, Vocabria: FDA - PRODUCT QUALITY REVIEW(S).
3. Lippert J., et al., 2019, CPT Pharmacometrics Syst Pharmacol. 8(12): 878–882.
4. Trezza C., et al., 2015, Current Opinion in Hiv and Aids vol. 10(4): 239–245.
5. Spreen W., et al., 2013, HIV clinical trials vol. 14(5): 192–203.
6. Min S., et al., 2009, The Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco
7. Parasrampuria R., et al., 2019, Clinical pharmacology in drug development vol. 8(5): 674–681

Conclusions

- A PBPK model was developed and qualified for cabotegravir, and doses (8-54 mg) and corresponding patch sizes (14-88 cm^2) were estimated for monthly therapeutic delivery to HIV positive children.
- Reducing the estimated patch sizes by shifting to weekly administration may be necessary for acceptability and manufacturing feasibility for most pediatric age groups, except for neonates where monthly administration is feasible.

Results

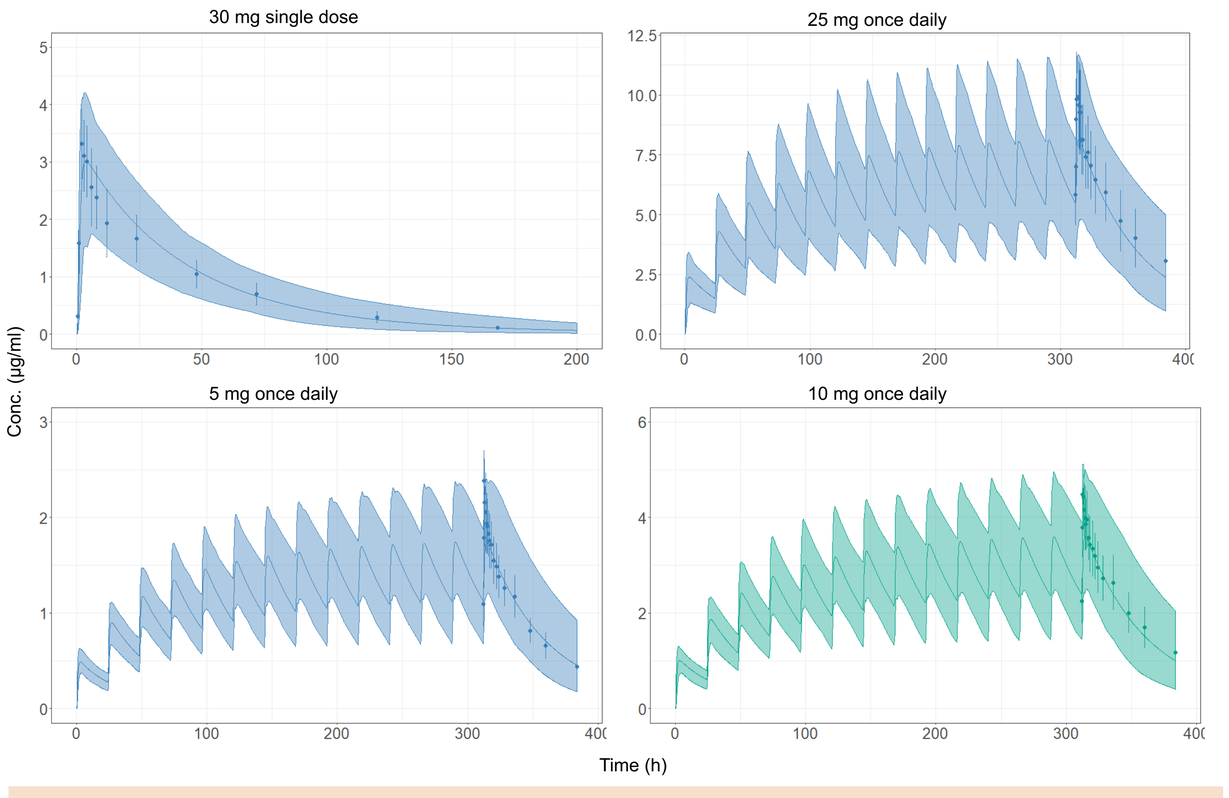

Figure 2. *Cabotegravir plasma concentration-time profiles after oral dosing for model development dataset (blue) and model qualification dataset (green). Observations are represented by dots [6,7]. Solid line and shaded area represent the simulated geometric mean and the 5-95% quantiles of the PBPK model for a virtual adult population (n=100).*

A PBPK model of CAB was established that could describe the available clinical data in adults (Figure 2). The in vitro measured capacity of recombinant UGT1A1 and UGT1A9 to metabolize CAB was used to inform the model on fraction metabolized by each enzyme. In addition, observed clinical data after multiple dosing suggested autoinhibition of metabolizing enzyme, thus this mechanism was included in the final PBPK model. Comparison of simulated and observed PK parameters for the model qualification data set demonstrated acceptable performance of the model as simulated-to-observed absolute average fold error was 1.23 for C_{max} and 1.08 for AUC.

Table 1. *Estimated effective doses, patch sizes and loaded doses for cabotegravir MAP for children in different weight bands.*

Weight band	Approximate age	Effective dose (mg)	Patch size (cm^2)	Loaded dose (mg)
3 to <6 kg	0 - 0.5 years	8.43	13.8	29.9
6 to <10 kg	0.5 - 1 years	18.2	29.8	64.3
10 to < 14 kg	1 - 3 years	27.4	44.9	97.0
14 to <20 kg	3 - 6 years	35.2	57.6	124
20 to <25 kg	6 - 8 years	45.0	73.8	159
25 to <35 kg	8 - 12 years	53.7	88.1	190

The PBPK model was used to estimate MAP sizes for pediatric populations in different weight bands by adopting age-dependent changes in anatomy, physiology, and enzyme ontogeny. The estimated sizes of the drug-loaded area of the MAP ranged from 14 to 88 cm^2, under the assumption that the drug release follows zero-order kinetics (Table 1).

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