Paper No. 18

Utilization of Physiologically Based Pharmacokinetic Modelling (PBPK) to predict the effect of UGT enzyme inhibition and induction on the systemic exposure of Cabotegravir

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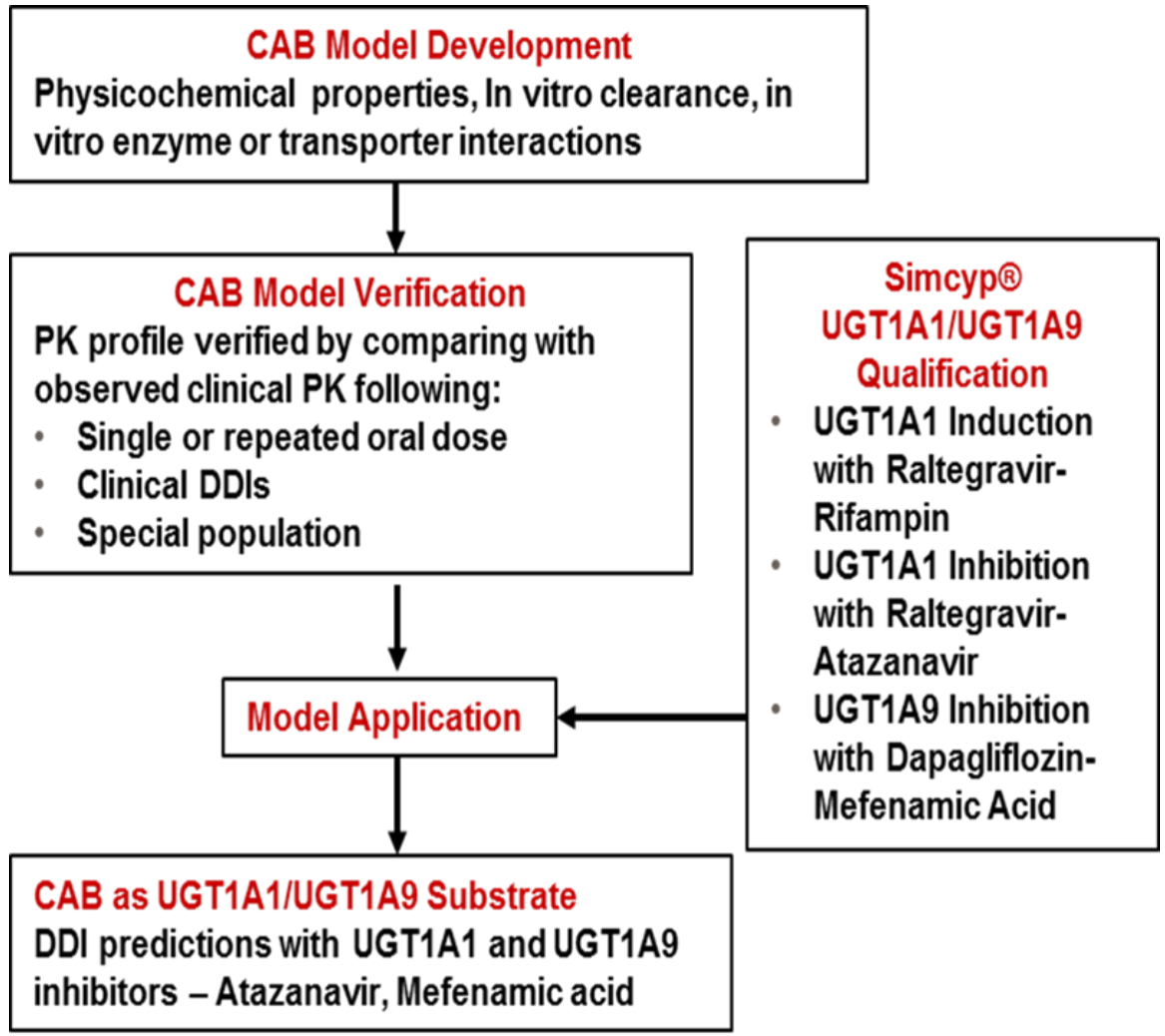
Disclosure

- Aarti Patel is a full time employee of GlaxoSmithKline

Introduction and PBPK Strategy

- Cabotegravir (CAB) is an HIV integrase inhibitor in development for HIV treatment for monthly administration as part of a combination dual therapy regimen with rilpivirine, and as monotherapy for HIV prevention.
- CAB undergoes glucuronidation via UGT1A1 with a minor contribution from UGT1A9.
- In HIV/TB coinfection, co-administration with anti-TB agents, rifampin or rifabutin, may be required. Rifampin is a potent UGT inducer and reduced oral plasma CAB exposure by 59% in the clinic. Reduction of only 21% was observed with rifabutin which is a weak UGT inducer.
- UGT inhibition effects on CAB exposure have not been clinically investigated.
- A physiologically based pharmacokinetic (PBPK) model of CAB was developed and verified to prospectively assess the impact of potent UGT inhibition by atazanavir (1A1) or mefenamic acid (1A9), and of a weak UGT1A1 inducer, phenobarbital.

Workflow for CAB PBPK Model Development, Verification, Application and Software Qualification

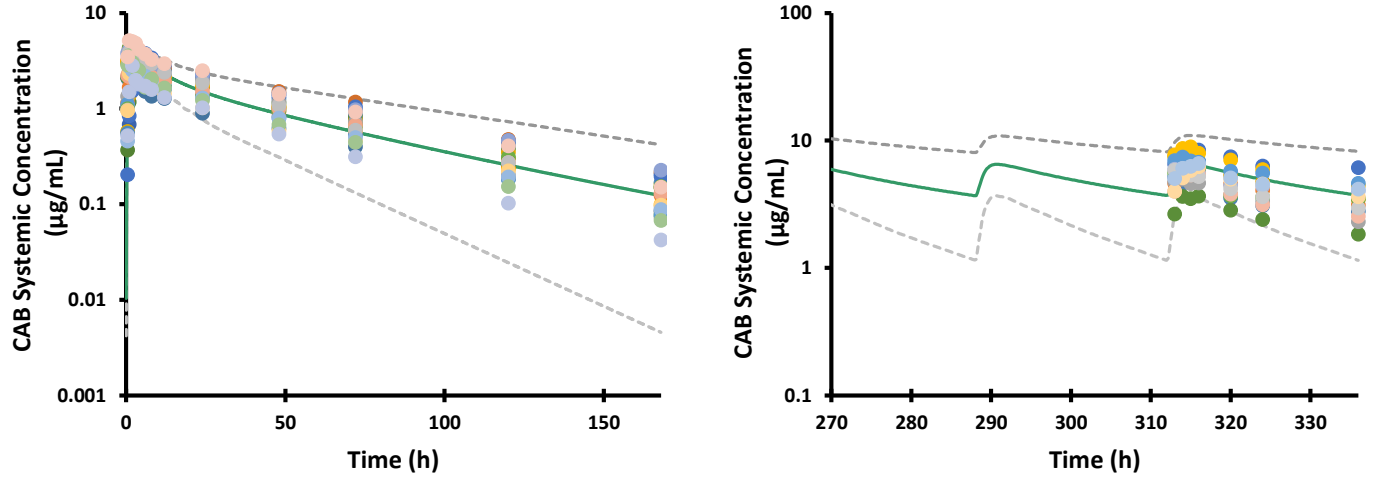


CAB Model Development, Verification and Software Qualification

Key Input parameters for CAB PBPK Model in Simcyp®v17

Parameter	Value	Source
Molecular Weight	405.4	Measured value
Log P	1.58	Measured value
pKa	7.71	Measured value
Fraction unbound in plasma (Fu)	0.006	Measured value from clinical and *in vitro* investigations.
Papp (10^{-6} cm/s)	25.6	Measured value (MDCK)
Vss (L/Kg)	0.12	Predicted by Simcyp® (Method 2)
Clearance – Enzymatic CL_{int} (µL/min/mg)	UGT1A1 – 4.5 UGT1A9 – 2.2	Measured value from *in vitro* investigations

Simulated and Observed CAB Plasma Profiles Following Single and Repeat 30 mg CAB Oral Dose



Solid Line – Simulated Mean CAB Plasma Profile; Dotted Lines – Simulated 5th-95th percentile; Dots – Observed Individual CAB Plasma profiles.

- CAB PBPK model was verified and deemed suitable for prospective DDI simulations as
  - Simulated CAB PK profiles were within 25 % of observed clinical PK parameters following single and repeat oral CAB 30mg administration qualifying the model as sensitive for predicting clinical DDIs..
  - Simulated PK profiles were further comparable to data in healthy and patient populations from clinical studies, including rifampin DDI, renal impairment, and individuals with UGT1A1 polymorphisms.
  - Similar CAB concentrations following oral and LA administration support extrapolation of predictions to CAB LA.
- Simulated PK parameters for UGT1A1 and UGT1A9 known inhibitor/inducer and substrate pairs (Rifampin, Atazanavir, Raltegravir, Dapagliflozin, Mefenamic acid) were comparable to the observed clinical DDIs qualifying the software for UGT DDI predictions.

Model Application and Conclusion

Predictions using CAB PBPK Model

Substrate – Inhibitor/Inducer DDI Enzyme	CAB AUC Ratio* Geometric Mean (5th-95th percentile) Predicted	CAB Cmax Ratio* Geometric Mean (5th-95th percentile) Predicted
Cabotegravir – Atazanavir UGT1A1 Inhibition	1.11 (1.04, 1.20)	1.02 (1.01, 1.04)
Cabotegravir – Mefenamic Acid UGT1A9 Inhibition	1.10 (1.04, 1.18)	1.02 (1.01, 1.03)
Cabotegravir – Phenobarbital UGT1A1 Induction	0.71 (0.46, 0.93)	0.97 (0.92. 0.99)

* AUC and Cmax Ratio of CAB with and without UGT inhibitor or inducer

- DDI simulations predicted a mean 11 and 10 % increase in plasma oral CAB exposure when co-administered with UGT1A1 and UGT1A9 inhibitors (atazanavir or mefenamic acid) respectively, and was within bioequivalence criteria for PO and LA CAB.
- DDI simulations with phenobarbital predicted a mean <30% decrease in oral CAB exposure, comparable to observed clinical rifabutin data and were well within the studied exposures for PO and LA CAB in the clinic.

Conclusions

- A PBPK model of oral CAB was developed and validated to accurately predict human pharmacokinetics and the impact of potential DDIs on oral and LA exposure.
- DDI simulations predicted minimal effects on CAB exposure from potent inhibitors of UGT1A1 or UGT1A9 suggesting no restrictions being required with this class of inhibitor.
- Clinical DDI data and PBPK simulations indicated that the impact of UGT inducers on CAB exposure was proportional to their *in vitro* induction potency. These data suggested that co-medication exclusions may not be required for weak and moderate inducers.