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.
CAB Model Development, Verification and Software Qualification

Key Input parameters for CAB PBPK Model in Simcyp®v17

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
<td>405.4</td>
<td>Measured value</td>
</tr>
<tr>
<td>Log P</td>
<td>1.58</td>
<td>Measured value</td>
</tr>
<tr>
<td>pKa</td>
<td>7.71</td>
<td>Measured value</td>
</tr>
<tr>
<td>Fraction unbound in plasma (Fu)</td>
<td>0.006</td>
<td>Measured value from clinical and in vitro investigations.</td>
</tr>
<tr>
<td>Papp (10^-6 cm/s)</td>
<td>25.6</td>
<td>Measured value (MDCK)</td>
</tr>
<tr>
<td>Vss (L/Kg)</td>
<td>0.12</td>
<td>Predicted by Simcyp® (Method 2)</td>
</tr>
<tr>
<td>Clearance – Enzymatic CL_int (µL/min/mg)</td>
<td></td>
<td>Measured value from in vitro investigations.</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>UGT1A9</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
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Simulated and Observed CAB Plasma Profiles Following Single and Repeat 30 mg CAB Oral Dose

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.
## Predictions using CAB PBPK Model

<table>
<thead>
<tr>
<th>Substrate – Inhibitor/Inducer</th>
<th>CAB AUC Ratio*</th>
<th>CAB Cmax Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDI Enzyme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB AUC Ratio*</td>
<td>Geometric Mean (5th-95th percentile)</td>
<td>Geometric Mean (5th-95th percentile)</td>
</tr>
<tr>
<td>Predicted</td>
<td>Predicted</td>
<td></td>
</tr>
</tbody>
</table>

### Cabotegravir – Atazanavir
- UGT1A1 Inhibition
  - Predicted: 1.11 (1.04, 1.20)
  - Predicted: 1.02 (1.01, 1.04)

### Cabotegravir – Mefenamic Acid
- UGT1A9 Inhibition
  - Predicted: 1.10 (1.04, 1.18)
  - Predicted: 1.02 (1.01, 1.03)

### Cabotegravir – Phenobarbital
- UGT1A1 Induction
  - Predicted: 0.71 (0.46, 0.93)
  - Predicted: 0.97 (0.92, 0.99)

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### 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.**

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* 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.