Population pharmacokinetics of rifapentine and its active metabolite in healthy volunteers: nonlinearities in clearance and bioavailability

*Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA*
Rifapentine

• Rifapentine (RPT): potent new drug that may help shorten TB treatment duration

• FDA-approved dose 600 mg twice weekly (intensive phase), 600 mg once weekly (continuation phase) too low

• In mouse model, daily RPT-containing regimen can shorten treatment duration to 2-3 months
Rifapentine dose optimization

- TBTC Study 29: two-month culture conversion similar for 10 mg/kg of RPT and RIF
- TBTC Study 29B: less than dose-proportional increases in exposure with increase in dose & time-dependent PK
- We performed nonlinear mixed effects (NLME) modeling of TBTC Study 29B data to evaluate:
  - Autoinduction and its relationship to dose
  - Drug/metabolite relationships
  - Absorption and clearance kinetics/saturability and relationship to dose
TBTC Study 29B Design

- Healthy volunteers were enrolled in Tuberculosis Trials Consortium Study 29B
  - RPT 5, 10, 15, or 20 mg/kg daily for 14 days with food (n=22)
  - RPT sampling at predose, 0.5, 1, 2, 4, 5, 8, 12, 24 (48, 72) hours after 1st and 14th dose (plus troughs)
  - Quantified using LCMS/MS

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Modeling Strategy & Methodology

Strategy:

• Develop a model for RPT
  – Evaluate different models for absorption
  – Understand bioavailability
  – Compare single dose PK with multiple dose PK
  – Understand changes in CL over time
• Develop a joint model for RPT and its metabolite

Methodology:

  – Nonlinear mixed effects (NONMEM 7)
  – FOCE method with interaction
## Simple empirical exercise

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose cohort (mg/kg)</th>
<th>MODEL I</th>
<th></th>
<th>MODEL II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OFV=8770</td>
<td>OFV=8732</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Single dose</td>
<td>Relative bioavailability</td>
<td>1</td>
<td>1.08</td>
<td>0.83</td>
</tr>
<tr>
<td>Multiple dose</td>
<td></td>
<td>0.82</td>
<td>0.94</td>
<td>0.65</td>
</tr>
<tr>
<td>Single dose</td>
<td>CL/F (L/h)</td>
<td>2.12</td>
<td>2.26</td>
<td>1.53</td>
</tr>
<tr>
<td>Multiple dose</td>
<td></td>
<td>2.76</td>
<td>2.74</td>
<td>2.21</td>
</tr>
</tbody>
</table>

- **Bioavailability**
  - Lower bioavailability at higher doses
  - Lower bioavailability after multiple doses compared to after a single dose

- **Clearance**
  - Increased clearance after multiple doses compared to after a single dose
  - No effect of dose on clearance

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Major findings (I)

- From single dose data - Relative bioavailability decreases with dose
- Linear decrease with dose
- However, minimum is not reached at total daily dose of 1800 mg
Major findings (II)

- Single dose data do not predict multiple dose data well
  - indicating autoinduction is present
Major findings (III):

- CL is increasing over time
- It does not reach saturation in 2 weeks
- Time course of autoinduction is, thus, hard to characterize
Now, adding the metabolite: Rifapentine-desRPT model
Visual predictive check, final model

Day 1

Day 14
What have we learned from this exercise?

• Bioavailability of RPT decreases with dose (2.5% decrease with each 100 mg increase in dose)

• Significant auto-induction and increase in CL (2-fold) for both parent and metabolite with multiple dosing

• Steady state is not reached by 14 days
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