Population pharmacokinetics and bacterial dynamics of sutezolid in patients with active tuberculosis

Kajal B. Larson¹, Kun Wang¹,², Lisa Beth Ferstenberg³, Carol Nacy³ and Edward P. Acosta¹

¹Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, Alabama
²Center for Drug Clinical Research, Shanghai University of Chinese Medicine, China
³Sequella, Inc
Pipeline of TB drugs

Discovery

Lead optimization

Diarylquinolines

InhA inhibitors

LeuRS inhibitors

Mycobacterial gyrase inhibitors

Pyrazinamide analogues

Riminophenazines

Ruthenium (II) complexes

Spectinamides

Translocase 1 inhibitors

Preclinical development

Preclinical development

CPZEN-45

DC-159a

Q201

SPR-10199

SQ609

SQ641

BTZ043

TBA-354

GLP toxicology

AZD5847

Bedaquiline (TMC207)

Linezolid

Novel regimens

PA-824

Rifapentine

SQ109

Sutezolid (PNU-100480)

Clinical development

Phase I

Delamanid (OPC67683)

Gatifloxacin

Moxifloxacin

Rifapentine

Phase II

Phase III

Chemical classes

- Fluoroquinolone
- Rifamycin
- Oxazolidinone
- Nitroimidazole
- Diarylquinoline
- Benzothiazinone
Oxazolidinone family

• Linezolid
  • Has activity against DR TB
  • Optic neuropathy, myelosuppresion

• Sutezolid (PNU-100480)
  • More potent than linezolid in murine models
  • Safe and well-tolerated in healthy human volunteers
  • Active metabolite: PNU-101603
    • Median plasma concentration is ~7 times higher than parent*

Sutezolid Clinical Studies

- Study B1171001
  - Phase 1, single ascending doses, healthy volunteers, fasted/fed (35-1500 mg)
- Study B1171002
  - Phase 1, placebo-controlled, multiple ascending doses, healthy volunteers (100, 300, 600 mg BID, 1200 mg QD)
- Study B1171003
  - Phase 2a, open-label, randomized, treatment-naïve sputum smear positive subjects with drug-sensitive pulmonary TB to assess early bactericidal activity (EBA) and whole blood activity (WBA); 600 mg BID, 1200 mg QD
Question

• What is the optimal sutezolid dose and dosing interval when administered as a single agent?
  • Second look at the EBA, WBA, and parent and metabolite concentration-time data collected in the B1171003 study
Methods

- Fifty treatment-naïve adults, sputum smear positive with drug sensitive TB
  - 14-day monotherapy
  - 25 received sutezolid at 600 mg BID
  - 25 received sutezolid at 1200 mg QD
- Patient demographics:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sutezolid 600 mg BID</th>
<th>Sutezolid 1200 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>32.3 ± 9.0</td>
<td>34.1 ± 11.7</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Race (Black/other)</td>
<td>11/14</td>
<td>8/17</td>
</tr>
<tr>
<td>BMI (kg/m², mean ± SD)</td>
<td>19.6 ± 2.9</td>
<td>18.3 ± 1.8</td>
</tr>
</tbody>
</table>
Methods

- Drug concentration measured by HPLC-MS/MS
- Sputum was collected for CFU counts
- Blood was also collected for WBA
- ADAPT 5 (MLEM algorithm) was used to
  - Develop a population pharmacokinetic model to describe the drug (parent and metabolite) concentrations
  - Link the PK model to bacterial dynamic model
PK model

Parent

\[ V_p/F \]

\[ Q/F \]

\[ k_a \]

\[ 2 \text{ gut} \]

\[ T_{lag} \]

\[ 1 \]

\[ V_c/F \]

\[ (1-fa)*CL/F \]

\[ fa*CL/F \]

\[ 3 \]

\[ V_p/F \]

\[ 4 \]

\[ V_m/f_m \]

\[ CL_m/f_m \]

\[ 5 \]

\[ k_{45} \]

\[ k_{54} \]

\[ \text{Metabolite} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (%RSE)</th>
<th>IIV CV% (%RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_t (L/h)</td>
<td>165 (5.33)</td>
<td>27.8 (16.8)</td>
</tr>
<tr>
<td>V_c/F (L)</td>
<td>162 (20.3)</td>
<td>71.1 (26.2)</td>
</tr>
<tr>
<td>Q/F (L/h)</td>
<td>32.4 (8.65)</td>
<td>14.8 (131)</td>
</tr>
<tr>
<td>K_a (1/h)</td>
<td>0.876 (7.23)</td>
<td>6.38 (210)</td>
</tr>
<tr>
<td>V_p/F (L)</td>
<td>258 (10.4)</td>
<td>33 (41.6)</td>
</tr>
<tr>
<td>T_{lag} (h)</td>
<td>0.846 (3.39)</td>
<td>10.7 (32.8)</td>
</tr>
<tr>
<td>CL_m/F_m (L/h)</td>
<td>17.5 (68.8)</td>
<td>16.5 (81.3)</td>
</tr>
<tr>
<td>V_m/F_m (L)</td>
<td>0.157 (92)</td>
<td>15.6 (193)</td>
</tr>
<tr>
<td>K_{45} (1/h)</td>
<td>59.4 (62.1)</td>
<td>3.68 (2520)</td>
</tr>
<tr>
<td>K_{54} (1/h)</td>
<td>0.347 (12.2)</td>
<td>26.5 (58.4)</td>
</tr>
<tr>
<td>fa</td>
<td>0.562 (67.5)</td>
<td>1.93 (2130)</td>
</tr>
</tbody>
</table>

\[ t_{1/2}-parent \] 6.72 hrs
\[ t_{1/2}-metabolite \] 5.71 hrs
PK Model Visual Predictive Check

dose=1200 mg QD

0  2  4  6  8  10  12
Time hr

0  2  4  6  8  10  12
Time hr

0  2  4  6  8  10  12
Time hr

0  2  4  6  8  10  12
Time hr

dose= 600 mg BID

0  2  4  6  8  10  12
Time hr

0  2  4  6  8  10  12
Time hr

0  2  4  6  8  10  12
Time hr

0  2  4  6  8  10  12
Time hr
PK model linked to bacterial model

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<tr>
<th>Parameter</th>
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<th>IIV CV% (%RSE)</th>
</tr>
</thead>
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<tr>
<td>EC$_{50}$ (mg/L)</td>
<td>0.02 (105)</td>
<td>63.6 (174)</td>
</tr>
<tr>
<td>k$_{death}$ (day$^{-1}$)</td>
<td>0.0281 (19.4)</td>
<td>31 (31.5)</td>
</tr>
<tr>
<td>k$_{growth}$ (day$^{-1}$)</td>
<td>0.0133</td>
<td>Fixed</td>
</tr>
<tr>
<td>B$_{max}$ (CFU/mL)</td>
<td>$10^9$</td>
<td>Fixed</td>
</tr>
</tbody>
</table>
Bacterial Model Goodness of Fit

![Graph showing standard residuals vs. time (hrs) and sputum individual predictions vs. observations.](image-url)
Dose-Response Simulation of Linked PK/Bacterial Model

• Simulation studies were conducted to explore exposure–response relationships using population mean parameters of the linked PK/Bacterial Model.

• Simulated doses ranged from 20 to 2000 mg twice daily (100 different doses).

• The pharmacodynamic determinant of response was the decrease in the time-averaged area under the \( \log_{10} \) sputum–time curve from 0 to 14 days minus baseline (AAUCMB).

• Simulated doses were linked to the bacterial model to calculate corresponding changes in AAUCMB and to determine the dose required to produce the \( EC_{50}, EC_{80}, EC_{85}, EC_{90}, \) and \( EC_{95} \) of the maximum drug effect (\( E_{\text{max}} \)).
Exposure–relationship curve

- The exposure–response relationship of dose and the decrease in AAUCMB was fitted using the following Emax model:

\[
\text{Decrease in AAUCMB} = E_0 + \frac{(E_{\text{max}}-E_0)\cdot\text{Dose}}{E_{C50}+\text{Dose}}
\]

\[\begin{align*}
E_{\text{max}} &= 1.1 \\
E_0 &= -0.6 \\
E_{C50} &= 167 \text{ mg} \\
E_{C80} &= 667 \text{ mg} \\
E_{C85} &= 945 \text{ mg} \\
E_{C90} &= 1501 \text{ mg} \\
E_{C95} &= 3168 \text{ mg}
\end{align*}\]
<table>
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<tr>
<th>Parameter</th>
<th>EBA AAUCMB (BID, mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>167</td>
</tr>
<tr>
<td>EC&lt;sub&gt;80&lt;/sub&gt;</td>
<td>667</td>
</tr>
<tr>
<td>EC&lt;sub&gt;85&lt;/sub&gt;</td>
<td>945</td>
</tr>
<tr>
<td>EC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>1501</td>
</tr>
<tr>
<td>EC&lt;sub&gt;95&lt;/sub&gt;</td>
<td>3168</td>
</tr>
</tbody>
</table>
Conclusions

• It is believed that U-480 is most active against intracellular TB and U-603 is more active against extracellular TB
• Our model linked the parent drug to EBA activity; future work will consider the metabolite model
  • It is very difficult to extract individual drug effects when both parent and metabolite are inherently present
• Our modeling and simulation exercises suggest a sutezolid dose of 1000 mg BID as a center point for further dose-ranging trials in patients
• Sutezolid and linezolid are structurally similar
  • Concern for mitochondrial protein synthesis toxicity
    • high exposures and longer duration