PNU-100480 (sutezolid)
Update

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Pfizer
Sutezolid: Preclinical and Clinical

• Preclinical
  – Superior bactericidal activity vs. LZD regardless of LZD dose
  – Earlier sterilization (1-2) with standard drugs
• Phase 1: SAD, MAD
  – Doses to 600 mg BID reasonably well absorbed and tolerated to 28d
  – No safety signals, incl. hematology
  – Superior bactericidal activity \textit{ex vivo} in whole blood culture (WBA) regardless of LZD dose or concentration
  – Killing linked to T > MIC
• Phase 2: EBA trial (nearly complete)
  – Sutezolid 600 mg BID, 1200 mg QD, HREZ
  – 14 days, Sputum (CFU and TTP) and WBA endpoints
  – Goal is to show activity in lung and assist in dose selection
Innovative development strategy

• Universal regimen
  – No cross-resistance to current TB drugs (excl. FQs, PZA)
  – Effective in DS, M/XDR-TB, HIV-TB

• Parallel studies in DS and M/XDR-TB
  – Larger DS-TB trial to inform M/XDR

• Adaptive licensing based on 2-month sputum culture
  – Also described as accelerated or provisional licensing
  – Initially in M/XDR, HIV-TB, later in DS-TB

• Global TB outcome registry during adaptive licensing
  – Report safety and effectiveness outcomes
Candidates for universal regimen

concentration-activity relationship in whole blood culture

[Graph showing concentration-activity relationship for SQ109, PA-824, Bedaquiline, and Sutezolid]
**UJ: additive whole blood culture**

### A Combined bactericidal activity ($\Delta \log/d$)

<table>
<thead>
<tr>
<th>TMC207 mg/L</th>
<th>0</th>
<th>0.1</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.216</td>
<td>-0.442</td>
<td>-0.664</td>
<td>-0.642</td>
</tr>
<tr>
<td>0.5</td>
<td>-0.129</td>
<td>-0.502</td>
<td>-0.884</td>
<td>-0.897</td>
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<tr>
<td>1.5</td>
<td>-0.327</td>
<td>-0.778</td>
<td>-0.973</td>
<td>-1.133</td>
</tr>
<tr>
<td>3</td>
<td>-0.472</td>
<td>-0.715</td>
<td>-1.036</td>
<td>-1.150</td>
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</tbody>
</table>

### Difference from sum of individual activities

<table>
<thead>
<tr>
<th>TMC207 mg/L</th>
<th>0</th>
<th>0.1</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.069</td>
<td>-0.091</td>
<td>-0.125</td>
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<tr>
<td>0.5</td>
<td>-0.010</td>
<td>0.017</td>
<td>-0.164</td>
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<tr>
<td>1.5</td>
<td>0.199</td>
<td>0.099</td>
<td>-0.035</td>
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</tr>
<tr>
<td>3</td>
<td></td>
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</tbody>
</table>

mean = -0.004±0.116

P = 0.912
Activity of novel combinations

<table>
<thead>
<tr>
<th>Drug combo</th>
<th>Overall effect</th>
<th>Difference from sum</th>
<th>P</th>
<th>Predicted cWBA at standard doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>USq</td>
<td>additive</td>
<td>-0.017</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>UJ</td>
<td>additive</td>
<td>-0.004</td>
<td>0.9</td>
<td>-0.41</td>
</tr>
<tr>
<td>JPa</td>
<td>&lt; additive</td>
<td>0.179</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>UPa</td>
<td>≤ additive</td>
<td>0.628</td>
<td>0.2</td>
<td>-0.34</td>
</tr>
<tr>
<td>UJPa</td>
<td>antagonistic</td>
<td>0.493</td>
<td>0.03</td>
<td>0</td>
</tr>
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</table>
Nitroimidazole antagonism: NO?

• In hypoxic, non-replicating cultures, nitroimidazoles-derived NO poisons the respiratory chain, resulting in depletion of ATP
  – Combinations of nitroimidazoles and TMC207 may be less than fully additive if they share a common mechanism of action.
• Whole blood cultures (and likely most in vivo conditions) are neither hypoxic nor fully replicating
• Under non-hypoxic conditions, NO triggers a dormancy response in Mtb through activation of DosR
  – This may reduce the activity of other drugs
• Nitroimidazoles are unlikely to become part of a UJ-containing universal regimen
Adaptive licensing based on 2-mo culture status

![Diagram showing treatment effect over time for DS-TB and M/XDR-TB with new regimen and registry indicated]
Summary

• Early clinical findings support superior efficacy and safety of sutezolid vs. linezolid
• Combinations including sutezolid, bedaquiline, SQ109 appear likely as candidates for a new universal regimen
• Innovative development strategies for sustainable TB drug development can enhance value to patients, physicians, and sponsors, yet address regulatory concerns regarding the approval of medicines that are safe and effective
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