SPR720: Novel Oral Therapy for Non-tuberculous Mycobacterial (NTM) Infections

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Non-Tuberculous Mycobacteria (NTM): A Rare Chronic Infectious Disease

Progressive lung disease
Infection caused by environmental pathogen
Common in COPD, bronchiectasis, asthma, and CF

Increasing Prevalence
50,000-100,000 patients in U.S. suffer from NTM
8% annual increase in prevalence predicted year-over-year in the U.S.

Significant Unmet Need
5-yr mortality rate of 35%
No currently approved oral agents for NTM
SOC has limited efficacy, high toxicity

• NTMfacts.com
**SPR720: Key Differentiating Factors**

- **Novel chemical class:** aminobenzimidazole
  - SPR720 is phosphate prodrug of the active parent SPR719
- **Mechanism-of-Action:** Gyrase inhibitor, not a fluoroquinolone
  - Inhibits ATPase subunits in Gyrase (GyrB) and Topoisomerase IV (ParE)
  - Target in mycobacteria is GyrB
- **No cross-resistance** with marketed antibiotics

**DNA Gyrase**
Primarily responsible for introducing negative supercoils into conformationally constrained DNA during bacterial DNA replication.
## In vitro Activity Against a Range of NTM Species

<table>
<thead>
<tr>
<th>NTM Species</th>
<th>N</th>
<th>SPR719 MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>SPR719 MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MIC ranges: standard of care agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AMK</td>
<td>CIP</td>
<td>CLR</td>
</tr>
<tr>
<td><strong>M. abscessus subsp. abscessus</strong></td>
<td>30</td>
<td>2</td>
<td>4</td>
<td>2 - 64</td>
</tr>
<tr>
<td><strong>M. abscessus subsp. massiliense</strong></td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>4 - 16</td>
</tr>
<tr>
<td><strong>M. chelonae</strong></td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>16 - 32</td>
</tr>
<tr>
<td><strong>M. immunogenenum</strong></td>
<td>10</td>
<td>4</td>
<td>8</td>
<td>8 - 16</td>
</tr>
<tr>
<td><strong>M. fortuitum group</strong></td>
<td>10</td>
<td>0.25</td>
<td>1</td>
<td>≤1</td>
</tr>
<tr>
<td><strong>M. avium complex</strong></td>
<td>41</td>
<td>0.5</td>
<td>2</td>
<td>8 - &gt;64</td>
</tr>
<tr>
<td><strong>M. simiae</strong></td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>8 - 32</td>
</tr>
</tbody>
</table>

Barbara Brown-Elliott at UT-Tyler, Texas, USA 2018; MIC values in μg/mL; ND = not determined

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<th>NTM Species</th>
<th>N</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>MBC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M. abscessus subsp. abscessus</strong></td>
<td>29</td>
<td>2</td>
<td>8</td>
<td>&gt;32 (static)</td>
</tr>
<tr>
<td><strong>M. avium complex</strong></td>
<td>12</td>
<td>1</td>
<td>2</td>
<td>&gt;32 (static for M. avium)</td>
</tr>
<tr>
<td><strong>M. kansasii</strong></td>
<td>10</td>
<td>&lt;0.03</td>
<td>0.06</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

Jakko van Ingen at Radboud University, Nijmegen, Netherlands 2018; MIC/MBC values in μg/mL

*SPR719 is the active parent of SPR720 and is used for in vitro testing


AMK: Amikacin  
CIP: Ciprofloxacin  
CLR: Clarithromycin  
MINO: Minocycline  
FOX: Cefoxitin
SPR720: Effective as Monotherapy & Combination Therapy in *M. abscessus* Murine Model of Infection

Controls

<table>
<thead>
<tr>
<th>Test Article</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPR719</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin</td>
<td>2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

Data from the lab of Diane Ordway (CSU).

- *M. abscessus* 1513
- SCID mice treated daily starting on day 28 for a total of 28 days (chronic model)

CLR: Clarithromycin
AMK: Amikacin
CFZ: Clofazimine
SPR720: Non-Clinical Data Supports Clinical Evaluation

• SPR720 converts rapidly to SPR719
• CYP inhibition IC$_{50}$ s >40 µM; no time or concentration dependent inhibition

• In vitro safety assessments predict no major issues
• hERG IC$_{50}$ > 30 µM; non-cytotoxic; non-genotoxic: in silico, Ames, chromosome aberration, in vivo micronucleus negative

• Repeat dose GLP 28-day rat and NHP toxicity studies completed
• Rat NOAEL = 100 mg/kg/day; NHP NOAEL = 300 mg/kg/day

• Exposures at the NOAEL provide a therapeutic index relative to the efficacious exposure using M. abscessus murine models
SPR720-101: Phase 1 SAD/MAD Study (Ongoing)

A Two-part, Randomized, Double-blind, Placebo-controlled, Phase I Study of the Safety, Tolerability and Pharmacokinetics of SPR720 Following Administration of Single and Multiple Ascending Oral Doses in Healthy Volunteers

- Objectives: Safety, Tolerability, PK (including Food Effect), TQT
- Single Center (Simbec, UK)
- Healthy volunteers, male and female (non-childbearing): 18-55 yo
- 8 Single Ascending Dose (SAD) Cohorts including 1 Food Effect Cohort
- 3 Multiple Ascending Dose (MAD) Cohorts (7-days duration)
- 88 subjects (planned); 3:1 randomization (n = 8/cohort: 6 SPR720, 2 placebo)
- Continuous Holter monitoring incorporated for downstream TQT analysis
Learn more about the Spero pipeline

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