BAY 73-7388, a novel aminomethylcycline, exhibits potent efficacy in pulmonary murine models of infection

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Objective: With the emergence of resistance to currently available antibiotics in the treatment of infectious diseases, the development of novel antibiotic classes has become of major importance. BAY 73-7388 is the first aminomethylcycline antibacterial agent and is characterised by potent activity in vitro against sensitive and multi-antibiotic resistant Gram-positive, Gram-negative and atypical bacteria. We have evaluated BAY 73-7388 in several murine pulmonary infection models with a range of pathogens in both neutropenic (Neut) and immunocompetent (IC) mice.

Methods: BAY 73-7388 and reference antibiotics were evaluated in acute, systemic lethal infections caused by multi-resistant (res) and susceptible (sus) Streptococcus pneumoniae (Spn); acute, lethal pulmonary Spn infection in Neut mice; chronic Spn lung model in IC mice; and chronic Haemophilus influenzae (Hflu) infection model in IC mice. In each infection BAY 73-7388 and other antibiotics were administered i.v.

Results: PD50 (survival) and ED50 (bacterial burden) results for BAY 73-7388 and comparators, vancomycin (VAN), linezolid (LIN), ciprofloxacin (CIP), azithromycin (AZI) and doxycycline (DOX) against sus and res strains of Spn and Hflu (sus), are detailed in the table below.

<table>
<thead>
<tr>
<th>Efficacy (mg/kg)</th>
<th>In Vivo model</th>
<th>BAY 73-7388</th>
<th>AZI</th>
<th>CIP</th>
<th>LIN</th>
<th>VAN</th>
<th>DOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, systemic Spn, IC(sus) (PD50)</td>
<td>0.09</td>
<td>2.2</td>
<td>&gt;5</td>
<td>3.5</td>
<td>1.4</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Acute, systemic Spn, Neut (res) (PD50)</td>
<td>0.14</td>
<td>18.9</td>
<td>21.3</td>
<td>7.1</td>
<td>0.14</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>Chronic Spn, IC (ED50)</td>
<td>7.4</td>
<td>5.1</td>
<td>&gt;5</td>
<td>&gt;4</td>
<td>&gt;40</td>
<td>31.6</td>
<td></td>
</tr>
<tr>
<td>Chronic Hflu, IC (ED50)</td>
<td>4.7</td>
<td>31.6</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Acute, pulmonary Spn, Neut (PD50)</td>
<td>11.0</td>
<td>7.5</td>
<td>31.6</td>
<td>&gt;4</td>
<td>7.2</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>Acute, pulmonary Spn, Neut (res) (PD50)</td>
<td>8.5</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>&gt;4</td>
<td>5.4</td>
<td>&gt;50</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions: Overall, BAY 73-7388 performed as well or better than the currently available therapeutic agents in all the models investigated in this study.

(BAY 73-7388 was discovered by Paratek Pharmaceuticals Inc., Boston, MA, and designated PTK 0796.)
**Abstract**

**Objectives**

With the emergence of resistance to currently available antibiotics in the treatment of infectious diseases, the development of novel antibiotic classes has become of major importance. BAY 73-7388 is a first aminomethylcycline antibacterial agent and is characterized by potent activity in vitro against sensitive and multi-resistant resistant gram-positive, gram-negative, and anaerobic bacteria. We have evaluated BAY 73-7388 in several murine pulmonary infection models with a range of pathogens in both neutropenic (Neut) and immunocompetent (IC) mice.

**Methods**

BAY 73-7388 and reference antibiotics were evaluated in acute, systemic lethal infections caused by multiresistant (res) and susceptible (sus) Streptococcus pneumoniae (SPn); acute, lethal pulmonary SPn infection in Neut mice; chronic SPn lung model in IC mice; and chronic Haemophilus influenzae (HFlu) infection model in IC mice. In each infection, BAY 73-7388 and other antibiotics were administered IV.

**Results**

PD50 (survival) and ED50 (bacterial burden) results for BAY 73-7388 and comparators, vancomycin (VAN), linezolid (LZD), ciprofloxacin (CIP), azithromycin (AZI), and doxycycline (DOX) against susceptible and resistant strains of SPn and HFlu (sus) are detailed in the table below.

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**Introduction**

Streptococcus pneumoniae and Haemophilus influenzae are important causes of upper and lower respiratory tract infections. Indeed, S. pneumoniae remains the most frequently isolated organism in community-acquired pneumonia and continues to cause significant mortality.

The prevalence of multidrug resistance among these pathogens is increasing.

BAY 73-7388 is a novel aminomethylcycline active against gram-positive, gram-negative, and anaerobic, and atypical bacteria, including those resistant to currently available classes of antibiotics.

This study investigated the efficacy of BAY 73-7388 in pulmonary models of infections caused by S. pneumoniae and H. influenzae.

**Characteristics of BAY 73-7388**

- Structure: 7-dimethylaminocyclo(2,3-dimethylpyrrol)aminomethylcycline
- Highly active against resistant gram-positive and gram-negative pathogens in vitro
- MIC50 for S. pneumoniae is 0.125 mg/L (range, 0.06-0.25 mg/L)
- MBC50 for H. influenzae is 2.0 mg/L (range, 0.5-8.0 mg/L)

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