**INTRODUCTION**

Staphylococcus aureus and Escherichia coli are leading causes of bacteremia often associated with serious complications. Nabriва’s ESP program is developing a new generation of pleuromutilin antibiotics with the target to extend the conventional pleuromutilin spectrum (Gram-positive, fastidious Gram-negative and atypical pathogens), to a broader Gram-negative spectrum, primarily Enterobacteriaceae, addressing a significant unmet medical need.

Following in vitro efficacy testing, selected ESP were evaluated in two in vivo efficacy models to assess activity compared to the control antibiotics linezolid and tigecycline. The selected EPS presented here were tested together with control antibiotics in mice suffering from a lethal sepsis induced by Staphylococcus aureus or Escherichia coli.

**METHODS**

**Bacterial isolates**

The minimal inhibitory concentrations (MIC) were determined by CLSI broth microdilution method.

**In vivo efficacy**

The in vivo antibacterial activity of the ESP, linezolid, and tigecycline against bloodstream infections was determined in two murine sepsis infection models in immuno-competent mice.

**RESULTS**

- All tested ESP showed good in vitro and in vivo efficacy against S. aureus induced sepsis when compared to the standard antibiotics linezolid and tigecycline (Table 1).
- Linezolid and tigecycline tested against S. aureus showed ED$_{50}$ values of 10.3 mg/kg/day and 0.99 mg/kg/day, respectively.
- BC-9514 showed with 0.12 mg/kg/day the lowest ED$_{50}$ dose of all tested compounds in the sepsis model caused by S. aureus.

**Table 2. Antibacterial activity and in vivo efficacy of ESP and tigecycline against E. coli ATCC 25922**

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC [mg/L]</th>
<th>ED$_{50}$ [mg/kg/day]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC-9505</td>
<td>≤0.03</td>
<td>0.36</td>
</tr>
<tr>
<td>BC-9514</td>
<td>0.015</td>
<td>2.08</td>
</tr>
<tr>
<td>BC-9520</td>
<td>0.06</td>
<td>0.47</td>
</tr>
<tr>
<td>BC-9529</td>
<td>≤0.015</td>
<td>10.3</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.25</td>
<td>2.15</td>
</tr>
</tbody>
</table>

**RESULTS continued**

- In the murine sepsis model caused by the E. coli the ED$_{50}$ values of the presented ESP ranged between 3.17 to 16.5 mg/kg/day (Table 2).
- Tigecycline showed an ED$_{50}$ of 2.15 mg/kg/day against E. coli.
- BC-9529 and BC-9514 showed with ED$_{50}$ values of 3.75 and 3.17 mg/kg against E. coli induced sepsis, respectively, similar efficacy as tigecycline.

**CONCLUSIONS**

- The extended spectrum pleuromutilins tested demonstrated excellent efficacy against severe murine septicemia caused by S. aureus and E. coli.
- Activity of the tested ESP against sepsis caused by S. aureus and E. coli was comparable to that of standard antibiotics linezolid or tigecycline.
- Based on the data presented above, ESP will be further investigated in vivo efficacy models including initial pre-clinical PK/PD studies.

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