Microbiological Activity and Outcome of the Pleuromutilin BC-3781 in a Clinical Phase 2 Trial In Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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ABSTRACT

Background: The novel pleuromutilin antibiotic BC-3781 has completed the first clinical phase 2 trial in patients with severe ABSSSI caused by Gram-positive (G+) pathogens. We present the antibacterial in vitro activity of BC-3781 and comparisons against the collected isolates and the microbiological responses in patients treated with BC-3781 (100 and 150 mg) i.v. in comparison to vancomycin (VAN, 1 g q12h) in comparison to vancomycin (VAN, 1 g q12h).

Methods: Susceptibility testing of BC-3781, VAN and other antibiotics was performed by broth microdilution according to CLSI guidelines. All S. aureus were evaluated for the presence of PVL. PFGE typing was performed for all MRSA.

Results: MIC50/90 was 0.03-0.06 µg/ml against 99.1% of S. aureus. BC-3781 displayed very good antibacterial activity in vitro with a 52.9% resistance rate among S. aureus (0.12-0.25 µg/ml). Against Staphylococcus spp. BC-3781 showed MIC50 of 0.03-0.06 µg/ml (VAN MIC50, 0.5-8 µg/ml). No resistance development was observed for BC-3781 in VAN during the study.

Conclusions: BC-3781 demonstrated very good activity with overall microbiological eradication rates of 80.0% and 84.3% (modified intent-to-treat population) at doses of 100 mg and 150 mg correlating well with the clinical success rates. For MRSA in particular, eradication rates were 82.4% and 87.5% (100 and 150 mg). These were comparable with VAN with eradication rates of 82.4% and 82.5%.

MATERIALS & METHODS

Table 1. MIC 50/90 [µg/ml] of BC-3781 and Comparators Against Key Microbiological Activity and Outcome of the Pleuromutilin BC-3781 in a Clinical Phase 2 Trial In Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Comparator</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
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<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>BC-3781</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>VAN</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>BC-3781</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>VAN</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>BC-3781</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>VAN</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>BC-3781</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>VAN</td>
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<td>8</td>
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</tbody>
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The clinical phase 2 trial was a multi-center, double-blind, parallel-group study involving 210 patients. The microbiological outcome was assessed at test of cure (TOC; 7-14 days post end of treatment) for the modified intent to treat (MITT) and the microbiological evaluable (ME) populations. The MITT population was defined as (n = 193), who had a documented Gram-positive baseline pathogen culture at baseline. The ME population was defined as (n = 129) with a confirmed diagnosis of ABSSSI who had received at least 50% of the study antibiotic and had a positive pathogen culture at baseline. The ME population was defined as (n = 129) with a confirmed diagnosis of ABSSSI who had received at least 50% of the study antibiotic and had a positive pathogen culture at baseline. The ME population was defined as (n = 129) with a confirmed diagnosis of ABSSSI who had received at least 50% of the study antibiotic and had a positive pathogen culture at baseline.

RESULTS

Baseline Infection Characteristics

- The baseline infection characteristics of the clinically evaluable and microbiologically evaluable in this clinical trial reflecting its excellent antibacterial activity in vitro.

- INTRODUCTION

- Acute bacterial skin and skin structure infections (ABSSSI) are characterized by a wide range of disease presentations including wound infection, cellulitis, erysipelas, cutaneous abscesses and burn infections. The majority of these infections are caused by Gram-positive bacteria such as Staphylococcus aureus including methicillin-resistant Staphylococcus aureus (MRSA), and the Gram-negative Haemophilus influenzae and Streptococcus pyogenes. Resistance development to current systemic antibiotic agents constantly increases the medical need for new agents overcoming the problem of resistant pathogens.

- BC-3781 is a novel semi-synthetic pleuromutilin antibiotic acting like pleuromutilin, a well-known broad-spectrum antimicrobial agent that transfers content of the large ribosomal subunit thereby inhibiting protein synthesis. In vitro, BC-3781 demonstrated potent activity against Staphylococcus spp., Streptococcus spp., Enterococcus faecium, H. influenzae and S. pyogenes including multi-resistant strains. It is therefore being developed for treatment of ABSSSI and community-acquired bacterial pneumonia (CAP) as an intravenous switch therapy.

- The study presents the microbiological results of the clinical phase 2 trial in patients with severe ABSSSI caused by Gram-positive pathogens treated with 100 or 150 mg i.v. BC-3781 for 5-14 days in comparison to vancomycin (VAN, 1 g, q12h).

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Microbiological and Clinical Outcome

- BC-3781 100 mg and 150 mg demonstrated consistently high efficacy rates across a wide range of microbiological and clinical outcomes at several time points including TOC (7-14 days post completion of therapy).

- Microbiological eradication and clinical success rates at TOC for the MITT and ME population for all pathogens, S. aureus, and separately MRSA are summarised in Table 2.

- Overall, the clinical success rates for BC-3781 100 mg at TOC by baseline pathogen were with 90.0% and 88.9% (CE) similar to those for the vancomycin group (92.2%). Similarly, clinical success rates for the MITT population were 82.0% and 84.2% for BC-3781 100 mg and 150 mg, respectively again similar to that of vancomycin (82.4%).

- BC-3781 displayed microbiological eradication rates of 80.0% and 84.3% at doses of 100 mg and 150 mg, respectively (MITT) and 84.0% and 97.1%, respectively, for MRSA (82.4%) and 97.1% PVL positive; 68.9% USA300), 4.5% S. agalactiae 100% of the USA100-1100 using a >80% cutoff for relatedness.


- The results of this clinical phase 2 trial provide the first proof of concept for the systemic use of a pleuromutilin antibiotic for the treatment of ABSSSI and support the continued clinical evaluation of BC-3781 in serious infections.

SELECTED REFERENCES


