**ABSTRACT**

Background: BC-3781, a novel pleuromutilin, is being developed for the treatment of acute bacterial infections such as skin and skin structure infections and pneumonia. BC-3781 shows excellent antimicrobial activity against relevant bacteria including methicillin-resistant Staphylococcus aureus (MRSA). Reported here are the results of an age and gender study conducted to support transition of BC-3781 to a patient population.

Methods: This single-centre, double-blind, randomized, placebo-controlled, cross-over study investigated the safety, tolerability and pharmacokinetics (PK) of BC-3781 administered to 12 healthy males and 12 healthy females aged 18-55 years and to 12 healthy elderly subjects ≥65 years. Subjects received 150 mg BC-3781 and placebo at separate sessions as single intravenous infusions over 60 minutes. Vital signs, laboratory safety parameters, adverse events and ECG were recorded and samples taken for PK.

Results: No adverse events of clinical concern nor clinically significant changes in vital signs and safety laboratory parameters were reported in any subject. BC-3781 was well tolerated but some signs of local intolerance were observed after BC-3781 and placebo administration. The plasma concentration curve showed a multi-Phase decline. Irrespective of age or gender of subjects, no significant differences in the pharmacokinetic parameters could be observed between the groups. BC-3781 is well distributed; the volume of distribution was large and tended to be slightly greater in the subjects aged ≥65 years. Covariate analysis indicated no effect of body weight, height and body mass index on any of the PK parameters.

The urinary excretion of unchanged BC-3781 was low, <1%. No major effect of age or gender on the renal excretion of BC-3781 could be detected.

Conclusions: BC-3781 was well tolerated in all groups and showed comparable PK irrespective of age or gender. These results indicate that no dosing adjustment is needed for subjects of different age and gender.

**INTRODUCTION**

BC-3781 is a semi-synthetic pleuromutilin derivative and a new representative of a new class of antibiotics for systemic use in humans which is being targeted for approval as an alternative to existing antibiotics. The present study evaluates the safety, tolerability and pharmacokinetics in healthy adult males, females and elderly subjects aged 18-55 years and 65 years.

BC-3781 interferes with bacterial protein synthesis by binding to the peptidyltransferase center of the 50S subunit of ribosomes. The uniqueness of this mechanism implies the lack of cross-resistance with other antibiotic classes. BC-3781 can be dosed either orally or intravenously. Reported here is a study examining the pharmacokinetics of BC-3781 in three different populations: males, females and the elderly.

**MATERIALS & METHODS**

**Primary objectives:**
- To assess the safety and tolerability of a single dose of BC-3781 when administered as a single intravenous infusion in male and female subjects aged 18 to 55 years and in elderly subjects ≥ 65 years.
- To assess local tolerability at the site of infusion.
- To derive the pharmacokinetics of BC-3781 when administered as a single IV infusion in male and female subjects aged 18 to 55 years and in elderly subjects ≥ 65 years.
- To assess local tolerability at the site of infusion.

**Secondary objectives:**
- Single-center, double-blind, randomized, placebo-controlled, cross-over study evaluated the safety, tolerability and pharmacokinetics (PK) of BC-3781 administered to 12 healthy males and 12 healthy females aged 18-55 years and to 12 healthy elderly subjects ≥65 years. Subjects received 150 mg BC-3781 and placebo at separate sessions as single intravenous infusions over 60 minutes. Vital signs, laboratory safety parameters, adverse events and ECG were recorded and samples taken for PK.

**RESULTS**

**Pharmacokinetics:**
- Blood samples for PK: 0, 15, 30, 60, 120, 240 and 36 hours post infusion start.
- BC-3781 concentrations in plasma and urine were determined using validated LC-MS/MS assays.
- The limits of quantification (LOQ) were 1.00 and 0.10 ng/mL in plasma and urine, respectively.
- For the pharmacokinetic evaluation, pre-dose values below the LOQ were set to zero.
- Non-compartmental pharmacokinetic analysis was performed using Professional Workbench Version 5.2.1 (Pharsight Corporation, Mountain View, CA, USA).

**Safety and tolerability:**
- Vital signs.
- ECG at 3 timepoints at each study session.
- Clinical biochemistry and hematology.
- Adverse events.
- Local signs at site of infusion.

**Safety and tolerability:**
- BC-3781 was safe and well tolerated. There were no changes in vital signs and safety laboratory parameters. BC-3781 was well tolerated in all groups and showed comparable PK irrespective of age or gender.
- The pharmacokinetic variables of BC-3781 were similar in males, females and elderly subjects.
- No major effect of gender on the renal excretion of BC-3781.
- BC-3781 interferes with bacterial protein synthesis by binding to the peptidyltransferase center of the 50S subunit of ribosomes. The uniqueness of this mechanism implies the lack of cross-resistance with other antibiotic classes. BC-3781 can be dosed either orally or intravenously.

**CONCLUSIONS**

- No significant age or gender related differences in PK parameters were found in this study.
- The pharmacokinetic variables of BC-3781 were similar in male and female subjects and young and elderly.
- The renal excretion of BC-3781 was low (<1%) and without any major effect of age or gender.
- BC-3781 was well tolerated in all groups.
- The number of AEs was similar after placebo and BC-3781 infusion and were self-limiting.
- There were no clinically meaningful treatment emergent abnormalities or changes from baseline in any safety parameter.
- No dose adjustment of BC-3781 is required because of age or gender.

**Table 3.** All reported possibly or probably related Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo</th>
<th>Male</th>
<th>Female</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

**Figure 1.** BC-3781 plasma concentration time curve in young and elderly subjects

**Figure 2.** BC-3781 plasma concentration time curve in female and male subjects

**Figure 3.** BC-3781 plasma concentration time curve in young, female and elderly subjects