**In Vivo Pharmacodynamic Activity of BC-3781**

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**Background:** BC-3781 is an antireceptor antibiotic of the pleuromutilin class, inhibiting the prolylreptokinase protein synthesis. BC-3781 is in clinical development for intravenous and oral treatment of skin and skin structure infections (SSSI) and community-acquired pneumonia (CAP). We examined the pharmacodynamics of BC-3781 against clinical isolates of Staphylococcus aureus, which are part of the predominant SSSI pathogens. The activity of BC-3781 against various strains of S. aureus and S. pneumoniae was evaluated against various gram-positive strains, including hospital acquired and community acquired strains. The pharmacodynamics of BC-3781 was similar for all S. aureus strains showing a good fit in vitro - in vivo correlation (MIC-static dose relationship). The total AUC/MIC values for each dose were calculated based on the PK parameters of infected mice and normalized over the free fraction, as determined in vitro experiments using equilibrium dialysis method. The individual efficacy of corresponding 24 h AUC/MIC ratios of eight S. aureus strains out of four studies, the sigmoid curve fit of mean and CI95 are depicted in Figure 4. The 24 h AUC/MIC necessary to produce a net static effect against S. aureus was 11.5 with a 95% confidence interval band of 8.69-13.4.

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**S. aureus**

**S. pneumoniae**

**BC-3781**

**Normal - Lung**

**Normal - Thigh**

**Neutropenic - Lung**

**Neutropenic - Thigh**

**Starting Drugs**

**Clinical Studies:** The above studies have characterized the in vivo pharmacodynamic activity of BC-3781 against various strains of S. pneumoniae and S. aureus:

- The drug appears to exhibit time-dependent killing but also produces modest in vivo PAEs.
- The 24 h AUC/MIC and the T_eff are the PK/PD indices most important for efficacy.
- The magnitude of the 24 h AUC/MIC required for the various strains of S. aureus was 11.5 (CI95 % = 8.69-13.4).
- The drug was more potent (about 3-4 fold) in the lung compared to the thigh in both neutropenic and normal mice.
- The presence of white blood cells had only a slight effect in enhancing the activity of the drug.

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**References:**