Introduction and Purpose

BC-3781 is an investigational semi-synthetic pleuromutilin derivative. Pleuromutilins are macroline antibiotics with a unique mode of action and a broad spectrum of antimicrobial activity against Gram-positive cocci relevant for skin and skin structure infections and Gram-negative pathogens associated with community-acquired bacterial pneumonia. BC-3781 is being developed for the treatment of serious skin infections and bacterial pneumonia caused by Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, and other bacteria, including multi-drug resistant strains such as MRSA and Vancomycin resistant Enterococcus faecalis. BC-3781 is under development for treatment of acute bacterial skin and skin structure infections (ABSSSIs) and hospital treated community-acquired pneumonia (HCAP) with intravenous and oral dosing formulations.

Many drugs interact with CYP450 enzymes as substrates, inhibitors or inducers. Thus, we investigated whether BC-3781 could affect or might be affected by other CYP450 interacting drugs in order to prevent adverse drug reactions caused by drug-drug interactions by standard in vitro assays in two clinical drug interaction studies.

Methods

Interaction of BC-3781 with CYP450 enzymes was investigated by reaction phenotyping using human recombinant CYP450 enzymes. Inhibition and induction was investigated in vitro using microsomes and human hepatocytes. The in vitro interaction of BC-3781 on the pharmacokinetics (PK) of midazolam and the interaction of ketocazole on the PK of BC-3781 were investigated in two cross over phase I studies in healthy subjects.

Results

In vitro reaction phenotyping: BC-3781 was incubated in duplicates at a final concentration of 0.5 µM (0.25 µg/ml) for 60 min at 37 °C. The final CYP enzyme concentrations were between 10-50 pmol/ml respectively. In parallel, the robustness of the assay was confirmed by testing respective standard CYP substrates (positive controls).

CYP inhibition: The potential of BC-3781 to inhibit CYP enzymes was analyzed by determining IC₅₀ values using a uridine diphosphate (UDP) glucuronosyltransferase (UDPGT) activity assay. IC₅₀ determinations identified CYP3A as primary target of BC-3781 displaying an IC₅₀ value of 5.5 µM (2.79 µg/ml) for midazolam hydroxylation while testosterone hydroxylation was affected to a much lesser extent (IC₅₀ value > 300 µM (152 µg/ml)).

CYP induction: The potential of BC-3781 to induce CYP enzyme activities was confirmed by incubating human liver microsomes and human hepatocytes with BC-3781. Inhibition experiments were carried out at a final protein concentration of 0.5 µM (0.25 µg/ml) for 15 min at 37 °C using recommended standard substrates.

A clinical study investigating the effect of BC-3781 on midazolam PK in healthy subjects demonstrated a very weak inhibitor of CYP3A. The AUC of midazolam increased by 1.17 (CI 90% 0.82-1.67) while Cmax was increased by a factor of 1.04 (CI 90% 0.82-1.30) in the presence of BC-3781. Inhibition of CYP3A with ketocazole identified BC-3781 as a weak CYP3A inhibitor in vitro with geometric mean AUC ratio estimates of 1.29 (CI 90% 1.00-1.64) and 1.02 (CI 90% 0.86-1.19) before the weak CYP3A interaction threshold of 1.25 and within the no-effect range.

Conclusions: While BC-3781 did not induce CYP1A2 and 3A4 it could be demonstrated that BC-3781 serves as a CYP3A4 substrate and inhibitor in vitro. Two clinical drug interaction studies with BC-3781 showed that the PM of CYP3A is only marginally affected in the presence of ketocazole and only a weak inhibition of CYP3A4 was observed. Therefore, in vitro assay results were confirmed in vivo. The data obtained in both studies suggest that BC-3781 can be classified as having only a weak interaction with CYP3A4. In two clinical drug interaction studies with either CYP3A substrates or inhibitors in a clinical setting, these results suggest that no major CYP450 mediated drug-drug interactions are expected with BC-3781.