ABSTRACT

Background: BC-3781 is a pleuromutilin antibiotic, developed for the treatment of infections caused by multidrug-resistant Gram-negative bacteria. The recent updated FDA guidance for industry on developing drugs for ABSSSI infection (2011) recommends pharmacodynamic modeling (PD) to gain insight into the bactericidal activity of the drug. The Day 1 total-drug AUC_{0-24} value, which has been previously associated with BC-3781 efficacy, was evaluated in patients with BC who were treated with pleuromutilin in a single-blind, randomized, controlled study (ABSD101; NCT01465776). The Day 1 total-drug AUC_{0-24} is a well established PK index, and the Day 1 total-drug AUC_{0-24} was not always significant at the 0.05 level for each clinical endpoints in the multifaceted study. Therefore, we investigated whether clinical endpoints were associated with the AUC_{0-24} values from patients with 5 adverse events. We applied logistic regression models for dichotomous, continuous, and time-to-event endpoints to determine the relationship between BC-3781 Day 1 total-drug AUC_{0-24} and observed clinical endpoints.

Methods: Results from the previously published ABSD101 study were used for this analysis. Patients were enrolled in the ABSD101 study if they were 18 to 65 years old, clinically infected with BC resistant to ≥1 drug. The patients were randomized 1:1 to receive pleuromutilin (40 mg/kg q8h) or matched placebo. The study endpoints were a total of 32 predefined efficacy and safety endpoints, which included: clinical cure, and microbiological response at Day 1 and 20, with or without cure.

Results: Non-inferiority of the BMD: 70% confidence intervals for the ratio of the predicted to the observed microbiological response probability at Day 1 and 20 were less than 1.5 with BC-3781 (Table 1). The BMD analyses revealed that BC-3781 Day 1 total-drug AUC_{0-24} response AUC_{0-24} was associated with a decrease in wound size and an increase in success rate observed at Day 20 (Table 2).

Conclusions: Our results revealed that BC-3781 Day 1 total-drug AUC_{0-24} is significantly associated with clinical endpoints and microbiological response at Day 20. These results indicate a potential use of BC-3781 Day 1 total-drug AUC_{0-24} as a novel PD index for BC-3781 ABSSSI.