The objectives of these analyses were to refine a previously-developed population pharmacokinetic (PK) model using pooled IV and PO PK data from healthy subjects. A three-compartment model with nonlinear protein binding and two parallel first-order absorption processes was developed in a sequential manner: one for the fasted condition and one for the fed condition. Once an appropriate structural model was identified, a covariate model was developed using forward selection followed by a backward elimination procedure. The covariate analyses showed that a high fat/high calorie meal resulted in slower absorption rate compared to those under the fasted condition. The final population PK model provided precise and unbiased estimates of lefamulin plasma concentrations. As shown by the VPC plots in Figure 1, since the bulk of the observed data was within the prediction limits, the final model provided precise and unbiased estimates of lefamulin plasma exposure. The refined PPK model provided precise and unbiased fits to lefamulin PK data after IV and PO administration. The unbalanced OSS provided an acceptable prediction of the AUC0-24 value at steady-state, regardless of food status, with mean r2 values of 0.761 and 0.772 for simulated subjects dined under fed and fed conditions, respectively.

**INTRODUCTION**

Lefamulin is an anti-microbial agent from the pleuromutilin clade with in vivo activity against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and co-linear bacterial and skin structure infections (ABSSSI), including multi-drug resistant strains of Streptococcus pneumoniae (SP). The final population PK model for describing lefamulin after IV and PO administration is an essential step in the implementation of which in Phase 3 will allow for pharmacometric evaluations of the safety and efficacy of lefamulin. The unbalanced OSS provided an acceptable prediction of the AUC0-24 value at steady-state, regardless of food status, with mean r2 values of 0.761 and 0.772 for simulated subjects dined under fed and fed conditions, respectively.

**METHODS**

Data were obtained from Study NAB-BC-3781-1107 (Study 1107), a Phase 1, single-cohort, randomized, four-period crossover study that was carried out to assess the population PK model was developed in a sequential manner: one for the fasted condition and one for the fed condition. Once an appropriate structural model was identified, a covariate model was developed using forward selection followed by a backward elimination procedure. The covariate analyses showed that a high fat/high calorie meal resulted in slower absorption rate compared to those under the fasted condition. The final population PK model provided precise and unbiased estimates of lefamulin plasma concentrations. As shown by the VPC plots in Figure 1, since the bulk of the observed data was within the prediction limits, the final model provided precise and unbiased estimates of lefamulin plasma exposure. The refined PPK model provided precise and unbiased fits to lefamulin PK data after IV and PO administration. The unbalanced OSS provided an acceptable prediction of the AUC0-24 value at steady-state, regardless of food status, with mean r2 values of 0.761 and 0.772 for simulated subjects dined under fed and fed conditions, respectively.

**RESULTS**

The results of the OSS based on IV PK data and assessment of optimal PK sampling strategy are shown in Table 2. The model of the observed and simulated lefamulin IV PK data from fasted and fed healthy subjects, stratified by treatment arm, the sold white line and gray shaded area represent the median and the 90% confidence interval, respectively, based on the simulated data, while the circles represent the observed PK data from the Phase 1 healthy volunteers.

**CONCLUSIONS**

The unbalanced OSS provided an acceptable prediction of the AUC0-24 value at steady-state, regardless of food status, with mean r2 values of 0.761 and 0.772 for simulated subjects dined under fed and fed conditions, respectively.