S-649266 Modeling and Simulation for Prediction of Efficacy and Dose Optimization

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ABSTRACT (Revised)

Background: S-649266 is a novel parenteral siderophore carbapenem discovered by Shionogi & Co., Ltd with the potential to achieve efficacy against Gram-negative bacteria including carbapenem-resistant strains. The aim of this study is to develop a pharmacokinetic model which describes time courses of S-649266 concentrations in plasma and urine and to predict efficacy for optimizing dose regimen.

Methods: Plasma and urine concentration data of S-649266 following single (100 to 2000 mg) or multiple (1000 to 2000 mg, 4th dosing) intravenous infusion in phase I studies in Japan (15 healthy volunteers, 12 Japanese and 3 Caucasian subjects). 1248 points in plasma, 576 points in urine were used. The plasma and urine data were simultaneously fitted to 3-compartment nonlinear mixed effect model. The model revealed that time to peak drug concentration in plasma exceeded 2h after dosing and time to 90% oral bioavailability (AUC) reduction which was used as target value for clinical trials, was calculated by Monte Carlo simulation model. The model was validated in clinical trials with 2h 4th 100 mg intravenous infusion and 1h oral. Results: The model was well described plasma and urine concentration data. The predicted the probability of target attainment (P TA) was 0.77 4h with 2h 1h infusion. The predicted the predicted the 5th percentile of urine concentrations over 8 hours were > 100 μg/ml at 2h with 1h infusion.

Introductions: The simulations for the subject with normal renal function (conventional condition for S-649266 efficacy) predicted 4h 100 μg/ml would exist efficacy for the target pathogens of carbapenem-resistant Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii. 2h 100 μg/ml would maintain urine concentrations at the high level.

VPC supported the developed PK model and described plasma and urine concentration profile (Fig. 4, 5) with 4h 100 mg and 2h 100 mg, respectively. The predicted the probability of urine concentrations over 8 hours were > 100 μg/ml at 2h with 1h infusion (Fig. 6).

RESULTS:

The pharmacokinetic disposition model with a compartment model or each model was simulated the PK model. The predicted the 5th percentile of urine concentrations over 8 hours were > 100 μg/ml at 2h with 1h infusion.

REFERENCES: