Population Pharmacokinetics (PPK) of CEM-102 in Healthy Subjects.

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Background:

CEM-102, an oral antibiotic with activity against methicillin-resistant *Staphylococcus aureus*, is being developed for the treatment of complicated skin and skin structure infections. Using Phase 1 data, PPK analysis was conducted to characterize the disposition of CEM-102 with and without food.

Methods:

Healthy subjects (n = 69) enrolled in 3 Phase 1 clinical studies received 500 – 2200 mg of CEM-102 orally as either single or multiple doses, with or without food. Food effect was assessed after a single 500 mg dose in a crossover study with 14 subjects. Serial pharmacokinetic (PK) samples were collected and assayed for CEM-102 using LC/MS/MS. Candidate PPK models were fit to the data using the Monte Carlo parametric expectation maximization algorithm in S-ADAPT 1.56.

Results:

The final PPK model, comprised of 2 disposition compartments, described the PK of CEM-102 well (overall r^2 was 0.96 for individual and 0.84 for population fits). This model included an auto-inhibition of clearance by a hypothetical inhibition compartment. Mean total clearance was 1.36 L/h (39% CV for between subject variability). Maximum extent of inhibition of clearance by the effect of the inhibition compartment was 45.1% and the associated IC50 was 48.2 mg/L (37% CV). The slower rate of absorption for evening vs. morning doses and slower rate of absorption in the fed state was modeled by a slower gastric release. The bioavailable fraction of dose was ~17.2% lower in the fed compared to fasting state. Front-loaded dose regimens achieved steady-state more rapidly than regimens without front-loading.

Conclusions:

The saturable elimination of CEM-102 was best described by an auto-inhibition of clearance. Extent of bioavailability was ~17.2% lower in the fed than in the fasted state. The PPK model described herein, in combination with a mechanism-based PK-PD model, will allow for the prediction of the effectiveness of different CEM-102 dosing regimens.