Population Pharmacokinetics (PPK) of CEM-101 Using Data from the Plasma and Epithelial Lining Fluid (ELF) of Healthy Subjects

Abstract A1-691

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Background:

CEM-101 is a fluoroketolide antibiotic with activity against typical and atypical bacterial respiratory organisms including *Streptococcus pneumoniae*. The objective of this analysis was to characterize CEM-101 PPK using plasma and ELF Phase 1 data.

Methods:

Healthy subjects in 1 of 3 Phase 1 studies received 50 -1600 mg of CEM-101 orally as either single or multiple doses. Plasma PK samples were collected intensively in all 3 studies; ELF samples were collected on Day 5 via bronchoalveolar lavage at 1 of 5 time points in subjects who received 400 mg daily for 5 days. Plasma and ELF samples were assayed for CEM-101 using LC/MS/MS. Urea in plasma and ELF was used to correct ELF CEM-101 concentrations. 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, which was based on data from 91 subjects, was a 3-compartment model (central, peripheral and ELF) with auto-inhibition of clearance, a Weibull absorption process with fitted lag times and a capacity-limited first-pass effect. The mean (%CV) of the total clearance was 292 L/hr (69). The maximum extent of the inhibition of clearance (%CV) was 80% (3.1) and the IC_{50} (%CV) associated with the inhibition process was 0.056 mg/L (26). Bi-directional rate constants (%CV) between ELF and plasma were 0.74 (61) and 0.057 (68) hr^{-1}, respectively. The PPK model provided excellent fits to the plasma and ELF data (r^2 = 0.94 and 0.99 for observed vs fitted concentrations, respectively). Goodness-of-fit diagnostics indicated an unbiased fit to the data. Mean (%CV) Day 5 ELF and plasma AUC_{0-24} for 400 mg were 7.2 (51) and 62 (102), respectively.

Conclusions:

A PPK model was successfully developed for CEM-101 and fit the data well. This model will be useful to support dose selection for future clinical trials.