Background:
CEM-102, an oral antibiotic with activity against Staphylococcus aureus, was developed for the treatment of complicated skin and skin-structure infections (SSIs). In Study 1, a population pharmacokinetic (PK) 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 either as single or multiple doses. Safety and tolerability were assessed after a single 500 mg dose in a crossover study with 14 subjects. Serial pharmacokinetic (PK) samples were collected and analyzed for CEM-102 using LC/MS/MS. Candidate PK parameters were fit to the data using a noncompartmental method and maximum a posteriori estimation algorithm in SADAPT 1.56.

Results:
CEM-102 is a two-compartment single and multiple dose absorption model, with a validated LC/MS/MS method with a lower limit of quantification of 0.2 (ng/mL) and an inter-day coefficient of variation (CV) of 7.6%.

Population PK Analysis:
Candidate population PK model selection was based on both a repletion of the exploratory data analysis results and prior knowledge of the PK of fusidic acid.
- Intersubject variability was estimated for every PK parameter, where possible, using an exponential between-subject variability model (assuming log-normally distributed errors) or a variance component where appropriate (to constrain estimates to the allowed domain).
- Residual variability was described using an additive plus proportional model.
- All population PK analyses were conducted using Monte Carlo parametric expectation maximization (MC-PERM), as implemented in the open-source software program, SADAPT 1.56.
- Model discrimination was performed by comparison of objective function values, with a validated Information Criterion for either nested or non-nested models.

Preliminary evaluation of the PK data revealed:
- 102 was a linearly reversible process in study B only,
- The primary PK data was obtained after a single 500 mg dose to each subject in the crossover study with 14 subjects.
- Serial pharmacokinetic samples were collected and analyzed for CEM-102 using LC/MS/MS. Candidate PK parameters were fit to the data using a noncompartmental method and maximum a posteriori estimation algorithm in SADAPT 1.56.

Methods:
- Study Design and Dose Administration (continued)
  - Study 102-A was a dose linearity study in which 28 subjects were randomized to receive a single 500 mg dose of CEM-102 without food. After a washout period, a subset of 14 subjects was randomly selected to receive CEM-102 with food.
  - In Study 102-B, 18 subjects were enrolled and randomized to receive a single 500 mg dose of CEM-102 in the fed state. After a washout period, a subset of 14 subjects was randomly selected to receive CEM-102 in the fasted state.
  - In Study 103, 30 subjects were enrolled and randomized to receive doses ranging from 500 mg to 2200 mg of CEM-102 as a single dose followed by multiple doses in the fed state. Serial blood samples were collected at various times during the study after the administration of a single dose and multiple doses.

Results:
The final model was a two-compartment absorption model, with and without food, for CEM-102 absorption. The parameters estimated and associated standard errors for the final model were provided in Table 1. The goodness of fit plots demonstrated that the population PK model described the data with overall r2 values of 10.87 for observed versus individual fitted plasma concentrations and an overall r2 value of 0.844 for the population fitted plasma concentrations (Figure 2B).

Conclusions:
- The population model developed can be used to describe the time course of total plasma concentrations of CEM-102 at various dose levels and after single- and multiple-doses.
- Depending on the dose level and the IC

References: