Pharmacokinetics-Pharmacodynamics (PK-PD) of CEM-102 against Methicillin-Resistant *Staphylococcus aureus* (MRSA) using an In Vitro PD Model (IVPM) and Mechanism-Based (MB) Modeling.

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Background:

The PK-PD of CEM-102, an oral antibiotic in development for the treatment of complicated skin and skin structure infections, was investigated against MRSA using an IVPM and MB modeling.

Methods:

Using an IVPM, the PK-PD of CEM-102 against MRSA, USA300 (MIC=0.25 mg/L), at an initial inoculum (CFU_0) of 10^6 CFU/mL, was evaluated over 48h. Broth was supplemented with human albumin (4g/dL). CEM-102 regimens (AUC:MIC ratio) included: 550mg q12h (7000), 1100 q24h (8030), front-loaded (FL) 550 q12h (10400), 1100 q12h (21300), 2200 q24h (24400), and FL 1100 q12h (32500). MB models were developed in NONMEM VI, fitting all data simultaneously.

Results:

CEM-102 regimens displayed the following net changes in log_{10} CFU/mL at 24h [48h]: 550q12h: -0.95 [1.79], 1100q24h: -1.28 [0.51], FL-550q12h: -1.13 [-1.07], 1100q12h: -1.54 [-1.67], 2200q24h: -1.85 [-1.56], and FL-1100q12h: -1.65 [-1.67]. The log_{10} of the area under the CFU/mL curve ($AUCFU_{Drug}$)/($AUCFU_{Control}$) for these regimens was -1.11, -2.03, -2.49, -2.72, -2.61, and -2.82 , respectively. An AUC_{48}:MIC ratio of 9433 was predictive of a -2.5 log decline in this area ratio. The MB model included a susceptible and a resistant subpopulation (10^{-4} of CFU_0). CEM-102 prolonged the mean generation time up to 3.7-fold with an IC_{50} of 5.45 mg/L for both subpopulations. CEM-102 also inhibited the probability of successful doubling by up to 66%. Data fits were unbiased and precise for all regimens (slope = 1.00; intercept = -0.02; r = 0.97 for population fitted vs. observed log CFU/mL).

Conclusions:

Bacterial killing by CEM-102 correlated well with AUC_{48}:MIC ratio. The MB model, which yielded excellent fits of the data, will be useful for further evaluations to support dose selection.