Pharmacokinetic-Pharmacodynamic (PK-PD) Analysis of CEM-101 Against *Streptococcus pneumoniae* Using Data from a Murine-Lung Infection Model

Abstract A1-688

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Background:

CEM-101 is a fluoroketolide with *in vitro* activity against typical and atypical pathogens associated with community-acquired bacterial pneumonia (CABP). Using a murine-lung infection model, epithelial lining fluid (ELF) and plasma PK-PD measures most closely associated with CEM-101 efficacy against *S. pneumoniae* and targets based on PK-PD relationships for such indices were identified.

Methods:

CEM-101 PK data were obtained from healthy mice administered single CEM-101 doses ranging from 0.625 - 40 mg/kg. Plasma and ELF were collected over 24 h (3 mice/time point) and assayed for CEM-101. Urea in plasma and ELF was used to correct ELF concentrations. Neutropenic mice infected with 10^8 CFU of 1 of 5 *S. pneumoniae* isolates via inhalation were administered daily CEM-101 doses (0.156 - 160 mg/kg) via oral gavage. Dose-fractionation was performed for 1 isolate; CEM-101 was administered to the other 4 isolates as a Q6h or Q12h regimen. PK and PK-PD were evaluated using S-ADAPT 1.56.

Results:

A 3-compartment model with a parallel first-order and capacity-limited clearance and a capacity-limited first pass effect with fitted lag-times best described the plasma and ELF data (r^2 = 0.98 and 0.83 for observed vs fitted concentrations, respectively). ELF to total- and free-drug (*f*) plasma (based on protein binding of 91.8% in mice) $AUC_{0\text{-}24}$ ratios were 0.22 and 2.7, respectively. ELF and *f* plasma $AUC_{0\text{-}24}$:MIC ratios were most predictive of efficacy (r^2 = 0.85 for ELF and *f* plasma). ELF and *f* plasma $AUC_{0\text{-}24}$:MIC ratios associated with net bacterial stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline were 1.26 and 1.65, 15.1 and 6.31, and 59.8 and 12.8, respectively.

Conclusions:

$AUC_{0\text{-}24}$:MIC ratio was the PK-PD index most predictive of efficacy. PK-PD targets based on these relationships will be used to support CEM-101 dose selection for future studies in patients with CABP.