Efficacy and Pharmacodynamic evaluation of CEM-101, a Novel Macrolide, in Murine Infection Models

Abstract P1098

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Objectives:
To evaluate the in vivo efficacy of CEM-101 against gram positive pathogens including community associated MRSA.

Methods:
Efficacy was evaluated in both a subcutaneous abscess model as well as neutropenic thigh infection model. Abscesses were induced in CD-1 female mice by s.c. injection of S. pneumoniae or S. pyogenes mixed with cytodex beads, CEM-101 or comparator test articles were administered as a single oral dose two hours post infection with bioburden levels assessed at 48 hours post infection. In addition, the neutropenic thigh infection model was utilized to determine target organ efficacy after a single oral dose. CD-1 female mice were rendered neutropenic with cyclophosphamide pre-treatment. Mice were infected with S. pneumoniae (SPN) or S. aureus via IM injection into the right thigh. At 1.5 hours post infection, mice received treatment via oral gavage with CEM-101 ranging from 1 to 25 mg/Kg. CFUs/ gram of thigh were determined at initiation of treatment and at 24 hour post start of treatment. Subsequently, for a preliminary evaluation of PK-PD relationship, mice, infected with SPN, were treated with 4 doses of CEM-101 fractionated into 1, 2, 3, or 4 doses over a 24 hour period. Single dose plasma PK was also performed.

Results:
In the abscess, a 10 mg/Kg QD dose of CEM-101 demonstrated a 2.3 log₁₀ decrease while clarithromycin only achieved a 0.9 log₁₀ reduction from untreated mice against SPN. Similarly, a 2.9 log₁₀ decrease was observed for CEM-101 against S. pyogenes; while clarithromycin demonstrated only a 0.59 log₁₀ reduction. In the thigh model, CEM-101 demonstrated efficacy after a single oral dose against both susceptible and MRSA isolates. Evaluation of PK-PD demonstrated concentration dependent killing with increased bacterial reduction for the single oral dose over the fractionated cohorts. The effect of CEM-101 on bacterial burden was combined with free drug concentrations to predict the most likely PK-PD parameter. C_{max}/MIC was the best predictor of in vivo efficacy with an r²=0.83.

Conclusions:
CEM-101 demonstrated significant in vivo activity in a subcutaneous abscess and neutropenic thigh infection model. Preliminary PK-PD suggests concentration dependent killing with C_{max}/MIC being the best predictor of efficacy against this isolate.