Population Pharmacokinetic (PPK) and Pharmacokinetic-Pharmacodynamic (PK-PD) Target Attainment (TA) Analyses for Solithromycin (SOL, CEM-101) to Support Intravenous (IV) Dose Selection in Patients with Community-Acquired Bacterial Pneumonia (CABP)

Abstract A-1269

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Background:

SOL is a novel fluoroketolide with activity against CABP bacterial pathogens including *S. pneumoniae* (MIC_{90} = 0.125 mg/L). PPK and PK-PD TA analyses were conducted to identify potential SOL IV dosing regimens for the treatment of CABP patients.

Methods:

Using Phase 1 PK data for SOL 25-800 mg IV (n = 40) and 50-1600 mg PO (n = 113; n = 30 for subjects with ELF PK) and Phase 2 PK data (n = 22), a previous PPK model (ICAAC 2010, A1-691) was refined. Using this model, PK-PD targets for *S. pneumoniae* from a murine-lung infection model (ELF and free-drug (*f*) plasma AUC_{0-24}:MIC ratios of 1.26 and 1.65 for net bacterial stasis, and 15.1 and 6.31 for a 1-log_{10} CFU reduction from baseline, respectively (ICAAC 2010, A1-688)), and Monte Carlo simulation, PK-PD TA analyses were conducted.

Results:

A 3-compartment PPK model (central, peripheral and ELF) with auto-inhibition of clearance via an effect compartment fit the data well (r^2 = 0.974 for observed vs. individual fitted plasma concentrations; r^2 = 0.984 for observed vs. individual fitted ELF concentrations). PK-PD TA probabilities by MIC on Days 1 and 5 based on ELF and *f* plasma AUC_{0-24} for the dosing regimens evaluated are presented in Table 1.

Conclusions:

For ELF PK-PD targets, high PK-PD TA probabilities for MIC ≤ 1 mg/L were seen for dosing regimens 1, 2 and 5; using the *f* plasma PK-PD target for net bacterial stasis, high probabilities were seen for MIC ≤ 0.5 mg/L for these same dosing regimens. Unlike for SOL PO (ICAAC 2010, A1-692), front-loading was not required for SOL IV 400 mg Q24h to achieve a high PK-PD TA probability at MIC = 1 mg/L for the ELF PK-PD target for 1-log_{10} CFU reduction. These data will be used to support Phase 3 SOL IV dose selection.

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