ZTI-01 Treatment Improves Survival of Animals Infected with Multidrug Resistant *Pseudomonas aeruginosa*

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Background: ZTI-01 (fosfomycin, FOS, for injection) is currently under US development to treat complicated urinary tract infections. ZTI-01 is unique compared to other antimicrobials in that it inhibits an early step in cell wall synthesis via covalent binding to MurA. ZTI-01 demonstrates broad *in vitro* activity against Gram-negative (GN) and -positive (GP) bacteria, including multidrug-resistant (MDR) organisms. Our study goals were to determine the efficacy of ZTI-01 as a monotherapy or in combination with meropenem against MDR *Pseudomonas aeruginosa* in a preclinical model of pulmonary infection.

Methods: 8 week old neutropenic mice were infected with a MDR strain of *P. aeruginosa* via intubation-mediated intratracheal (IMIT) instillation. Three hours after instillation, mice received treatment with ZTI-01, meropenem, or ZTI-01 plus meropenem (combination therapy) q8h for 5 days. Mice were monitored every 8 h for 7 days for development of disease and moribund animals were humanely euthanized. Lungs and spleens were harvested at euthanasia, or at 7 days for survivors, and processed for bacterial enumeration and development of pathology.

Results: Mice were challenged with a lethal dose of *P. aeruginosa* UNC-D. Mock treated animals succumbed to infection within 36 h post-infection. Animals that received 6 g/kg/day ZTI-01 showed an increase in the MTD (52 h) and 25% of the cohort were protected from lethal disease. Combining ZTI-01 with meropenem resulted in a significant increase in survival (≥75% of cohorts survived infection). Combination therapy also significantly decreased bacterial numbers in the lungs and inhibited dissemination to the spleens. Furthermore, animals receiving combination therapy were protected from significant inflammation in the lungs and the development of pneumonia.

Conclusion: Here we report that combination therapy with ZTI-01 and meropenem provides significant improvements in all disease manifestations over treatment with each drug individually in a preclinical model for pulmonary infection with MDR *P. aeruginosa*. These data strongly support further evaluation of ZTI-01 in combination with other antibiotics as potential therapies against pulmonary infections with MDR bacteria.