Evaluation of Pharmacokinetics/Pharmacodynamics of the Novel β-lactamase Inhibitor, ETX2514, in Combination with Sulbactam Against Acinetobacter baumannii


1Institute for Clinical Pharmacology, Inc., Schererton, NY, USA
2Tentia Therapeutics, Watimont, MA, USA
3Clinical Pharmacology & Therapeutics, Bucharest, Romania
4Department of Internal Medicine, Indiana University, Indianapolis, IN
5Clinical Pharmacology, University of Wisconsin, Madison, WI

Background: β-lactamase-producing Acinetobacter baumannii (A. baumannii) has become a common cause of severe infections associated with high mortality and morbidity. The majority of clinical isolates are classified as either multidrug-resistant (MDR) or extensively drug-resistant (XDR). In vitro susceptibility testing demonstrates that A. baumannii, a β-lactam-negative bacterium, is highly resistant to β-lactam antibiotics. ETX2514 is a novel β-lactamase inhibitor (BLI) that demonstrates intrinsic activity against A. baumannii. A beta-lactamase inhibitor (BLI) that demonstrates intrinsic activity against A. baumannii, ETX2514 is a broad-spectrum BLI that extends the antibiotic activity of sulbactam against MDR A. baumannii. This study presents preclinical data to support the clinical development of ETX2514 in combination with sulbactam against A. baumannii.

Methods: This is a laboratory and in vivo study in mice of ETX2514 in combination with sulbactam. The relative potency and efficacy of ETX2514 ± sulbactam was evaluated in a chemostat model in vitro, and an in vivo murine thigh infection model. Dose fractionation and PK/PD analysis were performed to support clinical dose selection.

Results: ETX2514 ± sulbactam demonstrated >32-fold increase in intrinsic activity against MDR A. baumannii relative to sulbactam alone, and was associated with a >90% decrease in bacterial growth across all MICs in the chemostat model. PK/PD analysis in the in vivo murine thigh infection model showed combinations of ETX2514 ± sulbactam achieved >T >0.75 mg/L >90% of the time (T>0.75 >%T), suggesting clinical efficacy in this murine infection model.

Conclusions: ETX2514 in combination with sulbactam is a promising new treatment option for patients with infections due to MDR A. baumannii. The combination of ETX2514 ± sulbactam extends the activity of sulbactam against MDR A. baumannii and warrants further study in clinical development.

REFERENCES