Background

VNRX-5133 is a broad-spectrum, selective, non-β-lactam, BS-BLI with in vitro activity against all four Ambler class enzymes, including Class B metallo-β-lactamasess. VNRX-5133 is being developed in combination with cefepime for the treatment of serious infections associated with β-lactamase producing bacteria. In order to optimize VNRX-5133 dosing, it is important to understand the PK-PD index associated with efficacy. To this end, a series of in vitro studies for VNRX-5133 in combination with cefepime were completed with the following objectives: 1) to identify the PK-PD index associated with VNRX-5133 efficacy; and 2) to determine the magnitude of the VNRX-5133 PK-PD index required for efficacy against cephalosporin and carbapenem-resistant Enterobacteriaceae (ENT) and Pseudomonas aeruginosa (PSA).

Methods

A 24 h one-compartment in vitro infection model was utilized in all studies. To identify the PK-PD index associated with VNRX-5133 efficacy, dose-fractionation studies were conducted using one isolate exposed to five VNRX-5133 exposures fractionated into regimens administered every 3, 6, 12, or 24 hours, in combination with a sub-clinical dose of cefepime administered q8h. In order to evaluate the inter-isolate variability in VNRX-5133 efficacy, dose-ranging studies were completed for five isolates (3 ENT and 2 PSA) producing a variety of serine- and/or metallo-β-lactamase enzymes (NDM-1, VIM-2, CTX-M-15, KPC-3, TEM-1, and SHV-11) in combination with cefepime 2 g q8h. Hill-type models were used to describe relationships between change in log_{10} CFU from baseline at 24 hours and each of VNRX-5133 AUC:MIC ratio, C_{max}:MIC ratio and %T>threshold concentration, where the cefepime MIC was determined in the presence of 4 mg/L of VNRX-5133.

Results

AUC:MIC ratio and %T>0.03 mg/L described the efficacy of VNRX-5133 well (r^2 of 0.763 and 0.760, respectively. The magnitudes of AUC:MIC ratio associated with net bacterial stasis and 1- and 2-log_{10} CFU reductions from baseline were 7.42, 14.7, and 31.9 for ENT and 0.57, 0.93, and 6.41 for PSA, respectively.

Conclusions

These data, which demonstrated similar in vitro activity of VNRX-5133 against serine- and metallo-β-lactamasess for both ENT and PSA, provide initial PK-PD targets for VNRX-5133 efficacy in combination with cefepime for the treatment of infections arising from carbapenem-resistant isolates.

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