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In Vivo pharmacodynamic profile of cefepime in combination with VNRX-5133 against serine β-lactamase-producing Gram-negative bacteria in the neutropenic murine thigh infection model

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INTRODUCTION

- VNRX-5133 is a cyclic boronate β-lactamase inhibitor with activity against Classes A, B (except IMP), C and D β-lactamases.
- Cefepime (FEP)/VNRX-5133 combination is currently under development for treatment of infections due to multi-drug resistant gram-negative bacteria.

OBJECTIVE

To determine the PK/PD index, relative to VNRX-5133 exposure, that correlated most closely with the efficacy of FEP/VNRX-5133 combination and the magnitude of index required for efficacy against serine β-lactamase-producing Enterobacteriaceae and *Pseudomonas aeruginosa* in the neutropenic murine thigh infection model.

MATERIALS & METHODS

Antimicrobial Test Agents

- VNRX-5133 $(HCl)_2$ (VenatoRx Pharmaceuticals, Inc.).
- Cefepime 2g vials (Sagent Pharmaceuticals, Inc.) and cefepime HCl (Tecoland) were used for *in vivo* and *in vitro* testing, respectively.

Neutropenic Murine Thigh Infection Model

- Female ICR mice were rendered neutropenic by cyclophosphamide; uranyl nitrate was given to induce renal impairment.
- Thighs were inoculated with 0.1 mL of 10^7 CFU/ml bacterial suspensions.

MATERIALS & METHODS (continued)

Dose-Fractionation Studies

- 2 KPC-producing isolates were examined.
- FEP human-simulated regimen (HSR) equivalent to a dose of 2g q8h (2h infusion) was given in combination with 2 total daily VNRX-5133 doses (1 or 5 mg/kg/day), each given with three dosing frequencies (q24h, q12h or q6h).
- Comparisons of bacterial burdens at 24h were made between the three different regimens of the same total daily dose using one-way Analysis of Variance (ANOVA) test followed by Tukey's test where the P value is < 0.05.

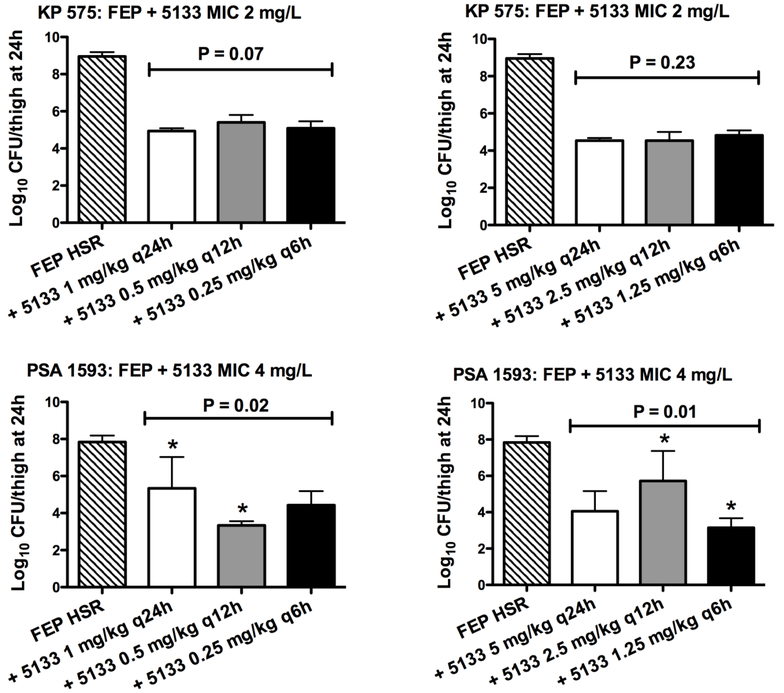
Dose-Ranging Studies

- Efficacy of FEP HSR in combination with escalating VNRX-5133 exposures was assessed against clinical FEP-resistant (MIC ≥256 mg/L) Enterobacteriaceae and *P. aeruginosa* isolates.
- Efficacy was measured as the change in log_{10}CFU/thigh at 24h compared with 0h controls.
- Pharmacokinetics of VNRX-5133 were assessed to determine the exposures of the regimens utilized; exposures required to achieve efficacy endpoints were estimated using the Hill-equation.
- FEP+VNRX-5133 MICs were determined at a fixed VNRX-5133 concentration of 4 mg/L.

RESULTS

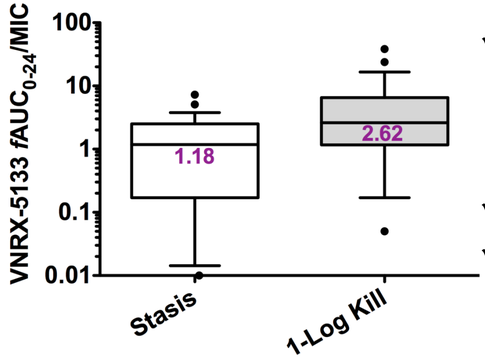
Figure 1. Bacterial burdens observed with FEP HSR alone and in combination with 2 total daily VNRX-5133 doses (1 or 5 mg/kg/day), each given with three dosing frequencies (q24h, q12h or q6h).

- Asterisks indicate P <0.05 with the post hoc test.



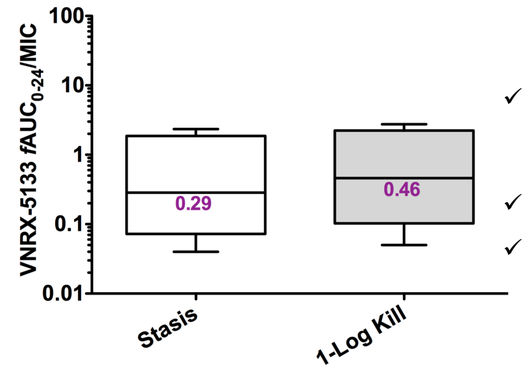
Dosing frequency had no impact on VNRX-5133 potentiation of FEP activity

Figure 2. VNRX-5133 PK/PD targets against **26 isolates of Enterobacteriaceae**. Whiskers represent 10th and 90th percentiles.



- ✓ Isolates expressed KPCs (n=9), OXA-48 (n=11), and/or extended-spectrum β-lactamases (SHV and CTX-M types, n=20)
- ✓ FEP MIC: 256 to >512 mg/L
- ✓ FEP + 5133 (fixed at 4 mg/L) MIC: 0.063 to 16 mg/L.

Figure 3. VNRX-5133 PK/PD targets against **4 isolates of *P. aeruginosa***. Whiskers represent 10th and 90th percentiles.



- ✓ Isolates were either KPC-producing (n=1), or AmpC over-producing (n=3)
- ✓ FEP MIC: 256 to >512 mg/L
- ✓ FEP + 5133 (fixed at 4 mg/L) MIC: 2 to 16 mg/L.

CONCLUSIONS

- The *f*AUC_{0-24}/MIC appeared to be the PK/PD driver for the activity of VNRX-5133.
- Given that the *f*AUC_{0-24} observed in humans with VNRX-5133 dose of 0.5 g every 8h was ~145 mg.h/L[1], our data predict that this dose should provide sufficient systemic exposure to acheive at least 1-log bacterial kill against highly FEP-resistant Enterobacteriaceae and *P. aeruginosa* isolates [2-4].
- These data support a VNRX-5133 dose of 0.5 g in combination with FEP 2g every 8h for Phase 3 studies.

REFERENCES

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