INTRODUCTION
- VN5313 is a cyclic boronate β-lactamase inhibitor with activity against Classes A, B, and D β-lactamas.

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 VN5313 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**
- VN5313 (HC1), (VenatoRx Pharmaceuticals, Inc.).
- Cefepime 2g vials (Sagent Pharmaceuticals, Inc.).
- Cefepime HCI (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 10⁹ CFU/ml bacterial suspensions.

**RESULTS**
- Figure 1. Bacterial burdens observed with FEP HSR alone and in combination with 2 total daily VN5313 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.

  - 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 VN5313 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 VN5313 exposures was assessed against clinical FEP-resistant (MIC ≥256 mg/L) Enterobacteriaceae and P. aeruginosa isolates.
    - Efficacy was measured as the change in log₁₀ CFU/thigh at 24h compared with 0h controls.
    - Pharmacokinetics of VN5313 were assessed to determine the exposures of the regimens utilized; exposures required to achieve efficacy endpoints were estimated using the Hill-equation.
    - FEP+VN5313 MICs were determined at a fixed VN5313 concentration of 4 mg/L.

**CONCLUSIONS**
- The fAUC₀-2₄/MIC appeared to be the PK/PD driver for the activity of VN5313.
- Given that the fAUC₀-2₄ observed in humans with VN5313 dose of 0.5 g every 8h was ~145 mg.h/L, our data predict that this dose should provide sufficient systemic exposure to achieve at least 1-log bacterial kill against highly FEP-resistant Enterobacteriaceae and P. aeruginosa isolates.
- These data support a VN5313 dose of 0.5 g in combination with FEP 2g every 8h for Phase 3 studies.

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