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Pharmacokinetics of VNRX-5133 in Combination with Cefepime and Metronidazole

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Background

The rapid emergence of multidrug-resistant (MDR) Gram-negative pathogens is increasingly recognized as a threat to effective treatment of serious infections due to the limited treatment options available (CDC 2013; WHO 2016). VNRX-5133 is a novel, non-β-lactam, β-lactamase inhibitor (BLI) with potent direct inhibitory activity against serine- and metallo-β-lactamases. Combined with cefepime, VNRX-5133 restored *in vivo* activity against resistant β-lactamase producing strains (Georgiou et al, 2018; Weiss et al, 2018). *In vitro* models of infection showed that VNRX-5133 plus cefepime had excellent activity against carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*, including those expressing Ambler Class A, B, C and D serine-β-lactamases, and against cefepime- and/or meropenem-resistant *P. aeruginosa* (Hackel and Sahm, 2018; Hamrick et al, 2018; Estabrook et al, 2018; Donnelly et al, 2018). A previous study in healthy volunteers found that intravenous (IV) administration of VNRX-5133 was well-tolerated, and exhibited a dose-proportional PK profile after single doses of 62.5 to 1500 mg and multiple doses of 250 to 750 mg q8h for 10 days (Geibel et al, 2018). VNRX-5133, combined with cefepime is being developed for the treatment of serious infections due to multidrug resistant Gram-negative bacteria, including ESBL-producing organisms and carbapenem-resistant Enterobacteriaceae and *P. aeruginosa*.

Objectives

- Evaluate the pharmacokinetics (PK) of IV VNRX-5133 and cefepime alone and in combination
- Evaluate the PK of co-administration of IV VNRX-5133 and cefepime with oral metronidazole

Methods

Study Design

- Phase 1, randomized study in healthy subjects
- 2-part, 5-period cross-over design with a randomized sequence **(Table 1)**
- Subjects were randomized into a single-dose assessment sequential 3-period crossover (Part 1A) phase (Treatment Sequences A, B, and C)
  - All subjects received all treatments in random order on Days 1, 4, and 7
- Subjects were re-randomized into a 2-period crossover (Part 1B) phase (Treatment Sequences D and E)
  - All subjects received both treatments in random order on Days 10 and 13
- VNRX-5133 and cefepime alone and in combination were administered as a 2 h IV infusion. Metronidazole was administered as a single oral dose of 0.5 g.

Table 1. Study Treatments

Study Part	Treatment Sequence	Drug/Dose
1A	A	VNRX-5133 0.75 g
	B	Cefepime 2 g
	C	VNRX-5133 0.75 g + cefepime 2 g
1B	D	VNRX-5133 0.75 g + cefepime 2 g + oral metronidazole 0.5 mg
	E	Placebo + oral metronidazole 0.5 mg

Study Subjects

- Healthy male or female subjects, aged 18 to 55 years
- Body weight ≥50 kg, body mass index between ≥18.5 and <30.0 kg/m^2
- At Screening, no clinically relevant abnormalities from physical examination, vital signs, clinical laboratory testing or ECG that could interfere with the conduct of the study

Study Assessments

- Blood samples were collected for determination of plasma concentrations of VNRX-5133 and cefepime prior to each infusion and at frequent intervals to 48 hours after starting the infusion.
- Plasma concentrations of metronidazole were determined for up to 48 hours after dose.
- Safety assessments included adverse events (AEs), vital signs, clinical laboratory, ECG, and physical examination.

Pharmacokinetic Analysis

- Plasma concentrations of study drugs were determined using validated methods (LC-MS/MS).
- PK variables were determined or calculated using noncompartmental analysis of the plasma concentration-time data.
- Geometric mean ratios (GMR) and 90% confidence intervals (CI) were used to compare C_{max} and $AUC_{0\text{-}inf}$ for treatment groups.
- No drug interaction was concluded if the 90% CI were within 80% to 125%

Results

- 18 subjects were enrolled. 17 completed; 1 was withdrawn for non-compliance.
- Baseline characteristics **(Table 2)**

Table 2. Baseline Characteristics

Characteristic	Subjects (N=18)
Mean age, years[(a)]	32.2 ± 9.0
Age range, years	19 – 47
Female, n (%)	10 (55.6)
Race, n (%)	
White	5 (27.8)
Black or African American	11 (61.1)
Other	2 (11.1)
Mean body weight, kg[(a)]	76.9 ± 11.4
Mean body mass index, kg/m^2[(a)]	26.6 ± 2.4

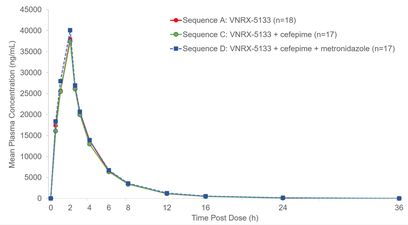
(a) Mean ± standard deviation

Pharmacokinetics

VNRX-5133

- Plasma VNRX-5133 concentration decreased in a multiphasic manner after reaching peak levels immediately after the end of infusion **(Figure 1).**
- Mean half-life was similar across groups, ranging from 3.1 to 3.3 hours.
- Mean CL of VNRX-5133 was similar across Treatment A, C, D (range: 5.5 to 5.9 L/h).
- All VNRX-5133 PK parameters had a relatively low degree of variability (CV% <20%).

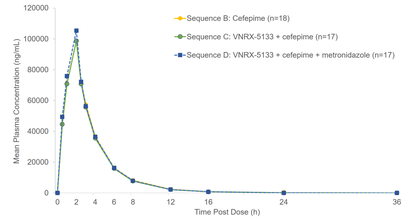
Figure 1. Mean VNRX-5133 Plasma Concentrations versus Time by Treatment.



Cefepime

- Plasma cefepime concentrations decreased in a monophasic manner after reaching peak levels immediately after the end of infusion **(Figure 2)**.
- Mean half-life was similar across groups, ranging from 2.3 to 2.4 hours across Treatment B, C, and D.
- Mean CL of cefepime was similar across Treatment B, C, and D (5.8 to 6.1 L/h).
- After a single IV dose, all cefepime PK parameters had a relatively low degree of variability (CV% <20%).

Figure 2. Mean Cefepime Plasma Concentrations versus Time by Treatment.



Metronidazole

- Metronidazole plasma concentration decreased in a monophasic manner after reaching peak levels **(Figure 3)**.
- Median T_{max} in Treatments D and E was 1.1 and 1.1, respectively.
- Mean half-life was 8.6 and 8.7 hours in Treatment D and E, respectively.

Figure 3. Mean Metronidazole Plasma Concentrations versus Time by Treatment.

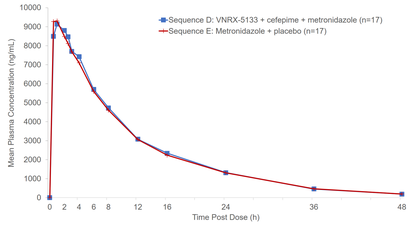


Table 3. Analysis of PK Parameters After Monotherapy and Co-administration of Study Treatments

		Geometric Mean Ratio (90% Confidence Intervals)	
Analyte	Test / Reference	C_{max} (ng/mL)	$AUC_{(0\text{-}inf)}$ (h*ng/mL)
VNRX-5133	C vs. A	0.991 (0.964, 1.018)	0.978 (0.952, 1.006)
	D vs. C	1.072 (1.029, 1.117)	1.073 (1.041, 1.106)
Cefepime	C vs. B	1.017 (0.980, 1.055)	1.001 (0.984, 1.018)
	D vs. C	1.071 (1.046, 1.097)	1.045 (1.011, 1.080)
Metronidazole	D vs. E	0.959 (0.871, 1.055)	1.009 (0.990, 1.029)

A=VNRX-5133; B=cefepime; C=VNRX-5133 + cefepime; D=VNRX-5133 + cefepime + metronidazole; E=metronidazole + placebo

Safety/Tolerability

- 9 (50%) subjects experienced 13 treatment-emergent AEs (Table 4).
- All AEs were mild, and no serious AEs or discontinuation for AEs occurred.
- Headache (5 [27.8%]), constipation (2 [11.1%]), and vaginal infection (2 [11.1%]) were the most common AEs.
- No safety concerns were identified:
- No clinically significant abnormal laboratory findings
- No AEs related to clinical laboratory findings
- No clinically significant changes in ECG, vital signs or physical examination

Table 4. Incidence of Treatment-emergent Adverse Events

	Number (%) of Subjects				
	VNRX-5133 (n=18)	Cefepime (n=18)	VNRX-5133 + Cefepime (n=17)	Metronidazole + VNRX-5133 + Cefepime (n=17)	Metronidazole + Placebo (n=17)
Subjects with any AE	1 (5.6)	3 (16.7)	5 (29.4)	0	2 (11.8)
Abdominal pain	0	0	1 (5.9)	0	0
Constipation	1 (5.6)	0	1 (5.9)	0	0
Headache	1 (5.6)	2 (11.1)	2 (11.8)	0	0
Nausea	1 (5.6)	0	0	0	0
Oropharyngeal pain	0	1 (5.6)	0	0	0
Skin irritation	0	0	0	0	1 (5.9)
Vaginal infection	0	0	1 (5.9)	0	1 (5.9)

Conclusions

- No drug-drug interactions were observed between VNRX-5133 and cefepime.
- No drug-drug interactions were observed when cefepime and VNRX-5133 were co-administered with metronidazole.
- Co-administration of cefepime/VNRX-5133 was safe and well tolerated.

References

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