O1601: Pharmacodynamics of VNRX-5133 in Combination with Cefepime Studied in an *in vitro* Model of Infection

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29th ECCMID Amsterdam April 2019

Background

- VNRX-5133 (VNRX) is a novel β-lactamase inhibitor with activity against serine and metallo β-lactamases including CTX-M-15, KPC, CMY, AmpC, OXA, NDM and VIM enzymes.
- VNRX-5133 is not active against IMP enzymes.
- In prior in vitro and in vivo infection models, VNRX-5133 fAUC/MIC was generally predictive of efficacy of the combination when human simulated regimens of cefepime and VNRX-5133 were administered.

Objective

- **The objective of the study was to define the pharmacodynamics (PD) of VNRX-5133 using human simulated exposures for a 2G cefepime + 500mg VNRX-5133 dose against Enterobacterales with CTX-M, KPC, AmpC and OXA-48 β-lactamases**.

Materials and methods

- An *in vitro* one compartment dilutional pharmacokinetic model was used. Free drug serum concentrations associated with CEF 2G by 2hr infusion 8hrly were simulated and VNRX-5133 was initially given by continuous infusion (CI): concentration range 0.003mg/L-10mg/L.
- VNRX-5133 was then fractionated, i.e. dosed once, twice and three times a day at three exposures across the response relationship. Reduction in viable count at 24h (log CFU/mL (d24)) was the primary end point.
- Four clinical strains were used: *E. coli* 35776 (CTX-M), *K. pneumoniae* 42421 (KPC), *E. coli* 75927 (AmpC) and *K. pneumoniae* 75927 (OXA-48).

Results:

- All isolates were resistant to cefepime; the addition VNRX-5133 (4mg/L) decreased cefepime MICs by >8fold.
- In the VNRX-5133 CI experiments with CEF 2G 8hrly, ≥4 log kill was attained with VNRX-5133 concentrations >0.005mg/L against CTX-M producing *E.coli* (inoculum 10^6cfu/mL; ≥0.5mg/L against KPC producing *K. pneumoniae*, ≥4mg/L against AmpC producing *E.coli* and OXA-48 producing *K. pneumoniae* (Figure 1).

Figure 1: Relationship between VNRX-5133concentrations and antibacterial effect

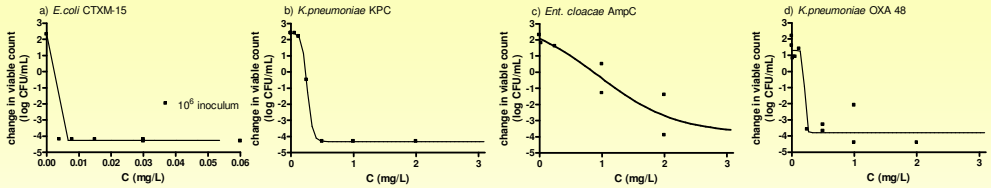

Table 1: VNRX-5133 Css required for maximum effect and PD driver

strain/enzyme	inoculum	Cefepime MIC (mg/L)	Cefepime + VNRX-5133 MIC (mg/L)	Css for maximum effect at 24h	PD driver R^2	
					AUC	T>threshold
E.coli / CTXM	1.00E+06	32	0.25	0.02	-	-
	1.00E+08			0.75	0.74	0.62
K.pneumoniae / KPC	1.00E+06	>4	1	0.75	0.70	0.72
E.coli / AmpC	1.00E+06	>128	8	7.00	0.64	0.52
K.pneumoniae / OXA 48	1.00E+06	16	2	0.50	0.67	0.94

- Combined analysis of CI and dose fractionation simulations were conducted to determine the VNRX-5133 PD (AUC, Cmax, Time (T) >threshold) for each strain (Figures 2 - 5, Tables 2, 3 and 4).
- For *E. coli* producing CTX-M, AUC (R^2 0.74) and T>0.5mg/L (R^2 0.62) using a 10^8 CFU/mL inoculum were best related to d24.
- For KPC producing *K.pneumoniae*, AUC (R^2 0.70) and T>0.25mg/L VNRX-5133 (R^2 0.72) were best related to d24.
- For AmpC producing *Ent.cloacae* C, AUC (R^2 0.64) and T>2mg/L (R^2 0.52) were best related to d24.
- For OXA-48 producer, AUC (R^2 0.67) and T>0.25mg/L (R^2 0.94) were best related to d24.

Figure 2: Relationship between AUC, Cmax and T>threshold for *E.coli* 35776 CTXM-15 producer

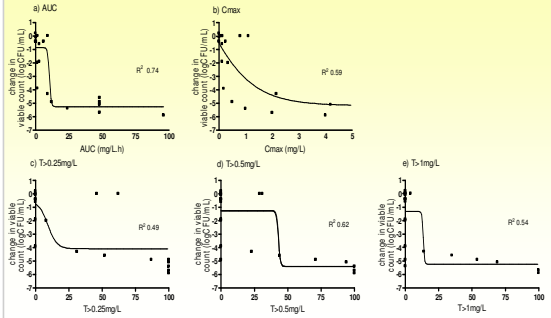

Figure 3: Relationship between AUC, Cmax and T>threshold for *K.pneumoniae* 42421 KPC producer

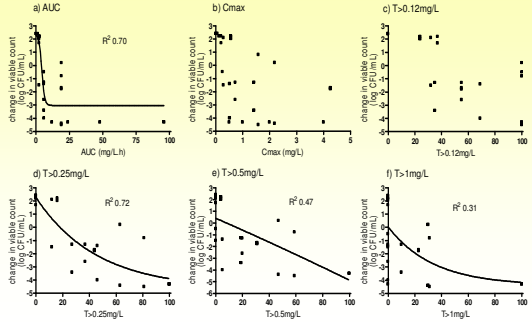

Figure 4: Relationship between AUC, Cmax and T>threshold for *E.coli* 48761 AmpC producer

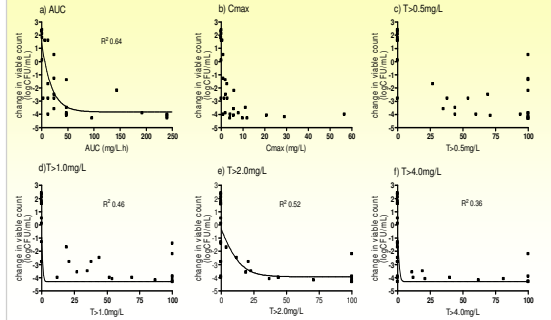

Figure 5: Relationship between AUC, Cmax and T>threshold for *K.pneumoniae* 75927 OXA-48 producer

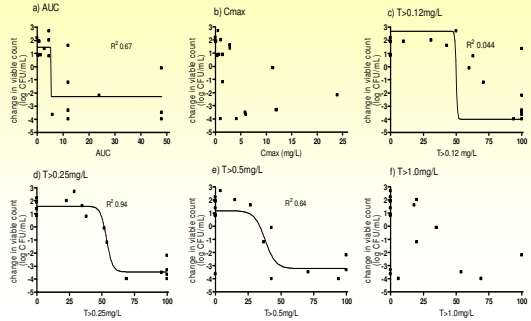

Table 2: VNRX-5133 AUC for a static, 1log, 2log reduction in viable count

strain/enzyme	Cefepime + VNRX-5133 MIC (mg/L)	antibacterial effect (mg/L.h)		
		static effect	1 log drop	2 log drop
E.coli / CTXM	0.5	-	-	-
K.pneumoniae / KPC	1	4.0	4.4	5.6
E.coli / AmpC	8	5.8	11.2	19.2
K.pneumoniae / OXA-48	2	5.1	5.2	5.3

Table 3: VNRX-5133 T>threshold required for a static, 1log, 2log reduction in viable count

strain/enzyme	Cefepime + VNRX-5133 MIC (mg/L)	T>VNRX-5133 threshold (mg/L)	antibacterial effect (%)		
			static effect	1 log drop	2 log drop
E.coli / CTXM	0.5	-	-	-	-
K.pneumoniae / KPC	1	0.25	17.8	28.8	41.9
E.coli / AmpC	8	2.0	0.0	2.3	8.0
K.pneumoniae / OXA-48	2	0.25	51.6	53.0	54.7

- The VNRX-5133 AUC to produce a static effect in viable count at 24h with each strain was 4.0-5.8mg/L.h, and a -1 log reduction in count 4.4-11.2mg/L.h.
- AUC/MIC, Cmax/MIC and T>MIC>4 could also be related to d24 in a pooled analysis including all four strains, however, curve fit was poor R^2<0.40.

Conclusions:

- VNRX-5133 was effective in combination with cefepime in producing bacterial clearance from the model for cefepime-resistant isolates of Enterobacterales with CTX-M15, KPC, AmpC and OXA-48 enzymes.
- The primary pharmacodynamic driver is AUC or time over threshold, both being closely related to antibacterial effect (no specific T>threshold concentration predicted efficacy).

This study was funded by VenatoRx Pharmaceuticals