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Oral Bioavailability of Novel β-Lactamase Inhibitor VNRX-7145 in Rats, Dogs, and Non-Human Primates

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Background

VNRX-7145 is a novel, orally bioavailable, cyclic boronate β-lactamase inhibitor (BLI) in development in combination with ceftibuten as an oral treatment for infections caused by serine-β-lactamase-producing Enterobacteriaceae. *In vivo*, VNRX-7145 undergoes biotransformation to the active BLI, VNRX-5236, that covalently and reversibly binds the active site serine of Ambler Class A, C and D β-lactamases[1]. Here, the oral bioavailability in rats, dogs, and non-human primates was investigated to determine the level of absorption. The rate and level of biotransformation of VNRX-7145 into the active BLI, VNRX-5236, was also determined.

Methods

Groups of rats (5), dogs (4), and NHPs (4) were given a single 10 mg/kg (1 mg/kg for NHPs) intravenous bolus (5 mL/kg) dose of VNRX-5236 in a formulation of sodium acetate/acetic acid buffer (pH 5). Groups of rats (6), dogs (4), and NHPs (4) were given a single oral gavage (5 mL/kg) of VNRX-7145 in a Solutol® HS-15:Water (20:80 for rats and NHPs, 10:90 for dogs) formulation at doses ranging from 10-1,000 mg/kg in rats and NHPs and 10-300 mg/kg in dogs.

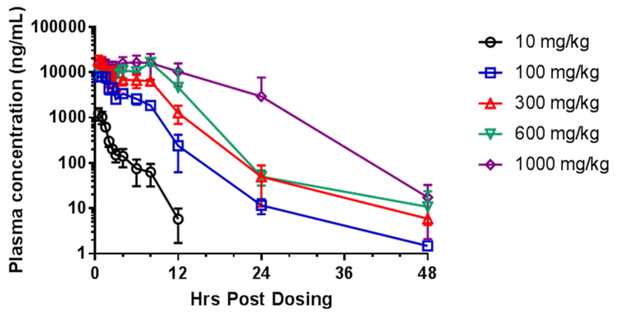
Blood samples were collected at various time points up to 48 hours post-dose in K_2EDTA tubes to which a 0.5M solution of citric acid was added. After centrifugation to collect plasma, 10% formic acid was added to the samples prior to freezing. These additions of acid were to provide esterase inhibition so that amounts of circulating VNRX-7145 could be determined without additional cleavage occurring post-sampling. Bioanalytical methods for VNRX-7145 and VNRX-5236 were developed and qualified in rat, dog, and NHP plasma. Pharmacokinetic parameters for both analytes were estimated with concentration-nominal time data for each animal by model independent methods using WinNonlin® Professional, Version 7.0 (Pharsight Corporation, a Certara company).

VNRX-5236 Plasma Levels after Oral Dosing of VNRX-7145

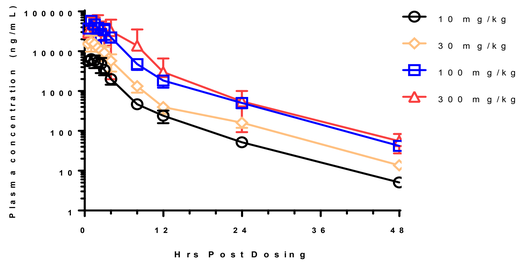
PO Dose of VNRX-7145 (mg/kg)	C_{max} (μg/mL)	AUC_{last} (μg*h/mL)	%F[a]
Rats			
10	1.25	2.42	53
100	8.92	36.1	80
300	19.2	90.3	67
600	17.7	157	58
1,000	19.6	285	64
Dogs			
10	6.42	26.4	100
30	19.2	68.2	87
100	58.4	228	88
300	57.1	298	39
100[b]	74.4	199	77
NHPs			
10	12.4	64.0	75
30	20.3	131	51
100	61.4	445	52
300	86.9	1,107	44
600	90.9	1,667	32
1,000	97.3	1,555	18
100[c]	62.3	461	54

[a] %F = Percent absolute oral bioavailability corrected for MW difference between VNRX-7145 and VNRX-5236.
[b] Fasted dogs.
[c] Fasted NHPs.
For a VNRX-5236 IV dose of 10 mg/kg, C_{max} and AUC_{last} were 23.7 μg/mL and 6.7 μg*h/mL, respectively, in rats; 54.5 μg/mL and 39.3 μg*h/mL, respectively, in dogs;
For a VNRX-5236 IV dose of 1 mg/kg in NHPs, C_{max} and AUC_{last} were 25.8 μg/mL and 12.7 μg*h/mL, respectively.

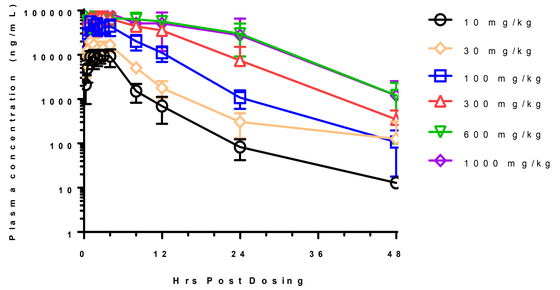
Plasma Concentrations of VNRX-5236 in Rats



Plasma Concentrations of VNRX-5236 in Dogs



Plasma Concentrations of VNRX-5236 in NHPs



Summary

Rat PK Study: A dose proportional increase in exposure of VNRX-5236 vs. VNRX-7145 dose (r^2=0.98) was observed. VNRX-7145 was converted rapidly and extensively to VNRX-5236 in vivo at all dose levels, with less than 2% of the VNRX-5236 exposure detected at any time point.
Dog PK Study: Emesis impacted data derived from dosing of dogs and resulted in a maximum dose administered of 300 mg/kg. VNRX-7145 was converted rapidly and extensively to VNRX-5236 in vivo at all dose levels, with less than 2% of the VNRX-5236 exposure detected at any time point. Prandial state of the dogs did not impact exposure significantly.
NHP PK Study: A dose-related increase in exposure was observed up to the 600 mg/kg dose of VNRX-7145. VNRX-7145 was converted rapidly and extensively to VNRX-5236 in vivo at all dose levels, with less than 2% of the VNRX-5236 exposure detected at any time point. Prandial state of the NHPs did not impact exposure significantly.

Conclusions

- Dose-proportional or dose-related increase in exposure of VNRX-5236 was observed in all three species.
- VNRX-7145 was converted rapidly and extensively to the active VNRX-5236 at all dose levels and at all time points in all three species.
- Up to a 1,000 mg/kg single dose was well-tolerated in both rats and non-human primates.
- The high absolute oral bioavailability observed across the three species coupled with in vitro metabolic biotransformation and Caco-2 permeability assay results support advancement of VNRX-7145 to human testing.[2]

References

1. Meyers, C. et al. 2019. Ceftibuten/VNRX-7145, an orally bioavailable β -lactam/ β-lactamase inhibitor combination active against serine- β -lactamase-producing Enterobacteriaceae. ECCMID poster #1182
2. Trout, R.E. et. al. 2019. In Vitro Permeability and Metabolic Biotransformation of Oral β-Lactamase Inhibitor VNRX-7145 Across Species. ASM poster #AAR-724

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