29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

O1064 *In vivo* pharmacodynamic profile of cefepime in combination with VNRX-5133 against serine beta-lactamase-producing Gram-negative bacteria in the neutropenic murine thigh infection model

Kamilia Abdelraouf*[1], Safa Almarzoky Abuhussain[1,2], David Nicolau[1]

[1] Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, United States, [2] Umm Al-Qura University, Makkah, Saudi Arabia

Background: Cefepime (FEP)/VNRX-5133 is a cephalosporin/cyclic boronate β-lactamase inhibitor combination under development for treatment of infections due to multi-drug resistant gram-negative bacteria. The objective of this study was 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 Enterobacteriaceae isolates (KPC-, OXA-48- and extended-spectrum β-lactamases-expressing) and against *Pseudomonas aeruginosa* (AmpC-overproducing and KPC-expressing) in the neutropenic murine thigh infection model.

Materials/methods: Thighs of neutropenic ICR mice were inoculated with bacterial suspensions (10^7 CFU/ml). Dose-fractionation studies were conducted against 2 KPC-producing isolates; FEP human-simulated regimen (HSR) equivalent to a clinical dose of 2g q8h as 2h infusion was given in combination with 2 total daily VNRX-5133 doses (1 or 5 mg/kg/day), each given with 3 dosing frequencies (q24h, q12h or q6h). Dose-ranging studies were conducted to assess the *in vivo* bactericidal activity of FEP HSR in combination with escalating VNRX-5133 exposures against 26 clinical Enterobacteriaceae (FEP/VNRX-5133 combination MICs 0.06 - 16 mg/L, at fixed VNRX-5133 concentration of 4 mg/L) and 4 *P. aeruginosa* isolates (FEP/VNRX-5133 combination MICs 2 - 16 mg/L). Efficacy was measured as the change in $\log_{10}$CFU/thigh at 24h compared with 0h controls. Pharmacokinetics of VNRX-5133 was assessed to determine the systemic exposures of the regimens utilized; exposures required to achieve various efficacy endpoints were estimated using the Hill-equation.

Results: Dosing frequency had no impact on VNRX-5133 potentiation of FEP activity as the bacterial burdens at 24h in the thighs of the groups of mice receiving the same VNRX-5133 total daily dose were comparable for each isolate. Relationship between the area under the free VNRX-5133 concentration–time curve to MIC ratios (fAUC$_{0\text{-}24}$/MIC) and the change in $\log_{10}$CFU/thigh at 24h for each isolate was examined; median fAUC$_{0\text{-}24}$/MIC values associated with static and 1-log kill endpoints for Enterobacteriaceae isolates were 1.18 and 2.62, respectively (median R^2 = 0.97), and for *P. aeruginosa* 0.29 and 0.46, respectively (median R^2 = 0.92).

Conclusions: The fAUC$_{0\text{-}24}$/MIC appeared to be the PK/PD driver for the activity of VNRX-5133. These data support VNRX-5133 dose selection for Phase 2 studies.