In vitro activity of cefepime alone and in combination with the broad-spectrum beta-lactamase inhibitor VNRX-5133 against ESBL and carbapenemases harbouring Enterobacteriaceae and Pseudomonas spp.

Ria Donnelly1,2, Wendy Kloezen2, Mark Goldman4, Anita C. Van Mil4, Claudia M. Lagarde2,4, Joseph Meletiadis2,3, Johan Mouton*2,4

1Radboud University Medical Center, Department of Medical Microbiology, Nijmegen, 2Erasmus Medical Center, Department of Medical Microbiology and Infectious Diseases, Rotterdam, Netherlands, 3Medical School, National and Kapodistrian University of Athens, Clinical Microbiology Laboratory, Attikon Hospital, Athens, Greece, 4Radboud University Medical Center, Department of Medical Microbiology, Nijmegen, Netherlands

**Background:** Extended spectrum β-lactamase (ESBL) and carbapenemase producing strains are increasing worldwide. VNRX-5133 is a newly developed broad-spectrum beta-lactamase inhibitor with potent and direct inhibitory activity against Ambler Class A (ESBL and KPC), B (NDM and VIM), C (AmpC) and D β-lactamases. To evaluate the potential clinical feasibility and concentrations to be used in MIC determinations in the clinical laboratory, we determined the inhibition of clinically and molecularly well-documented ESBL and carbapenemase producing strains.

**Materials/methods:** Clinically and molecularly well-documented ESBL and carbapenemase producing strains (42 Escherichia coli, 39 Klebsiella pneumoniae, 29 Pseudomonas aeruginosa, 16 Enterobacter cloacae, 2 Citrobacter freundii, 2 Enterobacter aerogenes) with a variety of resistance mechanisms were used. MICs were determined and evaluated following EUCAST and ISO compliant methods. Full checkerboard experiments were performed to study interactions with two-fold dilutions over the range of 0.063-256 mg/L FEP and 0.032-32 mg/L VNRX-5133 in duplicate.

**Results:** The MIC50 and MIC90 of cefepime for all Enterobacteriaceae isolates (n=101) were 32 and 256 mg/L, respectively. For P. aeruginosa isolates this was 32 and 128 mg/L, respectively. The 50th and 90th percentile concentration of VNRX-5133 required to reduce the MIC of cefepime to 8 mg/L (the current clinical breakpoint of cefepime high dose) for all Enterobacteriaceae isolates was ≤0.032/0.5 mg/L, while for P. aeruginosa isolates this was 1 and 32 mg/L. At a fixed concentration of 1 mg/L VNRX-5133, the MIC50 and MIC90 were reduced to 0.25 and 2 mg/L, respectively, for Enterobacteriaceae isolates, and to 16 and 64 mg/L, respectively, for P. aeruginosa isolates. To obtain a breakpoint MIC of ≤16 mg/L cefepime for 90% of the P. aeruginosa isolates, including strains with reduced permeability, 4 mg/L VNRX-5133 was required.

**Conclusions:** Increasing concentrations of VNRX-5133 resulted in a decreasing MIC of cefepime to clinically relevant values. At a fixed concentration of 4 mg/L VRNX-5133 all Enterobacteriaceae were susceptible. The combination cefepime/VNRX is a promising alternative treatment option for infections caused by ESBL harbouring Enterobacteriaceae strains and the majority of P. aeruginosa.