28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

P1039 In vitro activity of Nacubactam, a novel dual action diazabicyclooctane, alone and with meropenem, against beta-lactamase-positive Enterobacteriaceae

Ian Morrissey*[1], Sophie Magnet[1], Stephen Hawser[1], Séverine Louvel[3], Rusudan Okujava[2 3], Claudia Zampaloni[3], Kenneth Bradley[3]

[1]IHMA Europe Sàrl, Monthey, Switzerland, *[2]Roche, Basel, Switzerland*, *[3]Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd , Immunology, Inflammation and Infectious Diseases, Basel, Switzerland*

Background: Nacubactam (NAC, RG6080, OP0595) is a novel dual action diazabicyclooctane having both a beta-lactamase inhibitor activity and a direct antibacterial activity that can additionally translate to an “enhancer” effect when partnered with beta-lactams. This study investigated the effect of nacubactam alone and together with meropenem against recent clinical *Enterobacteriaceae* isolates that are positive for beta-lactamase genes.

Materials/methods: Isolates originating from US and European hospitals between 2013 and 2016 were investigated (n=1,553). The main species were *Klebsiella pneumoniae* (n=701), *Escherichia coli* (n=494) and *Enterobacter cloacae* (n=195). Beta-lactamases were identified by PCR amplification and gene sequencing. MICs were determined by broth microdilution following CLSI methodology. Meropenem and nacubactam were tested as fixed ratio (1:1 and 2:1) and fixed concentrations of nacubactam (2 and 4 mg/L).

Results: MIC50 and MIC90 data for meropenem, nacubactam and meropenem:nacubactam combinations against all *Enterobacteriaceae* and by class of beta-lactamase are shown in the Table. Nacubactam alone had a bimodal MIC distribution (2 and >32 mg/L) against the tested *Enterobacteriaceae* clinical isolates with an MIC50 of 2 mg/L. Meropenem:nacubactam demonstrated activity against class B-, class D- and KPC-producing *Enterobacteriaceae*. Meropenem and meropenem:nacubactam were similarly active against ESBL- and class C- producing isolates.

Isolate group:		NAC	MEM:NAC [1:1][1]	MEM:NAC [2:1][1]	MEM:NAC [2][2]	MEM:NAC [4][2]	MEM
All (n=1553)	MIC_{50}	2	0.12	0.25	≤ 0.004	≤ 0.004	0.5
	MIC_{90}	> 32	2	4	0.5	0.25	128
Class A (n= 577)	MIC_{50}	2	0.03	0.03	≤ 0.004	≤ 0.004	0.03
	MIC_{90}	> 32	0.06	0.06	0.015	0.015	0.12
Class B (n= 123)	MIC_{50}	4	2	4	0.008	≤ 0.004	32
	MIC_{90}	> 32	32	32	64	64	> 256
Class C (n= 254)	MIC_{50}	2	0.06	0.06	≤ 0.004	≤ 0.004	0.12
	MIC_{90}	> 32	0.25	0.25	0.06	0.015	0.5
Class D (n= 212)	MIC_{50}	32	1	2	0.25	0.12	4
	MIC_{90}	> 32	4	8	8	4	64
KPC (n= 381)	MIC_{50}	4	1	1	0.008	≤ 0.004	64
	MIC_{90}	> 32	2	4	0.5	0.25	256
GES (n=6)[3]	MIC range	1 - > 32	0.12 - 4	0.12 - 8	≤ 0.004 - 8	≤ 0.004 - 1	0.12 - 256

NAC, nacubactam; MEM; meropenem

[1]Fixed MEM:NAC ratio; [2]Fixed NAC concentration (mg/L); [3]GES-6 or GES-20 carbapenemase-positive

Conclusions: Nacubactam works as a beta-lactamase inhibitor and as an antibacterial agent that, partnered with meropenem, can have also an “enhancer” effect. These combined activities translate into the observed excellent *in vitro* activity of meropenem:nacubactam against beta-lactamase-producing *Enterobacteriaceae*.