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P1843 Antimicrobial activity of POL7306 tested against clinical isolates of Gram-negative bacteria collected worldwide

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Background: POL7306 belongs to a novel class of outer membrane protein target antibiotics (OMPTAs) with a novel mechanism of action. POL7306 is in development for the treatment of infections caused by antimicrobial resistant gram-negative bacteria.

Materials/methods: : A total of 891 isolates were collected by the SENTRY Antimicrobial Surveillance Program from 134 medical centres in Europe (n=424; 41 centres in 18 nations), United States (USA; 411 isolates from 67 centres), Asia-Pacific region (APAC; n=24; 15 centres in 6 nations), and Latin America (LATAM; n=32; 11 centres in 9 nations). The collection comprised 558 Enterobacteriaceae, 310 non-fermenters, and 23 fastidious organisms. Susceptibility testing was performed by reference broth microdilution method, and media was supplemented with 0.002% polysorbate-80 (P-80) for testing POL7306. Resistant subsets were characterized by whole genome sequencing.

Results: POL7306 was very active against Enterobacteriaceae, except against *Proteus mirabilis*, indole-positive Proteeae (IPP) and *Serratia* spp. When these organisms were excluded from the collection of randomly selected Enterobacteriaceae, POL7306 ($MIC_{50/90}$, 0.06/0.25 mg/L; highest MIC, 1 mg/L) was slightly more active than colistin ($MIC_{50/90}$, 0.12/0.25 mg/L; highest MIC, >8 mg/L) against the remaining isolates (Table). POL7306 was also highly active against carbapenem-resistant ($MIC_{50/90}$, 0.06/0.25 mg/L), ESBL-producing ($MIC_{50/90}$, 0.06/0.12 mg/L), KPC-producing ($MIC_{50/90}$, 0.12/0.25 mg/L), metallo-beta-lactamase-producing ($MIC_{50/90}$, 0.06/0.25 mg/L) Enterobacteriaceae. POL7306 ($MIC_{50/90}$, 0.12/0.25 mg/L) was 32-fold more potent than colistin ($MIC_{50/90}$, 4/8 mg/L) when tested against *mcr*-positive Enterobacteriaceae and retained good activity ($MIC_{50/90}$, 0.5/2 mg/L) against colistin-nonsusceptible (MIC >2 mg/L), *mcr*-negative *Klebsiella pneumoniae*. The *Pseudomonas aeruginosa* collection (n=154) included 102 extensively drug-resistant (XDR) isolates, and the highest POL7306 MIC value was only 0.5 mg/L ($MIC_{50/90}$, 0.25/0.25 mg/L). POL7306 exhibited good activity against XDR *Acinetobacter baumannii* (n=105; $MIC_{50/90}$, 0.06/0.12 mg/L) and *Stenotrophomonas maltophilia* ($MIC_{50/90}$, 0.06/0.25 mg/L).

Conclusions: POL7306 demonstrated potent activity against a large collection of gram-negative organisms collected worldwide that included colistin-resistant, XDR, and ESBL- and carbapenemase-producing isolates for which there are currently limited treatment options.

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:								
	0.03	0.06	0.12	0.25	0.5	1	2	4	>[a]
Enterobacteriaceae (272)[b]		54.4	86.4	98.2	99.3	100.0			
Carbapenem-resistant Enterobacteriaceae (53)	1.9	56.6	86.8	98.1	100.0				
ESBL-producing Enterobacteriaceae (24)		66.7	95.8	100.0					
KPC-producing Enterobacteriaceae (23)		47.8	87.0	100.0					
MBL-producing Enterobacteriaceae (12)		75.0	83.3	91.7	91.7	91.7	91.7	91.7	100.0
mcr-positive Enterobacteriaceae (75)		8.0	89.3	100.0					
Colistin-NS[c], *mcr*-negative *K. pneumoniae* (24)			4.2	33.3	79.2	87.5	95.8	100.0	
Pseudomonas aeruginosa (154)		1.3	40.9	96.8	100.0				
XDR *Acinetobacter baumannii* (105)	1.9	58.1	95.2	100.0					
Stenotrophomonas maltophilia (51)	13.7	56.9	78.4	100.0					

[a] Greater than the highest concentration tested.
[b] Randomly selected isolates, excluding indole-positive Proteeae and *Serratia* spp.
[c] NS, nonsusceptible, MIC >2 mg/L.