P0101 Global surveillance of *in vitro* activity of eravacycline and comparators against *Enterobacteriaceae*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus* and *Enterococcus* spp. collected during 2016

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Introduction

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic currently under review by the EMA and FDA for the treatment of complicated intra-abdominal infections.

The purpose of this study was to evaluate the activity of eravacycline and comparators against global isolates of *Enterobacteriaceae*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), and *Enterococcus* spp, including those that are multidrug-resistant (MDR).

Methods

- A total of 4544 clinical isolates collected in 2016 from urinary, intra-abdominal and respiratory infections were tested.
- Distribution of the isolates tested, including resistance phenotype, are shown in Figure 1.
- MDR was defined as resistance to ≥ 3 from cefepime/cefotaxime/ceftazidime/ceftriaxone (any one), aztreonam, gentamicin, a carbapenem (meropenem or ertapenem) levofloxacin, piperacillin-tazobactam, tetracycline or tigecycline.
- The geographic origins of the clinical isolates are shown in Figure 2.
- Minimal inhibitory concentration (MIC) values were determined by broth microdilution according to CLSI guidelines[1] for eravacycline and comparators.
- Quality control testing was performed each day of testing as specified by the CLSI using *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 28753 *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213.
- Antibiotic susceptibility was determined using EUCAST breakpoints.[2]

Figure 1. Percent distribution of isolates tested and resistance phenotype.

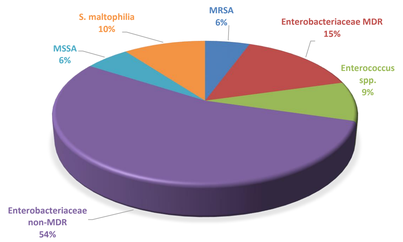
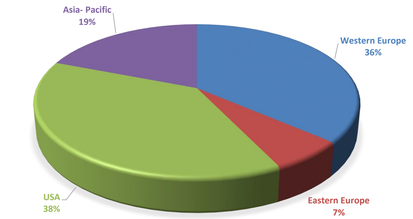


Figure 2. Percent distribution of all isolates by geographic origin.



Results

- Susceptibility data, $MIC_{50/90}$ values, and MIC ranges for eravacycline and comparators are shown in Tables 1 - 7.
- The susceptibility range of MDR *Enterobacteriaceae* was from 13.9% for cefotaxime to 94% for meropenem, with 67.8% of isolates susceptible to tigecycline.
- 78.5%, 87.1%, and 93.8% of MRSA were susceptible to tetracycline, minocycline and tigecycline, respectively.
- 80.4% of *E. faecalis* and *E. faecium* were susceptible to tigecycline.
- The MIC_{90} of eravacycline was at least 4-fold lower than tigecycline against *Enterobacteriaceae,* including against MDR isolates, MRSA and *Enterococcus* spp.

Table 1. Susceptibility of *Enterobacteriaceae* (n = 3,157) to eravacycline and comparators.

Drug	Breakpoints [S|I|R]	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Min	Max
Amikacin	≤8 | 16 | ≥32	97.5	0.9	1.6	1	4	≤ 0.25	> 64
Aztreonam	≤1 | 2-4 | ≥8	78.7	2.9	18.4	0.12	> 16	≤ 0.03	> 16
Cefepime	≤1 | 2-4 | ≥8	85.4	3.4	11.3	0.06	8	≤ 0.008	> 16
Cefotaxime	≤1 | 2 | ≥4	75.1	1.9	23.0	0.12	> 64	≤ 0.015	> 64
Ceftazidime	≤1 | 2-4 | ≥8	77.7	3.5	18.8	0.25	64	≤ 0.03	> 128
Ceftriaxone	≤1 | 2 | ≥4	75.7	1.0	23.4	0.12	> 4	≤ 0.015	> 4
Eravacycline	**NB**	**-**	**-**	**-**	**0.25**	**1**	**0.03**	**16**
Ertapenem	≤0.5 | 1 | ≥2	95.2	1.8	3.0	0.015	0.25	0.004	> 2
Gentamicin	≤2 | 4 | ≥8	87.6	1.2	11.3	0.5	16	≤ 0.12	> 16
Levofloxacin	≤0.5 | 1 | ≥2	78.8	3.4	17.7	0.06	8	≤ 0.004	> 8
Meropenem	≤2 | 4-8 | ≥16	98.6	1.4	0.0	0.03	0.12	≤ 0.004	> 4
Minocycline	NB	-	-	-	2	> 16	≤ 0.12	> 16
Piperacillin Tazobactam	≤8 | 16 | ≥32	81.6	5.3	13.1	2	64	≤ 0.25	> 128
Tetracycline	NB	-	-	-	2	> 64	≤ 0.25	> 64
Tigecycline	≤1 | 2 | ≥4	76.2	12.6	11.2	0.5	4	0.03	32

%S, %I, %R, percent susceptible, intermediate or resistant; NB, no defined breakpoint

Table 2. Susceptibility of MDR *Enterobacteriaceae* (n = 686) to eravacycline and comparators.

Drug	Breakpoints [S|I|R]	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Min	Max
Amikacin	≤8 | 16 | ≥32	90.1	2.6	7.3	2	8	≤ 0.25	> 64
Aztreonam	≤1 | 2-4 | ≥8	17.9	4.4	77.7	> 16	> 16	≤ 0.03	> 16
Cefepime	≤1 | 2-4 | ≥8	36.9	13.7	49.4	4	> 16	0.015	> 16
Cefotaxime	≤1 | 2 | ≥4	13.9	1.6	84.6	> 64	> 64	≤ 0.015	> 64
Ceftazidime	≤1 | 2-4 | ≥8	17.9	6.6	75.5	32	> 128	≤ 0.03	> 128
Ceftriaxone	≤1 | 2 | ≥4	14.1	0.9	85.0	> 4	> 4	≤ 0.015	> 4
Eravacycline	**NB**	**-**	**-**	**-**	**0.25**	**2**	**0.06**	**16**
Ertapenem	≤0.5 | 1 | ≥2	79.6	7.4	13.0	0.12	2	0.004	> 2
Gentamicin	≤2 | 4 | ≥8	51.3	1.2	47.5	2	> 16	≤ 0.12	> 16
Levofloxacin	≤0.5 | 1 | ≥2	35.0	6.9	58.2	4	> 8	0.015	> 8
Meropenem	≤2 | 4-8 | ≥16	94.0	6.0	0.0	0.06	0.5	≤ 0.004	> 4
Minocycline	NB	-	-	-	4	> 16	≤ 0.12	> 16
Piperacillin Tazobactam	≤8 | 16 | ≥32	36.0	10.8	53.2	32	> 128	≤ 0.25	> 128
Tetracycline	NB	-	-	-	32	> 64	0.5	> 64
Tigecycline	≤1 | 2 | ≥4	67.8	14.0	18.2	1	4	0.06	32

%S, %I, %R, percent susceptible, intermediate or resistant; NB, no defined breakpoint

Table 3. Susceptibility of *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae*, including MDR strains, to eravacycline and tigecycline.

		Eravacycline				Tigecycline			
Species		MIC_{50}	MIC_{90}	Min	Max	MIC_{50}	MIC_{90}	Min	Max
E. coli	all (n = 503)	0.12	0.25	0.03	2	0.25	0.5	0.06	4
	MDR (n = 128)	0.12	0.25	0.06	2	0.25	1	0.06	4
K. pneumoniae	all (n = 513)	0.25	1	0.06	16	0.5	2	0.06	8
	MDR (n = 138)	0.5	2	0.12	16	1	4	0.12	8
E. cloacae	all (n = 391)	0.25	0.5	0.06	8	0.5	2	0.12	8
	MDR (n = 117)	0.5	1	0.12	4	0.5	4	0.12	4

Table 4. Susceptibility of methicillin-susceptible *S. aureus*, MSSA (n = 256) to eravacycline and comparators.

Drug	Breakpoints [S|I|R]	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Min	Max
Amoxicillin/clavulanate	NB	-	-	-	1	1	0.12	> 1
Azithromycin	≤1 | 2 | ≥4	73.05	7.42	19.53	1	> 4	0.5	> 4
Ceftaroline	≤1 | -- | ≥2	100.0	0.0	0.0	0.25	0.25	0.12	0.5
Clindamycin	≤0.25 | 0.5 | ≥1	94.9	0.4	4.7	0.06	0.12	≤ 0.03	> 2
Daptomycin	≤1 | -- | ≥2	100.0	0.0	0.0	0.25	0.5	0.25	0.5
Eravacycline	NB	-	-	-	0.06	0.12	0.03	0.5
Levofloxacin	≤1 | -- | ≥2	92.2	0.0	7.8	0.12	0.5	0.06	> 4
Linezolid	≤4 | -- | ≥8	100.0	0.0	0.0	1	2	≤ 0.5	2
Minocycline	≤0.5 | 1 | ≥2	98.8	0.0	1.2	≤ 0.06	0.12	≤ 0.06	> 8
Oxacillin	≤2 | -- | ≥4	100.0	0.0	0.0	0.25	0.5	≤ 0.06	2
Penicillin	≤0.12 | -- | ≥0.25	32.0	0.0	68.0	2	> 2	≤ 0.12	> 2
Tetracycline	≤1 | 2 | ≥4	93.4	0.4	6.3	0.25	0.5	0.12	> 16
Tigecycline	≤0.5 | -- | ≥1	98.8	0.0	1.2	0.12	0.25	0.06	1
Vancomycin	≤2 | -- | ≥4	100.0	0.0	0.0	0.5	1	0.5	2

%S, %I, %R, percent susceptible, intermediate or resistant; NB, no defined breakpoint

Table 5. Susceptibility of methicillin-resistant *S. aureus* MRSA (n = 256) to eravacycline and comparators.

Drug	Breakpoints [S|I|R]	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Min	Max
Amoxicillin/clavulanate	NB	-	-	-	> 1	> 1	0.5	> 1
Azithromycin	≤1 | 2 | ≥4	26.95	3.52	69.53	> 4	> 4	0.5	> 4
Ceftaroline	≤1 | -- | ≥2	92.2	0.0	7.8	1	1	0.12	> 4
Clindamycin	≤0.25 | 0.5 | ≥1	68.0	0.0	32.0	0.12	> 2	≤ 0.03	> 2
Daptomycin	≤1 | -- | ≥2	100.0	0.0	0.0	0.5	0.5	0.12	1
Eravacycline	NB	-	-	-	0.06	0.12	0.015	1
Levofloxacin	≤1 | -- | ≥2	35.9	0.0	64.1	4	> 4	0.06	> 4
Linezolid	≤4 | -- | ≥8	100.0	0.0	0.0	1	2	≤ 0.5	2
Minocycline	≤0.5 | 1 | ≥2	87.1	0.0	12.9	0.12	8	≤ 0.06	> 8
Oxacillin	≤2 | -- | ≥4	0.0	0.0	100.0	> 2	> 2	> 2	> 2
Penicillin	≤0.12 | -- | ≥0.25	0.0	0.0	100.0	> 2	> 2	0.25	> 2
Tetracycline	≤1 | 2 | ≥4	78.5	1.6	19.9	0.25	> 16	≤ 0.06	> 16
Tigecycline	≤0.5 | -- | ≥1	93.8	0.0	6.3	0.25	0.5	0.06	2
Vancomycin	≤2 | -- | ≥4	100.0	0.0	0.0	0.5	1	0.5	1

%S, %I, %R, percent susceptible, intermediate or resistant; NB, no defined breakpoint

Table 6. Susceptibility of *E. faecalis* and *E. faecium* combined (n = 414) to eravacycline and comparators.

Drug	Breakpoints [S|I|R]	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Min	Max
Amoxicillin/clavulanate	≤4 | 8 | ≥16	100.0	0.0	0.0	1	> 1	0.5	> 1
Ampicillin	≤4 | 8 | ≥16	65.2	0.5	34.3	2	> 8	0.5	> 8
Daptomycin	NB	-	-	-	1	2	≤ 0.03	4
Eravacycline	**NB**	**-**	**-**	**-**	**0.06**	**0.06**	**0.008**	**0.5**
Levofloxacin	≤4 | -- | ≥8	49.5	0.0	50.5	> 8	> 8	0.25	> 8
Linezolid	≤4 | -- | ≥8	99.3	0.0	0.7	1	2	≤ 0.12	> 4
Minocycline	NB	-	-	-	8	> 8	≤ 0.03	> 8
Penicillin	NB	-	-	-	4	> 8	0.5	> 8
Tetracycline	NB	-	-	-	> 32	> 32	≤ 0.06	> 32
Tigecycline	≤0.25 | 0.5 | ≥1	80.4	4.6	15.0	0.12	1	0.03	2
Vancomycin	≤4 | -- | ≥8	87.7	0.0	12.3	1	> 16	≤ 0.25	> 16

Table 7. Susceptibility of *S. maltophilia* (n= 469) to eravacycline and comparators.

Drug	Breakpoints [S|I|R]	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Min	Max
Amikacin	NB	-	-	-	> 64	> 64	0.12	> 64
Ampicillin Sulbactam	NB	-	-	-	> 64	> 64	2	> 64
Aztreonam	NB	-	-	-	> 64	> 64	0.06	> 64
Cefepime	NB	-	-	-	32	> 64	0.06	> 64
Ceftazidime	NB	-	-	-	16	> 64	0.12	> 64
Ceftriaxone	NB	-	-	-	> 64	> 64	0.12	> 64
Colistin	NB	-	-	-	2	16	0.12	> 32
Eravacycline	**NB**	**-**	**-**	**-**	**1**	**2**	**0.06**	**8**
Gentamicin	NB	-	-	-	64	> 64	0.06	> 64
Levofloxacin	NB	-	-	-	1	8	0.06	> 64
Meropenem	NB	-	-	-	> 64	> 64	0.06	> 64
Minocycline	NB	-	-	-	1	2	0.25	64
Piperacillin Tazobactam	NB	-	-	-	> 128	> 128	2	> 128
Tetracycline	NB	-	-	-	16	32	2	> 64
Tigecycline	NB	-	-	-	2	4	0.25	> 16
Trimethoprim/Sulfamethoxazole	≤4 | -- | ≥8	93.2	0.0	6.8	0.5	4	≤ 0.03	> 64

%S, %I, %R, percent susceptible, intermediate or resistant; NB, no defined breakpoint

Conclusions

- Eravacycline demonstrated potent *in vitro* activity against *Enterobacteriaceae*, including MDR phenotypes, as well as clinically important Gram-positive organisms and *S. maltophilia* collected globally in 2016.
- Eravacycline demonstrated lower MIC_{90} values than tigecycline against *Enterobacteriaceae, S. aureus, Enterococcus* spp, and *S. maltophilia*, including MDR organisms.

References

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Acknowledgements

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