Poster # 630

Global *in vitro* activity of eravacycline and comparators against *Enterobacteriaceae, Acinetobacter baumannii, Stenotrophomonas maltophilia*, *Staphylococcus aureus* and *Enterococcus spp*. including multidrug-resistant (MDR) isolates from 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, Acinetobacter baumanii, Stenotrophomonas maltophilia, Staphylococcus aureus* (including methicillin-resistant *S. aureus*, MRSA) and *Enterococcus* spp, including those that are multidrug-resistant (MDR).

Methods

- A total of 6719 clinical isolates collected in 2016 from genito-urinary, gastro-intestinal, body fluids, and respiratory sources were tested.
- Global distribution of the clinical isolates 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.
- 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 CLSI 2016 breakpoints[2], with the exception of tigecycline where FDA breakpoints were used.

References

1. CLSI, 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Tenth Edition M07-A10. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 26th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.

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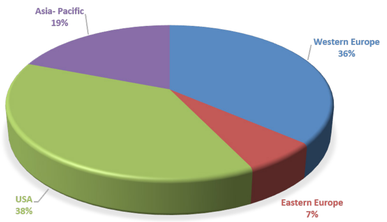
Methods (continued)

Figure 1. 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 - 8.
- The susceptibility range of MDR *Enterobacteriaceae* was from 22% for ceftriaxone to 93% for meropenem, with 81.1% of isolates susceptible to tigecycline (Table 2).
- Against *Enterobacteriaceae*, the MIC_{90} for eravacycline was 4-fold lower than tigecycline (Table 1).
- Similarly, against MDR *Enterobacteriaceae* (Table 2), including versus specific strains (Table 3) eravacycline was observed to be at least 2-fold more potent than tigecycline and at least 8-fold more potent than minocycline.
- 80.1% and 93.8% of MRSA were susceptible to tetracycline and tigecycline, respectively (Table 5).
- The MIC_{90} of eravacycline was at least 4-fold lower than tigecycline against *S aureus*, including MRSA (Table 5).
- Versus *A. baumannii*, eravacycline demonstrated 8-fold greater potency compared to tigecycline and minocycline (Table 8).

Results (continued)

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

Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**0.25**	**1**	**0.03**	**16**
Amikacin	<=16 | 32 | >=64	98.42	0.38	1.2	1	4	<= 0.25	> 64
Aztreonam	<=4 | 8 | >=16	81.63	1.58	16.79	0.12	> 16	<= 0.03	> 16
Cefepime	<=2 | 4-8 | >=16	87.23	2.79	9.98	0.06	8	<= 0.008	> 16
Ceftazidime	<=4 | 8 | >=16	81.18	1.68	17.14	0.25	64	<= 0.03	> 128
Ceftriaxone	<=1 | 2 | >=4	75.67	0.98	23.35	0.12	> 4	<= 0.015	> 4
Ertapenem	<=0.5 | 1 | >=2	95.15	1.84	3.01	0.015	0.25	0.004	> 2
Gentamicin	<=4 | 8 | >=16	88.72	0.86	10.42	0.5	16	<= 0.12	> 16
Levofloxacin	<=2 | 4 | >=8	84.99	1.9	13.11	0.06	8	<= 0.004	> 8
Meropenem	<=1 | 2 | >=4	98.23	0.35	1.43	0.03	0.12	<= 0.004	> 4
Piperacillin Tazobactam	<=16/4 | 32/4-64/4 | >=128/4	86.89	5.48	7.63	2	64	<= 0.25	> 128
Tetracycline	<=4 | 8 | >=16	64.05	4.53	31.42	2	> 64	<= 0.25	> 64
Tigecycline	<=2 | 4 | >=8	88.85	8.71	2.44	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 = 666) to eravacycline and comparators.

Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**0.5**	**2**	**0.03**	**16**
Amikacin	<=16 | 32 | >=64	92.49	1.8	5.71	2	16	<= 0.25	> 64
Aztreonam	<=4 | 8 | >=16	31.53	2.55	65.92	> 16	> 16	<= 0.03	> 16
Cefepime	<=2 | 4-8 | >=16	43.09	11.56	45.35	8	> 16	<= 0.008	> 16
Ceftazidime	<=4 | 8 | >=16	31.98	5.56	62.46	32	> 128	<= 0.03	> 128
Ceftriaxone	<=1 | 2 | >=4	22.22	1.2	76.58	> 4	> 4	<= 0.015	> 4
Ertapenem	<=0.5 | 1 | >=2	79.43	7.21	13.36	0.12	2	0.004	> 2
Gentamicin	<=4 | 8 | >=16	48.95	3.15	47.9	8	> 16	<= 0.12	> 16
Levofloxacin	<=2 | 4 | >=8	43.54	4.8	51.65	8	> 8	0.015	> 8
Meropenem	<=1 | 2 | >=4	92.64	1.2	6.16	0.06	0.5	<= 0.004	> 4
Piperacillin Tazobactam	<=16/4 | 32/4-64/4 | >=128/4	56.31	11.41	32.28	16	> 128	<= 0.25	> 128
Tetracycline	<=4 | 8 | >=16	30.48	3.75	65.77	64	> 64	0.5	> 64
Tigecycline	<=2 | 4 | >=8	81.08	11.71	7.21	1	4	0.06	32

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

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

Organism	Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	Maximum
C. freundii MDR (54)	**Eravacycline**	**No Breakpoints Defined**	–	–	–	**0.25**	**1**	**4**
	Minocycline	<=4 | 8 | >=16	50	14.81	35.19	4	> 16	> 16
	Tetracycline	<=4 | 8 | >=16	55.56	12.96	31.48	4	> 64	> 64
	Tigecycline	<=2 | 4 | >=8	94.44	5.56	0	0.5	2	4
E. cloacae MDR (N=95)	**Eravacycline**	**No Breakpoints Defined**	–	–	–	**0.5**	**2**	**4**
	Minocycline	<=4 | 8 | >=16	56.84	14.74	28.42	4	> 16	> 16
	Tetracycline	<=4 | 8 | >=16	50.53	4.21	45.26	4	> 64	> 64
	Tigecycline	<=2 | 4 | >=8	86.32	13.68	0	1	4	4
E. coli MDR (15)	**Eravacycline**	**No Breakpoints Defined**	–	–	–	**0.12**	**0.25**	**2**
	Minocycline	<=4 | 8 | >=16	64.24	10.6	25.17	2	> 16	> 16
	Tetracycline	<=4 | 8 | >=16	14.57	0	85.43	> 64	> 64	> 64
	Tigecycline	<=2 | 4 | >=8	98.01	1.99	0	0.25	1	4
K. pneumoniae MDR (142)	**Eravacycline**	**No Breakpoints Defined**	–	–	–	**0.5**	**2**	**16**
	Minocycline	<=4 | 8 | >=16	45.07	21.13	33.8	8	> 16	> 16
	Tetracycline	<=4 | 8 | >=16	33.8	4.93	61.27	> 64	> 64	> 64
	Tigecycline	<=2 | 4 | >=8	88.03	6.34	5.63	1	4	8

%S, %I, %R, percent susceptible, intermediate or resistant; NB, no defined breakpoint; MDR, multi-drug resistant

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}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**0.06**	**0.12**	**0.03**	**0.5**
Clindamycin	<=0.5 | 1-2 | >=4	95.31	0	4.69	0.06	0.12	<= 0.03	> 2
Daptomycin	<=1 | – | –	100	0	0	0.25	0.5	0.25	0.5
Levofloxacin	<=1 | 2 | >=4	92.19	0.78	7.03	0.12	0.5	0.06	> 4
Linezolid	<=4 | – | >=8	100	0	0	1	2	<= 0.5	2
Oxacillin	<=2 | – | >=4	100	0	0	0.25	0.5	<= 0.06	2
Penicillin	<=0.12 | – | >=0.25	32.03	0	67.97	2	> 2	<= 0.12	> 2
Tetracycline	<=4 | 8 | >=16	94.92	0	5.08	0.25	0.5	0.12	> 16
Tigecycline	<=0.5 | – | –	98.83	0	1.17	0.12	0.25	0.06	1
Vancomycin	<=2 | 4-8 | >=16	100	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}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**0.06**	**0.12**	**0.015**	**1**
Clindamycin	<=0.5 | 1-2 | >=4	68	0	32	0.12	> 2	<= 0.03	> 2
Daptomycin	<=1 | – | –	100	0	0	0.5	0.5	0.12	1
Levofloxacin	<=1 | 2 | >=4	35.9	5.5	58.6	4	> 4	0.06	> 4
Linezolid	<=4 | – | >=8	100	0	0	1	2	<= 0.5	2
Oxacillin	<=2 | – | >=4	0	0	100	> 2	> 2	> 2	> 2
Penicillin	<=0.12 | – | >=0.25	0	0	100	> 2	> 2	0.25	> 2
Tetracycline	<=4 | 8 | >=16	80.1	0.4	19.5	0.25	> 16	<= 0.06	> 16
Tigecycline	<=0.5 | – | –	93.75	0	6.25	0.25	0.5	0.06	2
Vancomycin	<=2 | 4-8 | >=16	100	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 = 397) to eravacycline and comparators.

Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**0.06**	**0.06**	**0.008**	**0.5**
Ampicillin	<=8 | – | >=16	65.7	0	34.3	2	> 8	0.5	> 8
Daptomycin	<=4 | – | –	100	0	0	1	2	<= 0.03	4
Levofloxacin	<=2 | 4 | >=8	48.3	1.2	50.5	> 8	> 8	0.25	> 8
Linezolid	<=2 | 4 | >=8	98.8	0.5	0.7	1	2	<= 0.12	> 4
Penicillin	<=8 | – | >=16	62.8	0	37.2	4	> 8	0.5	> 8
Tigecycline	<=0.25 | – | –	80.4	0	19.56	0.12	1	0.03	2
Vancomycin	<=4 | 8-16 | >=32	87.7	0	12.3	1	> 16	<= 0.25	> 16

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

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

Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**1**	**2**	**0.06**	**8**
Amikacin	No Breakpoints Defined	0	0	0	> 64	> 64	0.12	> 64
Levofloxacin	<=2 | 4 | >=8	76.8	9.6	13.6	1	8	0.06	> 64
Meropenem	No Breakpoints Defined	0	0	0	> 64	> 64	0.06	> 64
Minocycline	<=4 | 8 | >=16	99.2	0.2	0.6	1	2	0.25	64
Piperacillin Tazobactam	No Breakpoints Defined	0	0	0	> 128	> 128	2	> 128
Tetracycline	No Breakpoints Defined	0	0	0	16	32	2	> 64
Tigecycline	No Breakpoints Defined	0	0	0	2	4	0.25	> 16
Trimethoprim Sulfa	<=2/38 | – | >=4/76	89.3	0	10.7	0.5	4	<= 0.03	> 64

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

Table 8 Susceptibility of *A baumannii* (N=503) to eravacycline and comparators

Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	Minimum	Maximum
Eravacycline	**No Breakpoints Defined**	–	–	–	**0.5**	**1**	**<= 0.015**	**16**
Amikacin	<=16 | 32 | >=64	50	2.6	47.4	32	> 64	0.25	> 64
Ampicillin Sulbactam	<=8/4 | 16/8 | >=32/16	30.4	9.7	59.9	32	> 64	1	> 64
Cefepime	<=8 | 16 | >=32	23.9	5.7	70.4	64	> 64	<= 0.03	> 64
Ceftazidime	<=8 | 16 | >=32	30.8	2.6	66.6	> 64	> 64	0.12	> 64
Colistin	<=2 | – | >=4	96.6	0	3.4	0.5	1	0.12	> 32
Levofloxacin	<=2 | 4 | >=8	29.4	3.4	67.2	16	64	<= 0.03	> 64
Meropenem	<=2 | 4 | >=8	32.4	3	64.6	64	> 64	<= 0.03	> 64
Minocycline	<=4 | 8 | >=16	64.4	20.5	15.1	2	16	0.06	> 64
Tigecycline	No Breakpoints Defined	0	0	0	4	8	0.12	> 16

%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 compared to tigecycline against *Enterobacteriaceae, S. aureus, Enterococcus* spp, and *S. maltophilia*, including MDR organisms.
- This global surveillance investigation highlights eravacycline's broad spectrum potency against Gram-negative and Gram-positive bacteria, including MDR strains and further underscores its potential benefit for treatment of polymicrobial infections caused by resistant pathogens.