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## Assessment of Eravacycline Against Recent Gastro-Intestinal (GI) and Genito-Urinary (GU) Clinical Isolates Collected During 2013-2014

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### Abstract

**Background** Eravacycline is a novel, fully synthetic fluorocycline antibiotic with broad-spectrum activity available in intravenous and oral formulations. Eravacycline has completed enrolment in Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

**Methods:** MICs were determined by CLSI broth microdilution against 1,736 GI and 1,877 GU isolates represented in a 2013-2014 global collection.

**Results:** Eravacycline MIC data ( $\mu\text{g/ml}$ ) for species where N  $\geq$ 50 from each infection type are shown in the following Table:

GU (n)	MIC <sub>50</sub>	MIC Range	GI (n)	MIC <sub>50</sub>	MIC Range
<i>A. baumannii</i> (68)	1	0.03 - 4	<i>A. baumannii</i> (67)	1	0.03 - 2
<i>C. freundii</i> (70)	0.5	0.12 - 1	<i>C. freundii</i> (81)	1	0.06 - 2
<i>C. koseri</i> (121)	0.25	0.12 - 1	<i>E. aerogenes</i> (56)	0.5	0.25 - 2
<i>E. aerogenes</i> (154)	1	0.12 - 8	<i>E. cloacae</i> (112)	1	0.12 - 8
<i>E. cloacae</i> (154)	1	0.12 - 8	<i>E. faecalis</i> (98)	0.12	0.015 - 0.5
<i>E. faecalis</i> (209)	0.06	0.008 - 0.12	<i>E. faecium</i> (98)	0.06	0.015 - 1
<i>E. faecium</i> (128)	0.06	0.008 - 0.5	<i>E. coli</i> (241)	0.25	0.06 - 2
<i>K. oxytoca</i> (135)	0.25	0.06 - 2	<i>K. oxytoca</i> (100)	0.5	0.12 - 8
<i>M. morgani</i> (73)	2	0.25 - 8	<i>K. pneumoniae</i> (252)	2	0.12 - 8
<i>P. mirabilis</i> (146)	2	0.25 - 4	<i>P. mirabilis</i> (89)	2	0.25 - 4
<i>P. vulgaris</i> (83)	1	0.25 - 2	<i>P. aeruginosa</i> (185)	16	1.0 - 32
<i>P. aeruginosa</i> (76)	16	1.0 - 32	<i>S. marcescens</i> (50)	4	1.0 - 4
<i>S. marcescens</i> (113)	2	0.5 - 8	<i>S. aureus</i> MRSA (56)	0.5	0.03 - 1
<i>S. haemolyticus</i> (79)	0.5	0.015 - 1			
<i>S. agalactiae</i> (72)	0.03	0.008 - 0.06			

**Conclusions:** For isolates from GU, the eravacycline MIC<sub>90</sub> was 2  $\mu\text{g/ml}$  or lower except against *P. aeruginosa* (MIC<sub>90</sub> = 16  $\mu\text{g/ml}$ ). For GI isolates the eravacycline MIC<sub>90</sub> was also 2  $\mu\text{g/ml}$  or lower except against *P. aeruginosa* (MIC<sub>90</sub> = 16  $\mu\text{g/ml}$ ) and *S. marcescens* (MIC<sub>90</sub> = 4  $\mu\text{g/ml}$ ). Eravacycline showed promising activity against most isolates from GU or GI infections and data from the recently completed Phase 3 trials will be used in determining the clinical breakpoints.

### Introduction

Eravacycline is a novel, fully synthetic fluorocycline antibiotic with broad-spectrum activity available in intravenous and oral formulations for the treatment of multidrug-resistant (MDR) infections, including those caused by MDR Gram-negative bacteria. Eravacycline was investigated in Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

The current study assessed the activity of eravacycline against a recent clinical isolates from Gastro-intestinal (GI) and Genito-urinary (GU) infections.

### Methods

- A total of 1,736 GI (732 from Europe & 1004 from USA) and 1,877 GU (678 from Europe & 1199 from USA) clinical isolates (collected from 2013-2014) were tested.
- Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1).
- Quality control testing was performed each day of testing as specified by the CLSI using *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Enterococcus faecalis* ATCC 29212, *H. influenzae* ATCC 49247, *H. influenzae* ATCC 49766, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619.
- Antibiotic susceptibility was determined using CLSI 2015 breakpoints (2), with the exception of tigecycline where FDA breakpoints were used (3).

**Table 1. Summary MIC data from eravacycline against isolates from GI infections (where n  $\geq$ 20).**

Organism	N	MIC ( $\mu\text{g/ml}$ )			
		MIC <sub>50</sub>	MIC <sub>90</sub>	Min	Max
<i>Acinetobacter baumannii</i>	67	0.5	1	0.03	2
<i>Citrobacter freundii</i>	81	0.25	1	0.06	2
<i>Citrobacter koseri</i>	26	0.12	0.25	0.12	0.5
<i>Enterobacter aerogenes</i>	56	0.25	0.5	0.25	2
<i>Enterobacter cloacae</i>	112	0.5	1	0.12	8
<i>Enterococcus faecalis</i>	68	0.06	0.12	0.015	0.5
<i>Enterococcus faecium</i>	98	0.06	0.06	0.015	1
<i>Escherichia coli</i>	241	0.12	0.25	0.06	2
<i>Klebsiella oxytoca</i>	100	0.25	0.5	0.12	8
<i>Klebsiella pneumoniae</i>	252	0.5	2	0.12	8
<i>Morganella morganii</i>	45	1	2	0.25	4
<i>Proteus mirabilis</i>	89	1	2	0.25	4
<i>Proteus vulgaris</i>	29	1	1	0.25	1
<i>Pseudomonas aeruginosa</i>	185	8	16	1	32
<i>Serratia marcescens</i>	50	1	4	1	4
MRSA	56	0.06	0.5	0.03	1
MSSA	43	0.06	0.12	0.03	0.25
<i>Staphylococcus epidermidis</i>	39	0.12	0.5	0.03	1
<i>Stenotrophomonas maltophilia</i>	24	0.5	2	0.12	2
<i>Streptococcus anginosus</i>	25	0.008	0.03	<=0.001	0.06

**Table 2. Summary MIC data from eravacycline against isolates from GU infections (where n  $\geq$ 20).**

Organism	N	MIC ( $\mu\text{g/ml}$ )			
		MIC <sub>50</sub>	MIC <sub>90</sub>	Min	Max
<i>Acinetobacter baumannii</i>	68	0.25	1	0.03	4
<i>Citrobacter freundii</i>	70	0.25	0.5	0.12	1
<i>Citrobacter koseri</i>	121	0.25	0.25	0.12	1
<i>Enterobacter aerogenes</i>	154	0.5	1	0.12	8
<i>Enterobacter cloacae</i>	154	0.5	1	0.12	8
<i>Enterococcus faecalis</i>	209	0.06	0.06	0.008	0.12
<i>Enterococcus faecium</i>	128	0.06	0.06	0.008	0.5
<i>Klebsiella oxytoca</i>	135	0.25	0.25	0.06	2
<i>Morganella morganii</i>	73	1	2	0.25	8
<i>Proteus mirabilis</i>	146	1	2	0.25	4
<i>Proteus vulgaris</i>	83	1	1	0.25	2
<i>Providencia stuartii</i>	42	1	2	0.5	16
<i>Pseudomonas aeruginosa</i>	76	8	16	1	32
<i>Serratia marcescens</i>	113	1	2	0.5	8
MSSA	26	0.06	0.12	0.015	0.12
<i>Staphylococcus epidermidis</i>	46	0.25	0.5	0.015	1
<i>Staphylococcus haemolyticus</i>	79	0.12	0.5	0.015	1
<i>Stenotrophomonas maltophilia</i>	33	0.5	1	0.06	2
<i>Streptococcus agalactiae</i>	72	0.03	0.03	0.008	0.06

**Table 5. Summary MIC data and susceptibility for *Acinetobacter baumannii* from GI infections (n=67) & GU infections (n=68).**

Antibiotic	CLSI Breakpoints (S  R)	Source	Percentage			MIC ( $\mu\text{g/ml}$ )			
			S	I	R	MIC <sub>50</sub>	MIC <sub>90</sub>	Min	Max
Aztreonam	No Breakpoints Defined	GI	-	-	-	>16	>16	2	>16
		GU	-	-	-	>16	>16	1	>16
Cefepime	<=8   16   >=32	GI	28.4	10.5	61.2	>16	>16	0.5	>16
		GU	41.2	17.7	41.2	16	>16	<= 0.25	>16
Ceftazidime	<=8   16   >=32	GI	23.9	1.5	74.6	>16	>16	1	>16
		GU	36.8	2.9	60.3	>16	>16	<= 0.5	>16
Ceftriaxone	<=8   16-32   >=64	GI	17.9	7.5	74.6	>32	>32	2	>32
		GU	26.5	11.8	61.8	>32	>32	2	>32
Colistin	<=2   --   >=4	GI	92.5	0.0	7.5	1	2	0.5	>4
		GU	95.6	0.0	4.4	1	2	0.25	>4
Eravacycline	No Breakpoints Defined	GI	-	-	-	0.5	1	0.03	2
		GU	-	-	-	0.25	1	0.03	4
Gentamicin	<=4   8   >=16	GI	23.9	7.5	68.7	>8	>8	1	>8
		GU	47.1	8.8	44.1	8	>8	0.5	>8
Imipenem	<=2   4   >=8	GI	38.8	1.5	59.7	>8	>8	<= 0.25	>8
		GU	52.9	1.5	45.6	2	>8	<= 0.25	>8
Levofloxacin	<=2   4   >=8	GI	14.9	3.0	82.1	>4	>4	<= 0.25	>4
		GU	32.4	2.9	64.7	>4	>4	<= 0.25	>4
Pip/Taz	<=16/4   32/4-64/4   >=128/4	GI	26.9	4.5	68.7	>64	>64	<= 0.5	>64
		GU	32.4	8.8	58.8	>64	>64	<= 0.5	>64
Tetracycline	<=4   8   >=16	GI	28.4	9.0	62.7	>8	>8	<= 0.25	>8
		GU	38.2	7.4	54.4	>8	>8	0.5	>8
Tigecycline	No Breakpoints Defined	GI	-	-	-	1	4	0.06	4
		GU	-	-	-	1	2	0.12	8

S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

### Results

**Table 3. Summary MIC data and susceptibility for *Enterobacteriaceae* from GI infections (n=1,094) & GU infections (n=1,113).**

Antibiotic	CLSI Breakpoints (S  R)	Source	Percentage			MIC ( $\mu\text{g/ml}$ )			
			S	I	R	MIC <sub>50</sub>	MIC <sub>90</sub>	Min	Max
Aztreonam	<=4   8   >=16	GI	81.5	0.8	17.6	<=0.5	>16	<=0.5	>16
		GU	87.0	1.2	11.9	<=0.5	16	<=0.5	>16
Cefepime	<=8   16   >=32	GI	92.1	1.4	6.5	<=0.25	4	<=0.25	>16
		GU	97.4	1.5	1.1	<=0.25	1	<=0.25	>16
Ceftazidime	<=4   8   >=16	GI	82.0	1.6	16.5	<=0.5	>16	<=0.5	>16
		GU	87.2	1.3	11.5	<=0.5	16	<=0.5	>16
Ceftriaxone	<=1   2   >=4	GI	78.9	1.8	19.3	<=0.5	>32	<=0.5	>32
		GU	80.0	2.3	17.7	<=0.5	16	<=0.5	>32
Colistin	No Breakpoints Defined	GI	-	-	-	1	>4	<=0.12	>4
		GU	-	-	-	1	>4	<=0.12	>4
Eravacycline	No Breakpoints Defined	GI	-	-	-	0.25	2	0.06	8
		GU	-	-	-	0.5	2	0.06	16
Gentamicin	<=4   8   >=16	GI	89.9	0.8	9.3	0.5	8	<=0.25	>8
		GU	91.1	1.1	7.8	1	4	<=0.25	>8
Imipenem	<=1   2   >=4	GI	78.1	12.3	9.7	0.5	2	<=0.25	>8
		GU	63.9	20.7	15.5	1	4	<=0.25	>8
Levofloxacin	<=2   4   >=8	GI	83.6	1.7	14.7	<=0.25	>4	<=0.25	>4
		GU	86.2	3.2	10.6	<=0.25	>4	<=0.25	>4
Pip/Taz	<=16/4   32/4-64/4   >=128/4	GI	86.7	8.6	4.8	2	32	<=0.5	>64
		GU	89.0	8.7	2.3	2	32	<=0.5	>64
Tetracycline	<=4   8   >=16	GI	63.4	5.5	31.1	2	>8	<=0.25	>8
		GU	56.8	6.2	37.0	4	>8	0.5	>8
Tigecycline	<=2   4   >=8*	GI	91.5	7.3	1.2	0.5	2	0.12	16
		GU	88.2	9.7	2.1	1	4	<=0.015	32

\* FDA breakpoints were used for Tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

**Table 6. Summary MIC data and susceptibility for *P. aeruginosa* from GI infections (n=185) & GU infections (n=76).**

Antibiotic	CLSI Breakpoints (S  R)	Source	Percentage			MIC ( $\mu\text{g/ml}$ )			
			S	I	R	MIC <sub>50</sub>	MIC <sub>90</sub>	Min	Max
Aztreonam	<=8   16   >=32	GI	46.5	21.6	31.9	16	>16	2	>16
		GU	40.8	15.8	43.4	16	>16	<=0.5	>16
Cefepime	<=8   16   >=32	GI	76.8	13.5	9.7	4	16	0.5	>16
		GU	80.3	10.5	9.2	4	16	1	>16
Ceftazidime	<=8   16   >=32	GI	77.8	4.9	17.3	4	>16	<=0.5	>16
		GU	80.3	6.6	13.2	4	>16	<=0.5	>16
Ceftriaxone	No Breakpoints Defined	GI	-	-	-	>32	>32	4	>32
		GU	-	-	-	>32	>32	2	>32
Colistin	<=2   4   >=8	GI	95.7	3.8	0.5	2	2	0.5	>4
		GU	96.1	4.0	0.0	2	2	0.5	4
Eravacycline	No Breakpoints Defined	GI	-	-	-	8	16	1	32
		GU	-	-	-	8	16	1	32
Gentamicin	<=4   8   >=16	GI	80.0	6.5	13.5	2	>8	<=0.25	>8
		GU	84.2	4.0	11.8	2	>8	<=0.25	>8
Imipenem	<=2   4   >=8	GI	59.5	9.2	31.4	2	>8	0.5	>8
		GU	55.3	11.8	32.9	2	>8	0.5	>8
Levofloxacin	<=2   4   >=8	GI	61.1	4.9	34.1	1	>4	<=0.25	>4
		GU	60.5	7.9	31.6	1	>4	<=0.25	>4
Pip/Taz	<=16/4   32/4-64/4   >=128/4	GI	67.0	15.1	17.8	8	>64	1	>64
		GU	65.8	18.4	15.8	16	>64	<=0.5	>64
Tetracycline	No Breakpoints Defined	GI	-	-	-	>8	>8	8	>8
		GU	-	-	-	>8	>8	8	>8
Tigecycline	No Breakpoints Defined	GI	-	-	-	16	32	1	>32
		GU	-	-	-	16	16	2	>32