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Assessment of Eravacycline against a Recent Global Collection of 4,462 *Enterobacteriaceae* Clinical Isolates (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 for the treatment of multidrug-resistant (MDR) infections, including MDR Gram-negative bacteria. Eravacycline has completed enrollment 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 4,462 *Enterobacteriaceae* collected worldwide.

Methods: A total of 4,462 *Enterobacteriaceae* clinical isolates (collected from 2013-2014) were tested. MICs were determined by CLSI broth microdilution. Quality control testing was performed on each day of testing as specified by the CLSI. Susceptibility was assessed using CLSI breakpoints except for tigecycline where FDA breakpoints were used.

Results: Results are shown in the following Table:

	MIC (µg/ml)		%S*	%I	%R
	MIC ₅₀	MIC ₉₀			
Eravacycline	0.5	2	-	-	-
Tetracycline	2	> 8	59.8	6.6	33.6
Tigecycline	0.5	2	91.1	7.3	1.6
Aztreonam	≤ 0.5	> 16	84.7	1.3	14.1
Cefepime	≤ 0.25	2	94.8	1.5	3.7
Ceftazidime	≤ 0.5	> 16	85.3	1.1	13.5
Ceftriaxone	≤ 0.5	32	80.3	2.0	17.7
Colistin	1	> 4	-	-	-
Gentamicin	0.5	4	91.5	1.0	7.5
Imipenem	0.5	4	72.0	16.8	11.3
Levofloxacin	≤ 0.25	> 4	86.8	1.9	11.3
Piperacillin/tazobactam	2	32	87.4	9.0	3.6

*%S, I, R; percent susceptible, intermediate or resistant

Conclusions: Against a total of 4,462 *Enterobacteriaceae* clinical isolates, eravacycline exhibited the lowest MIC₉₀ of 2 µg/ml (equal to cefepime and tigecycline). Eravacycline exhibited excellent activity against the majority of isolates and shows promise for the treatment of infections caused by *Enterobacteriaceae*. 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 large collection of recent clinical isolates of *Enterobacteriaceae* from both the USA and Europe.

Methods

A total of 4,462 *Enterobacteriaceae* clinical isolates (collected from 2013-2014) were tested. The majority were from body fluid sources (n = 1277, 27.6% of total), genito-urinary sources (n = 1113, 24%), gastro-intestinal sources (n = 1,094, 23.7%), respiratory sources (n = 545, 11.8%) and skin (n = 359, 7.8%). The remainder were from other sources that included blood, bone, head/ear/nose/throat, lymph, muscle and medical devices (catheters, tubes).

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 and ATCC 35218.

Antibiotic susceptibility was determined using CLSI 2015 breakpoints (2), with the exception of tigecycline where FDA breakpoints were used (3).

Table 1. Summary of *Enterobacteriaceae* species and geographical origin

Organism	Number of isolates from country:																		Grand Total								
	AT	BE	CZ	DK	FR	DE	EL	HU	IE	IT	LV	NL	PL	PT	RO	RU	RS	ES		SE	CH	TR	UK	All EUR	USA		
<i>Citrobacter freundii</i>				2	2	3			2		19			2										32	137	286	
<i>Citrobacter koseri</i>					19	3			3		2			2										32	69	218	
<i>Enterobacter aerogenes</i>		15			2	15			2					15							15	15	15	96	349	499	
<i>Enterobacter asburiae</i>																									3	3	
<i>Enterobacter cloacae</i>					15	15	15			15			15		14	15						14		148	347	495	
<i>Escherichia coli</i>					15	16	15			15			15	1	16	15						15	15	153	349	502	
<i>Klebsiella oxytoca</i>					15	15	15			15			15		15	15						15	15	150	347	497	
<i>Klebsiella pneumoniae</i>					15	15	15			15			14		15	14						15	15		35	497	
<i>Morganella morganii</i>				15	15	2	1	1	15					19	1										95	67	216
<i>Proteus mirabilis</i>				15	15	2	15		15					15	15	15						15	15	150	258	408	
<i>Proteus vulgaris</i>	1	1	9		15	2	1							15	15	1		2	15						77	6	209
<i>Providencia rettgeri</i>	2	1	1	1	4	7	3	1	1	1	1		3	4	1	4									38	13	51
<i>Providencia stuartii</i>	3	2	7		4	2	9	3	1	8		2		1	1	3	3	8							57	27	84
<i>Serratia marcescens</i>					15	15	15	15	15	15			15	15	15							15	150	347	497		

Total 15 28 82 1 187 215 97 39 1 184 1 41 77 110 92 116 3 212 18 16 100 104 1739 2723 4462
AT, Austria; BE, Belgium; CZ, Czech Republic; DK, Denmark; FR, France; DE, Germany; EL, Greece; HU, Hungary; IE, Republic of Ireland; IT, Italy; LV, Latvia; NL, Netherlands; PL, Poland; PT, Portugal; RO, Romania; RU, Russia; RS, Republic of Serbia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.

Figure 1. Cumulative percentage MIC distribution for eravacycline, tetracycline and tigecycline against *Enterobacteriaceae* from the USA (n=2,723)

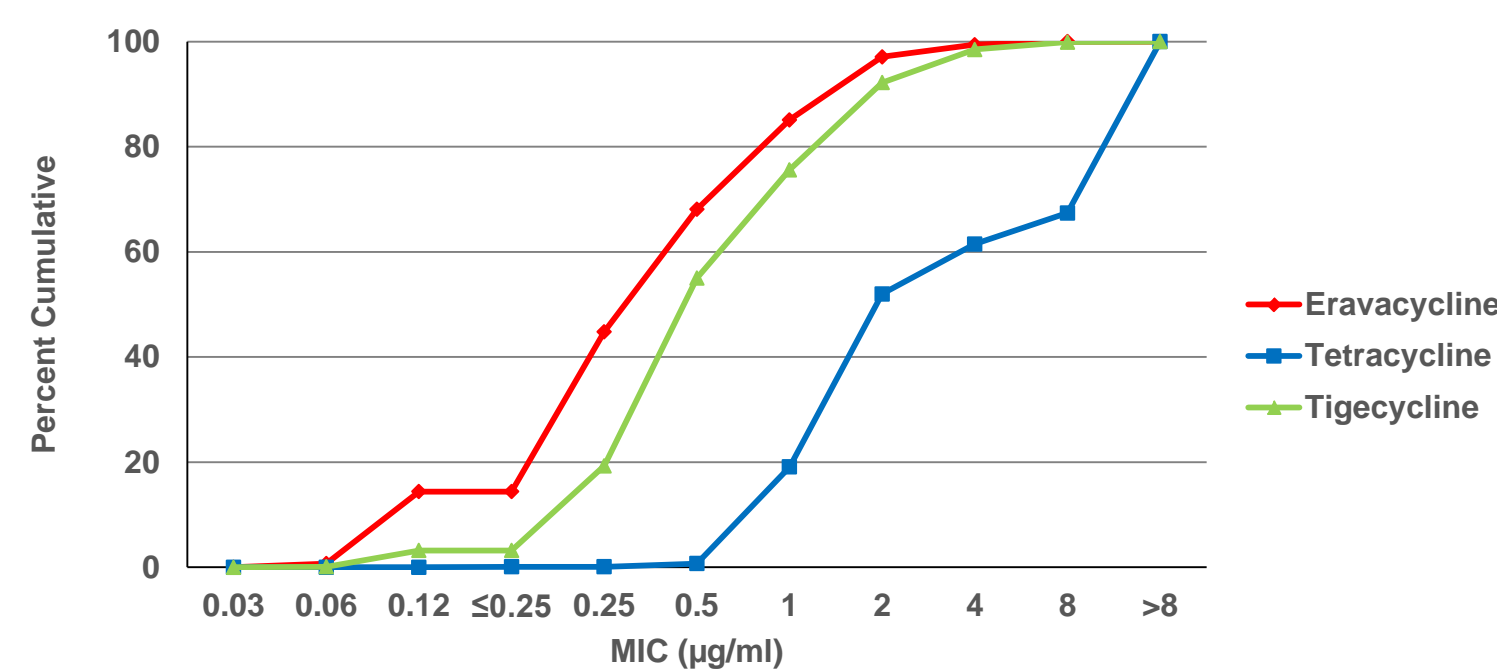
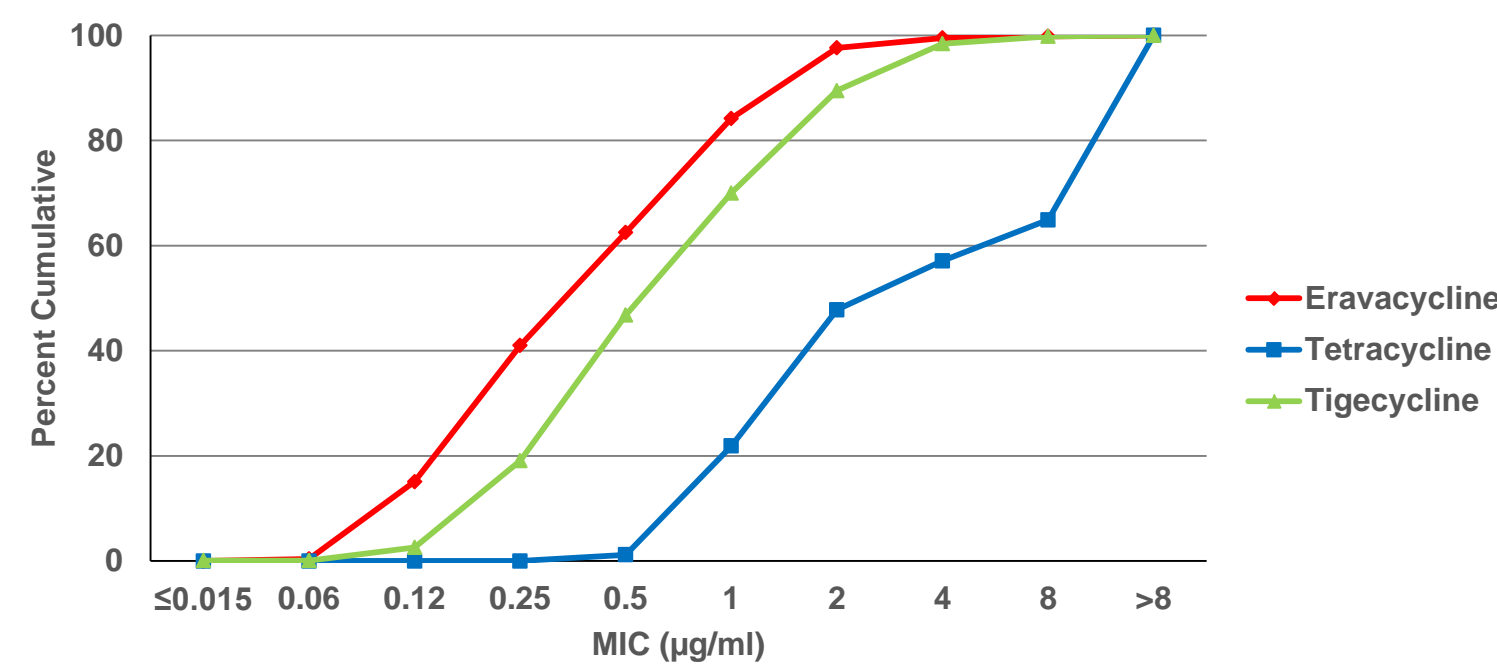


Figure 2. Cumulative percentage MIC distribution for eravacycline, tetracycline and tigecycline against *Enterobacteriaceae* from Europe (n=1,739)



Results

Table 2. Summary MIC data and susceptibility for all *Enterobacteriaceae* (n = 4,462)

Antibiotic	CLSI Breakpoints [S I R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC ₅₀	MIC ₉₀	Min	Max
Aztreonam	<=4 8 >=16	84.7	1.3	14.1	<= 0.5	> 16	<= 0.5	> 16
Cefepime	<=8 16 >=32	94.8	1.5	3.7	<= 0.25	2	<= 0.25	> 16
Ceftazidime	<=4 8 >=16	85.3	1.1	13.5	<= 0.5	> 16	<= 0.5	> 16
Ceftriaxone	<=1 2 >=4	80.3	2.0	17.7	<= 0.5	32	<= 0.5	> 32
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	16
Gentamicin	<=4 8 >=16	91.5	1.0	7.5	0.5	4	<= 0.25	> 8
Imipenem	<=1 2 >=4	72.0	16.8	11.3	0.5	4	<= 0.25	> 8
Levofloxacin	<=2 4 >=8	86.8	1.9	11.3	<= 0.25	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 32/4-64/4 >=128/4	87.4	9.0	3.6	2	32	<= 0.5	> 64
Tetracycline	<=4 8 >=16	59.8	6.6	33.6	2	> 8	<= 0.25	> 8
Tigecycline	<=2 4 >=8 *	91.1	7.3	1.6	0.5	2	<= 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 3. Summary MIC data and susceptibility for *Enterobacteriaceae* from the USA (n = 2,723)

Antibiotic	CLSI Breakpoints [S I R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC ₅₀	MIC ₉₀	Min	Max
Aztreonam	<=4 8 >=16	81.9	1.6	16.5	<= 0.5	> 16	<= 0.5	> 16
Cefepime	<=8 16 >=32	91.8	2.0	6.2	<= 0.25	4	<= 0.25	> 16
Ceftazidime	<=4 8 >=16	82.4	1.3	16.4	<= 0.5	> 16	<= 0.5	> 16
Ceftriaxone	<=1 2 >=4	76.5	2.1	21.4	<= 0.5	> 32	<= 0.5	> 32
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	16
Gentamicin	<=4 8 >=16	89.2	0.9	9.9	1	8	<= 0.25	> 8
Imipenem	<=1 2 >=4	63.5	20.2	16.3	1	4	<= 0.25	> 8
Levofloxacin	<=2 4 >=8	86.6	2.1	11.3	<= 0.25	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 32/4-64/4 >=128/4	86.5	8.8	4.7	2	32	<= 0.5	> 64
Tetracycline	<=4 8 >=16	57.1	7.8	35.1	4	> 8	<= 0.5	> 8
Tigecycline	<=2 4 >=8 *	89.5	8.9	1.6	1	4	<= 0.015	32

Table 4. Summary MIC data and susceptibility for *Enterobacteriaceae* from Europe (n = 1,739)

Antibiotic	CLSI Breakpoints [S I R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC ₅₀	MIC ₉₀	Min	Max
Aztreonam	<=4 8 >=16	86.5	1.1	12.5	<= 0.5	> 16	<= 0.5	> 16
Cefepime	<=8 16 >=32	96.7	1.1	2.2	<= 0.25	1	<= 0.25	> 16
Ceftazidime	<=4 8 >=16	87.2	1.1	11.7	<= 0.5	> 16	<= 0.5	> 16
Ceftriaxone	<=1 2 >=4	82.7	1.9	15.4	<= 0.5	32	<= 0.5	> 32
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	8
Gentamicin	<=4 8 >=16	93.0	1.0	6.0	0.5	2	<= 0.25	> 8
Imipenem	<=1 2 >=4	77.3	14.6	8.1	0.5	2	<= 0.25	> 8
Levofloxacin	<=2 4 >=8	87.0	1.8	11.3	<= 0.25	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 32/4-64/4 >=128/4	88.0	9.1	2.9	2	32	<= 0.5	> 64
Tetracycline	<=4 8 >=16	61.6	5.9	32.6	2	> 8	<= 0.25	> 8
Tigecycline	<=2 4 >=8 *	92.2	6.3	1.5	0.5	2	0.03	16

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

Table 5. Summary MIC data for eravacycline against individual species of *Enterobacteriaceae* from Europe and the USA

Organism	Europe			USA		
	N	MIC ₅₀	MIC ₉₀	N	MIC ₅₀	MIC ₉₀
<i>Citrobacter freundii</i>	149	0.25	0.5	137	0.25	0.5
<i>Citrobacter koseri</i>	149	0.25	0.25	69	0.25	0.25
<i>Enterobacter aerogenes</i>	150	0.5	0.5	349	0.5	1
<i>Enterobacter cloacae</i>	148	0.5	1	347	0.5	1
<i>Escherichia coli</i>	153	0.12	0.25	349	0.12	0.25
<i>Klebsiella oxytoca</i>	150	0.25	0.25	347	0.25	0.5
<i>Klebsiella pneumoniae</i>	147	0.5	1	350	0.5	1
<i>Morganella morganii</i>	149	1	2	67	2	4
<i>Proteus mirabilis</i>	150	2	2	258	1	2
<i>Proteus vulgaris</i>	149	1	1	60	1	1
<i>Providencia rettgeri</i>	38	2	2	13	2	2
<i>Providencia stuartii</i>	57	1	4	27	1	4
<i>Serratia marcescens</i>	150	1	2	347	1	2

Figure