Presentation 780

Activity of Eravacycline against North American and European *Enterobacteriaceae*, Including Multidrug-Resistant Isolates, Collected in 2013-14

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Revised Abstract

Background: Eravacycline is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity in development for the treatment of multidrug-resistant (MDR) infections. Eravacycline has recently completed two Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

Methods: Clinical isolates of *Enterobacteriaceae* (ENT) from Europe and North America collected in 2013-2014 (n=4,462) comprising 15 species and MDR isolates were tested. MICs were determined by broth microdilution according to CLSI guidelines for eravacycline and comparators. MDR was defined as resistant to 3 or more antibiotics from the following classes: cefepime/ceftazidime/ceftriaxone (any one), gentamicin, imipenem, levofloxacin, piperacillin-tazobactam or tetracycline. Quality control testing was performed on each day of testing as specified by the CLSI.

Results: Eravacycline results for all ENT and major species collected are shown in the Table. The MIC_{90} values ranged from 0.25 - 4 µg/ml in both geographical regions, with no statistically relevant regional differences.

Organism/MIC (µg/ml)	Europe					North America				
	N	MIC_{50}	MIC_{90}	MIN	MAX	N	MIC_{50}	MIC_{90}	MIN	MAX
All ENT	1739	0.5	2	0.06	16	2723	0.5	2	0.06	8
All ENT (MDR)	269	0.5	2	0.06	16	285	1	4	0.06	8
C. freundii	149	0.25	0.5	0.12	1	137	0.25	0.5	0.06	4
C. koseri	149	0.25	0.25	0.12	1	69	0.25	0.25	0.12	0.5
E. aerogenes	150	0.5	0.5	0.12	2	349	0.5	1	0.12	8
E. cloacae	148	0.5	1	0.12	8	347	0.5	1	0.12	8
E. cloacae (MDR)	29	1	4	0.25	8	45	0.5	4	0.25	8
E. coli	153	0.12	0.25	0.06	2	349	0.12	0.25	0.06	2
E. coli (MDR)	42	0.12	0.25	0.06	0.5	56	0.25	0.5	0.06	2
K. oxytoca	150	0.25	0.25	0.12	2	347	0.25	0.5	0.06	8
K. pneumoniae	147	0.5	1	0.12	2	350	0.5	1	0.12	8
K. pneumoniae (MDR)	55	0.5	1	0.12	2	47	1	2	0.25	4
M. morganii	149	1	2	0.25	8	67	2	4	0.25	8
P. mirabilis	150	2	2	0.25	4	258	1	2	0.25	8
P. mirabilis (MDR)	31	2	2	0.5	4	43	2	4	0.25	4
P. stuartii	57	1	4	0.5	16	27	1	4	0.5	8
S. marcescens	150	1	2	0.5	8	347	1	2	0.5	8

MIN, minimum MIC; MAX, maximum MIC

Conclusions: Eravacycline demonstrated potent in vitro activity against *Enterobacteriaceae* collected from Europe and North America. The MDR phenotype had little or no effect on eravacycline MIC. Overall, eravacycline showed promising activity and data from the Phase 3 trials will be used in determining the clinical breakpoints.

Introduction

Eravacycline is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity in development 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 collection of recent *Enterobacteriaceae* collected from Europe and USA.

Methods and Materials

Isolates

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 = 1094, 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).

MIC determination

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 *E. coli* ATCC 35218.

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

Multidrug-resistant (MDR) was defined as resistant to 3 or more of the following antibiotics: cefepime/ceftazidime/ceftriaxone (any one), gentamicin, imipenem, levofloxacin, piperacillin-tazobactam or tetracycline.

Results

- A breakdown of the 4,462 *Enterobacteriaceae* collected by country of origin is shown in Table 1.
- Summary MIC data for eravacycline against all *Enterobacteriaceae* and individual species where N ≥20, including MDR strains, are given in Table 3.
- Eravacycline MIC_{90} values ranged from 0.25 - 4 µg/ml against MDR isolates from both Europe and the USA.
- Summary susceptibility and MIC data for eravacycline and comparators against all isolates combined and those from Europe and the USA, including MDR strains, are shown in Tables 2, 3 and 5.
- A comparison of ratio of tigecycline versus eravacycline MIC is shown in Figure 1.

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

Organism \ Region	Number of isolates from country: 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	Grand Total
Citrobacter freundii			20		20	30				20		19		20				20					149	137	286
Citrobacter koseri					19	30				30		20		20				30					149	69	218
Enterobacter aerogenes		15			20	15				20				15				20		15	15	15	150	349	499
Enterobacter asburiae																								3	3
Enterobacter cloacae					15	15	15			15			15		14	15		15			15	14	148	347	495
Escherichia coli					15	16	15			15			15	1	16	15		15			15	15	153	349	502
Klebsiella oxytoca					15	15	15			15			15		15	15		15			15	15	150	347	497
Klebsiella pneumoniae					15	15	15			15			14		15	14		14			15	15	147	350	497
Morganella morganii			15		15	20	10	10		15				19		10		25			10		149	67	216
Proteus mirabilis			15		15	15	15			15					15	15		15			15	15	150	258	408
Proteus vulgaris	10	10	9		15	20		10						15	15	10		20	15				149	60	209
Providencia rettgeri	2	1	1	1	4	7	3	1		1	1		3	4	1	4			3	1			38	13	51
Providencia stuartii	3	2	7		4	2	9	3	1	8		2		1	1	3	3	8					57	27	84
Serratia marcescens			15		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**	**1,739**	**2,723**	**4,462**

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 of Great Britain and Northern Ireland; USA, United States of America.

Results

Table 2. Summary MIC data and susceptibility for all *Enterobacteriaceae* (n = 4,462) and MDR *Enterobacteriaceae* (n=554)

Antibiotic	Breakpoints (S|I|R)		Percentage S	Percentage I	Percentage R	MIC (µg/ml): MIC_{50}	MIC_{90}	Min	Max
Aztreonam	<=4 | 8 | >=16	All	84.7	1.3	14.1	<= 0.5	> 16	<= 0.5	> 16
		MDR	28.0	3.3	68.8	> 16	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	All	94.8	1.5	3.7	<= 0.25	2	<= 0.25	> 16
		MDR	60.7	10.3	29.1	4	> 16	<= 0.25	> 16
Ceftazidime	<=4 | 8 | >=16	All	85.3	1.1	13.5	<= 0.5	> 16	<= 0.5	> 16
		MDR	31.1	4.5	64.4	> 16	> 16	<= 0.5	> 16
Ceftriaxone	<=1 | 2 | >=4	All	80.3	2.0	17.7	<= 0.5	32	<= 0.5	> 32
		MDR	16.3	2.2	81.6	> 32	> 32	<= 0.5	> 32
Colistin	No Breakpoints Defined	All	-	-	-	1	> 4	<= 0.12	> 4
		MDR	-	-	-	1	> 4	0.25	> 4
Eravacycline	**No Breakpoints Defined**	**All**	**-**	**-**	**-**	**0.5**	**2**	**0.06**	**16**
		MDR	**-**	**-**	**-**	**1**	**2**	**0.06**	**16**
Gentamicin	<=4 | 8 | >=16	All	91.5	1.0	7.5	0.5	4	<= 0.25	> 8
		MDR	47.1	3.4	49.5	8	> 8	<= 0.25	> 8
Imipenem	<=1 | 2 | >=4	All	72.0	16.8	11.3	0.5	4	<= 0.25	> 8
		MDR	56.1	12.8	31.1	1	8	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	All	86.8	1.9	11.3	<= 0.25	> 4	<= 0.25	> 4
		MDR	36.1	4.7	59.2	> 4	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	All	87.4	9.0	3.6	2	32	<= 0.5	> 64
		MDR	53.3	19.3	27.4	16	> 64	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	All	59.8	6.6	33.6	2	> 8	<= 0.25	> 8
		MDR	26.9	7.8	65.3	> 8	> 8	1	> 8
Tigecycline	<=2 | 4 | >=8 *	All	91.1	7.3	1.6	0.5	2	<= 0.015	32
		MDR	80.5	13.7	5.8	1	4	0.12	32

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

Table 3. Activity of eravacycline against *Enterobacteriaceae* from Europe and the USA and individual species where N ≥20

Organism	Region	N	MIC (µg/ml): MIC_{50}	MIC_{90}	Min	Max
Enterobacteriaceae	Europe	1739	0.5	2	0.06	16
	USA	2723	0.5	2	0.06	8
Enterobacteriaceae (MDR)	Europe	269	0.5	2	0.06	16
	USA	285	1	4	0.06	8
C. freundii	Europe	149	0.25	0.5	0.12	1
	USA	137	0.25	0.5	0.06	4
C. koseri	Europe	149	0.25	0.25	0.12	1
	USA	69	0.25	0.25	0.12	0.5
E. aerogenes	Europe	150	0.5	0.5	0.12	2
	USA	349	0.5	1	0.12	8
E. cloacae	Europe	148	0.5	1	0.12	8
	USA	347	0.5	1	0.12	8
E. cloacae (MDR)	Europe	29	1	4	0.25	8
	USA	45	0.5	4	0.25	8
E. coli	Europe	153	0.12	0.25	0.06	2
	USA	349	0.12	0.25	0.06	2
E. coli (MDR)	Europe	42	0.12	0.25	0.06	0.5
	USA	56	0.25	0.5	0.06	2
K. oxytoca	Europe	150	0.25	0.25	0.12	2
	USA	347	0.25	0.5	0.06	8
K. pneumoniae	Europe	147	0.5	1	0.12	2
	USA	350	0.5	1	0.12	8
K. pneumoniae (MDR)	Europe	55	0.5	1	0.12	2
	USA	47	1	2	0.25	4
M. morganii	Europe	149	1	2	0.25	8
	USA	67	2	4	0.25	8
P. mirabilis	Europe	150	2	2	0.25	4
	USA	258	1	2	0.25	8
P. mirabilis (MDR)	Europe	31	2	2	0.5	4
	USA	43	2	4	0.25	4
P.vulgaris	Europe	149	1	1	0.12	2
	USA	60	1	1	0.5	2
P. stuartii	Europe	57	1	4	0.5	16
	USA	27	1	4	0.5	8
S. marcescens	Europe	150	1	2	0.5	8
	USA	347	1	2	0.5	8

Table 4. Summary MIC data and susceptibility for *Enterobacteriaceae* (n = 2,723) and MDR *Enterobacteriaceae* (n=285) from the USA

Antibiotic	Breakpoints (S|I|R)		Percentage S	Percentage I	Percentage R	MIC (µg/ml): MIC_{50}	MIC_{90}	Min	Max
Aztreonam	<=4 | 8 | >=16	All	86.5	1.1	12.5	<= 0.5	> 16	<= 0.5	> 16
		MDR	26.7	3.5	69.8	> 16	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	All	96.7	1.1	2.2	<= 0.25	1	<= 0.25	> 16
		MDR	70.5	9.8	19.7	2	> 16	<= 0.25	> 16
Ceftazidime	<=4 | 8 | >=16	All	87.2	1.1	11.7	<= 0.5	> 16	<= 0.5	> 16
		MDR	31.9	5.3	62.8	> 16	> 16	<= 0.5	> 16
Ceftriaxone	<=1 | 2 | >=4	All	82.7	1.9	15.4	<= 0.5	32	<= 0.5	> 32
		MDR	19.0	3.2	77.9	32	> 32	<= 0.5	> 32
Colistin	No Breakpoints Defined	All	-	-	-	1	> 4	<= 0.12	> 4
		MDR	-	-	-	1	> 4	0.25	> 4
Eravacycline	**No Breakpoints Defined**	**All**	**-**	**-**	**-**	**0.5**	**2**	**0.06**	**8**
		MDR	**-**	**-**	**-**	**1**	**4**	**0.06**	**8**
Gentamicin	<=4 | 8 | >=16	All	93.0	1.0	6.0	0.5	2	<= 0.25	> 8
		MDR	50.9	4.9	44.2	4	> 8	<= 0.25	> 8
Imipenem	<=1 | 2 | >=4	All	77.3	14.6	8.1	0.5	2	<= 0.25	> 8
		MDR	61.1	10.2	28.8	1	8	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	All	87.0	1.8	11.3	<= 0.25	> 4	<= 0.25	> 4
		MDR	32.3	6.3	61.4	> 4	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	All	88.0	9.1	2.9	2	32	<= 0.5	> 64
		MDR	51.9	21.4	26.7	16	> 64	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	All	61.6	5.9	32.6	2	> 8	<= 0.25	> 8
		MDR	27.0	9.1	63.9	> 8	> 8	1	> 8
Tigecycline	<=2 | 4 | >=8 *	All	92.2	6.3	1.5	0.5	2	0.03	16
		MDR	79.3	15.1	5.6	1	4	0.12	8

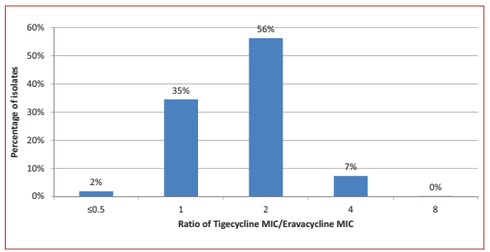
* FDA breakpoints were used for Tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

Table 5. Summary MIC data and susceptibility for *Enterobacteriaceae* (n = 1,739) and MDR *Enterobacteriaceae* (n=269) from Europe

Antibiotic	Breakpoints (S|I|R)		Percentage S	Percentage I	Percentage R	MIC (µg/ml): MIC_{50}	MIC_{90}	Min	Max
Aztreonam	<=4 | 8 | >=16	All	81.9	1.6	16.5	<= 0.5	> 16	<= 0.5	> 16
		MDR	29.4	3.0	67.7	> 16	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	All	91.8	2.0	6.2	<= 0.25	4	<= 0.25	> 16
		MDR	50.2	10.8	39.0	8	> 16	<= 0.25	> 16
Ceftazidime	<=4 | 8 | >=16	All	82.4	1.3	16.4	<= 0.5	> 16	<= 0.5	> 16
		MDR	30.1	3.7	66.2	> 16	> 16	<= 0.5	> 16
Ceftriaxone	<=1 | 2 | >=4	All	76.5	2.1	21.4	<= 0.5	> 32	<= 0.5	> 32
		MDR	13.4	1.1	85.5	> 32	> 32	<= 0.5	> 32
Colistin	No Breakpoints Defined	All	-	-	-	1	> 4	<= 0.12	> 4
		MDR	-	-	-	1	> 4	0.25	> 4
Eravacycline	**No Breakpoints Defined**	**All**	**-**	**-**	**-**	**0.5**	**2**	**0.06**	**16**
		MDR	**-**	**-**	**-**	**0.5**	**2**	**0.06**	**16**
Gentamicin	<=4 | 8 | >=16	All	89.2	0.9	9.9	1	4	<= 0.25	> 8
		MDR	43.1	1.9	55.0	> 8	> 8	<= 0.25	> 8
Imipenem	<=1 | 2 | >=4	All	63.5	20.2	16.3	1	4	<= 0.25	> 8
		MDR	50.9	15.6	33.5	1	> 8	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	All	86.6	2.1	11.3	<= 0.25	> 4	<= 0.25	> 4
		MDR	40.2	3.0	56.9	> 4	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	All	86.5	8.8	4.7	2	32	<= 0.5	> 64
		MDR	54.7	17.1	28.3	16	> 64	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	All	57.1	7.8	35.1	4	> 8	0.5	> 8
		MDR	26.8	6.3	66.9	> 8	> 8	1	> 8
Tigecycline	<=2 | 4 | >=8 *	All	89.5	8.9	1.6	1	4	<= 0.015	32
		MDR	81.8	12.3	6.0	1	4	0.12	32

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

Figure 1. Ratio of Tigecycline MIC and Eravacycline MIC (all isolates).



Conclusions

- Against a total of 4,462 *Enterobacteriaceae* clinical isolates, eravacycline exhibited the lowest MIC_{90} of 2 µg/ml (equal to cefepime and tigecycline) compared with antibiotics in the testing panel.
- Eravacycline had a lower MIC distribution than tetracycline or tigecycline, with 64% of isolates having an eravacycline MIC ≥2-fold lower than tigecycline.
- Eravacycline in vitro activity was similar against isolates from the USA and Europe.
- The MDR phenotype had little or no effect on eravacycline MIC.
- These data along with data from the recently completed Phase 3 trials will be used in determining breakpoints for eravacycline.
- Eravacycline exhibited potent *in vitro* activity against the majority of isolates, including MDR strains.

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