Presentation 008
Monday

Eravacycline *In Vitro* Activity Against Clinical Isolates Obtained from Genitourinary (GU) and Gastrointestinal (GI) Sources from Patients in the United States

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Abstract

Background: Eravacycline (ERV) is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. ERV is in phase 3 clinical development for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis. The purpose of this study was to evaluate the activity of ERV against key pathogens from the US isolated from GU and GI sources.

Methods: MIC results for ERV and comparator agents were determined by CLSI broth microdilution against 1004 GI and 1199 GU isolates collected from US hospitals in 2013-2014. MDR was defined as resistant to ≥3 of the following antibiotics: cefepime/ceftazidime/ceftriaxone (any one), gentamicin, imipenem, levofloxacin, piperacillin-tazobactam or tetracycline.

Results: ERV MIC data for species where n ≥ 30 from each infection type are shown in the Table.

GI (n)	$MIC_{50/90}$	MIC range	GU (n)	$MIC_{50/90}$	MIC Range
Gram-negatives					
C. freundii (36)	0.25/1	0.06-2	*A. baumannii* (43)	0.25/1	0.03-4
E. cloacae (77)	0.5/0.5	0.12-8	*C. freundii* (45)	0.25/0.5	0.12-1
E. coli (170)	0.12/0.25	0.06-2	*E. aerogenes* (102)	0.5/1	0.12-8
K. oxytoca (63)	0.25/1	0.12-8	*E. cloacae* (133)	0.5/1	0.12-8
K. pneumoniae (189)	0.5/2	0.12-8	*K. oxytoca* (101)	0.25/0.25	0.06-1
P. mirabilis (54)	1/2	0.25-4	*M. morganii* (30)	2/2	0.25-4
P. aeruginosa (145)	8/16	2-32	*P. mirabilis* (104)	1/2	0.25-4
MDR *P. aeruginosa* (40)	8/32	8-32	*P. aeruginosa* (63)	8/16	2-32
S. marcescens (31)	1/2	1-4	*S. marcescens* (98)	1/2	0.5-8
Gram-positives					
E. faecium (40)	0.06/0.12	0.03-0.5	*E. faecalis* (187)	0.06-0.06	0.008-0.12
VR *E. faecium* (26)	0.06/0.12	0.03-0.5	*E. faecium* (104)	0.06-0.06	0.008-0.5
S. aureus (56)	0.06/0.12	0.03-0.5	VR *E. faecium* (79)	0.06-0.06	0.03-0.5
MRSA (37)	0.06/0.12	0.03-0.5	*S. agalactiae* (47)	0.03/0.03	0.008-0.06

$MIC_{50/90}$, minimal inhibitory concentration (mg/L) required to inhibit growth of 50/90% of isolates; MRSA, methicillin-resistant *S. aureus*; VR, vancomycin-resistant

Conclusion: For GI and GU isolates, the ERV MIC_{90} was ≤ 2 mg/L, except for *P. aeruginosa*. ERV showed activity against clinically-important Gram-negative and -positive isolates from GU or GI infections from the US.

Introduction

Gram-negative bacteria are common causes of intra-abdominal infections and urinary tract infections, and resistance amongst these pathogens is increasing. Eravacycline is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class in development for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. ERV is in phase 3 clinical development for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis.

The pharmacokinetics and pharmacodynamics of eravacycline have been studied in animals and during clinical trials. Two doses of eravacycline were used in clinical trials of cIAI that produced favorable results in terms of efficacy, safety and pharmacokinetic evaluations: 1.5 mg/kg q24h and 1 mg/kg q12h (1, 2). In a phase 1 multiple-ascending dose study in healthy volunteers, the C_{max} values after a 60-minute infusion were 2.7 and 2.1 mg/L at day 1, respectively, and 1.9 and 1.8 mg/L at day 10, respectively, based on a four-compartment model (3). AUC_{ss} values were 8.7 and 12.7 mg·hr/L for the 1.5 mg/kg q24h dose and 1 mg/kg q12h dose, respectively (3).

Renal clearance of 3.0-3.5 L/h was reported in healthy volunteers with approximately 16% excreted unchanged in the urine. In healthy subjects who received multiple IV doses of 1.5 mg/kg q24h over 60 minutes, eravacycline concentrations in urine collected from 0–8 h were 6.9 ± 1.2 mg/L on day 1 and 13.3 ± 3.4 mg/L on day 10 (2).

The purpose of this study was to assess the *in vitro* activity of eravacycline against recent US clinical isolates of key pathogens from gastrointestinal (GI) and genitourinary (GU) infections.

Methods

- A total of 1004 GI and 1199 GU clinical isolates, collected from 2013-2014 from 43 US hospitals, were tested.
- Minimal inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (4).
- 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, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619.
- Antibiotic susceptibility was determined using CLSI 2015 breakpoints (5), with the exception of tigecycline where FDA breakpoints were used (6).
- MDR was defined as resistant to 3 or more of the following antibiotic classes: cefepime/ceftazidime/ceftriaxone (any one), gentamicin, imipenem, levofloxacin, piperacillin-tazobactam or tetracycline.

Results

- For GI and GU isolates shown in Table 1, the ERV MIC_{90} was ≤ 2 mg/L, except for *P. aeruginosa* (MIC_{90} = 16 mg/L).

Table 1. Summary MIC (mg/L) data for eravacycline against isolates from GI (n = 1004) and GU (n = 1199) infections (where n ≥ 10)

GI (n)	$MIC_{50/90}$	MIC range	GU (n)	$MIC_{50/90}$	MIC range
Gram-negative Organisms					
Acinetobacter baumannii (22)	0.25/1	0.03-2	*Acinetobacter baumannii* (43)	0.25/1	0.03-4
Citrobacter freundii (36)	0.25/1	0.06-2	*Citrobacter freundii* (45)	0.25/0.5	0.12-1
Citrobacter koseri (16)	0.12/0.25	0.12-0.5	*Citrobacter koseri* (29)	0.25/0.25	0.12-0.25
Enterobacter aerogenes (25)	0.25/0.5	0.25-2	*Enterobacter aerogenes* (102)	0.5/1	0.12-8
Enterobacter cloacae (77)	0.5/0.5	0.12-8	*Enterobacter cloacae* (133)	0.5/1	0.12-8
Escherichia coli (170)	0.12/0.25	0.06-2	*Klebsiella oxytoca* (101)	025/0.25	0.06-1
Klebsiella oxytoca (63)	0.25/1	0.12-8	*Morganella morganii* (30)	2/2	0.25-4
Klebsiella pneumoniae (189)	0.5/2	0.12-8	*Proteus mirabilis* (104)	1/2	0.25-4
Morganella morganii (11)	1/2	0.5-2	*Proteus vulgaris* (24)	1/1	0.5-2
Proteus mirabilis (54)	1/2	0.25-4	*Providencia stuartii* (17)	1/2	0.5-2
Proteus vulgaris (10)	0.5/1	0.5-1	*Pseudomonas aeruginosa* (63)	8/16	2-32
Pseudomonas aeruginosa (145)	8/16	2-32	*Serratia marcescens* (98)	1/2	0.5-8
Serratia marcescens (31)	1/2	1-4			
Stenotrophomonas maltophilia (13)	0.5/2	0.12-2			
Gram-positive Organisms					
Enterococcus faecalis (23)	0.06/0.12	0.015-0.25	*Enterococcus faecalis* (187)	0.06/0.06	0.008-0.12
Enterococcus faecium (40)	0.06/0.12	0.03-0.5	*Enterococcus faecium* (104)	0.06/0.06	0.008-0.5
Staphylococcus aureus (56)	0.06/0.12	0.03-0.5	*Staphylococcus aureus* (26)	0.06/0.12	0.015-0.12
			Staphylococcus epidermidis (20)	0.25/0.5	0.03-1

- ERV MIC_{90} values did not increase in resistant phenotypes (carbapenem-resistant, multidrug-resistant, vancomycin-resistant, or methicillin-resistant phenotypes) for *C. freundii, K. pneumoniae, M. morganii, P. vulgaris, E. faecium, S. aureus, S. epidermidis* (Table 2).
  - Carbapenem-resistant organisms had ERV MIC_{90} values ≤ 2 mg/L, with the exception of *P. aeruginosa*.
  - MDR organisms had ERV MIC_{90} values ≤ 2 mg/L, with the exception of *E. aerogenes*, *P. mirabilis*, and *P. aeruginosa*.

Table 2. MIC distribution (cumulative %) of eravacycline against pertinent organisms by resistance phenotype from GI and GU sources (where n ≥ 10)

	Number of isolates (cumulative %) inhibited at eravacycline MIC (mg/L) of:												
Organism (n)	<0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16	MIC_{50}	MIC_{90}
Gram-negative:													
A. baumannii (65)		8 (12.3)	8 (24.6)	7 (35.4)	15 (58.5)	15 (81.5)	6 (90.8)	5 (98.5)	1 (100)			0.25	1
MDR *A. baumannii* (42)				1 (2.4)	14 (35.7)	15 (71.4)	6 (85.7)	5 (97.6)	1 (100)			0.5	2
CR *A. baumannii* (30)				1 (3.3)	8 (30)	10 (63.3)	5 (80)	5 (96.7)	1 (100)			0.5	2
C. freundii (81)			1 (1.2)	21 (27.2)	45 (82.7)	5 (88.9)	8 (98.8)	1 (100)				0.25	1
MDR *C. freundii* (10)				1 (10)	4 (50)	2 (70)	2 (90)	1 (100)				0.25	1
C. koseri (45)				18 (40)	26 (97.8)	1 (100)						0.25	0.25
E. aerogenes (127)				3 (2.4)	54 (44.9)	55 (88.2)	6 (92.9)	4 (96.1)	4 (99.2)	1 (100)		0.5	1
MDR *E. aerogenes* (10)					1 (10)	2 (30)		4 (70)	2 (90)	1 (100)		2	4
E. cloacae (210)				2 (1)	42 (21)	140(87.6)	15 (94.8)	5 (97.1)	3 (98.6)	3 (100)		0.5	1
MDR *E. cloacae* (33)					5 (15.2)	13 (54.6)	8 (78.8)	4 (90.9)	2 (97)	1 (100)		0.5	2
E. coli (170)			8 (4.7)	102(64.7)	48 (92.9)	8 (97.7)	2 (98.8)	2 (100)				0.12	0.25
MDR *E. coli* (25)			1 (4)	7 (32)	14 (88)	2 (96)	1 (100)					0.25	0.5
K. oxytoca (164)			1 (0.6)	36 (22.6)	110(89.6)	8 (94.5)	6 (98.2)	2 (99.4)		1 (100)		0.25	0.5
K. pneumoniae (189)				3 (1.6)	78 (42.9)	57 (73)	27 (87.3)	17 (96.3)	5 (98.9)	2 (100)		0.5	2
MDR *K. pneumoniae* (26)					2 (7.7)	6 (30.8)	13 (80.8)	5 (100)				1	2
CR *K. pneumoniae* (10)					2 (20)	2 (40)	4 (80)	2 (100)				1	2
M. morganii (41)					2 (4.9)	3 (12.2)	16 (51.2)	18 (95.1)	2 (100)			1	2
MDR *M. morganii* (10)					1 (10)	1 (20)	4 (60)	3 (90)	1 (100)			1	2
CR *M. morganii* (33)					2 (6.1)	2 (12.1)	14 (54.6)	14 (97)	1 (100)			1	2
P. mirabilis (158)					5 (3.2)	26 (19.6)	61 (58.2)	56 (93.7)	10 (100)			1	2
MDR *P. mirabilis* (33)						4 (12.1)	7 (33.3)	14 (75.8)	8 (100)			2	4
CR *P. mirabilis* (64)						7 (10.9)	22 (45.3)	29 (90.6)	6 (100)			2	2
P. vulgaris (34)						11 (32.4)	22 (97.1)	1 (100)				1	1
CR *P. vulgaris* (13)						4 (30.8)	9 (100)					1	1
P. rettgeri (10)							1 (10)	8 (90)	1 (100)			2	2
P. stuartii (22)						1 (4.6)	13 (63.6)	5 (86.4)	2 (95.5)	1 (100)		1	4
P. aeruginosa (208)								4 (1.9)	20 (11.5)	100(59.6)	84(100)	8	≥16
MDR *P. aeruginosa* (57)								1 (1.8)	2 (5.3)	25 (49.1)	29 (100)	≥16	≥16
CR *P. aeruginosa* (62)								1 (1.6)	3 (6.5)	24(45.2)	34 (100)	≥16	≥16
S. marcescens (129)						6 (4.7)	73 (61.2)	40 (92.3)	9 (99.2)	1 (100)		1	2
S. maltophilia (19)			1 (5.3)	1 (10.5)	4 (31.6)	7 (68.4)	3 (84.2)	3 (100)				0.5	2
CR *S. maltophilia* (19)			1 (5.3)	1 (10.5)	4 (31.6)	7 (68.4)	3 (84.2)	3 (100)				0.5	2
Gram-positive:													
E. faecalis (210)	6 (2.9)	48 (25.7)	144(94.3)	11 (99.5)	1 (100)							0.06	0.06
E. faecium (144)	3 (2.1)	47 (34.7)	82 (91.7)	5 (95.1)	3 (97.2)	4 (100)						0.06	0.06
VR *E. faecium* (105)		35 (33.3)	60 (90.5)	3 (93.3)	3 (96.2)	4 (100)						0.06	0.06
S. aureus (82)	2 (2.4)	5 (8.5)	63 (85.4)	8 (95.1)	1 (96.3)	3 (100)						0.06	0.12
MRSA (38)		4 (10.5)	28 (84.2)	3 (92.1)		3 (100)						0.06	0.12
S. epidermidis (25)		1 (4)	6 (28)	1 (32)	7 (60)	9 (96)	1 (100)					0.25	0.5
MRSE (20)			4 (20)	1 (25)	7 (60)	7 (95)	1 (100)					0.25	0.5
S. agalactiae (53)	25(47.2)	27 (98.1)	1 (100)									0.03	0.03

Red text = MIC_{90}; Underlined = MIC_{50}; MDR = Multi-drug Resistant; CR = Carbapenem-resistant; VR = Vancomycin-resistant; MR = Methicillin-resistant

- Based on MIC_{90} values for Enterobacteriaceae pathogens, the potency of ERV was comparable to or up to 2-fold greater than that of TGC.
- Based on MIC_{90} values for *A. baumannii*, the potency of ERV was 2-fold greater than that of TGC (Table 4).

Table 3. Antimicrobial activity of eravacycline and comparator agents against *Enterobacteriaceae* isolates from GI (n = 691) and GU (n = 691) sources

Organism (n)/ Antimicrobial Agent	MIC (mg/L)			%S / %I / %R[a]
	MIC_{50}	MIC_{90}	Range	CLSI
***Enterobacteriaceae* (1382)**				
Aztreonam	≤ 0.5	> 16	≤ 0.5-> 16	86 / 0.9 / 13.1
Cefepime	≤ 0.25	1	≤ 0.25-> 16	94.1 / 3.0 / 2.9
Ceftazidime	≤ 0.5	> 16	≤ 0.5-> 16	86.5 / 1.2 / 12.3
Ceftriaxone	≤ 0.5	32	≤ 0.5-> 32	81.7 / 2.2 / 16.1
Colistin	1	> 4	≤ 0.12-> 4	– / – / –
Eravacycline	**0.5**	**2**	**0.06-8**	– / – / –
Gentamicin	0.5	4	≤ 0.25-> 8	91.2 / 1.2 / 7.5
Imipenem	0.5	2	≤ 0.25-> 8	76.4 / 14.0 / 9.6
Levofloxacin	≤ 0.25	> 4	≤ 0.25-> 4	84.4 / 2.5 / 13.2
Piperacillin/tazobactam	2	32	≤ 0.5-> 64	88.3 / 8.7 / 3.0
Tetracycline	4	> 8	0.25-> 8	60.4 / 5.0 / 34.6
Tigecycline	0.5	2	0.03-16	90.3 / 8.0 / 1.7
***Citrobacter* spp.[b] (126)**				
Aztreonam	≤ 0.5	16	≤ 0.5-> 16	84.9 / 0.8 / 14.3
Cefepime	≤ 0.25	1	≤ 0.25-> 16	98.4 / 0.8 / 0.8
Ceftazidime	≤ 0.5	> 16	≤ 0.5-> 16	84.1 / 1.6 / 14.3
Ceftriaxone	≤ 0.5	32	≤ 0.5-> 32	82.5 / 1.6 / 15.9
Colistin	1	1	≤ 0.12-> 4	– / – / –
Eravacycline	**0.25**	**0.5**	**0.06-2**	– / – / –
Gentamicin	1	2	≤ 0.25-> 8	96.0 / 0 / 4.0
Imipenem	0.5	2	≤ 0.25-> 8	89.7 / 8.7 / 1.6
Levofloxacin	≤ 0.25	1	≤ 0.25-> 4	93.7 / 4.0 / 2.4
Piperacillin/tazobactam	2	16	≤ 0.5-> 64	90.5 / 4.0 / 5.6
Tetracycline	1	> 8	≤ 0.25-> 8	87.3 / 0.8 / 11.9
Tigecycline	0.5	0.5	0.06-2	100 / 0 / 0
***Enterobacter* spp.[c] (339)**				
Aztreonam	≤ 0.5	> 16	≤ 0.5-> 16	70.2 / 1.8 / 28.0
Cefepime	≤ 0.25	2	≤ 0.25-> 16	92.6 / 6.2 / 1.2
Ceftazidime	≤ 0.5	> 16	≤ 0.5-> 16	70.5 / 0.9 / 28.6
Ceftriaxone	≤ 0.5	> 32	≤ 0.5-> 32	64.9 / 1.5 / 33.6
Colistin	0.5	1	≤ 0.12-> 4	– / – / –
Eravacycline	**0.5**	**1**	**0.12-8**	– / – / –
Gentamicin	0.5	1	≤ 0.25-> 8	94.4 / 0.9 / 4.7
Imipenem	1	2	≤ 0.25-> 8	81.1 / 17.4 / 1.5
Levofloxacin	≤ 0.25	1	≤ 0.25-> 4	93.8 / 1.8 / 4.4
Piperacillin/tazobactam	4	64	≤ 0.5-> 64	73.8 / 22.1 / 4.1
Tetracycline	2	8	0.5-> 8	87.3 / 3.2 / 9.4
Tigecycline	0.5	1	0.03-8	96.5 / 2.7 / 0.9
***E. coli* (170)**				
Aztreonam	≤ 0.5	16	≤ 0.5-> 16	87.1 / 1.2 / 11.8
Cefepime	≤ 0.25	2	≤ 0.25-> 16	90.6 / 1.2 / 8.2
Ceftazidime	≤ 0.5	8	≤ 0.5-> 16	87.7 / 2.4 / 10.0
Ceftriaxone	≤ 0.5	32	≤ 0.5-> 32	85.9 / 0.6 / 13.5
Colistin	0.5	1	0.25-2	– / – / –
Eravacycline	**0.12**	**0.25**	**0.06-2**	– / – / –
Gentamicin	1	> 8	≤ 0.25-> 8	79.4 / 1.2 / 19.4
Imipenem	≤ 0.25	0.5	≤ 0.25-1	100 / 0 / 0
Levofloxacin	≤ 0.25	> 4	≤ 0.25-> 4	64.1 / 0.6 / 35.3
Piperacillin/tazobactam	2	8	≤ 0.5-> 64	94.7 / 4.7 / 0.6
Tetracycline	2	> 8	1-> 8	61.2 / 1.8 / 37.1
Tigecycline	0.25	0.5	0.12-2	100 / 0 / 0
Indole + *Proteeae*[d] (107)				
Aztreonam	≤ 0.5	1	≤ 0.5-> 16	97.2 / 1.9 / 0.9
Cefepime	≤ 0.25	0.5	≤ 0.25-> 16	96.3 / 2.8 / 0.9
Ceftazidime	≤ 0.5	2	≤ 0.5-> 16	95.3 / 1.9 / 2.8
Ceftriaxone	≤ 0.5	4	≤ 0.5-16	84.1 / 5.6 / 10.3
Colistin	> 4	> 4	> 4-> 4	– / – / –
Eravacycline	**1**	**2**	**0.25-8**	– / – / –
Gentamicin	2	> 8	≤ 0.25-> 8	83.2 / 2.8 / 14.0
Imipenem	2	4	≤ 0.25-8	17.8 / 35.5 / 46.7
Levofloxacin	≤ 0.25	> 4	≤ 0.25-> 4	70.1 / 9.4 / 20.6
Piperacillin/tazobactam	≤ 0.5	4	≤ 0.5-8	100 / 0 / 0
Tetracycline	>8	> 8	1-> 8	30.8 / 11.2 / 57.9
Tigecycline	2	4	0.25-8	77.6 / 18.7 / 3.7
***Klebsiella* spp.[e] (353)**				
Aztreonam	≤ 0.5	> 16	≤ 0.5-> 16	88.7 / 0.6 / 10.8
Cefepime	≤ 0.25	1	≤ 0.25-> 16	93.2 / 2.3 / 4.5
Ceftazidime	≤ 0.5	4	≤ 0.5-> 16	90.7 / 1.1 / 8.2
Ceftriaxone	≤ 0.5	4	≤ 0.5-> 32	88.4 / 1.4 / 10.2
Colistin	1	1	≤ 0.12-2	– / – / –
Eravacycline	**0.25**	**1**	**0.06-8**	– / – / –
Gentamicin	≤ 0.25	1	≤ 0.25-> 8	95.2 / 1.4 / 3.4
Imipenem	≤ 0.25	1	≤ 0.25-> 8	94.3 / 2.8 / 2.8
Levofloxacin	≤ 0.25	4	≤ 0.25-> 4	89.0 / 1.7 / 9.4
Piperacillin/tazobactam	2	32	≤ 0.5-> 64	89.2 / 5.7 / 5.1
Tetracycline	2	> 8	0.5-> 8	81.3 / 6.2 / 12.5
Tigecycline	0.5	2	0.12-16	94.9 / 3.7 / 1.4
***P. mirabilis* (158)**				
Aztreonam	≤ 0.5	≤ 0.5	≤ 0.5-> 16	98.1 / 0 / 1.9
Cefepime	≤ 0.25	1	≤ 0.25-16	94.3 / 3.8 / 1.9
Ceftazidime	≤ 0.5	≤ 0.5	≤ 0.5-16	97.5 / 1.3 / 1.3
Ceftriaxone	≤ 0.5	1	≤ 0.5-32	90.5 / 3.2 / 6.3
Colistin	> 4	> 4	>4-> 4	– / – / –
Eravacycline	**1**	**2**	**0.25-4**	– / – / –
Gentamicin	2	> 8	≤ 0.25-> 8	86.1 / 1.9 / 12.0
Imipenem	2	4	≤ 0.25-> 8	22.8 / 36.7 / 40.5
Levofloxacin	≤ 0.25	> 4	≤ 0.25-> 4	73.4 / 2.5 / 24.1
Piperacillin/tazobactam	≤ 0.5	1	≤ 0.5-> 64	98.1 / 0.6 / 1.3
Tetracycline	> 8	> 8	0.5-> 8	1.9 / 0 / 98.1
Tigecycline	2	4	0.5-8	53.8 / 40.5 / 5.7
***S. marcescens* (129)**				
Aztreonam	≤ 0.5	1	≤ 0.5-> 16	95.4 / 0 / 4.7
Cefepime	≤ 0.25	0.5	≤ 0.25-16	98.5 / 0.8 / 0.8
Ceftazidime	≤ 0.5	1	≤ 0.5-> 16	97.0 / 0 / 3.1
Ceftriaxone	≤ 0.5	2	≤ 0.5-> 32	88.4 / 4.7 / 7.0
Colistin	> 4	> 4	1-> 4	– / – / –
Eravacycline	**1**	**2**	**0.5-8**	– / – / –
Gentamicin	1	2	≤ 0.25-> 8	96.1 / 0.8 / 3.1
Imipenem	1	2	≤ 0.25-4	85.3 / 13.2 / 1.6
Levofloxacin	≤ 0.25	4	≤ 0.25-> 4	89.9 / 1.6 / 8.5
Piperacillin/tazobactam	2	16	≤ 0.5-64	91.5 / 8.5 / 0
Tetracycline	> 8	> 8	4-> 8	1.6 / 15.5 / 83.0
Tigecycline	2	2	0.5-16	94.6 / 3.9 / 1.6

[a]Criteria as published by the CLSI (2015); [b]Includes: *C. freundii* (81 strains) and *C. koseri* (45 strains); [c]Includes: *E. cloacae* (210 strains), *E. aerogenes* (127 strains) and *E. asburiae* (2 strains); [d]Includes: *M. morganii* (41 strains), *P. vulgaris* (34 strains), *P. stuartii* (22 strains), and *P. rettgeri* (10 strains); [e]Includes: *K. pneumoniae* (189 strains) and *K. oxytoca* (164 strains)
"--" = No breakpoint defined

Table 4. Antimicrobial activity of eravacycline and comparator agents against *A. baumannii* isolates from GI (n = 22) and GU (n = 43) sources

Organism (n)/ Antimicrobial Agent	MIC (mg/L)			%S / %I / %R[a]
	MIC_{50}	MIC_{90}	Range	CLSI
***A. baumannii* (65)**				
Aztreonam	> 16	> 16	2-> 16	– / – / –
Cefepime	16	> 16	≤ 0.25-> 16	41.5 / 15.4 / 43.1
Ceftazidime	> 16	> 16	≤ 0.5-> 16	36.9 / 3.1 / 60.0
Ceftriaxone	> 32	> 32	2-> 32	27.7 / 10.8 / 61.5
Colistin	1	1	0.25-> 4	98.5 / – / 1.5
Eravacycline	**0.25**	**1**	**0.03-4**	**-- / -- / --**
Gentamicin	> 8	> 8	0.5-> 8	41.5 / 4.6 / 53.9
Imipenem	2	> 8	≤ 0.25-> 8	53.9 / 0 / 46.2
Levofloxacin	> 4	> 4	≤ 0.25-> 4	26.2 / 3.1 / 70.8
Piperacillin/tazobactam	> 64	> 64	≤ 0.5-> 64	36.9 / 10.8 / 52.3
Tetracycline	8	> 8	≤ 0.25-> 8	35.4 / 15.4 / 49.2
Tigecycline	1	2	0.12-8	– / – / –

[a]Criteria as published by the CLSI (2015)
"--" = No breakpoint defined

- Based on MIC_{90} values for Gram-positive pathogens, the potency of ERV was up to 4-fold greater than that of TGC (Table 5).

Table 5. Antimicrobial activity of eravacycline and comparator agents against Gram-positive isolates from GI (n = 130) and GU (n = 384) sources

Organism (n)/ Antimicrobial Agent	MIC (mg/L)			%S / %I / %R[a]
	MIC_{50}	MIC_{90}	Range	CLSI
***E. faecalis* (210)**				
Amoxicillin/clavulanate	1	2	0.25-2	– / – / –
Azithromycin	> 8	> 8	0.12-> 8	– / – / –
Ceftriaxone	> 64	> 64	≤ 0.5-> 64	– / – / –
Daptomycin	2	4	≤ 0.06-> 4	99.5 / – / 0.5
Eravacycline	**0.06**	**0.06**	**0.008-0.25**	– / – / –
Levofloxacin	2	>8	0.5-> 8	66.2 / 1.0 / 32.9
Linezolid	2	2	1-4	99.1 / 1.0 / 0
Minocycline	8	> 8	≤ 0.03-> 8	33.8 / 21.0 / 45.2
Penicillin	2	4	≤ 0.12-8	100 / – / 0
Tetracycline	32	> 32	0.12-> 32	25.7 / 0.5 / 73.8
Tigecycline	0.12	0.25	≤ 0.015-0.5	98.6 / – / 1.4
Vancomycin	1	4	0.25-> 32	90.9 / 0 / 9.1
***E. faecium* (144)**				
Amoxicillin/clavulanate	> 16	> 16	≤ 0.12-> 16	– / – / –
Azithromycin	> 8	> 8	0.5-> 8	– / – / –
Ceftriaxone	> 64	> 64	2-> 64	– / – / –
Daptomycin	4	> 4	0.25-> 4	88.2 / – / 11.8
Eravacycline	**0.06**	**0.06**	**0.008-0.5**	– / – / –
Levofloxacin	>8	> 8	0.5-> 8	3.5 / 5.6 / 91.0
Linezolid	2	2	≤ 0.5-4	98.6 / 1.4 / 0
Minocycline	8	> 8	≤ 0.03-> 8	41.0 / 15.3 / 43.8
Penicillin	> 8	> 8	0.5-> 8	5.6 / – / 94.4
Tetracycline	32	> 32	0.12-> 32	18.8 / 0 / 81.3
Tigecycline	0.12	0.25	0.03-1	94.4 / – / 5.6
Vancomycin	> 32	> 32	0.5-> 32	24.5 / 2.1 / 73.4
***S. aureus* (82)**				
Amoxicillin/clavulanate	2	16	≤ 0.12-> 16	– / – / –
Azithromycin	> 8	> 8	0.5-> 8	37.8 / 0 / 62.2
Ceftriaxone	8	> 64	2-> 64	– / – / –
Daptomycin	0.5	1	0.25-1	100 / – / –
Eravacycline	**0.06**	**0.12**	**0.015-0.5**	– / – / –
Levofloxacin	0.5	> 8	0.12-> 8	52.4 / 0 / 47.6
Linezolid	2	2	≤ 0.5-2	100 / – / –
Minocycline	0.12	0.25	≤ 0.03-> 8	97.5 / 0 / 2.5
Penicillin	> 8	> 8	≤ 0.12-> 8	17.1 / – / 82.9
Tetracycline	0.5	0.5	≤ 0.06-> 32	95.1 / 0 / 4.9
Tigecycline	0.12	0.25	0.03-0.5	100 / – / 0
***S. epidermidis* (25)**				
Amoxicillin/clavulanate	2	2	0.25-16	– / – / –
Azithromycin	> 8	> 8	0.25-> 8	36.0 / 0 / 64.0
Ceftriaxone	16	32	1-> 64	– / – / –
Daptomycin	0.5	1	0.5-2	96.0 / – / 4.0
Eravacycline	**0.25**	**0.5**	**0.03-1**	– / – / –
Levofloxacin	8	> 8	0.25-> 8	44.0 / 0 / 56.0
Linezolid	2	2	≤ 0.5-2	100 / – / –
Minocycline	0.5	0.5	0.06-1	100 / 0 / 0
Penicillin	2	> 8	≤ 0.12-> 8	12.0 / – / 88.0
Tetracycline	2	8	0.25-> 32	88.0 / 4.0 / 8.0
Tigecycline	0.5	0.5	0.12-1	96.0 / – / 4.0
***S. agalactiae* (53)**				
Amoxicillin/clavulanate	0.12	0.25	0.06-0.25	– / – / –
Azithromycin	0.12	> 2	≤ 0.03-> 2	50.9 / 0 / 49.1
Ceftriaxone	0.06	0.12	≤ 0.03-0.12	100 / – / –
Daptomycin	0.25	0.5	0.12-0.5	100 / – / –
Eravacycline	**0.03**	**0.03**	**0.008-0.06**	– / – / –
Levofloxacin	1	2	0.5-2	100 / 0 / 0
Linezolid	2	2	1-2	100 / – / –
Minocycline	> 8	> 8	≤ 0.03-> 8	– / – / –
Penicillin	≤ 0.06	≤ 0.06	≤ 0.06-≤ 0.06	100 / – / –
Tetracycline	> 8	> 8	0.12-> 8	17.0 / 0 / 83.0
Tigecycline	0.03	0.03	≤ 0.008-0.06	100 / – / –

[a]Criteria as published by the CLSI (2015)
"--" = No breakpoint defined

Conclusions

- Eravacycline was active against most isolates from GU or GI infections, including MDR and CR isolates, from the US.

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Presented at ASM Microbe 2016, June 16 - June 20, Boston, Massachusetts, USA