

# Eravacycline *in vitro* activity against clinical isolates obtained from urinary and gastrointestinal sources, including drug-resistant pathogens,

## from patients in Europe

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### 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 with broad-spectrum activity in development for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. Eravacycline has been evaluated in phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis. The purpose of this study was to assess the *in vitro* activity of eravacycline against recent European clinical isolates of key pathogens from gastrointestinal (GI) and genitourinary (GU) infections.

### Methods

- A total of 732 GI and 678 GU clinical isolates, collected from 2013-2014 from amongst 134 European hospitals, 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, *Haemophilus influenzae* ATCC 4924T, *H. influenzae* ATCC 49766, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619.
- Antibiotic susceptibility was determined using EUCAST 2015 breakpoints (2).
- MDR was defined as resistant to 3 or more of the following antibiotic classes: cefepime/ceftriaxone/ceftriaxone (any one), gentamicin, imipenem, levofloxacin, piperacillin-tazobactam or tetracycline.

### Results

- The organisms tested were comparably distributed across European countries with proportions from Germany, France, Italy, Spain and UK being 15%, 9%, 9%, 9% and 6%, respectively. Organisms from Eastern Europe represented 25% of the total (Czech Republic, Hungary, Poland, Romania and Russia).
- For GI and GU isolates shown in Table 1, the eravacycline MIC<sub>90</sub> was  $\leq 2$  mg/L except for *Providencia stuartii* (GU MIC<sub>90</sub> = 4 mg/L), *Pseudomonas aeruginosa* (GI and GU MIC<sub>90</sub> = 16 mg/L), and *Serratia marcescens* (GI MIC<sub>90</sub> = 4 mg/L).
- Eravacycline MIC<sub>90</sub> values did not increase in resistant phenotypes (defined as carbapenem-resistant (CR), multidrug-resistant (MDR), vancomycin-resistant (VR), or methicillin-resistant (MR)) for *Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecium*, *Staphylococcus epidermidis*, and *Staphylococcus haemolyticus* (Table 2).
- Carbapenem-resistant organisms had eravacycline MIC<sub>90</sub> values  $\leq 2$  mg/L, with the exception of *Pseudomonas aeruginosa*.
- Multidrug-resistant organisms had eravacycline MIC<sub>90</sub> values  $\leq 2$  mg/L, with the exception of *Providencia stuartii* and *Pseudomonas aeruginosa*.
- Based on MIC<sub>90</sub> values in certain pathogens represented in Tables 3-5, the potency of eravacycline was generally 2-fold greater than that of tigecycline.

### Results (cont'd)

Table 1. Summary MIC (mg/L) data from eravacycline against isolates from GI (n = 732) and GU (n = 678) infections (where n  $\geq$  10)

GI (n)	MIC <sub>50%</sub>	MIC range	GU (n)	MIC <sub>50%</sub>	MIC range
<b>Gram-negatives</b>					
<i>Acinetobacter baumannii</i> (45)	0.5/1	0.03-2	<i>Acinetobacter baumannii</i> (25)	0.25/1	0.03-4
<i>Citrobacter freundii</i> (45)	0.25/0.5	0.12-1	<i>Citrobacter freundii</i> (25)	0.25/0.5	0.12-1
<i>Citrobacter koseri</i> (10)	0.12/0.25	0.12-0.5	<i>Citrobacter koseri</i> (9)	0.12/0.25	0.12-1
<i>Enterobacter aerogenes</i> (31)	0.5/0.5	0.25-1	<i>Enterobacter aerogenes</i> (52)	0.5/0.5	0.25-2
<i>Enterobacter cloacae</i> (35)	0.5/2	0.25-4	<i>Enterobacter cloacae</i> (21)	0.5/1	0.5-4
<i>Escherichia coli</i> (71)	0.12/0.25	0.06-2	<i>Klebsiella oxytoca</i> (34)	0.25/0.25	0.12-2
<i>Klebsiella oxytoca</i> (37)	0.25/0.25	0.12-0.5	<i>Morganella morganii</i> (43)	1/2	0.25-8
<i>Klebsiella pneumoniae</i> (63)	0.5/1	0.12-2	<i>Proteus mirabilis</i> (42)	2/2	0.25-4
<i>Morganella morganii</i> (34)	1/2	0.25-4	<i>Proteus vulgaris</i> (59)	1/1	0.25-2
<i>Proteus mirabilis</i> (35)	1/2	0.5-4	<i>Providencia rettgeri</i> (10)	2/2	0.25-2
<i>Proteus vulgaris</i> (19)	1/1	0.25-1	<i>Providencia stuartii</i> (25)	1/4	0.5-16
<i>Pseudomonas aeruginosa</i> (40)	8/16	1-32	<i>Pseudomonas aeruginosa</i> (13)	8/16	1-16
<i>Serratia marcescens</i> (19)	1/4	1-4	<i>Serratia marcescens</i> (15)	1/2	0.5-2
<i>Stenotrophomonas maltophilia</i> (11)	1/1	0.12-2	<i>Stenotrophomonas maltophilia</i> (27)	0.5/1	0.12-2
<b>Gram-positives</b>					
<i>Enterococcus faecalis</i> (45)	0.06/0.12	0.015-0.5	<i>Enterococcus faecalis</i> (22)	0.06/0.06	0.03-0.12
<i>Enterococcus faecium</i> (58)	0.06/0.06	0.015-1	<i>Enterococcus faecium</i> (24)	0.03/0.06	0.015-0.06
<i>Staphylococcus aureus</i> (43)	0.06/0.25	0.03-1	<i>Staphylococcus aureus</i> (11)	0.06/0.12	0.06-1
<i>Staphylococcus epidermidis</i> (34)	0.12/0.5	0.03-1	<i>Staphylococcus epidermidis</i> (26)	0.25/0.5	0.015-0.5
<i>Staphylococcus agalactiae</i> (10)	0.03/0.03	0.008-0.03	<i>Staphylococcus haemolyticus</i> (76)	0.12/0.5	0.03-1
<i>Streptococcus anginosus</i> (23)	0.008/0.03	$\leq 0.001-0.06$	<i>Streptococcus agalactiae</i> (25)	0.015/0.03	0.008-0.06

Table 2. Cumulative MIC distribution of eravacycline against pertinent organisms by resistance phenotype from GI and GU sources (where n  $\geq$  5)

Organism (n)	Number of isolates (cumulative % inhibited at eravacycline MIC (mg/L) of:												
	<0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	8	$\geq 16$	MIC <sub>50%</sub>	MIC <sub>90%</sub>
<b>Gram-negatives:</b>													
A. baumannii (20)		6 (30.0)	11 (55.0)	8 (75.0)	4 (61.3)	2 (29.8)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	0.5	1
MDR A. baumannii (38)		1 (2.6)	4 (10.5)	2 (5.3)	13 (34.2)	10 (26.3)	1 (2.6)	1 (2.6)	1 (2.6)	1 (2.6)	1 (2.6)	0.5	1
CR A. baumannii (45)		1 (2.2)	4 (8.9)	2 (4.4)	12 (26.7)	10 (22.2)	1 (2.2)	1 (2.2)	1 (2.2)	1 (2.2)	1 (2.2)	0.5	1
C. freundii (70)		11 (15.7)	36 (51.4)	6 (8.6)	4 (5.7)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	0.25	0.5
MDR C. freundii (14)		4 (28.6)	2 (14.3)	1 (7.1)	2 (14.3)	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	0.25	0.5
C. koseri (10)		2 (20.0)	4 (40.0)	7 (70.0)	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	0.12	0.25
E. aerogenes (33)		37 (44.8)	3 (3.6)	4 (4.8)	4 (4.8)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	0.25	0.5
MDR E. aerogenes (28)		10 (35.7)	13 (46.4)	2 (7.1)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	0.25	0.5
E. cloacae (56)		4 (7.1)	27 (48.2)	8 (14.3)	8 (14.3)	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)	0.5	2
MDR E. cloacae (28)		4 (14.3)	13 (46.4)	8 (28.6)	3 (10.7)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	1 (3.6)	0.5	2
E. coli (72)		4 (5.6)	48 (66.7)	17 (23.6)	3 (4.2)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	0.12	0.25
MDR E. coli (21)		1 (4.8)	14 (66.7)	4 (19.0)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	0.12	0.25
K. oxytoca (71)		23 (32.4)	30 (42.3)	7 (9.9)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	0.25	0.5
K. pneumoniae (64)		1 (1.6)	5 (7.8)	22 (34.4)	10 (15.6)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	0.5	1
MDR K. pneumoniae (25)		1 (4.0)	1 (4.0)	3 (12.0)	2 (8.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1	1
CR K. pneumoniae (7)		4 (57.1)	3 (42.9)										
M. morganii (17)		4 (23.5)	12 (70.6)	21 (94.8)	3 (98.7)	3 (98.7)	3 (98.7)	3 (98.7)	3 (98.7)	3 (98.7)	3 (98.7)	1	2
MDR M. morganii (9)		1 (11.1)	1 (11.1)	5 (55.6)	2 (22.2)	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)	0.5	2
MDR P. mirabilis (8)		1 (12.5)	3 (37.5)	3 (37.5)	3 (37.5)	3 (37.5)	3 (37.5)	3 (37.5)	3 (37.5)	3 (37.5)	3 (37.5)	2	2
MDR P. mirabilis (21)		1 (4.8)	8 (38.1)	11 (52.4)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	1 (4.8)	0.25	1
P. vulgaris (78)		5 (6.5)	34 (43.6)	26 (33.3)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	1	1
P. mirabilis (54)		1 (1.9)	11 (20.4)	33 (61.1)	8 (14.8)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	0.5	2
P. stuartii (25)		5 (20.0)	13 (52.0)	8 (32.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	2	4
MDR P. stuartii (11)		2 (18.2)	1 (9.1)	2 (18.2)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	2	16
P. aeruginosa (53)		2 (3.8)	5 (9.4)	2 (3.8)	2 (3.8)	3 (5.7)	3 (5.7)	3 (5.7)	3 (5.7)	3 (5.7)	3 (5.7)	8	16
MDR P. aeruginosa (17)		2 (11.8)	1 (5.9)	3 (17.6)	3 (17.6)	3 (17.6)	3 (17.6)	3 (17.6)	3 (17.6)	3 (17.6)	3 (17.6)	16	32
CR P. aeruginosa (16)		2 (12.5)	3 (18.8)	11 (68.8)	4 (25.0)	3 (18.8)	3 (18.8)	3 (18.8)	3 (18.8)	3 (18.8)	3 (18.8)	$\geq 16$	$\geq 16$
S. marcescens (24)		2 (8.3)	13 (54.2)	11 (45.8)	1 (4.2)	1 (4.2)	1 (4.2)	1 (4.2)	1 (4.2)	1 (4.2)	1 (4.2)	1	2
MDR S. marcescens (6)		1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	0.5	1
S. maltophilia (38)		3 (7.9)	10 (26.3)	11 (28.9)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	0.5	1
CR S. maltophilia (38)		3 (7.9)	10 (26.3)	11 (28.9)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	18 (47.4)	0.5	1
<b>Gram-positives:</b>													
E. faecalis (97)		1 (1.0)	15 (15.5)	40 (41.3)	4 (9.7)	1 (2.6)	1 (2.6)	1 (2.6)	1 (2.6)	1 (2.6)	1 (2.6)	0.06	0.06
E. faecium (82)		2 (2.4)	36 (44.0)	21 (25.6)	1 (9.7)	1 (9.7)	1 (9.7)	1 (9.7)	1 (9.7)	1 (9.7)	1 (9.7)	0.06	0.06
VRE faecium (22)		1 (4.5)	9 (40.9)	12 (54.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)	0.06	0.06
S. aureus (54)		4 (7.4)	24 (44.4)	8 (14.8)	4 (7.4)	2 (3.7)	2 (3.7)	2 (3.7)	2 (3.7)	2 (3.7)	2 (3.7)	0.06	0.25
MRSA (29)		1 (3.4)	12 (41.4)	4 (13.8)	3 (10.3)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	0.06	0.5
S. epidermidis (66)		1 (1.5)	5 (7.6)	19 (28.8)	12 (18.2)	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	0.12	0.5
MDR S. epidermidis (29)		1 (3.4)	12 (41.4)	12 (41.4)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	1 (3.4)	0.12	0.5
S. haemolyticus (83)		1 (1.2)	12 (14.5)	23 (27.8)	18 (21.8)	18 (21.8)	18 (21.8)	18 (21.8)	18 (21.8)	18 (21.8)	18 (21.8)	0.12	0.5
MDR S. haemolyticus (54)		1 (1.9)	14 (27.8)	11 (21.9)	16 (32.0)	10 (20.4)	2 (4.1)	2 (4.1)	2 (4.1)	2 (4.1)	2 (4.1)	0.25	0.5
S. agalactiae (35)		18 (51.4)	1 (2.9)	1 (2.9)								0.015	0.03
E. agalactiae (25)		1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.0)	0.008	0.03
S. pneumoniae (23)		1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	0.008	0.03
S. pneumoniae (23)		1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	1 (4.3)	0.008	0.03

Red text = MIC<sub>50%</sub>, Underlined = MIC<sub>90%</sub>, \*\* = MIC<sub>50%</sub> or MIC<sub>90%</sub> not applicable for species with isolates of N < 10; CR = carbapenem-resistant

Table 3. Antimicrobial activity of eravacycline and comparator agents against Enterobacteriaceae isolates from GI (n = 403) and GU (n = 422) sources.

Organism/Antimicrobial Agent (No. Tested)	MIC (mg/L)			%S / %I / %R*
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	
<b>Enterobacteriaceae (825)</b>				
Aztreonam	$\leq 0.5$	$> 16$	$\leq 0.5 \rightarrow 16$	78.3 / 3.2 / 18.6
Cefepime	$\leq 0.25$	8	$\leq 0.25 \rightarrow 16$	85.8 / 3.8 / 10.4
Ceftazidime	$\leq 0.5$	$> 16$	$\leq 0.5 \rightarrow 16$	76.4 / 5.2 / 18.4
Ceftriaxone	$\leq 0.5$	$> 32$	$\leq 0.5 \rightarrow 32$	75.6 / 1.9 / 22.4
Colistin	1	$> 4$	$\leq 0.12 \rightarrow 4$	62.8 / - / 37.2
Eravacycline	0.5	2	0.015-16	- / - / -
Gentamicin	1	$> 8$	$\leq 0.25 \rightarrow 8$	83.8 / 5.5 / 10.8
Imipenem	1	4	$\leq 0.25 \rightarrow 8$	82.4 / 15.9 / 1.7
Levofloxacin	$\leq 0.25$	$> 4$	$\leq 0.25 \rightarrow 4$	81.7 / 4.1 / 14.2
Piperacillin/tazobactam	2	32	$\leq 0.5 \rightarrow 64$	83.6 / 3.4 / 13
Tetracycline	4	$> 8$	$0.25 \rightarrow 32$	- / - / -
Tigecycline	1	4	$\leq 0.015 \rightarrow 32$	70.3 / 18.8 / 10.9
<b>Citrobacter spp.<sup>b</sup> (172)</b>				
Aztreonam	$\leq 0.5$	16	$\leq 0.5 \rightarrow 16$	84.3 / 1.7 / 14
Cefepime	$\leq 0.25$	1	$\leq 0.25 \rightarrow 16$	95.9 / 1.2 / 2.9
Ceftazidime	$\leq 0.5$	$> 16$	$\leq 0.5 \rightarrow 16$	83.7 / 2.9 / 13.4
Ceftriaxone	$\leq 0.5$	32	$\leq 0.5 \rightarrow 32$	88.0 / 0 / 15.1
Colistin	0.5	1	$\leq 0.12 \rightarrow 4$	98.3 / - / 1.7
Eravacycline	0.25	0.5	0.12-1	- / - / -
Gentamicin	0.5	1	$\leq 0.25 \rightarrow 8$	96.5 / 0.6 / 2.9
Imipenem	$\leq 0.25$	2	$\leq 0.25 \rightarrow 8$	94.0 / 0 / 0.6
Levofloxacin	$\leq 0.25$	$\leq 0.25$	$\leq 0.25 \rightarrow 4$	91.7 / 1.7 / 1.2
Piperacillin/tazobactam	2	16	$\leq 0.5 \rightarrow 64$	89.5 / 2.9 / 7.6
Tetracycline	1	4	0.5-8	- / - / -
Tigecycline	0.5	0.5	$\leq 0.015 \rightarrow 2$	99.4 / 0.6 / 0
<b>Enterobacter spp.<sup>c</sup> (139)</b>				
Aztreonam	$\leq 0.5$	$> 16$	$\leq 0.5 \rightarrow 16$	55.4 / 2.2 / 42.5
Cefepime	$\leq 0.25$	4		