

# In vitro activity of eravacycline and comparators in Gram-negative organisms, including drug-resistant phenotypes, isolated from respiratory sources, in Europe

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## Introduction

Infections caused by resistant Gram-negative bacteria are a serious global public health concern. 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. To date, eravacycline has been evaluated in studies for the treatment of complicated intra-abdominal infections (cIA) and complicated urinary tract infections (cUTI), including pyelonephritis. *In vitro* surveillance study data for eravacycline were collected on clinical isolates from various infection sources in 2013-2014 in the EU. The purpose of this portion of the study was to evaluate the *in vitro* activity of eravacycline and comparators against key Gram-negative pathogens isolated from respiratory cultures from patients in the EU.

## Methods

**Isolates**  
Gram-negative clinical isolates, including multidrug-resistant (MDR) organisms, were collected from respiratory sources between 2013 and 2014. Isolates were collected based on a target number for specific organisms. Preference was given first to gastrointestinal infection sources, second to genitourinary sources followed by respiratory tract sources and then other infections. As a result of preferential collection, a total of 271 Gram-negative clinical isolates comprising 13 species were collected and tested.

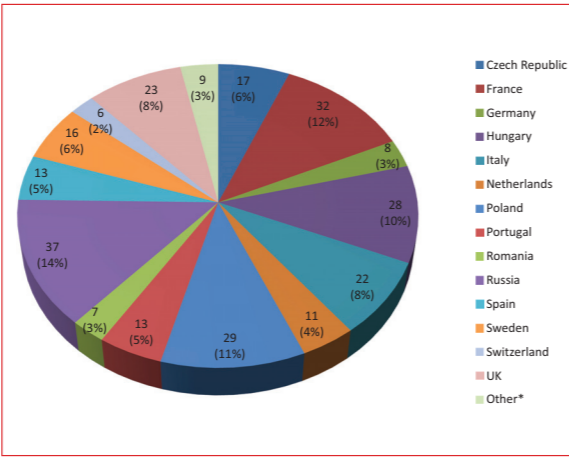
- MIC determination**
- Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1).
  - Quality control testing was performed each day of testing as specified by the CLSI using *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Haemophilus influenzae* ATCC 49247, *H. influenzae* ATCC 49766, *Pseudomonas aeruginosa* ATCC 27853.
  - Antibiotic susceptibility was determined using EUCAST 2015 breakpoints (2).
  - 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

- The geographical distribution, shown in Figure 1, of the 271 Gram-negative isolates collected from respiratory sources in this study was comparable to the represented regions of Europe.
- All isolates maintained an eravacycline MIC<sub>90</sub> range ≤ 1 mg/L, except for *Morganella morganii* and *Serratia marcescens* (Table 1).
- Eravacycline MIC<sub>90</sub> values did not increase by resistant phenotypes (multidrug-resistant or carbapenem-resistant pathogens) for *Acinetobacter baumannii* (Table 1).
- Based on MIC<sub>90</sub> values for certain pathogens, the potency of eravacycline was comparable to or up to 4-fold greater than that of tigecycline.
- Based on MIC<sub>90</sub> values, the potency of eravacycline was 2-fold greater than that of tigecycline in carbapenem-resistant and multidrug-resistant *Acinetobacter baumannii*.

## Results (cont'd)

Figure 1. Country of origin [n (%)] for the 271 Gram-negative clinical isolates tested



UK, United Kingdom of Great Britain and Northern Ireland; \*Countries included as "Other" (Austria, Belgium, Denmark, and Greece) had less than 5 isolates each.

Table 1. Cumulative MIC distribution of eravacycline against Gram-negative organisms, including resistance phenotypes, from respiratory sources (N=271)

Gram-negative Organism (n)	Number of isolates (cumulative %) inhibited at eravacycline MIC (mg/L) of:								MIC (mg/L)		
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Acinetobacter baumannii</i> (17)		1 (5.9)	1 (11.8)	7 (52.9)	3 (70.6)	5 (100)				0.25	1
MDR A. baumannii (10)		1 (10)	5 (50)	1 (70)	3 (100)					0.25	1
CR A. baumannii (12)		1 (8.3)	5 (50)	3 (75)	3 (100)					0.25	1
<i>Citrobacter freundii</i> (4)				3 (75)	1 (100)						
<i>Citrobacter koseri</i> (4)			1 (25)	2 (75)	1 (100)						
<i>Enterobacter aerogenes</i> (11)		1 (9.1)	4 (45.5)	6 (100)						0.5	0.5
MDR E. aerogenes (5)		1 (20)	4 (100)								
<i>Enterobacter cloacae</i> (5)		1 (20)	4 (100)								
MDR E. cloacae (1)		2 (1.5)	4 (4.6)	6 (65.5)	55 (97)	4 (100)				0.12	0.25
<i>Haemophilus influenzae</i> (131)				1 (100)							
MDR H. influenzae (1)				1 (100)							
<i>Klebsiella oxytoca</i> (6)				6 (100)							
<i>Morganella morganii</i> (11)			1 (9.1)	4 (45.5)	4 (81.8)	2 (100)				1	2
<i>Proteus vulgaris</i> (14)				6 (42.9)	8 (100)					1	1
<i>Providencia rettgeri</i> (3)				1 (33.3)	1 (66.7)	1 (100)					
<i>Providencia stuartii</i> (5)				1 (20)	2 (60)	2 (100)					
MDR P. stuartii (2)				2 (100)							
<i>Serratia marcescens</i> (32)				1 (3.1)	14 (46.9)	13 (87.5)	4 (86.9)	1 (100)		2	4
MDR S. marcescens (8)				1 (12.5)	1 (25)	4 (75)	2 (100)				
<i>Stenotrophomonas maltophilia</i> (28)		1 (3.6)	6 (25)	9 (57.1)	9 (89.3)	3 (100)				0.25	1
CR S. maltophilia (28)		1 (3.6)	6 (25)	9 (57.1)	9 (89.3)	3 (100)				0.25	1

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; MDR = multidrug-resistant; CR = carbapenem-resistant

Table 2. Antimicrobial activity of eravacycline and comparators against Gram-negative isolates from respiratory sources (where N>10)

Organism/Antimicrobial Agent (No. Tested)	MIC (mg/L)			%S / %I / %R* EUCAST
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	
<b>A. baumannii (17)</b>				
Aztreonam	> 16	> 16	8-> 16	- / - / -
Cefepime	> 16	> 16	0.5-> 16	- / - / -
Ceftazidime	> 16	> 16	2-> 16	- / - / -
Ceftriaxone	> 32	> 32	8-> 32	- / - / -
Colistin	1	1	0.5-2	100 / - / 0
<b>Eravacycline</b>	<b>0.25</b>	<b>1</b>	<b>0.06-1</b>	<b>- / - / -</b>
Gentamicin	> 8	> 8	2-> 8	17.7 / - / 82.4
Imipenem	> 8	> 8	≤ 0.25-> 8	29.4 / 0 / 70.6
Levofloxacin	> 4	> 4	≤ 0.25-> 4	5.9 / 0 / 94.1
Piperacillin/tazobactam	> 64	> 64	≤ 0.5-> 64	- / - / -
Tetracycline	> 8	> 8	1-> 8	- / - / -
Tigecycline	1	2	0.12-2	- / - / -
<b>Enterobacter spp.<sup>b</sup> (16)</b>				
Aztreonam	≤ 0.5	> 16	≤ 0.5-> 16	50 / 6.3 / 43.8
Cefepime	≤ 0.25	2	≤ 0.25-> 16	87.5 / 6.3 / 6.3
Ceftazidime	≤ 0.5	> 16	≤ 0.5-> 16	50 / 6.3 / 43.8
Ceftriaxone	≤ 0.5	> 32	≤ 0.5-> 32	50 / 0 / 50
Colistin	0.5	1	0.5-2	100 / - / 0
<b>Eravacycline</b>	<b>0.5</b>	<b>0.5</b>	<b>0.12-0.5</b>	<b>- / - / -</b>
Gentamicin	0.5	1	≤ 0.25-1	100 / 0 / 0
Imipenem	1	2	≤ 0.25-2	100 / 0 / 0
Levofloxacin	≤ 0.25	0.5	≤ 0.25-1	100 / 0 / 0
Piperacillin/tazobactam	4	64	1-> 64	56.3 / 6.3 / 37.5
Tetracycline	2	4	2-> 8	- / - / -
Tigecycline	0.5	1	0.25-1	100 / 0 / 0
<b>H. influenzae (131)</b>				
Aztreonam	0.06	0.06	≤ 0.03-0.12	- / - / -
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25-0.5	97.7 / - / 2.3
Ceftazidime	≤ 0.06	0.12	≤ 0.06-0.25	- / - / -
Ceftriaxone	≤ 0.03	≤ 0.03	≤ 0.03-0.06	100 / - / 0
Colistin	ND	ND	ND	- / - / -
<b>Eravacycline</b>	<b>0.12</b>	<b>0.25</b>	<b>0.03-0.5</b>	<b>- / - / -</b>
Gentamicin	ND	ND	ND	- / - / -
Imipenem	1	2	≤ 0.12-8	94.7 / - / 5.3
Levofloxacin	0.015	0.03	0.008-> 2	99.2 / - / 0.8
Piperacillin/tazobactam	ND	ND	ND	- / - / -
Tetracycline	0.5	1	0.25-8	97.7 / 0.8 / 1.5
Tigecycline	0.12	0.25	≤ 0.004-0.25	- / - / -
<b>M. morganii (11)</b>				
Aztreonam	≤ 0.5	≤ 0.5	≤ 0.5-> 0.5	100 / 0 / 0
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25-> 0.25	100 / 0 / 0
Ceftazidime	≤ 0.5	≤ 0.5	≤ 0.5-> 0.5	100 / 0 / 0
Ceftriaxone	≤ 0.5	≤ 0.5	≤ 0.5-1	100 / 0 / 0
Colistin	> 4	> 4	> 4-> 4	0 / - / 100
<b>Eravacycline</b>	<b>1</b>	<b>2</b>	<b>0.25-2</b>	<b>- / - / -</b>
Gentamicin	1	2	0.5-8	90.9 / 0 / 9.1
Imipenem	4	4	2-4	45.5 / 54.6 / 0
Levofloxacin	≤ 0.25	2	≤ 0.25-4	81.8 / 9.1 / 9.1
Piperacillin/tazobactam	≤ 0.5	1	≤ 0.5-8	100 / 0 / 0
Tetracycline	> 8	> 8	1-> 8	- / - / -
Tigecycline	1	2	1-2	54.6 / 45.5 / 0
<b>P. vulgaris (14)</b>				
Aztreonam	≤ 0.5	≤ 0.5	≤ 0.5-> 0.5	100 / 0 / 0
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25-0.5	100 / 0 / 0
Ceftazidime	≤ 0.5	≤ 0.5	≤ 0.5-1	100 / 0 / 0
Ceftriaxone	≤ 0.5	1	≤ 0.5-1	100 / 0 / 0
Colistin	> 4	> 4	2-> 4	14.3 / - / 85.7
<b>Eravacycline</b>	<b>1</b>	<b>1</b>	<b>0.5-1</b>	<b>- / - / -</b>
Gentamicin	2	2	1-2	100 / 0 / 0
Imipenem	2	4	1-8	50 / 50 / 0
Levofloxacin	≤ 0.25	≤ 0.25	≤ 0.25-0.5	100 / 0 / 0
Piperacillin/tazobactam	≤ 0.5	≤ 0.5	≤ 0.5-> 0.5	100 / 0 / 0
Tetracycline	8	8	2-> 8	- / - / -
Tigecycline	2	4	1-4	21.4 / 57.1 / 21.4

Table 3. Antimicrobial activity of eravacycline and comparator agents against MDR and CR isolates (N>10) (Continued)

Organism/Antimicrobial Agent (No. Tested)	MIC (mg/L)			%S / %I / %R* EUCAST
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	
<b>S. marcescens (32)</b>				
Aztreonam	≤ 0.5	> 16	≤ 0.5-> 16	78.1 / 0 / 21.9
Cefepime	≤ 0.25	16	≤ 0.25-> 16	81.3 / 3.1 / 15.6
Ceftazidime	≤ 0.5	16	≤ 0.5-> 16	78.1 / 9.4 / 12.5
Ceftriaxone	≤ 0.5	32	≤ 0.5-> 32	78.1 / 0 / 21.9
Colistin	> 4	> 4	> 4-> 4	0 / - / 100
<b>Eravacycline</b>	<b>2</b>	<b>4</b>	<b>0.5-8</b>	<b>- / - / -</b>
Gentamicin	1	2	0.5-> 8	93.8 / 0 / 6.3
Imipenem	1	2	≤ 0.25-2	100 / 0 / 0
Levofloxacin	≤ 0.25	2	≤ 0.25-> 4	84.4 / 6.3 / 9.4
Piperacillin/tazobactam	2	64	≤ 0.5-> 64	84.4 / 3.1 / 12.5
Tetracycline	> 8	> 8	8-> 8	- / - / -
Tigecycline	2	4	1-4	43.8 / 43.8 / 12.5
<b>S. maltophilia (28)</b>				
Aztreonam	> 16	> 16	2-> 16	- / - / -
Cefepime	> 16	> 16	0.5-> 16	- / - / -
Ceftazidime	16	> 16	1-> 16	- / - / -
Ceftriaxone	> 32	> 32	1-> 32	- / - / -
Colistin	1	> 4	≤ 0.12-> 4	- / - / -
<b>Eravacycline</b>	<b>0.25</b>	<b>1</b>	<b>0.03-1</b>	<b>- / - / -</b>
Gentamicin	8	> 8	≤ 0.25-> 8	- / - / -
Imipenem	> 8	> 8	> 8-> 8	- / - / -
Levofloxacin	1	2	≤ 0.25-4	- / - / -
Piperacillin/tazobactam	32	64	2-> 64	- / - / -
Tetracycline	8	> 8	2-> 8	- / - / -
Tigecycline	0.5	1	0.06-2	- / - / -
<b>MDR A. baumannii (10)</b>				
Aztreonam	> 16	> 16	16-> 16	- / - / -
Cefepime	> 16	> 16	16-> 16	- / - / -
Ceftazidime	> 16	> 16	16-> 16	- / - / -
Ceftriaxone	> 32	> 32	> 32-> 32	- / - / -
Colistin	1	1	0.5-2	100 / - / 0
<b>Eravacycline</b>	<b>0.25</b>	<b>1</b>	<b>0.12-1</b>	<b>- / - / -</b>
Gentamicin	> 8	> 8	4-> 8	16.7 / - / 83.3
Imipenem	> 8	> 8	> 8-> 8	0 / 0 / 100
Levofloxacin	> 4	> 4	> 4-> 4	0 / 0 / 100
Piperacillin/tazobactam	> 64	> 64	> 64-> 64	- / - / -
Tetracycline	> 8	> 8	2-> 8	- / - / -
Tigecycline	1	2	0.5-2	- / - / -

\*Criteria as published by the EUCAST (2015); \*Includes: E. aerogenes (11 strains) and E. cloacae (5 strains) ND, Not Determined; "-": no breakpoint defined;

Table 3. Antimicrobial activity of eravacycline and comparator agents against MDR and CR isolates (N>10)

Table 3. Antimicrobial activity of eravacycline and comparator agents against MDR and CR isolates (N>10) (Continued)

Organism/Antimicrobial Agent (No. Tested)	MIC (mg/L)			%S / %I / %R* EUCAST
	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	
<b>MDR Enterobacteriaceae (16)</b>				
Aztreonam	16	> 16	1-> 16	6.3 / 12.5 / 81.3
Cefepime	2	16	≤ 0.25-> 16	43.8 / 12.5 / 43.8
Ceftazidime	16	> 16	≤ 0.5-> 16	6.3 / 18.8 / 7.5
Ceftriaxone	32	> 32	1-> 32	6.3 / 0 / 93.8
Colistin	> 4	> 4	0.5-> 4	37.5 / - / 62.5
<b>Eravacycline</b>	<b>1</b>	<b>4</b>	<b>0.25-4</b>	<b>- / - / -</b>
Gentamicin	1	> 8	≤ 0.25-> 8	75 / 0 / 25
Imipenem	1	8	≤ 0.25-8	87.5 / 12.5 / 0
Levofloxacin	0.5	> 4	≤ 0.25-> 4	56.3 / 12.5 / 31.3
Piperacillin/tazobactam	32	> 64	2-> 64	31.3 / 6.3 / 62.5
Tetracycline	8	> 8	2-> 8	- / - / -
Tigecycline	1	4	0.25-4	56.3 / 18.8 / 25
<b>CR S. maltophilia (28)</b>				
Aztreonam	> 16	> 16	2-> 16	- / - / -
Cefepime	> 16	> 16	0.5-> 16	- / - / -
Ceftazidime	16	> 16	1-> 16	- / - / -
Ceftriaxone	> 32	> 32	1-> 32	- / - / -
Colistin	1	> 4	≤ 0.12-> 4	- / - / -
<b>Eravacycline</b>	<b>0.25</b>	<b>1</b>	<b>0.03-1</b>	<b>- / - / -</b>
Gentamicin	8	> 8	≤ 0.25-> 8	- / - / -
Imipenem	> 8	> 8	> 8-> 8	- / - / -
Levofloxacin	1	2	≤ 0.25-4	- / - / -
Piperacillin/tazobactam	32	> 64	2-> 64	- / - / -
Tetracycline	8	> 8	2-> 8	- / - / -
Tigecycline	0.5	1	0.06-2	- / - / -