

# In vitro activity of eravacycline and comparators against *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and *Enterobacteriaceae*, including carbapenem-resistant and ESBL phenotype subgroups, collected from European hospitals in 2015

Ian Morrissey<sup>1</sup>, Matteo Bassetti<sup>2</sup>, Sophie Magnet<sup>1</sup>, Stephen Hawser<sup>1</sup>, Melanie Olesky<sup>3</sup>, Corey Fyfe<sup>3</sup>

<sup>1</sup>IHMA Europe Sarl, Monthey, Switzerland; <sup>2</sup>Univ. of Udine, Udine, Italy; <sup>3</sup>Tetraphase Pharmaceuticals, Watertown, MA

Contact:  
Tetraphase Pharmaceuticals Medical Information (TPMI)  
medinfo@tphase.com  
617-715-3600

## Introduction

Resistance percentages for Gram-negative pathogens, including for carbapenem- and 3rd generation cephalosporin-resistant organisms, are high and increasing throughout Europe.<sup>1</sup> In a recent report by the World Health Organization (WHO), carbapenem-resistant (CR) *Acinetobacter baumannii* and CR- and 3rd-generation cephalosporin-resistant *Enterobacteriaceae* have been designated as two of three critical priority (tier 1) global pathogens for which new antibiotics are urgently needed within Europe.<sup>2</sup>

Eravacycline (ERV) is a novel, fully-synthetic fluorocycline antibiotic 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 (cIA) and complicated urinary tract infections (cUTI), including pyelonephritis.

Previous global surveillance studies of eravacycline have demonstrated potent *in vitro* activity against many Gram-negative pathogens.<sup>3</sup> The purpose of this study was to demonstrate the *in vitro* activity of eravacycline and comparators against *A. baumannii*, *Stenotrophomonas maltophilia* and *Enterobacteriaceae*, including extended spectrum beta-lactamase (ESBL) and carbapenem-resistant (CR) phenotypes, isolated from patients in Europe.

## Methods

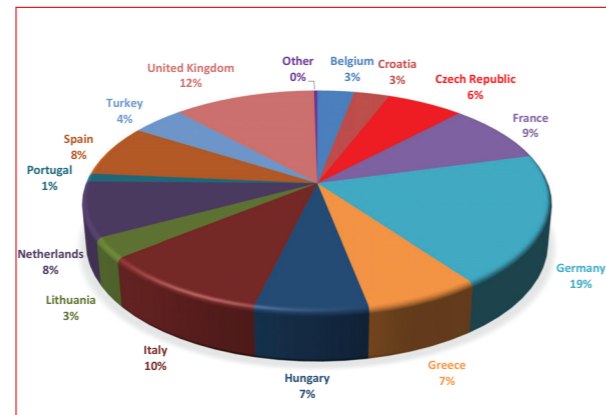
- Enterobacteriaceae* (N=1284), *A. baumannii* (N=270), and *S. maltophilia* (N=293) clinical isolates, collected from various body sites from hospitals in Europe in 2015, were tested.
- Breakdowns by country and site of infection are given in Figures 1 and 2, respectively.
- Minimal inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines.<sup>4</sup>
- Quality control testing was performed each day of testing as specified by the CLSI using *Escherichia coli* ATCC 25922 and *E. coli* ATCC 35218.
- ESBL was defined phenotypically according to CLSI guidelines (*Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae* and *Proteus mirabilis* only).<sup>4</sup>
- CR was defined as isolates that were resistant to ertapenem or meropenem.
- Antibiotic susceptibility was determined using EUCAST version 6.0 breakpoints<sup>5</sup>.

## Results

- Clinical isolates were comparably represented among diverse geographic locations throughout Europe (Fig. 1), with the largest numbers isolated from Germany (19%), UK (12%) and Italy (10%)
- Most isolates were collected from respiratory and genito-urinary sources, followed by gastro-intestinal and other body fluid sources (Fig. 2)

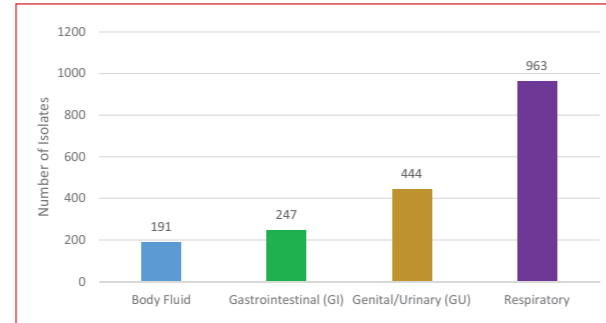
## Results (cont'd)

Figure 1. Distribution (%) by country of origin for the 1847 isolates collected in 2015 in Europe



Countries included as "Other" (Latvia and Russia) had less than 5 isolates each.

Figure 2. Isolate counts by source of infection (N=1845)



Note: Reproductive infection source (N=2) not included in chart. Body fluid includes bile and fluids from abdominal, peritoneal and pleural cavities.

- Summary MIC data for ERV and comparators are shown in Tables 1-3.
  - Overall, ERV MIC<sub>90</sub> values for *Enterobacteriaceae* (all species combined), *S. maltophilia* or *A. baumannii* isolates were 2 mg/L, and were unaffected by CR or ESBL phenotype. ERV MIC<sub>90</sub> values for *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp. and *E. coli* specifically were 0.5 mg/L
  - ERV MIC<sub>90</sub> values were generally 2 to 4-fold lower than tigecycline MIC<sub>90</sub> values, including for CR and ESBL isolates; however, the numbers of CR and ESBL isolates were relatively small.
  - Tigecycline susceptibility against all *Enterobacteriaceae* was 68.3% and 52.9% against CR isolates. CR isolates showed low susceptibility (≤ 52.9% susceptible) to all other antibacterial agents, except amikacin (88.2% susceptible) and colistin (100% susceptible)

Table 1. Antimicrobial activity of ERV and comparator agents against Gram-negative pathogens, including resistant strains, collected from Europe in 2015

Organism/Antimicrobial Tested (No. Tested)	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC (mg/L) MIN	MAX	%S	EUCAST %	%R
<b>All Enterobacteriaceae (N=1284)</b>							
Amikacin	2	4	<0.025	>64	99.1	0.4	0.6
Amoxicillin-clavulanate	>16	>32	<0.025	>64	44	56	56
Aztreonam	0.12	>16	<0.03	>16	81	3.2	15.8
Cefepime	0.06	1	<0.008	>16	90.6	9	6.4
Cefotaxime	0.12	64	<0.015	>64	80.3	1.7	18
Ceftazidime	0.25	32	<0.03	>128	82	2.3	15.7
Ceftiozone	0.12	>4	<0.015	>4	79	1.4	19.6
Colistin	0.5	>1	0.25	>1	100	—	—
Eravacycline	0.5	2	0.06	8	—	—	—
Ertapenem	0.015	0.25	0.004	>2	96.5	2.2	1.3
Gentamicin	0.5	2	<0.12	>16	92	0.5	7.6
Levofloxacin	0.06	2	<0.004	>8	98.2	2.9	9.9
Meropenem	0.03	0.12	0.008	>4	99.4	0.6	0
Piperacillin-tazobactam	2	64	<0.25	>128	82.9	4.7	12.4
Tetracycline	2	>64	0.5	>64	—	—	—
Tigecycline	1	4	0.12	>16	68.3	13.8	17.9
Trimethoprim-sulfamethoxazole	0.12	>4	<0.06	>4	82.9	0.2	16.8
<b>Klebsiella spp. (N=293)</b>							
Amikacin	1	2	<0.25	>64	98.2	0.3	1.5
Amoxicillin-clavulanate	4	32	>1	>32	78.1	—	21.9
Aztreonam	0.12	>16	<0.03	>16	81.9	—	16.1
Cefepime	0.03	2	<0.015	>16	89.1	2.4	8.5
Cefotaxime	0.03	2	<0.015	>64	87.5	2.7	9.7
Ceftazidime	0.12	2	<0.03	>128	88.5	2.4	9.1
Ceftiozone	0.06	>4	<0.015	>4	83	1.5	15.5
Colistin	0.5	0.5	0.25	>1	100	—	0
Eravacycline	0.25	0.5	0.12	1	—	—	—
Ertapenem	0.008	0.06	0.004	>2	96.7	0.9	2.4
Gentamicin	0.5	1	<0.12	>16	94.2	0	5.8
Levofloxacin	0.06	1	0.015	>8	90.6	0.9	8.5
Meropenem	0.03	0.12	0.008	>4	98.8	1.2	0
Piperacillin-tazobactam	2	>128	<0.25	>128	82.7	3.7	13.7
Tetracycline	1	16	0.5	>64	—	—	—
Tigecycline	0.5	2	0.25	>16	87.8	8.8	3.3
Trimethoprim-sulfamethoxazole	0.12	>4	<0.06	>4	87.8	0	12.2
<b>Enterobacter spp. (N=313)</b>							
Amikacin	1	2	<0.25	>8	100	0	0
Amoxicillin-clavulanate	>32	>32	<0.25	>32	2.8	—	97.1
Aztreonam	0.12	>16	<0.03	>16	66.1	4.8	29.1
Cefepime	0.06	2	0.015	>16	89.1	4.2	6.7
Cefotaxime	0.5	>64	0.03	>64	52.5	1.9	24.5
Ceftazidime	0.5	128	0.06	>128	65.5	1.9	32.6
Ceftiozone	0.25	>4	<0.015	>4	64.9	1	34.2
Colistin	0.5	0.5	0.25	>1	100	—	—
Eravacycline	0.5	0.5	0.12	4	—	—	—
Ertapenem	0.06	0.5	0.004	>2	92.7	6.1	1.3
Gentamicin	0.5	1	<0.12	>16	93.3	0	6.7
Levofloxacin	0.06	1	<0.004	>8	92	2.9	5.1
Meropenem	0.06	0.12	0.015	>4	99.7	0.3	0
Piperacillin-tazobactam	4	64	<0.25	>128	71.3	8.3	20.5
Tetracycline	2	2	>64	>64	—	—	—
Tigecycline	1	1	0.25	>8	90.1	6.1	3.8
Trimethoprim-sulfamethoxazole	0.12	>4	<0.06	>4	87.9	0	12.1
<b>Citrobacter spp. (N=164)</b>							
Amikacin	1	2	<0.25	>64	98.8	0.6	0.6
Amoxicillin-clavulanate	>32	>32	<0.25	>32	40.2	—	59.8
Aztreonam	0.12	>16	<0.03	>16	81.1	1.8	17.1
Cefepime	0.03	1	0.015	>16	95.1	1.8	3.1
Cefotaxime	0.12	32	<0.015	>64	80.5	1.2	18.3
Ceftazidime	0.25	128	<0.03	>128	78.1	3.7	18.3
Ceftiozone	0.12	>4	<0.015	>4	80.5	1.2	18.3
Colistin	0.5	>1	0.25	>1	100	—	—
Eravacycline	0.25	0.5	0.12	2	—	—	—
Ertapenem	0.015	0.25	0.008	>2	97	2.4	0.6
Gentamicin	0.5	1	<0.12	>16	98.2	0	1.8
Levofloxacin	0.03	0.5	0.015	>8	95.7	0.6	3.7
Meropenem	0.03	0.06	0.015	>25	100	0	0
Piperacillin-tazobactam	2	64	0.5	>128	77.4	6.1	16.5
Tetracycline	2	8	1	>64	—	—	—
Tigecycline	0.5	1	0.25	>16	90.2	7.3	2.4
Trimethoprim-sulfamethoxazole	<0.06	0.25	<0.06	>4	93.9	0	6.1
<b>Escherichia coli (N=139)</b>							
Amikacin	2	8	0.5	>16	98.6	1.4	0
Amoxicillin-clavulanate	16	32	<0.25	>32	43.2	—	56.8
Aztreonam	0.12	>16	<0.03	>16	81.3	4.9	14.4
Cefepime	0.06	>16	<0.008	>16	84.2	2.9	13.0
Cefotaxime	0.06	>64	<0.015	>64	82.7	0	17.3
Ceftazidime	0.25	16	0.06	>128	82.7	2.2	15.1
Ceftiozone	0.06	>4	<0.015	>4	82.0	0.7	17.3
Colistin	0.5	0.5	0.25	>1	100	—	0
Eravacycline	0.12	0.5	0.06	1	—	—	—
Ertapenem	0.008	0.06	0.004	>2	99.3	0	0.7
Gentamicin	0.5	>16	<0.12	>16	83.5	0.7	15.8
Levofloxacin	0.03	>8	0.008	>8	75.5	0	24.5
Meropenem	0.03	0.06	0.008	>2	100	0	0
Piperacillin-tazobactam	2	16	<0.25	>128	86.3	4.3	9.4
Tetracycline	2	>64	1	>64	—	—	—
Tigecycline	0.25	1	0.12	>4	91.4	7.2	1.4
Trimethoprim-sulfamethoxazole	0.12	>4	<0.06	>4	69.8	0	30.2
<b>Proteus mirabilis (N=17)</b>							
Amikacin	2	4	1	8	100	0	0
Amoxicillin-clavulanate	1	32	0.5	>32	81.4	—	18.6
Aztreonam	<0.03	0.06	<0.03	>4	95.9	4.1	0
Cefepime	0.06	1	0.015	>4	95.4	4.7	0
Cefotaxime	<0.015	0.25	<0.015	>64	90.1	0	9.9
Ceftazidime	<0.06	0.25	<0.03	>64	93	1.7	5.2
Ceftiozone	<0.015	1	<0.015	>4	91.9	1.2	7.0
Colistin	>1	>1	>1	>1	100	—	0
Eravacycline	2	2	0.25	4	—	—	—
Ertapenem	0.015	0.015	0.008	>2	99.4	0	0.6
Gentamicin	1	16	0.25	>16	84.9	1.7	13.1
Levofloxacin	0.06	4	0.008	>8	78.5	10.5	11.4
Meropenem	0.06	0.12	0.015	>4	99.4	0.6	0
Piperacillin-tazobactam	0.5	2	<0.25	>128	97.1	0.6	2.3
Tetracycline	64	64	1	>64	—	—	—
Tigecycline	4	4	1	>16	6.4	6.4	8.8
Trimethoprim-sulfamethoxazole	0.25	>4	<0.06	>4	63.4	0.6	35.1

Organism/Antimicrobial Tested (No. Tested)	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC (mg/L) MIN	MAX	%S	EUCAST %	%R
<b>Serratia marcescens (N=112)</b>							
Amikacin	2	4	1	32	98.2	0.9	0.9
Amoxicillin-clavulanate	>32	>32	<0.25	>32	4	—	96.2
Aztreonam	0.12	2	<0.03	>16	87.5	2.7	9.8
Cefepime	0.12	1	0.03	>16	90.2	1.8	8
Cefotaxime	0.5	8	0.06	>64	83	3.6	12.4
Ceftazidime	0.25	1	0.06	>128	90.2	1.8	8
Ceftiozone	0.25	4	0.03	>4	85.7	2.7	11.6
Colistin	>1	>1	0.5	>1	100	—	0
Eravacycline	2	2	0.12	4	—	—	—
Ertapenem	0.03	0.12	0.015	>2	96.4	1.8	1.8
Gentamicin	1	2	<0.12	>16	91.1	1.8	7.1
Levofloxacin	0.12	2	0.03	>8	87.5	5.4	7.1
Meropenem	0.06	0.12	0.03	>4	98.2	1.8	0
Piperacillin-tazobactam	2	8	0.5	>128	90.2	4.5	5.4
Tetracycline	64	>64	4	>64	—	—	—
Tigecycline	2	4	1	8	19.5	66.1	14.3
Trimethoprim-sulfamethoxazole	0.5	4	0.12	>4	88.4	1.8	9.8
<b>Acinetobacter baumannii (N=270)</b>							
Amikacin	64	>64	0.12	>64	38.5	0.4	61.1
Amoxicillin-substant	64	>64	1	>64	—	—	—
Aztreonam	>64	>64	4	>64	—	—	—
Cefepime	>64	>64	0.5	>64	—	—	—
Ceftazidime	>64	>64	1	>64	—	—	—
Ceftiozone	>64	>64	4	>64	—	—	—
Colistin	>64	>64	<0.03	>32			