

# *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

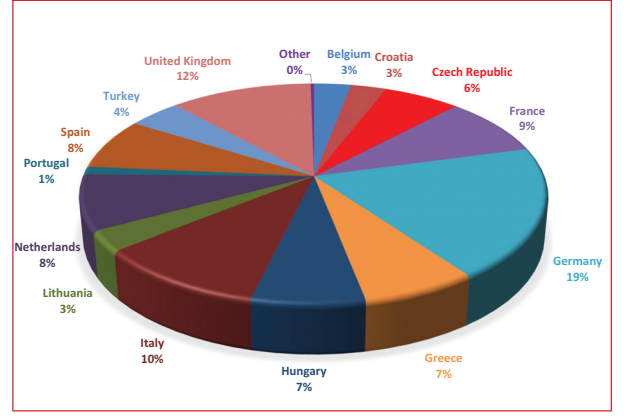
- *Enterobacteriaceae* (N=1284), *A. baumannii* (N=270), and *S. maltophilia* (N=293) clinical isolates, collected from various body sites from hospitals in Europe in 2015, were tested.
- Breakdowns by country and site of infection are given in Figures 1 and 2, respectively.
- Minimal inhibitory concentration (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)

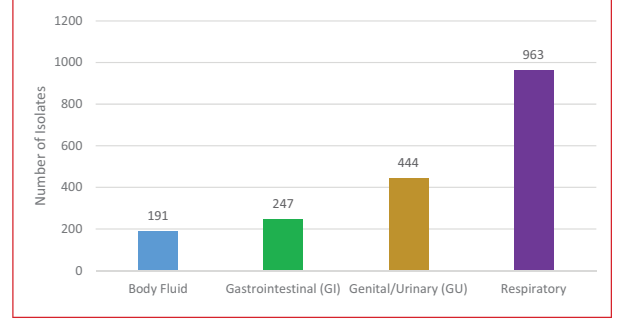
## Results (cont'd)

**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	> 0.25	> 64	44	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	–	–	
<b>Eravacycline</b>	0.5	2	0.06	4	–	–	–	
Ertapenem	0.015	0.25	0.004	> 2	96.5	2.2	1.3	
Gentamicin	0.5	2	> 0.12	> 16	52	0.5	7.6	
Levofloxacin	0.06	2	≤ 0.004	> 8	88.2	2.9	8.9	
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=929)</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	86.5	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	–	–	
<b>Eravacycline</b>	0.25	0.5	0.12	4	–	–	–	
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	8.3	
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	–	–	
<b>Eravacycline</b>	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	59.3	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	1	> 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	–	99.8	
Aztreonam	0.12	> 16	> 0.03	> 16	81	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	18.9	
Ceftiozone	0.12	> 4	≤ 0.015	> 4	80.5	1.2	18.3	
Colistin	0.5	1	0.25	> 1	100	–	–	
<b>Eravacycline</b>	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	64	90.2	7.3	2.4	
Trimethoprim-sulfamethoxazole	≤ 0.06	0.25	> 0.06	> 4	93.9	0	6.1	
<b>Klebsiella 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	92.7	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	–	–	
<b>Eravacycline</b>	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	4	95.9	4.1	9	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	> 64	≤ 0.015	> 64	93	1.7	5.2	
Ceftiozone	≤ 0.015	1	≤ 0.015	> 4	91.9	1.2	7.0	
Colistin	0.5	> 1	> 1	> 1	100	–	–	
<b>Eravacycline</b>	2	8	0.2	4	–	–	–	
Ertapenem	0.015	0.015	0.006	> 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	8	1	16	6.4	6.4	8.8	
Trimethoprim-sulfamethoxazole	0.25	> 4	> 0.06	> 4	63.4	0.6	35.1	

**Table 2. Antimicrobial activity of ERV and comparator agents against CR-Enterobacteriaceae and CR-A. baumannii 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>Serratia marcescens (N=112)</b>								
Amikacin	2	4	1	32	98.2	0.9	0.9	
Amoxic								