

# In vitro activity of eravacycline and comparators against *Staphylococcus aureus* and enterococci, including methicillin-resistant and vancomycin-resistant subgroups, collected from European hospitals in 2015

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## Introduction

The European Centre for Disease Prevention and Control (ECDC) estimates ~37,000 deaths per year in Europe to be attributed to acquired healthcare-associated infections, with Gram-positive organisms such as *Staphylococcus aureus*, *Enterococcus* spp. and coagulase-negative staphylococci among the contributable pathogens.<sup>1</sup> While the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) has stabilized/decreased, it remains ~17% in EU/EAA countries.<sup>2</sup> However, the proportion of MRSA typically associated with healthcare-associated infections has increased in the community-onset setting.<sup>2</sup> The occurrence of vancomycin-resistant *Enterococcus faecium* at 8.3% has shown an increasing trend among almost half of EU/EAA countries.<sup>2</sup> In a recent report by the World Health Organization (WHO), both MRSA and vancomycin-resistant enterococci (VRE) have been designated as high priority (tier 2) global pathogens for which new antibiotics are urgently needed within Europe.<sup>3</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 specific Gram-positive pathogens.<sup>4</sup> The purpose of this study was to demonstrate the *in vitro* activity of eravacycline and comparators against *S. aureus*, *Enterococcus* spp. and coagulase-negative staphylococci, including resistant phenotypes, isolated from patients in Europe during 2015.

## Methods

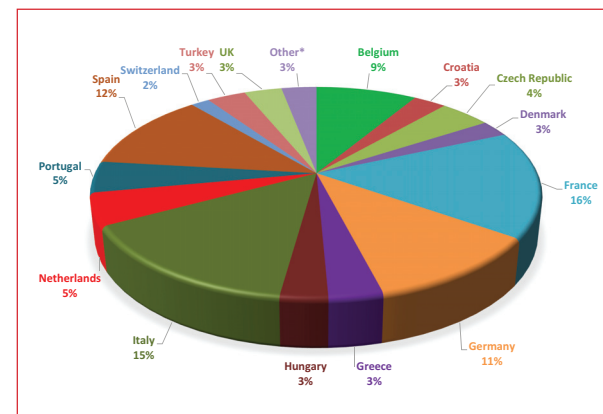
A total of 998 staphylococci (N=544) and enterococci (N=454) clinical isolates, collected from various body sites from hospitals in Europe in 2015, were tested.

- 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>5</sup>
- Quality control testing was performed each day of testing as specified by the CLSI using *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213.
- Antibiotic susceptibility was determined using EUCAST version 6.0 breakpoints<sup>6</sup>.

## Results

- Clinical isolates were comparably represented among diverse geographic locations throughout Europe (Fig. 1), with the largest numbers isolated from France (16%), Italy (15%), Spain (12%), and Germany (11%).

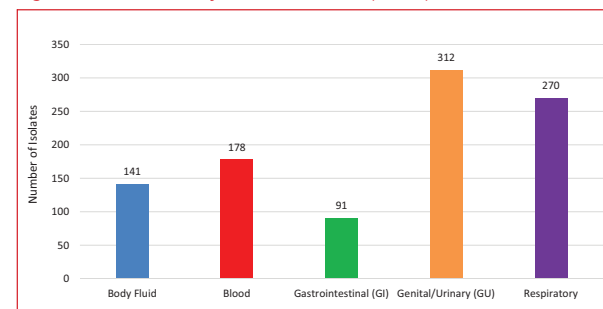
Figure 1. Isolate distribution (%) by country of origin for the 998 isolates collected in 2015 in Europe



UK, United Kingdom; \*Other\* (Austria, Ireland, Poland, Romania, and Russia) had 10 or less isolates

- Most isolates were collected from genito-urinary and respiratory sources, followed by blood, other body fluid and gastro-intestinal sources (Fig. 2).

Figure 2. Isolate counts by source of infection (N=992)



Note: Throat infection source (N=6) not included in chart.  
Body fluid includes bile and fluids from abdominal, peritoneal and pleural cavities.

- Tables 1 and 2 show MIC data for staphylococci and enterococci, respectively.
  - ERV MIC<sub>50/90</sub> values were 0.06/0.25 mg/L for all staphylococci combined and were 0.06/0.06 mg/L for both methicillin-sensitive *S. aureus* (MSSA) and MRSA
  - MIC<sub>50/90</sub> values for ERV against all enterococci combined, VS (vancomycin-susceptible) *E. faecium*, and VRE strains were 0.03/0.06 mg/L and were 0.06/0.06 mg/L for VS *E. faecalis*.

Table 1. Antimicrobial activity of ERV and comparator agents against *Staphylococcus* spp., including resistant strains, collected from Europe in 2015

Organism/Antimicrobial Tested (No. Tested)	MIC (mg/L)				EUCAST		
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIN	MAX	%S	%I	%R
<b>All Staphylococcus spp. (N=544)*</b>							
Amoxicillin-clavulanate	>1	>1	≤0.06	>1	--	--	--
Azithromycin	>4	>4	≤0.25	>4	44.3	0.2	55.5
Clindamycin	0.06	>2	≤0.03	>2	77.2	1.1	21.7
Daptomycin	0.25	0.5	≤0.06	>2	99.6	--	0.4
<b>Eravacycline</b>	<b>0.06</b>	<b>0.25</b>	<b>≤0.008</b>	<b>2</b>	--	--	--
Gentamicin	0.25	>8	≤0.06	>8	67.3	--	32.7
Levofloxacin	4	>4	0.06	>4	44.1	3.9	52
Linezolid	1	2	≤0.5	>4	99.5	--	0.6
Minocycline	0.12	0.25	≤0.06	4	98.4	1.5	0.2
Oxacillin	>2	>2	≤0.06	>2	--	--	--
Penicillin	>2	>2	≤0.12	>2	--	--	--
Tetracycline	0.25	4	≤0.06	>16	82.4	3.9	13.8
Tigecycline	0.12	0.25	0.03	1	99.8	--	0.2
Vancomycin	1	2	≤0.25	4	--	--	--
<b>MSSA (N=105)</b>							
Amoxicillin-clavulanate	>1	>1	0.25	>1	--	--	--
Azithromycin	0.5	>4	≤0.25	>4	88.6	1.0	10.5
Clindamycin	0.06	0.12	≤0.03	0.25	100	0	0
Daptomycin	0.25	0.5	0.12	0.5	100	--	0
<b>Eravacycline</b>	<b>0.06</b>	<b>0.06</b>	<b>≤0.008</b>	<b>0.12</b>	--	--	--
Gentamicin	0.25	0.5	≤0.06	1	100	--	0
Levofloxacin	0.12	0.5	0.06	>4	99.5	0	9.5
Linezolid	1	2	≤0.5	2	100	--	0
Minocycline	0.12	0.12	≤0.06	0.25	100	0	0
Oxacillin	0.25	0.5	0.12	0.5	100	--	0
Penicillin	1	>2	≤0.12	>2	23.8	--	76.2
Tetracycline	0.25	0.25	≤0.06	>16	99.1	0	1.0
Tigecycline	0.12	0.25	0.06	0.25	100	--	0
Vancomycin	1	1	≤0.25	2	100	--	0
<b>MRSA (N=104)</b>							
Amoxicillin-clavulanate	>1	>1	1	>1	--	--	--
Azithromycin	>4	>4	≤0.25	>4	33.7	0	66.4
Clindamycin	0.12	>2	≤0.03	>2	58.7	0	41.4
Daptomycin	0.25	0.5	0.25	1	100	--	0
<b>Eravacycline</b>	<b>0.06</b>	<b>0.06</b>	<b>0.015</b>	<b>0.25</b>	--	--	--
Gentamicin	0.25	0.5	0.12	>8	96.2	--	3.9
Levofloxacin	>4	>4	0.06	>4	16.4	1.9	81.7
Linezolid	1	2	1	2	100	--	0
Minocycline	0.12	0.12	≤0.06	0.5	100	0	0
Oxacillin	>2	>2	1	>2	1	--	99
Penicillin	>2	>2	≤0.12	>2	1.9	--	98.1
Tetracycline	0.25	0.5	≤0.06	>16	95.2	0	4.8
Tigecycline	0.25	0.25	0.06	0.5	100	--	0
Vancomycin	1	1	≤0.25	1	100	--	0
<b>Staphylococcus epidermidis (N=148)</b>							
Amoxicillin-clavulanate	>1	>1	≤0.06	>1	--	--	--
Azithromycin	>4	>4	≤0.25	>4	41.2	0	58.8
Clindamycin	0.06	>2	≤0.03	>2	66.2	3.4	30.4
Daptomycin	0.5	0.5	≤0.06	1	100	--	0
<b>Eravacycline</b>	<b>0.06</b>	<b>0.25</b>	<b>≤0.008</b>	<b>1</b>	--	--	--
Gentamicin	0.12	>8	≤0.06	>8	52.7	--	47.3
Levofloxacin	>4	>4	0.12	>4	39.2	11.5	49.3
Linezolid	≤0.5	1	≤0.5	>4	98.7	--	1.4
Minocycline	0.12	0.5	≤0.06	4	98	1.4	0.7
Oxacillin	2	>2	≤0.06	>2	22.3	--	77.7
Penicillin	>2	>2	≤0.12	>2	--	--	--
Tetracycline	1	8	≤0.06	>16	75	10.8	14.2
Tigecycline	0.12	0.25	0.03	0.5	100	--	0
Vancomycin	2	2	0.5	2	100	--	0
<b>Staphylococcus haemolyticus (N=135)</b>							
Amoxicillin-clavulanate	>1	>1	0.12	>1	--	--	--
Azithromycin	>4	>4	≤0.25	>4	18.5	0	81.5
Clindamycin	0.06	>2	≤0.03	>2	83.7	0	16.3
Daptomycin	0.5	0.5	0.12	1	100	--	0
<b>Eravacycline</b>	<b>0.12</b>	<b>0.25</b>	<b>0.015</b>	<b>2</b>	--	--	--
Gentamicin	8	>8	≤0.06	>8	27.4	--	72.6
Levofloxacin	>4	>4	0.06	>4	18.5	0.7	80.7
Linezolid	1	1	≤0.5	2	100	--	0
Minocycline	0.25	0.25	≤0.06	1	95.6	4.4	0
Oxacillin	>2	>2	≤0.06	>2	17.8	--	82.2
Penicillin	>2	>2	≤0.12	>2	--	--	--
Tetracycline	1	>16	0.12	>16	68.2	2.2	29.6
Tigecycline	0.25	0.5	0.06	1	99.3	--	0.7
Vancomycin	2	2	0.5	4	100	--	0

\*Includes *S. aureus* (209), *S. capitis* (4), *S. epidermidis* (148), *S. haemolyticus* (135), *S. hominis* (16), *S. lugdunensis* (9), *S. pasteurii* (1), *S. saprophyticus* (13), *S. schleiferi* (1), *S. sciuri* (2), *S. simulans* (2), *S. warneri* (2), CNSA, non-specified (1), non-specified (1)  
MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; "--" represents lack of an established breakpoint

Table 2. Antimicrobial activity of ERV and comparator agents against *Enterococcus* spp., including resistant strains, collected from Europe in 2015

Organism/Antimicrobial Tested (No. Tested)	MIC (mg/L)				EUCAST		
	MIC <sub>50</sub>	MIC <sub>90</sub>	MIN	MAX	%S	%I	%R
<b>All Enterococcus spp. (N=454)*</b>							
Amoxicillin-clavulanate	1	>1	≤0.12	>1	100	0	0
Ampicillin	1	>8	≤0.25	>8	67.2	0.4	32.4
Daptomycin	2	4	0.12	8	--	--	--
<b>Eravacycline</b>	<b>0.03</b>	<b>0.06</b>	<b>0.015</b>	<b>1</b>	--	--	--
Levofloxacin	2	>8	0.25	>8	52	--	48
Linezolid	1	1	0.5	4	100	--	0
Minocycline	8	>8	≤0.03	>8	--	--	--
Penicillin	2	>8	≤0.06	>8	--	--	--
Tetracycline	32	>32	0.12	>32	--	--	--
Tigecycline	0.12	0.12	0.03	8	98.9	0.4	0.7
Vancomycin	1	2	≤0.25	>16	95.6	--	4.4
<b>Enterococcus faecalis, VSE (N=281)</b>							
Amoxicillin-clavulanate	1	1	≤0.12	>1	100	0	0
Ampicillin	1	1	≤0.25	>8	98.9	0	1.1
Daptomycin	1	2	0.12	8	--	--	--
<b>Eravacycline</b>	<b>0.06</b>	<b>0.06</b>	<b>0.015</b>	<b>0.12</b>	--	--	--
Levofloxacin	1	>8	0.25	>8	72.6	--	27.4
Linezolid	1	1	0.5	2	100	--	0
Minocycline	8	>8	≤0.03	>8	--	--	--
Penicillin	2	4	0.5	>8	--	--	--
Tetracycline	>32	>32	0.12	>32	--	--	--
Tigecycline	0.12	0.25	0.03	8	98.9	0.7	0.4
Vancomycin	1	2	0.5	2	100	--	0
<b>Enterococcus faecium, VSE (N=143)</b>							
Amoxicillin-clavulanate	>1	>1	≤0.12	>1	100	0	0
Ampicillin	>8	>8	≤0.25	>8	11.2	1.4	87.4
Daptomycin	4	4	0.12	4	--	--	--
<b>Eravacycline</b>	<b>0.03</b>	<b>0.06</b>	<b>0.015</b>	<b>0.25</b>	--	--	--
Levofloxacin	>8	>8	0.5	>8	15.4	--	84.6
Linezolid	1	2	0.5	4	100	--	0
Minocycline	0.06	>8	0.06	>8	--	--	--
Penicillin	>8	>8	≤0.06	>8	--	--	--
Tetracycline	0.25	>32	0.12	>32	--	--	--
Tigecycline	0.06	0.12	0.03	8	99.3	0	0.7
Vancomycin	0.5	1	≤0.25	2	100	--	0
<b>VRE (N=20)*</b>							
Amoxicillin-clavulanate	>1	>1	1	>1	100	0	0
Ampicillin	>8	>8	1	>8	15	0	85
Daptomycin	2	4	1	4	--	--	--
<b>Eravacycline</b>	<b>0.03</b>	<b>0.06</b>	<b>0.03</b>	<b>1</b>	--	--	--
Levofloxacin	>8	>8	0.5	>8	10	--	90
Linezolid	1	1	1	1	100	--	0
Minocycline	0.06	8	0.06	>8	--	--	--
Penicillin	>8	>8	2	>8	--	--	--
Tetracycline	0.25	>32	0.25	>32	--	--	--
Tigecycline	0.06	0.25	0.06	1	95	0	5
Vancomycin	>16	>16	>16	>16	0	--	100

\*Includes *E. avium* (2), *E. casseliflavus* (1), *E. durans* (1), *E. faecalis* (284), *E. faecium* (160), *E. gallinarum* (3), *E. hirae* (1), *E. raffinosus* (2)

\*Includes vancomycin-resistant *E. faecalis* (N=3) and vancomycin-resistant *E. faecium* (N=17)

VSE, vancomycin-sensitive enterococci; VRE, vancomycin-resistant enterococci; "--" represents lack of an established breakpoint

- The *in vitro* activity (as measured by MIC<sub>90</sub> values) for ERV against *S. aureus*, including MRSA, was 4-fold more potent than tigecycline (TGC) and 2-fold more potent than minocycline (MIN). ERV exhibited up to 4-fold greater activity than TGC, >64-fold greater activity than MIN, and at least 16-fold greater activity than vancomycin against enterococci. All *S. aureus*, 99% of VSE and 95% of VRE were TGC-susceptible. Fig. 3 and Fig. 4 show MIC distributions for ERV, MIN and TGC.
- While staphylococci combined had varied susceptibilities to comparators, MSSA were ~90% susceptible to most agents except penicillin (24% susceptible) and MRSA were poorly susceptible to most agents except gentamicin (96% susceptible), tetracyclines (≥95% susceptible), daptomycin (100% susceptible), linezolid (100% susceptible) and vancomycin (100% susceptible). VS *E. faecalis* were ≥90% susceptible to most agents, except levofloxacin (73%). VS *E. faecium* and VRE showed reduced susceptibilities to ampicillin (11-15%) and levofloxacin (10-15%).