# **Oritavancin Activity against Staphylococcus aureus Clinical Isolates Causing Serious Infections in Hospitalized Patients in** Europe (2017–2018)

Cecilia G. Carvalhaes<sup>1</sup>, Helio S. Sader<sup>1</sup>, Jennifer M. Streit<sup>1</sup>, Robert K. Flamm<sup>1</sup>, Rodrigo E. Mendes<sup>1</sup> <sup>1</sup> JMI Laboratories, North Liberty, Iowa, USA

## Introduction

- Oritavancin, a potent lipoglycopeptide antibiotic, with a convenient single dose regimen, is a desirable option for serious Gram-positive infections as well as for those requiring prolonged treatment courses
- Oritavancin has potent bactericidal activity by inhibiting peptidoglycan synthesis at 2 stages and by causing depolarization of the bacterial cell membrane
- The European Medicines Agency and the United States Food and Drug Administration approved oritavancin for the treatment of skin and soft tissue infections in 2015
- This study assessed the activity of oritavancin and comparators against a contemporary collection of Staphylococcus aureus isolates causing serious infections in Europe

# Materials and Methods

#### **Organism collection**

- A total of 1.232 S. aureus isolates were included that were deemed to be the primary organisms responsible for invasive infections during 2017–2018 in 33 medical centres in 13 European and adjacent countries/regions
- The list of participating countries, sites, and number of isolates is shown in Table 1
- Only 1 isolate per patient infection episode was included
- Bacterial identification was confirmed by matrix-assisted laser desorption ionizationtime of flight mass spectrometry (Bruker Daltonics, Massachusetts, USA) following the manufacturer's instructions

#### Antimicrobial susceptibility testing

- Susceptibility testing was performed by broth microdilution according to European Committee of Antimicrobial Susceptibility Testing (EUCAST) methods and determinations were based on EUCAST (2019) breakpoint criteria
- Oritavancin minimal inhibitory concentrations (MICs) were determined in the presence of polysorbate-80 (0.002%)
- Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event
- Quality assurance was performed by concurrently testing EUCAST-recommended quality control (QC) reference strains (S. aureus ATCC 29213 and Enterococcus faecalis ATCC 29212), and all results were within published acceptable ranges



## Results

Country	No. of sites	No. of isolates
Belgium	1	9
France	5	238
Germany	5	144
Greece	1	12
Ireland	2	61
Italy	4	311
Poland	1	1
Portugal	1	47
Russia	3	72
Spain	3	90
Sweden	2	87
Turkey	2	69
United Kingdom	3	91
Total	33	1,232

S. aureus was most frequently recovered from bloodstream infections (BSIs; 77.8% of all isolates), followed by pneumonia (17.2%), bone and joint infections (BJIs; 3.1%), and intra-abdominal infections (IAIs; 1.9%, Figure 1)

Oritavancin (MIC<sub>50</sub>/MIC<sub>90</sub>, 0.03/0.06 mg/L) inhibited all S. aureus isolates at the susceptible breakpoint of  $\leq 0.12 \text{ mg/L}$  (Table 2)

Testing against methicillin-resistant S. aureus (MRSA; 23.3% of all S. aureus) and methicillin-susceptible S. aureus (MSSA) groups yielded similar oritavancin MIC<sub>50</sub> (0.03 mg/L) and MIC<sub>90</sub> (0.03-0.06 mg/L) results, regardless of infection type (Table 4) MRSA rates varied greatly among European countries (0%-46.6%; Table 3), but oritavancin MIC<sub>50</sub> and MIC<sub>90</sub> values remained at 0.03 mg/L and 0.03-0.06 mg/L, respectively (data not shown)

MSSA isolates showed high overall susceptibility rates to oritavancin (100%), vancomycin (100%), teicoplanin (99.9%), linezolid (100%), and clindamycin (98.6%), regardless of infection type

Oritavancin, vancomycin, teicoplanin, and linezolid remained active against MRSA isolates, regardless of infection type (Figure 2)

Oritavancin had  $MIC_{50}/MIC_{90}$  results (0.03/0.06 mg/L) 16- to 32-fold lower than vancomycin (MIC<sub>50</sub>/MIC<sub>90</sub>, 1/1 mg/L), teicoplanin (MIC<sub>50</sub>/MIC<sub>90</sub>, 0.5 / 1 mg/L), and linezolid ( $MIC_{50}/MIC_{90}$ , 1 / 2 mg/L, Table 4)

Decreased susceptibility to vancomycin (MIC, 2 mg/L) was observed in 8 MRSA isolates causing bloodstream infection, which exhibited oritavancin MIC values of 0.03 mg/L (4 isolates), 0.06 mg/L (3 isolates), and 0.12 mg/L (1 isolate)

Three teicoplanin-resistant S. aureus isolates (MIC, >2 mg/L) were observed; 2 of them also showed reduced susceptibility of vancomycin (MIC, 2 mg/L) and showed oritavancin MIC values of 0.03-0.12 mg/L

#### Table 1 List of European countries and number of S. aureus isolates causing serious infections

### Table 2 MIC distribution of oritavancin and comparator agents against 1,232 S. aureus isolates

Antimicrobial	Antimicrobial	No. and cumulative % of isolates inhibited at MIC (mg/L) of:										MIC <sub>50</sub>	MIC <sub>90</sub>			
agent	range (mg/L)	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	> <sup>a</sup>	(mg	;/L)
Oritavancin 0.004 - 1	0.004 1	17	344	747	99	25									0.02	0.06
	0.004 - 1	1.4%	29.3%	89.9%	98.0%	100.0%									0.03	
Clindamycin ≤0.03 - ≍				290	830	41	5	2	0	0				64	0.06	0.06
	≤0.03 - >2			23.5%	90.9%	94.2%	94.6%	94.8%	94.8%	94.8%				100.0%	0.06	0.06
Levofloxacin ≤0.03	< 0.02 > 1			1	5	224	679	48	10	3	13			249	0.25	
	≤0.03 - >4			0.1%	0.5%	18.7%	73.8%	77.7%	78.5%	78.7%	79.8%			100.0%	0.25	>4
Linezolid ≤0.12 - >8							0	54	798	375	5				1	2
	≤0.12 - <i>&gt;</i> 8						0.0%	4.4%	69.2%	99.6%	100.0%				Ŧ	
Teicoplanin	≤0.12 - 16					6	282	857	71	13	2	1			0 5	
						0.5%	23.4%	92.9%	98.7%	99.8%	99.9%	100.0%			0.5	0.5
Vancomycin	≤0.12 - 4					0	4	255	952	20					1	1
						0.0%	0.3%	21.0%	98.4%	100.0%					Т	T
<b>a</b>																

Greater than the highest concentration tested.

### Figure 2 Oritavancin and comparators activity against MRSA isolates



<sup>a</sup> Susceptibility rate based on EUCAST v.9.0 criteria.

#### Table 4 Activity of oritavancin and comparators against S. aureus isolates by infection type in Europe

Infection type		MIC <sub>50/90</sub> (mg/L)						
(no. of isolates)	Oritavancin	Vancomycin	Teicoplanin	Linezolid	Clindamycin	Lev		
MSSA (945)	0.03 / 0.03	1/1	0.5 / 0.5	1/2	0.06 / 0.06	0.2		
BSI (712)	0.03 / 0.03	1/1	0.5 / 0.5	1/2	0.06 / 0.06	0.2		
Pneumonia (185)	0.03 / 0.06	1/1	0.5 / 0.5	1/2	0.06 / 0.06	0.2		
IAI (17)	0.03 / 0.06	1/1	0.5 / 0.5	1/2	0.06 / >2	0.2		
BJI (31)	0.03 / 0.03	1/1	0.5 / 0.5	1/2	0.06 / 0.06	0.2		
MRSA (287)	0.03 / 0.06	1/1	0.5 / 1	1/2	0.06 / >2	>		
BSI (247)	0.03 / 0.06	1/1	0.5 / 1	1/2	0.06 / >2	>		
Pneumonia (27)	0.03 / 0.06	1/1	0.5 / 1	1/2	0.06 / >2	>		
IAI (6)	0.03 / -	1/-	0.5 / -	1/-	0.06 / -	0		
BJI (7)	0.03 / -	1/-	0.5 / -	1/-	0.06 / -			

Susceptibility rate based on EUCAST v.9.0 criteria.

Linezolid Teicoplanin Clindamycin Levofloxacin Antimicrobial Bloodstream infection (n = 247) Pneumonia (n = 27) Total MRSA (n = 287)

#### Table 3 MRSA rates among European countries and surroundings

Country	Total isolates	% MRSA	TZD MIC <sub>50</sub> (mg/L)
Italy	311	46.60%	0.03
Turkey	69	27.50%	0.03
Spain	90	25.60%	0.03
Germany	144	19.40%	0.03
Portugal	47	19.10%	0.03
Russia	72	18.10%	0.03
Ireland	61	16.40%	0.03
France	238	12.20%	0.03
United Kingdom	91	9.90%	0.03
Greece	12	8.30%	0.03
Sweden	87	1.10%	0.03
Belgium	9	0.00%	0.03
Poland	1	0.00%	0.03
Total	1232	23.30%	0.03

<sup>b</sup> MSSA, methicillin-susceptible S. aureus; MRSA, methicillin-resistant S. aureus; BSI, bloodstream infection; IAI, intra-abdominal infection; BJI, bone and joint infection

TZD MIC <sub>90</sub> (mg/L)
0.03
0.06
0.03
0.06
0.03
0.06
0.06
0.03
0.03
0.06
0.06
0.06
0.06

### floxacin 5 / 0.25 / 0.25 / 0.25 25 / 0.5 5 / 0.25 / >4 / >4 / >4 25 / -

## Conclusions

- Oritavancin showed good activity ( $MIC_{50}/MIC_{90}$ , 0.03/0.06 mg/L) against this 2017–2018 European collection of S. aureus isolates responsible for pneumonia, intra-abdominal, bone and joint, and bloodstream infections
- All isolates were susceptible to oritavancin, vancomycin, and linezolid, regardless of infection type or methicillin resistance
- Oritavancin showed 16- to 32-fold higher activity than vancomycin, teicoplanin, and linezolid against S. aureus isolates causing serious infections
- Oritavancin was also active against MRSA isolates displaying reduced susceptibility to vancomycin and/or teicoplanin
- A prolonged half-life and high potency may support oritavancin as a good option for treating serious S. aureus infections

## Acknowledgements

Funding for this research was provided by Melinta Therapeutics, Morristown, NJ, USA.

## References

Clinical and Laboratory Standards Institute (2019). M100Ed29E. Performance standards for antimicrobial susceptibility testing: 29th informational supplement. Wayne, PA: CLSI.

EUCAST (2019). Breakpoint tables for interpretation of MIC's and zone diameters. Version 9.0, January 2019. Available at: http://www.eucast.org/fileadmin/src/media /PDFs/EUCAST\_files/Breakpoint\_tables/v\_9.0\_Breakpoint\_Tables.pdf. Accessed January 2019.

Lowy FD. Staphylococcus aureus infections. N Engl J Med 1998;339:520–32.

European Centre for Disease Prevention and Control. Point prevalence survey of healthcareassociated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2013.

van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus bacteremia. Clin Microbiol Rev. 2012; 25:362–86.

## Contact

Rodrigo E. Mendes, PhD JMI Laboratories 345 Beaver Kreek Centre, Suite A North Liberty, IA 52317 Phone: (319) 665-3370 Fax: (319) 665-3371 Email: rodrigo-mendes@jmilabs.com



To obtain a PDF of this poster: Scan the QR code or visit https://www .jmilabs.com/data/posters/ECCMID19 -oritavancin-staphylococci.pdf

Charges may apply. No personal information is stored.