

Anti-Enterococcal Activity Profile of Orbitavancin, a Potent Lipoglycopeptide under Development for Use against Gram-Positive Infections

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ABSTRACT

Background: Orbitavancin (ORI) is a bactericidal lipoglycopeptide under clinical development for the treatment of infections caused by a variety of gram-positive species, including enterococci. This surveillance initiative established a current *in vitro* activity profile of ORI against both *E. faecalis* (E) and *E. faecium* (EM) populations, including those resistant (R) to currently available agents that may be used to treat enterococcal infections. **Methods:** Recent (2005) clinical isolates of EU (n=909) and EM (n=389) collected from hospital sites in the US (60), EU (35), and Israel (1) were centrally tested by broth microdilution (CLSI; M7-A7). ORI assays included a 0.002% polyorbital-80 throughout. Specific susceptible (S) and R phenotypes (e.g. non-susceptible [NS] to linezolid [LIN], daptomycin [DAP], and vancomycin [VAN]) were examined for ORI. Additional analysis was performed for Van A (VAN-R, telicoplanin [TEI]-R) and Van B (VAN-R, TEI-S) phenotypes. **Results:**

Organism	Phenotype	n	MIC range µg/mL	MIC ₅₀
EF	All	909	≤0.0005-4	0.12
	VAN S	850	≤0.0005-0.5	0.06
	VAN NS	59	0.015-4	1
	Van A	48	0.034-1	
	Van B	7	0.015-0.03	NA
EM	All	389	≤0.0005-0.25	0.25
	VAN S	120	≤0.0005-0.06	0.015
	VAN NS	269	≤0.0005-0.25	
	Van A	234	0.004-2	0.25
	Van B	24	0.004-0.06	0.03

NA=not applicable for <10 isolates; NS=non-susceptible (intermediate and R)
ORI MICs were 0.12 and 0.5 for 2 DAP-NS EF and ranged from 0.015-0.5 for DAP-NS EM (n=15). ORI MICs were 0.03, 0.06, and 0.5 for LHN-SEF (n=43); and ranged from 0.004-0.5 for LHN-SEM (n=6).

Conclusions: ORI showed potent activity against all enterococci encountered in this study, including strains NS to VAN (both Van A and Van B phenotypes), LIN, or DAP. Based on these findings, ORI may provide a useful alternative for the management of infections caused by enterococci, including those resistant to other agents frequently used to manage such infections.

INTRODUCTION

Orbitavancin (ORI) is a bactericidal lipoglycopeptide under clinical development for the treatment of infections caused by a variety of gram-positive species, including enterococci. This surveillance initiative established a current *in vitro* activity profile of ORI against both *E. faecalis* and *E. faecium* populations, including those resistant to currently available agents that may be used to treat enterococcal infections.

METHODS

Clinical isolates of *E. faecalis* (n=909) and *E. faecium* (n=389) from 60 hospital sites in the US, 35 hospital sites in Europe (*E. faecalis* only) and 1 site in Israel (*E. faecalis* only) were collected during 2005. The US sites were located across all nine US Bureau of Census regions and the sites in Europe were located in the following countries: Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Slovakia, Spain, and the United Kingdom.

All isolates were centrally tested by broth microdilution (CLSI; M7-A7) against ORI and other relevant comparators. ORI assays included 0.002% polyorbital-80 throughout. ORI activity was examined according to vancomycin susceptibility patterns, including Van A (vancomycin-resistant, telicoplanin-resistant) and Van B (vancomycin-resistant, telicoplanin-susceptible) phenotypes. Additionally, ORI activity was measured against populations that were non-susceptible to linezolid or daptomycin. All results were interpreted according to CLSI M100-S162 criteria, where applicable.

RESULTS

- The ORI MIC₅₀ for *E. faecalis* (all vancomycin phenotypes) was 0.12 µg/mL (Table 1).
- ORI MIC₅₀s for vancomycin-susceptible *E. faecalis* and vancomycin-resistant *E. faecalis* were 0.06 µg/mL and 1 µg/mL, respectively (Table 1). Although ORI MICs were higher among the Van A isolates than among the Van B isolates, no strain with an MIC exceeding 4 µg/mL was encountered.
- Against *E. faecium*, the ORI MIC₅₀ (0.25 µg/mL) all vancomycin phenotypes) was one doubling dilution higher than that obtained with *E. faecalis* (0.12 µg/mL; Tables 1 and 2).
- ORI MIC₅₀s for vancomycin-susceptible *E. faecium* and vancomycin-resistant *E. faecium* were 0.015 µg/mL and 0.25 µg/mL, respectively (Table 2). ORI MICs were higher among the Van A isolates than among the Van B isolates; however, the MIC never exceeded 2 µg/mL (Table 2).
- Analysis of MIC distributions for both *E. faecalis* (Figure 1) and *E. faecium* (Figure 2) demonstrated higher ORI MICs associated with vancomycin non-susceptible populations of both species; however, the MICs did not exceed 4 µg/mL for *E. faecalis* or 2 µg/mL for *E. faecium*.
- For both *E. faecalis* and *E. faecium* isolates, ORI maintained potent *in vitro* activity against strains that were non-susceptible to either daptomycin or linezolid (Table 3).

Figure 1. MIC distributions of ORI against *E. faecalis* according to vancomycin susceptibility status

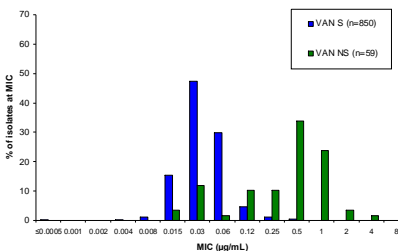


Table 1. Activity of ORI and comparators against *E. faecalis* according to vancomycin status

Agent	Phenotype*	Total n	MIC µg/mL					nS	%S	nI	%I	nR	%R
			Range	Mode	MIC ₅₀	MIC ₉₀	CC ₅₀						
Orbitavancin	All	909	≤0.0005-4	0.03	0.03	0.12	850	93.5	0	0	0	0	0
	VAN S	850	≤0.0005-0.5	0.03	0.03	0.06	850	100	0	0	0	0	0
	VAN NS	59	0.015-4	0.5	0.5	1	0	0	0	0	0	0	0
	Van A	48	0.034-1	0.5	0.5	1	0	0	0	0	0	0	0
	Van B	7	0.015-0.03	0.03	NA	NA	7	100	0	0	0	0	0
Vancomycin	All	909	0.5-256	1	1	2	850	93.5	3	0.3	56	6.2	0
	VAN S	850	0.5-4	1	1	2	850	100	0	0	0	0	0
	VAN NS	59	8-256	>256	>256	>256	0	0	0	3	5.1	56	94.9
	Van A	48	256-256	>256	>256	>256	0	0	0	0	0	48	100
	Van B	7	32-256	256	NA	NA	0	0	0	0	0	7	100
Telicoplanin	All	909	0.035-256	0.25	0.25	0.80	846	93.1	6	0.7	48	5.3	0
	VAN S	850	0.03-2	0.25	0.25	0.80	850	100	0	0	0	0	0
	VAN NS	59	0.12-256	128	64	256	10	16.9	1	1.7	48	81.4	0
	Van A	48	32-256	128	64	256	0	0	0	0	48	100	
	Van B	7	0.12-0.5	0.25	NA	NA	7	100	0	0	0	0	0
Linezolid	All	909	0.25-32	1	1	908	99.7	0	0	0	0	0.3	
	VAN S	850	0.25-32	1	1	848	99.8	0	0	0	2	0.2	
	VAN NS	59	0.5-16	1	1	58	98.3	0	0	0	1	1.7	
	Van A	48	0.5-16	1	1	47	97.9	0	0	1	2.1		
	Van B	7	1-2	1	1	7	100	0	0	0	0	0	
Daptomycin	All	909	0.25-4	1	1	907	99.8	0	0	0	0	0	
	VAN S	850	0.25-4	1	1	849	99.9	0	0	0	0	0	
	VAN NS	59	0.5-4	1	1	58	98.3	0	0	0	0	0	
	Van A	48	0.5-4	1	1	47	97.9	0	0	0	0	0	
	Van B	7	0.5-2	1	1	7	100	0	0	0	0	0	
Ampicillin	All	907	≤0.25-32	1	1	908	99.9	0	0	1	0.1	0	
	VAN S	850	≤0.25-32	1	1	849	99.9	0	0	0	0	0	
	VAN NS	59	≤0.25-2	1	1	59	100	0	0	0	0	0	
	Van A	48	≤0.25-2	1	1	48	100	0	0	0	0	0	
	Van B	7	≤0.25-1	1	1	7	100	0	0	0	0	0	

*Vancomycin non-susceptible (VAN NS) category includes Van A, Van B and others.
†Shaded line indicates that CLSI breakpoints are currently unavailable for interpretation as susceptible (S), intermediate (I), and/or resistant (R).

Figure 2. MIC distributions of ORI against *E. faecium* according to vancomycin susceptibility status

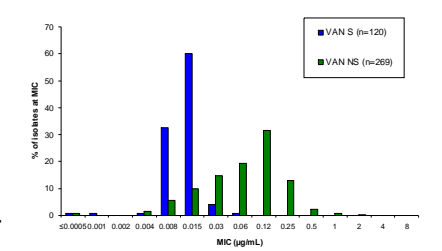


Table 2. Activity of ORI and comparators against *E. faecium* according to vancomycin status

Agent	Phenotype*	Total n	MIC µg/mL					nS	%S	nI	%I	nR	%R
			Range	Mode	MIC ₅₀	MIC ₉₀	CC ₅₀						
Orbitavancin	All	389	≤0.0005-2	0.015	0.03	0.25	389	100	0	0	0	0	0
	VAN S	120	≤0.0005-0.06	0.015	0.015	0.015	120	100	0	0	0	0	0
	VAN NS	269	≤0.0005-2	0.12	0.12	0.25	0	0	0	1.5	265	98.5	
	Van A	234	0.004-2	0.12	0.12	0.25	0	0	0	0	234	100	
	Van B	24	0.004-0.06	0.008	0.015	0.03	24	100	0	0	0	0	
Vancomycin	All	389	0.03-256	>256	>256	>256	120	30.6	4	1.0	265	68.1	
	VAN S	120	0.03-4	0.5	0.5	1	120	100	0	0	0	0	
	VAN NS	269	8-256	>256	>256	>256	0	0	0	1.5	265	98.5	
	Van A	234	32-256	>256	>256	>256	0	0	0	0	234	100	
	Van B	24	64-256	64	128	256	0	0	0	0	24	100	
Telicoplanin	All	389	0.015-256	64	32	128	147	37.8	8	2.1	234	60.2	
	VAN S	120	≤0.015-8	0.5	0.5	1	120	100	0	0	0	0	
	VAN NS	269	0.12-256	64	64	128	27	10.0	8	3.0	234	87.0	
	Van A	234	32-256	64	64	128	0	0	0	0	234	100	
	Van B	24	0.12-0.5	0.25	NA	NA	24	100	0	0	0	0	
Linezolid	All	389	≤0.12-16	1	1	2	383	98.3	3	0.8	3	0.8	
	VAN S	120	≤0.12-4	1	1	2	118	98.3	2	1.7	0	0.0	
	VAN NS	269	0.5-16	1	1	2	265	98.6	1	0.4	3	1.1	
	Van A	234	0.5-8	1	1	2	232	99.1	0	0	2	0.9	
	Van B	24	1-16	1	1	2	22	91.7	1	4.2	1	4.2	
Daptomycin	All	389	≤0.12-4	2	2	4	378	97.2	0	0	0	0	
	VAN S	120	≤0.12-4	2	2	4	116	96.7	0	0	0	0	
	VAN NS	269	≤0.12-4	2	2	4	262	97.4	0	0	0	0	
	Van A	234	1-4	2	2	4	229	97.9	0	0	0	0	
	Van B	24	0.25-4	2	2	4	22	91.7	0	0	0	0	
Ampicillin	All	389	≤0.25-256	>256	128	>256	48	12.3	3	0.8	341	87.6	
	VAN S	120	≤0.25-256	>256	64	>256	41	34.2	2	1.7	79	65.8	
	VAN NS	269	1-256	>256	128	>256	7	2.6	32	12	262	97.4	
	Van A	234	1-256	>256	128	>256	4	1.7	230	98.3	0	0	
	Van B	24	8-256	128	128	>256	1	4.2	23	95.8	0	0	

*Vancomycin non-susceptible (VAN NS) category includes Van A, Van B and others.
†Shaded line indicates that CLSI breakpoints are currently unavailable for interpretation as susceptible (S), intermediate (I), and/or resistant (R).

Table 3. Antibiograms of enterococcal isolates non-susceptible to daptomycin or linezolid

Phenotype	Organism	Isolate No.	MIC (µg/mL) CLSI Interpretation					AMP	
			ORI	TEI	VAN	DAP	LIN		
DAP NS	<i>E. faecalis</i>	1562354	0.12	1	>256	R	S	2	2
		1562369	0.12	1	>256	R	S	2	2
		1562362	0.03	64	>256	R	S	1	>256
		1562771	0.015	0.5	S	>4	NS	2	128
		1562926	0.12	128	>256	R	S	1	>256
DAP NS	<i>E. faecium</i>	1563156	0.25	128	>256	R	S	1	128
		1563191	0.015	1	S	>4	NS	2	256
		1563200	0.015	1	S	>4	NS	1	128
		1563201	0.015	1	S	>4	NS	1	256
		1563370	0.26	64	>256	R	S	1	>256
DAP NS	<i>E. faecalis</i>	1563417	0.015	1	>256	R	S	1	256
		1563416	0.015	0.5	S	>4	NS	2	256
		1563542	0.25	128	>256	R	S	1	16
		1563228	0.08	0.25	S	1	S	16	S
		1563360	0.001	0.25	S	1	S	2	S
DAP NS	<i>E. faecium</i>	1563506	0.5	64	256	R	1	S	16
		1562762	0.12						