C-1054 Update of Oritavancin and Comparator Agent *In Vitro* Activities Against Gram-positive Clinical Isolates Responsible for Documented Skin and Skin Structure Infections in the USA (2014)

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Abstract

Background: Oritavancin was approved in the USA (2014) for the treatment of acute bacterial skin and skin structure infections (SSSI) caused by Gram-positive pathogens. This study provides an updated *in vitro* activity for oritavancin against indicated species collected in 2014.

Methods: 1,774 isolates were collected from documented SSSI in 27 sites in the nine USA Census regions, as part of the SENTRY Antimicrobial Surveillance Program for 2014. Bacteria were identified by standard algorithms and MALDI-TOF. Susceptibility testing was performed by CLSI methods (M07-A10); interpretation of MIC results used FDA (oritavancin), CLSI (2015) and/or EUCAST (2015) criteria.

Results: Oritavancin had $MIC_{50/90}$ values of 0.03/0.06 μg/mL against *S. aureus* (99.9% susceptible). Oritavancin MICs were ≥8-fold lower than those obtained for vancomycin, daptomycin or linezolid against *S. aureus*, regardless of methicillin (oxacillin) susceptibility. *E. faecalis* (one VanA-phenotype) had oritavancin $MIC_{50/90}$ values of 0.015/0.03 μg/mL; ampicillin, vancomycin, daptomycin and linezolid had $MIC_{50/90}$ values (1/1-2 μg/mL) that were 32- to 64-fold higher than those of oritavancin. Oritavancin, daptomycin and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL) were similarly active against *S. pyogenes*; these agents had MIC_{90} values that were ≥four-fold lower than vancomycin. Linezolid, clindamycin and levofloxacin were also active against *S. pyogenes* (≥92.8% susceptible). Oritavancin and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL) were the most active agents tested against *S. agalactiae* and oritavancin was the most active agent tested against the *S. anginosus* group. Penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL), oritavancin, daptomycin, vancomycin and clindamycin ($MIC_{50/90}$, ≤0.12/≤0.25 μg/mL) were active against *S. dysgalactiae*.

Conclusions: Oritavancin had potent *in vitro* activity against this contemporary collection of Gram-positive isolates causing SSSI. Moreover, these *in vitro* potency results were greater than comparators currently prescribed for serious SSSI.

Background

Acute bacterial skin and skin structure infections (ABSSSIs) are often caused by aerobic Gram-positive cocci, most often *Staphylococcus aureus* and β-hemolytic streptococci. The epidemiology of *S. aureus* has been represented by several waves, and the latest comprises the emergence of methicillin-resistant (MRSA) isolates causing infections in community settings. This scenario has added further difficulties to empiric therapy. Therefore, the Infectious Diseases Society of America established a new treatment algorithm for ABSSSI, which focuses on antimicrobial therapies against *Streptococcus* spp. and *S. aureus*, and particularly when suspected of MRSA infection.

Oritavancin is a semisynthetic bactericidal lipoglycopeptide approved by the Food and Drug Administration (FDA, August 2014) and European Medicines Agency (EMA, March 2015) for the treatment of adults with ABSSSI. Oritavancin has demonstrated potent *in vitro* antimicrobial activities against Gram-positive organisms, such as staphylococci, enterococci and streptococci, including organisms with decreased susceptibility to vancomycin. This study provides an *in vitro* susceptibility benchmark for oritavancin and comparator agents against pathogens causing SSSIs in USA medical centers during the SENTRY surveillance program for 2014.

Methods

Bacterial strain collection. A total of 1,774 Gram-positive clinical isolates responsible for SSSI, per local guidelines, in 27 medical centers located in the nine USA Census regions were included. Selected isolates were submitted to the reference monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program. Isolates were primarily identified by the participating laboratory and identification was confirmed by the monitoring laboratory by standard algorithms and supported by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods. Susceptibility of isolates to oritavancin and comparator agents was determined by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document. Susceptibility testing was performed centrally using panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These panels provide oritavancin results equivalent to the CLSI-approved broth microdilution method supplemented with 0.002% polysorbate-80. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event.

Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619). All QC results were within published acceptable ranges (M100-S25). MIC interpretations for oritavancin were based on the FDA and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2015) breakpoint criteria. Interpretive criteria from CLSI and EUCAST were applied for comparator agents, as available.

Results

Staphylococci:

- Oritavancin (99.9% susceptible) showed modal MIC, MIC_{50} and MIC_{90} results of 0.03, 0.03 and 0.06 μg/mL, respectively, against all *S. aureus,* with similar activity results for methicillin-susceptible (MSSA) and MRSA isolates (Table 1).
- Oritavancin MIC results were at least eight-fold lower than those obtained for daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL), vancomycin ($MIC_{50/90}$, 1/1 μg/mL), or linezolid ($MIC_{50/90}$, 1/1 μg/mL) against MRSA (Table 2).
- Tetracycline ($MIC_{50/90}$, ≤0.5/1 μg/mL; 90.6 - 93.4% susceptible) and trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 μg/mL; 98.2% susceptible) were also active against the collection of MRSA (Table 2).
- Oritavancin demonstrated MIC_{50} results against coagulase-negative staphylococci ($MIC_{50/90}$, 0.015/0.06 μg/mL) two-fold lower than that obtained against *S. aureus* ($MIC_{50/90}$, 0.03/0.06 μg/mL; Tables 1 and 2).

***E. faecalis*:**

- *E. faecalis* (one VanA-phenotype) had oritavancin MIC_{50} and MIC_{90} values of 0.015 and 0.03 μg/mL, while ampicillin, vancomycin, daptomycin and linezolid had MIC_{50} and MIC_{90} results of 1 and 1-2 μg/mL, respectively against these isolates. These comparator MIC results were 32- to 64-fold higher than those of oritavancin (Table 2).

Streptococci:

- Oritavancin, daptomycin, linezolid and vancomycin (all 100.0% susceptible) were the most potent antimicrobial agents tested against viridans group streptococci, inhibiting all isolates at ≤0.12, ≤1, ≤1 and ≤1 μg/mL, respectively (Table 2). Penicillin was also active against most isolates ($MIC_{50/90}$, ≤0.06/0.25 μg/mL; 89.9 - 94.9% susceptible).
  - Among indicated streptococcal isolates, oritavancin had lowest MIC_{50} value against the *S. anginosus* group (MIC_{50}, 0.008 μg/mL), followed by *S. agalactiae* (MIC_{50}, 0.015 μg/mL), *S. pyogenes* (MIC_{50}, 0.03 μg/mL) and *S. dysgalactiae* (MIC_{50}, 0.12 μg/mL; Tables 1 and 2).
- Overall, oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL), daptomycin ($MIC_{50/90}$, ≤0.06/0.25 μg/mL) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL) were similarly active against the entire population of β-hemolytic streptococci (Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.12 μg/mL), penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL) and daptomycin ($MIC_{50/90}$, ≤0.06/0.12 μg/mL) were the most active agents tested against *S. pyogenes*. Linezolid, clindamycin and levofloxacin were also active against *S. pyogenes* (≥92.8% susceptible; Table 3).
- Oritavancin ($MIC_{50/90}$, 0.015/0.06 μg/mL) and penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL) were the most active agents tested against *S. agalactiae* and oritavancin was the most active agent tested against the *S. anginosus* group (Table 3).
- Penicillin ($MIC_{50/90}$, ≤0.06/≤0.06 μg/mL), oritavancin ($MIC_{50/90}$, 0.12/0.25 μg/mL), daptomycin ($MIC_{50/90}$, ≤0.06/0.12 μg/mL), vancomycin ($MIC_{50/90}$, 0.25/0.25 μg/mL) and clindamycin ($MIC_{50/90}$, ≤0.12/≤0.25 μg/mL; data not shown) were active against *S. dysgalactiae* (Table 3).

Table 1. Antimicrobial activity and MIC distribution of oritavancin against contemporary (2014) clinical isolates from USA medical centers causing skin and skin structure infections.

	MIC (μg/mL)		Number of isolates (cumulative %) inhibited at oritavancin MIC (μg/mL)							
Organism[a] (No. tested)	**50%**	**90%**	**≤0.004**	**0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**
S. aureus (1,374)	0.03	0.06	5 (0.4)	31 (2.6)	436 (34.4)	526 (72.6)	302 (94.6)	73 (99.9)	1 (100.0)	
MSSA (702)	0.03	0.06	3 (0.4)	17 (2.8)	209 (32.6)	276 (71.9)	163 (95.2)	33 (99.9)	1 (100.0)	
MRSA (672)	0.03	0.06	2 (0.3)	14 (2.4)	227 (36.2)	250 (73.4)	139 (94.0)	40 (100.0)		
CoNS (86)	0.015	0.06	12 (14.0)	24 (41.9)	12 (55.8)	21 (80.2)	14 (96.5)	3 (100.0)		
E. faecalis (75)	0.015	0.03	3 (4.0)	24 (36.0)	35 (82.7)	9 (94.7)	3 (98.7)	0 (98.7)	0 (98.7)	1 (100.0)[b]
VGS[c] (59)	0.008	0.06	21 (35.6)	17 (64.4)	12 (84.7)	3 (89.8)	2 (93.2)	4 (100.0)		
S. anginosus group (38)	0.008	0.015	18 (47.4)	14 (84.2)	6 (100.0)					
BHS (287)	0.03	0.12	4 (1.4)	29 (11.5)	79 (39.0)	61 (60.3)	45 (76.0)	45 (91.6)	22 (99.3)	2 (100.0)
S. pyogenes (152)	0.03	0.12	2 (1.3)	15 (11.2)	34 (33.6)	27 (51.3)	31 (71.7)	30 (91.4)	13 (100.0)	
S. agalactiae (96)	0.015	0.06	1 (1.0)	10 (11.5)	44 (57.3)	27 (85.4)	9 (94.8)	4 (99.0)	1 (100.0)	
S. dysgalactiae (39)	0.12	0.25	1 (2.6)	4 (12.8)	1 (15.4)	7 (33.3)	5 (46.2)	11 (74.4)	8 (94.9)	2 (100.0)

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci; BHS = β-hemolytic streptococci.
b. All vancomycin-susceptible *E. faecalis* were susceptible to oritavancin (i.e. all inhibited below breakpoint; i.e. ≤0.12 μg/mL). One *E. faecalis* displaying a VanA-phenotype (i.e. vancomycin and teicoplanin MIC values of >4 and >8 μg/mL, respectively) had an oritavancin MIC result of 0.5 μg/mL.
c. Includes *S. canis* (four isolates), *S. constellatus* (eight), *S. gordonii* (three), *S. anginosus group* (five), *S. mitis group* (two), *S. mitis/oralis* (two), *S. parasanguinis* (two), *S. salivarius group* (one), *S. anginosus* (20), *S. intermedius* (five), *S. oralis* (seven).

Table 3. Summary of antimicrobial activity of oritavancin and comparator agents tested against contemporary (2014) β-hemolytic streptococcal clinical isolates from USA medical centers causing skin and skin structure infections.

	Oritavancin			Vancomycin			Daptomycin			Linezolid			Penicillin			Levofloxacin		
	MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)			MIC (μg/mL)		
Organism[a] (No. tested)	**50%**	**90%**	**%S[a]**	**50%**	**90%**	**%S[a]**	**50%**	**90%**	**%S[a]**	**50%**	**90%**	**%S[a]**	**50%**	**90%**	**%S[a]**	**50%**	**90%**	**%S[a]**
S. pyogenes (152)	0.03	0.12	100.0	0.25	0.5	100.0	≤0.06	0.12	100.0	0.5	1	100.0	≤0.06	≤0.06	100.0	0.5	1	99.3/97.4
S. agalactiae (96)	0.015	0.06	100.0	0.5	0.5	100.0	0.25	0.25	100.0	0.5	1	100.0	≤0.06	≤0.06	100.0	0.5	1	99.0
S. dysgalactiae (39)	0.12	0.25	94.9	0.25	0.25	100.0	≤0.06	0.12	100.0	0.5	1	100.0	≤0.06	≤0.06	100.0	0.5	1	100.0
S. anginosus group[b] (38)	0.008	0.015	100.0	0.5	1	100.0	0.25	0.5	100.0	0.5	1	100.0	≤0.06	0.12	92.1/97.4	0.5	1	100.0

a. %S = percentage susceptible according to oritavancin package insert, CLSI (2015) and EUCAST (2015). Percentage susceptible described if distinct breakpoints are available from regulatory agencies (i.e. *S. pyogenes* vs levofloxacin; and *S. anginosus* group vs penicillin).
b. Consists of *S. anginosus* (25), *S. constellatus* (8), *S. intermedius* (5).

Table 2. Antimicrobial activity of oritavancin and comparator agents against contemporary (2014) clinical isolates from USA medical centers causing skin and skin structure infections.

		MIC (μg/mL)		% Susceptible/%Intermediate/%Resistant[b]					
Organism (No. tested) Antimicrobial agent[a]	Range	50%	90%	CLSI			EUCAST		
MRSA (672)									
Oritavancin	≤0.0005 — 0.12	0.03	0.06	100.0	-[c]	-	100.0	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	80.2	0.1	19.7	80.2	0.0	19.8
Daptomycin	0.12 — 2	0.25	0.5	99.9	-	-	99.9	-	0.1
Erythromycin	≤0.12 — >16	>16	>16	12.9	1.9	85.1	13.1	0.6	86.3
Levofloxacin	≤0.12 — >4	4	>4	39.7	0.6	59.7	39.7	0.6	59.7
Linezolid	0.25 — 2	1	1	100.0	-	0.0	100.0	-	0.0
Tetracycline	≤0.5 — >8	≤0.5	1	93.4	0.6	6.0	90.6	1.5	7.9
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	98.2	-	1.8	98.2	0.3	1.5
Vancomycin	0.5 — 2	1	1	100.0	0.0	0.0	100.0	-	0.0
CoNS (86)									
Oritavancin	0.002 — 0.12	0.015	0.06	-	-	-	-	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	76.7	1.2	22.1	72.1	4.7	23.3
Daptomycin	≤0.06 — 1	0.25	0.5	100.0	-	-	100.0	-	0.0
Erythromycin	≤0.12 — >16	0.25	>16	58.1	1.2	40.7	58.1	0.0	41.9
Levofloxacin	≤0.12 — >4	0.25	>4	75.6	1.2	23.3	75.6	1.2	23.3
Linezolid	0.25 — 1	0.5	0.5	100.0	-	0.0	100.0	-	0.0
Oxacillin	≤0.25 — >2	1	>2	57.0	-	43.0	57.0	-	43.0
Tetracycline	≤0.5 — >8	≤0.5	>8	87.1	1.2	11.8	81.2	2.4	16.5
TMP-SMX	≤0.5 — >4	≤0.5	4	89.5	-	10.5	89.5	8.1	2.3
Vancomycin	0.5 — 2	1	2	100.0	0.0	0.0	100.0	-	0.0
***E. faecalis* (75)**									
Oritavancin	0.004 — 0.5	0.015	0.03	98.7[d]	-	-	-	-	-
Ampicillin	0.5 — 2	1	1	100.0	-	0.0	100.0	0.0	0.0
Daptomycin	≤0.06 — 2	1	2	100.0	-	-	-	-	-
Levofloxacin	0.25 — >4	1	>4	70.7	0.0	29.3	-	-	-
Linezolid	0.25 — 1	1	1	100.0	0.0	0.0	-	-	-
Tetracycline	≤0.5 — >8	>8	>8	26.7	1.3	72.0	-	-	-
Vancomycin	0.25 — >16	1	2	98.7	0.0	1.3	98.7	-	1.3
VGS[e] (59)									
Oritavancin	≤0.0005 — 0.12	0.008	0.06	100.0	-	-	100.0	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	78.0	0.0	22.0	78.0	-	22.0
Daptomycin	≤0.06 — 1	0.25	1	100.0	-	-	-	-	-
Erythromycin	≤0.12 — >16	0.5	>16	49.2	5.1	45.8	-	-	-
Levofloxacin	≤0.12 — >4	0.5	1	98.3	0.0	1.7	-	-	-
Linezolid	≤0.12 — 1	0.5	1	100.0	-	-	-	-	-
Penicillin	≤0.06 — >8	≤0.06	0.25	89.8	6.8	3.4	94.9	1.7	3.4
Tetracycline	≤0.5 — >8	4	>8	49.2	10.2	40.7	-	-	-
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	-	-	-	-	-	-
Vancomycin	≤0.12 — 1	0.5	1	100.0	-	-	100.0	-	0.0
BHS[f] (287)									
Oritavancin	0.004 — 0.5	0.03	0.12	99.3	-	-	99.3	-	-
Clindamycin	≤0.25 — >2	≤0.25	>2	85.0	0.3	14.7	85.3	-	14.7
Daptomycin	≤0.06 — 0.5	≤0.06	0.25	100.0	-	-	100.0	-	0.0
Erythromycin	≤0.12 — >16	≤0.12	>16	71.4	1.0	27.5	71.4	1.0	27.5
Levofloxacin	0.25 — >4	0.5	1	99.3	0.0	0.7	98.3	1.0	0.7
Linezolid	0.5 — 1	0.5	1	100.0	-	-	100.0	0.0	0.0
Penicillin	≤0.06 — 0.12	≤0.06	≤0.06	100.0	-	-	100.0	-	0.0
Tetracycline	≤0.5 — >8	≤0.5	>8	58.2	2.1	39.7	57.5	0.7	41.8
TMP-SMX	≤0.5 — >4	≤0.5	≤0.5	-	-	-	97.6	0.0	2.4
Vancomycin	0.25 — 0.5	0.25	0.5	100.0	-	-	100.0	-	0.0

a. MRSA = methicillin-resistant *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci; BHS = β-hemolytic streptococci.
b. Breakpoint criteria for oritavancin according to the FDA package insert (CLSI column) and EUCAST, as available. *S. aureus* at ≤0.12 μg/mL for susceptible; *E. faecalis* at ≤0.12 μg/mL for susceptible (FDA breakpoint for vancomycin-susceptible only); breakpoint for VGS was that from *S. anginosus* group (≤0.25 μg/mL for susceptible); while the interpretive criterion for *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* (≤0.25 μg/mL for susceptible) was applied for BHS. Breakpoint criteria for comparator agents were those from CLSI (M100-S25, 2015) and EUCAST (2015), as available.
c. Breakpoint not available.
d. 98.7% of all *E. faecalis* and 100.0% of vancomycin-susceptible *E. faecalis* were susceptible to oritavancin. One *E. faecalis* displaying a VanA-phenotype (i.e. vancomycin and teicoplanin MIC values of >4 and >8 μg/mL, respectively) had an oritavancin MIC of 0.5 μg/mL.
e. Includes *S. canis* (four isolates), *S. constellatus* (eight), *S. gordonii* (three), *S. anginosus group* (five), *S. mitis group* (two), *S. mitis/oralis* (two), *S. parasanguinis* (two), *S. salivarius group* (one), *S. anginosus* (20), *S. intermedius* (five), *S. oralis* (seven).
f. Includes *S. pyogenes* (152 isolates), *S. agalactiae* (96) and *S. dysgalactiae* (39).

Conclusions

- Oritavancin exhibited potent *in vitro* activity relative to comparator agents against this contemporary collection of Gram-positive isolates causing SSSI in USA medical centers during 2014.
- Oritavancin inhibited 99.8% of indicated pathogens at or below the FDA- and EUCAST-approved breakpoint criteria.
- This study provides a susceptibility benchmark for oritavancin against indicated clinical species and other pathogens causing SSSI as it enters clinical use in the USA.

Disclosures

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References

1. Clinical and Laboratory Standards Institute (2015). *M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard- tenth edition*. Wayne, PA, USA.
2. Clinical and Laboratory Standards Institute (2015). *M100-S25. Performance standards for antimicrobial susceptibility testing; 25th informational supplement.* Wayne, PA, USA.
3. EUCAST (2015). Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
4. EUCAST Addendum (2015). Clinical breakpoints and QC recommendations for the new agents dalbavancin, oritavancin and tedizolid. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Addenda/New_EUCAST_breakpoints_final.pdf. Accessed August 2015.
5. Orbactiv™ Package Insert (2015). Available at http://www.orbactiv.com. Accessed August 7, 2015.
6. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC (2014). Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 59: 10-52.
7. Talan DA, Krishnadasan A, Gorwitz RJ, Fosheim GE, Limbago B, Albrecht V, Moran GJ (2011). Comparison of *Staphylococcus aureus* from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. *Clin Infect Dis* 53: 144-149.
8. Zervos MJ, Freeman K, Vo L, Haque N, Pokharna H, Raut M, Kim M (2012). Epidemiology and outcomes of complicated skin and soft tissue infections in hospitalized patients. *J Clin Microbiol* 50: 238-245.

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