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Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe: Report from the SENTRY Antimicrobial Surveillance Program, 2016 to 2018

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ABSTRACT Omadacycline is a broad-spectrum aminomethylcycline approved in October 2018 by the U.S. Food and Drug Administration for treating acute bacterial skin and skin structure infections and community-acquired pneumonia as both an oral and intravenous once-daily formulation. In this report, the activities of omadacycline and comparators were tested against 49,000 nonduplicate bacterial isolates collected prospectively during 2016 to 2018 from medical centers in Europe (24,500 isolates, 40 medical centers [19 countries]) and the United States (24,500 isolates, 33 medical centers [23 states and all 9 U.S. census divisions]). Omadacycline was tested by broth microdilution following the methods in Clinical and Laboratory Standards Institute document M07 (*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard*, 11th ed., 2018). Omadacycline ($MIC_{50/90}$, 0.12/0.25 mg/liter) inhibited 98.6% of *Staphylococcus aureus* isolates at ≤0.5 mg/liter, including 96.3% of methicillin-resistant *S. aureus* isolates and 99.8% of methicillin-susceptible *S. aureus* isolates. Omadacycline potency was comparable for *Streptococcus pneumoniae* ($MIC_{50/90}$, 0.06/0.12 mg/liter), viridans group streptococci ($MIC_{50/90}$, 0.06/0.12 mg/liter), and beta-hemolytic streptococci ($MIC_{50/90}$, 0.12/0.25 mg/liter), regardless of species and susceptibility to penicillin, macrolides, or tetracycline. Omadacycline was active against all *Enterobacterales* tested ($MIC_{50/90}$, 1/8 mg/liter; 87.5% of isolates were inhibited at ≤4 mg/liter) except *Proteus mirabilis* ($MIC_{50/90}$, 16/>32 mg/liter) and indole-positive *Proteus* spp. ($MIC_{50/90}$, 8/32 mg/liter) and was most active against *Escherichia coli* ($MIC_{50/90}$, 0.5/2 mg/liter), *Klebsiella oxytoca* ($MIC_{50/90}$, 1/2 mg/liter), and *Citrobacter* spp. ($MIC_{50/90}$, 1/4 mg/liter). Omadacycline inhibited 92.4% of *Enterobacter cloacae* species complex and 88.5% of *Klebsiella pneumoniae* isolates at ≤4 mg/liter. Omadacycline was active against *Haemophilus influenzae* ($MIC_{50/90}$, 0.5/1 mg/liter), regardless of β-lactamase status, and against *Moraxella catarrhalis* ($MIC_{50/90}$, ≤0.12/0.25 mg/liter). The potent activity of omadacycline against Gram-positive and -negative bacteria indicates that omadacycline merits further study in serious infections in which multidrug resistance and mixed Gram-positive and Gram-negative bacterial infections may be a concern.

KEYWORDS tetracycline, omadacycline, SENTRY, surveillance, susceptibility

The tetracycline class of antimicrobial agents has been an important element in the outpatient treatment of acute bacterial skin and skin structure infection and community-acquired bacterial pneumonia (1, 2). Unfortunately, heavy usage of the tetracyclines has gradually eroded the activity of this class of agents due to the development of resistance (1–4). Tetracycline-resistant pathogens most commonly express efflux and ribosomal protection mechanisms that greatly reduce the utility of this class against many of the clinically relevant pathogens that were previously

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TABLE 1 U.S. Food and Drug Administration-identified breakpoint interpretive criteria for omadacycline[a]

Pathogen	Indication	MIC (μg/ml)			Disk diffusion zone diam[b] (mm)		
		S	I	R	S	I	R
Enterobacteriaceae[c,d]	ABSSSI	≤4	8	≥16	≥18	16–17	≤15
Staphylococcus aureus (including methicillin-resistant isolates)	ABSSSI	≤0.5	1	≥2	≥21	19–20	≤18
Staphylococcus lugdunensis	ABSSSI	≤0.12	0.25	≥0.5	≥29	26–28	≤25
Enterococcus faecalis	ABSSSI	≤0.25	0.5	≥1	≥18	16–17	≤15
Streptococcus anginosus group[e]	ABSSSI	≤0.12	0.25	≥0.5	≥24	18–23	≤17
Streptococcus pyogenes	ABSSSI	≤0.12	0.25	≥0.5	≥19	16–18	≤15
Enterobacteriaceae[d,f]	CABP	≤4	8	≥16	≥18	16–17	≤15
Staphylococcus aureus (methicillin-susceptible isolates only)	CABP	≤0.25	0.5	≥1	≥23	21–22	≤20
Haemophilus species[g]	CABP	≤2	4	≥8	≥20	17–19	≤16
Streptococcus pneumoniae	CABP	≤0.12	0.25	≥0.5	≥20	17–19	≤16

[a]Abbreviations: S, susceptible; I, intermediate; R, resistant; ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumonia.
[b]Determined with a 30-μg omadacycline disk.
[c]*Klebsiella pneumoniae* and *Enterobacter cloacae* only.
[d]Omadacycline is not active *in vitro* against *Morganella* spp., *Proteus* spp., and *Providencia* spp.
[e]The *Streptococcus anginosus* group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.
[f]*Klebsiella pneumoniae* only.
[g]*Haemophilus* species includes *H. influenzae* and *H. parainfluenzae*.

covered by these agents (2–5). The search for a safe and effective oral agent that is active against bacteria expressing tetracycline resistance mechanisms has led to the development of omadacycline (3–7).

Omadacycline is a semisynthetic derivative of minocycline and the first member of the novel class of aminomethylcyclines (5, 8–11). Omadacycline remains active against tetracycline-resistant bacterial isolates expressing ribosomal protection and efflux resistance mechanisms (3, 5, 9–11). Omadacycline has potent *in vitro* activity against difficult-to-treat pathogens, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, carbapenem-resistant *Enterobacteriaceae*, and multidrug-resistant (resistant to ≥3 classes of agents) strains of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* (5, 11, 12). Omadacycline is approved by the U.S. Food and Drug Administration (FDA) for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections by susceptible organisms (Table 1) (6, 13, 14). Phase 2 studies for the use of omadacycline to treat uncomplicated urinary tract infections (UTIs; ClinicalTrials.gov registration number NCT03425396) and acute pyelonephritis (ClinicalTrials.gov registration number NCT03757234) in women have been completed (11, 15, 16). In both studies, omadacycline showed levels of clinical success generally comparable to those of either nitrofurantoin or levofloxacin, as determined by the investigator's assessment of the clinical response at the posttreatment evaluation. However, the microbiological responses were generally lower than those of the comparators (Paratek, data on file).

Due to the exploratory intent and the small numbers of subjects enrolled in each dose group in these phase 2 studies, the sponsor has identified dose regimens that require additional investigation before determining any future development plans for these indications. Additional analyses are ongoing, including the pathogen-specific level of efficacy and the relationships of both clinical and microbiological responses to urinary pharmacokinetic (PK) data.

In the present study, we evaluated the antimicrobial activities of omadacycline and comparator agents against 49,000 isolates of Gram-positive cocci (GPC) and Gram-negative bacilli collected between 2016 and 2018 from 73 individual academic and/or tertiary care medical centers in the United States (33 medical centers and all 9 census divisions) and Europe (40 medical centers from 19 countries) as part of the SENTRY Antimicrobial Surveillance Program. Evaluations of resistant organism subsets were included in the analysis, when available.

RESULTS

Number of organisms and key resistance phenotypes. The 49,000 isolates tested included 10,016 *S. aureus* isolates, 1,437 coagulase-negative staphylococci, 2,506 *Enterococcus* isolates (including 1,577 *Enterococcus faecalis* isolates and 851 *Enterococcus faecium* isolates), 3,153 *Streptococcus pneumoniae* isolates, 615 viridans group streptococci, 216 *Streptococcus anginosus* group isolates, 2,141 beta-hemolytic streptococci (including 1,030 *Streptococcus pyogenes* isolates, 776 *Streptococcus agalactiae* isolates, and 335 isolates of other beta-hemolytic streptococci), 20,028 *Enterobacterales* (including 8,749 *Escherichia coli* isolates, 4,220 *Klebsiella pneumoniae* isolates, 939 *Klebsiella oxytoca* isolates, 1,666 *Enterobacter cloacae* species complex isolates, 837 *Citrobacter* isolates, 1,144 *Proteus mirabilis* isolates, 750 indole-positive *Proteus* isolates, and 865 *Serratia marcescens* isolates), 892 *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex isolates, 4,564 *Pseudomonas aeruginosa* isolates, 604 *S. maltophilia* isolates, 1,886 *Haemophilus influenzae* isolates, 71 *Haemophilus parainfluenzae* isolates, and 984 *Moraxella catarrhalis* isolates (Tables 2 and 3).

Isolates with key resistant phenotypes included 3,326 (33.2%) methicillin-resistant *S. aureus* (MRSA) isolates, 880 (61.2%) methicillin-resistant (MR) coagulase-negative staphylococci, 330 (38.8%) vancomycin-nonsusceptible *E. faecium* isolates, 336 (10.7%) penicillin-resistant *S. pneumoniae* isolates, 1,784 (20.4%) extended-spectrum-β-lactamase-phenotype *E. coli* isolates, 13 (0.1%) carbapenem-resistant *E. coli* isolates, 1,383 (32.8%) extended-spectrum-β-lactamase-phenotype *K. pneumoniae* isolates, 388 (9.2%) carbapenem-resistant *K. pneumoniae* isolates, and 478 (28.7%) ceftazidime-nonsusceptible *E. cloacae* species complex isolates (Table 2). A total of 11,729 isolates were tetracycline resistant, including 514 *S. aureus* isolates (5.1% of all *S. aureus* isolates), 177 coagulase-negative staphylococci (12.3% of all coagulase-negative staphylococci), 1,178 *E. faecalis* isolates (74.7% of all *E. faecalis* isolates), 486 *E. faecium* isolates (57.1% of all *E. faecium* isolates), 656 *S. pneumoniae* isolates (20.8% of all *S. pneumoniae* isolates), 191 viridans group streptococci (31.1% of all viridans group streptococci), 923 beta-hemolytic streptococci (43.1% of all beta-hemolytic streptococci), 6,870 *Enterobacteriaceae* (34.3% of all *Enterobacteriaceae*), 544 *A. baumannii* isolates (61.0% of all *A. baumannii* isolates), and 15 *H. influenzae* isolates (0.8% of all *H. influenzae* isolates) (data not shown).

Overall omadacycline activity. The MIC distributions for omadacycline and each organism or organism group from the 73 participating medical centers are shown in Table 2. Omadacycline demonstrated essentially identical activity against the key target pathogens from the United States and Europe (Table 3). As such, the data sets were combined for further comparison.

Omadacycline had potent activity against *S. aureus* (10,016 isolates tested; $MIC_{50/90}$, 0.12/0.25 mg/liter) (Table 2). A subset of 9,880 (98.6%) isolates were inhibited by $\leq$0.5 mg/liter of omadacycline, including 99.8% of methicillin-susceptible *S. aureus* isolates and 96.3% of methicillin-resistant *S. aureus* isolates (Table 2). The omadacycline $MIC_{50/90}$ values for all coagulase-negative staphylococci were 0.12/0.5 mg/liter (Table 2). Overall, 92.4% of coagulase-negative staphylococci were inhibited by $\leq$0.5 mg/liter of omadacycline. Tetracycline resistance had little effect on omadacycline MIC values against *S. aureus* (omadacycline $MIC_{50/90}$, 0.12/0.5 mg/liter) or coagulase-negative staphylococci (omadacycline $MIC_{50/90}$, 0.25/1 mg/liter). Among the tetracycline-resistant isolates, 95.1% of *S. aureus* isolates and 89.2% of coagulase-negative staphylococci were inhibited by $\leq$0.5 mg/liter of omadacycline (data not shown).

Omadacycline was as active against *E. faecium* ($MIC_{50/90}$, 0.06/0.12 mg/liter; 97.3% of isolates were inhibited at $\leq$0.25 mg/liter) as it was against *E. faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/liter; 97.6% of isolates were inhibited at $\leq$0.25 mg/liter), and its activity was not adversely affected by resistance to vancomycin or tetracycline when tested against these organism groups (Table 2).

Omadacycline potency was comparable for *S. pneumoniae* ($MIC_{50/90}$, 0.06/0.12 mg/liter), viridans group streptococci ($MIC_{50/90}$, 0.06/0.12 mg/liter), and beta-hemolytic

TABLE 2 Antimicrobial activity of omadacycline tested against the main organisms and organism groups

Organism/organism group (no. of isolates)	No. (cumulative %) of isolates inhibited at MIC (mg/liter) of:													MIC (mg/liter)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]	50%	90%
Staphylococcus aureus (10,016)	5 (<0.1	84 (0.9)	1,696 (17.8)	6,512 (82.8)	1,412 (96.9)	171 (98.6)	103 (99.7)	26 (99.9)	4 (>99.9)	3 (100.0)				0.12	0.25
Methicillin susceptible (6,690)	4 (0.1)	54 (0.9)	1,093 (17.2)	4,511 (84.6)	958 (99.0)	58 (99.8)	11 (>99.9)	1 (100.0)						0.12	0.25
Methicillin resistant (3,326)	1 (<0.1)	30 (0.9)	603 (19.1)	2,001 (79.2)	454 (92.9)	113 (96.3)	92 (99.0)	25 (99.8)	4 (99.9)	3 (100.0)				0.12	0.25
Coagulase-negative staphylococci (1,437)	13 (0.9	119 (9.2)	374 (35.2)	331 (58.2)	209 (72.8)	282 (92.4)	103 (99.6)	5 (99.9)	1 (100.0)					0.12	0.5
Methicillin susceptible (557)	11 (2.0)	73 (15.1)	213 (53.3)	134 (77.4)	43 (85.1)	59 (95.7)	23 (99.8)	1 (100.0)						0.06	0.5
Methicillin resistant (880)	2 (0.2)	46 (5.5)	161 (23.8)	197 (46.1)	166 (65.0)	223 (90.3)	80 (99.4)	4 (99.9)	1 (100.0)					0.25	0.5
Staphylococcus lugdunensis (151)	8 (5.3)	39 (31.1)	81 (84.8)	20 (98.0)	1 (98.7)	1 (99.3)	0 (99.3)	1 (100.0)						0.06	0.12
Enterococcus spp. (2,506)	12 (0.5)	139 (6.0)	981 (45.2)	1,008 (85.4)	305 (97.6)	49 (99.5)	9 (99.9)	2 (>99.9)	0 (>99.9)	1 (100.0)				0.12	0.25
Vancomycin susceptible (MIC, ≤4 mg/liter) (2,136)	7 (0.3)	112 (5.6)	829 (44.4)	855 (84.4)	288 (97.9)	38 (99.7)	5 (99.9)	2 (100.0)						0.12	0.25
Vancomycin nonsusceptible (MIC, >4 mg/liter) (370)	5 (1.4)	27 (8.6)	152 (49.7)	153 (91.1)	17 (95.7)	11 (98.6)	4 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)				0.12	0.12
Enterococcus faecalis (1,577)	6 (0.4)	69 (4.8)	525 (38.0)	661 (80.0)	278 (97.6)	33 (99.7)	3 (99.9)	2 (100.0)						0.12	0.25
Vancomycin susceptible (MIC, ≤4 mg/liter) (1,547)	4 (0.3)	69 (4.7)	518 (38.2)	646 (80.0)	273 (97.6)	32 (99.7)	3 (99.9)	2 (100.0)						0.12	0.25
Vancomycin nonsusceptible (MIC, >4 mg/liter) (30)	2 (6.7)	0 (6.7)	7 (30.0)	15 (80.0)	5 (96.7)	1 (100.0)								0.12	0.25
Enterococcus faecium (851)	6 (0.7)	64 (8.2)	421 (57.7)	311 (94.2)	26 (97.3)	16 (99.2)	6 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)				0.06	0.12
Vancomycin susceptible (MIC, ≤4 mg/liter) (521)	3 (0.6)	38 (7.9)	277 (61.0)	181 (95.8)	14 (98.5)	6 (99.6)	2 (100.0)							0.06	0.12
Vancomycin nonsusceptible (MIC, >4 mg/liter) (330)	3 (0.9)	26 (8.8)	144 (52.4)	130 (91.8)	12 (95.5)	10 (98.5)	4 (99.7)	0 (99.7)	0 (99.7)	1 (100.0)				0.06	0.12
Other *Enterococcus* spp. (78)	0 (0.0)	6 (7.7)	35 (52.6)	36 (98.7)	1 (100.0)									0.06	0.12
Streptococcus pneumoniae (3,153)	33 (1.0)	477 (16.2)	2,032 (80.6)	576 (98.9)	33 (99.9)	1 (>99.9)	1 (100.0)							0.06	0.12
Penicillin susceptible oral (MIC, ≤0.06 mg/liter) (2,150)	29 (1.3)	389 (19.4)	1,398 (84.5)	314 (99.1)	19 (>99.9)	1 (100.0)								0.06	0.12
Penicillin intermediate oral (MIC, >0.06 mg/liter and ≤1 mg/liter) (637)	3 (0.5)	71 (11.6)	407 (75.5)	148 (98.7)	7 (99.8)	0 (99.8)	1 (100.0)							0.06	0.12
Penicillin-resistant oral (≥2 mg/liter; CLSI) (366)	1 (0.3)	17 (4.9)	227 (66.9)	114 (98.1)	7 (100.0)									0.06	0.12
Tetracycline resistant (MIC, ≥4 mg/liter; CLSI) (657)	3 (0.5)	70 (11.1)	365 (66.7)	201 (97.3)	17 (99.8)	0 (99.8)	1 (100.0)							0.06	0.12
Viridans group streptococci (615)	32 (5.2)	120 (24.7)	286 (71.2)	135 (93.2)	37 (99.2)	4 (99.8)	0 (99.8)	1 (100.0)						0.06	0.12
Penicillin susceptible (MIC, ≤0.12 mg/liter; CLSI) (457)	32 (7.0)	101 (29.1)	212 (75.5)	88 (94.7)	22 (99.6)	1 (99.8)	0 (99.8)	1 (100.0)						0.06	0.12
Penicillin resistant (MIC, ≥4 mg/liter; CLSI) (33)	0 (0.0)	2 (6.1)	20 (66.7)	8 (90.9)	2 (97.0)	1 (100.0)								0.06	0.12
Streptococcus anginosus group (216)	31 (14.4)	63 (43.5)	101 (90.3)	21 (100.0)										0.06	0.06
Beta-hemolytic streptococci (2,141)	0 (0.0)	29 (1.4)	952 (45.8)	927 (89.1)	194 (98.2)	37 (99.9)	2 (100.0)							0.12	0.25
Streptococcus pyogenes (1,030)	0 (0.0)	17 (1.7)	714 (71.0)	279 (98.1)	18 (99.8)	2 (100.0)								0.06	0.12
Macrolide resistant (erythromycin MIC, ≥1 mg/liter; CLSI) (123)		0 (0.0)	54 (43.9)	58 (91.1)	10 (99.2)	1 (100.0)								0.12	0.12
Streptococcus agalactiae (776)	0 (0.0)	9 (1.2)	164 (22.3)	474 (83.4)	121 (99.0)	8 (100.0)								0.12	0.25
Macrolide resistant (erythromycin MIC, ≥1 mg/liter; CLSI) (355)	0 (0.0)	2 (0.6)	58 (16.9)	225 (80.3)	68 (99.4)	2 (100.0)								0.12	0.25

(Continued on next page)

TABLE 2 (Continued)

Organism/organism group (no. of isolates)	No. (cumulative %) of isolates inhibited at MIC (mg/liter) of:													MIC (mg/liter)	
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]	50%	90%
Enterobacterales (20,028)			3 (<0.1)	13 (0.1)	489 (2.5)	4,852 (26.7)	6,203 (57.7)	4,163 (78.5)	1,801 (87.5)	964 (92.3)	873 (96.7)	509 (99.2)	158 (100.0)	1	8
Escherichia coli (8,749)			3 (<0.1)	9 (0.1)	431 (5.1)	4,194 (53.0)	2,734 (84.2)	1,018 (95.9)	283 (99.1)	55 (99.7)	18 (>99.9)	4 (100.0)		0.5	2
Non-ESBL[b] phenotype (6,965)			3 (<0.1)	8 (0.2)	385 (5.7)	3,671 (58.4)	2,068 (88.1)	627 (97.1)	162 (99.4)	30 (99.8)	10 (>99.9)	1 (100.0)		0.5	2
ESBL phenotype[c] (1,784)			0 (0.0)	1 (0.1)	46 (2.6)	523 (32.0)	666 (69.3)	391 (91.2)	121 (98.0)	25 (99.4)	8 (99.8)	3 (100.0)		1	2
Carbapenem resistant (13)					0 (0.0)	5 (38.5)	5 (76.9)	2 (92.3)	1 (100.0)					1	2
Klebsiella pneumoniae (4,220)			0 (0.0)	1 (<0.1)	14 (0.4)	212 (5.4)	1,591 (43.1)	1,384 (75.9)	533 (88.5)	284 (95.2)	143 (98.6)	47 (99.7)	11 (100.0)	2	8
Non-ESBL phenotype (2,837)			0 (0.0)	1 (<0.1)	12 (0.5)	153 (5.9)	1,311 (52.1)	1,035 (88.5)	166 (94.4)	92 (97.6)	59 (99.7)	7 (>99.9)	1 (100.0)	1	4
ESBL phenotype[b] (1,383)				0 (0.0)	2 (0.1)	59 (4.4)	280 (24.7)	349 (49.9)	367 (76.4)	192 (90.3)	84 (96.4)	40 (99.3)	10 (100.0)	4	8
Carbapenem resistant (388)					0 (0.0)	6 (1.5)	65 (18.3)	102 (44.6)	108 (72.4)	70 (90.5)	29 (97.9)	7 (99.7)	1 (100.0)	4	8
Klebsiella oxytoca (939)				0 (0.0)	2 (0.2)	114 (12.4)	660 (82.6)	87 (91.9)	48 (97.0)	22 (99.4)	5 (99.9)	1 (100.0)		1	2
Other *Klebsiella* spp. (584)					0 (0.0)	26 (4.5)	285 (53.3)	209 (89.0)	25 (93.3)	14 (95.7)	24 (99.8)	1 (100.0)		1	4
Enterobacter cloacae species complex (1,666)				0 (0.0)	3 (0.2)	33 (2.2)	458 (29.7)	912 (84.4)	134 (92.4)	69 (96.6)	44 (99.2)	12 (99.9)	1 (100.0)	2	4
Ceftazidime susceptible (MIC, ≤4 mg/liter) (1,188)				0 (0.0)	2 (0.2)	22 (2.0)	363 (32.6)	678 (89.6)	69 (95.5)	26 (97.6)	20 (99.3)	7 (99.9)	1 (100.0)	2	4
Ceftazidime nonsusceptible (MIC, ≥8 mg/liter) (478)				0 (0.0)	1 (0.2)	11 (2.5)	95 (22.4)	234 (71.3)	65 (84.9)	43 (93.9)	24 (99.0)	5 (100.0)		2	8
Citrobacter spp. (837)				0 (0.0)	7 (0.8)	216 (26.6)	350 (68.5)	174 (89.2)	47 (94.9)	29 (98.)3	13 (99.9)	1 (100.0)		1	4
Proteus mirabilis (1,144)							0 (0.0)	21 (1.8)	51 (6.3)	126 (17.3)	445 (56.2)	386 (89.9)	115 (100.0)	16	>32
Indole-positive *Proteus* spp. (750)					0 (0.0)	1 (0.1)	6 (0.9)	55 (8.3)	179 (32.1)	268 (67.9)	164 (89.7)	51 (96.5)	26 (100.0)	8	32
Serratia marcescens (865)					0 (0.0)	1 (0.1)	13 (1.6)	251 (30.6)	484 (86.6)	89 (96.9)	16 (98.7)	6 (99.4)	5 (100.0)	4	8
Other *Serratia* spp. (45)				0 (0.0)	1 (2.2)	6 (15.6)	25 (71.1)	9 (91.1)	4 (100.0)					1	2
Salmonella spp. (6)					0 (0.0)	2 (33.3)	1 (50.0)	3 (100.0)						1	
Acinetobacter baumannii (892)			3 (0.3)	33 (4.0)	148 (20.6)	75 (29.0)	60 (35.8)	104 (47.4	260 (76.6)	164 (95.0)	36 (99.0)	8 (99.9)	1 (100.0)	4	8
Other *Acinetobacter* spp. (93)	0 (0.0)	1 (1.1)	2 (3.2)	19 (23.7)	41 (67.7)	23 (92.5)	7 (100.0)							0.25	0.5
Pseudomonas aeruginosa (4,564)			0 (0.0)	1 (<0.1)	1 (<0.1)	9 (0.2)	9 (0.4)	45 (1.4)	67 (2.9)	163 (6.5)	681 (21.4)	1,675 (58.1)	1,913 (100.0)	32	>32
Stenotrophomonas maltophilia (604)				0 (0.0)	3 (0.5)	14 (2.8)	62 (13.1)	182 (43.2)	220 (79.6)	81 (93.0)	29 (97.8)	10 (99.5)	3 (100.0)	4	8
Haemophilus influenzae (1,886)				3 (0.2)	46 (2.6)	925 (51.6)	777 (92.8)	128 (99.6)	6 (99.9)	0 (99.9)	1 (100.0)			0.5	1
β-Lactamase positive (494)				1 (0.2)	7 (1.6)	249 (52.0)	201 (92.7)	33 (99.4)	3 (100.0)					0.5	1
β-Lactamase negative (1,392)				2 (0.1)	39 (2.9)	676 (51.5)	576 (92.9)	95 (99.7)	3 (99.9)	0 (99.9)	1 (100.0)			0.5	1
Haemophilus parainfluenzae (71)				0 (0.0)	2 (2.8)	20 (31.0)	24 (64.8)	20 (93.0)	4 (98.6)	0 (98.6)	1 (100.0)			1	2
β-Lactamase positive (4)				0 (0.0)	1 (25.0)	1 (50.0)	1 (75.0)	1 (100.0)						0.5	
β-Lactamase negative (67)				0 (0.0)	1 (1.5)	19 (29.9)	23 (64.2)	19 (92.5)	4 (98.5)	0 (98.5)	1 (100.0)			1	2
Moraxella catarrhalis (984)				593 (60.3)	379 (98.8)	12 (100.0)								≤0.12	0.25
Other *Moraxella* spp. (9)				1 (11.1)	3 (44.4)	3 (77.8)	2 (100.0)							0.5	

[a]>, greater than the highest concentration tested.

[b]ESBL, extended-spectrum β-lactamase.

[c]The extended-spectrum β-lactamase phenotype was defined as having a MIC value of ≥2 mg/liter for ceftazidime, ceftriaxone, or aztreonam (confirmatory testing was not performed).

TABLE 3 Summary of omadacycline activity stratified by geographic region

Organism	$MIC_{50/90}$ (mg/liter)	
	United States	Europe
S. aureus	0.12/0.25	0.12/0.25
Methicillin-susceptible *S. aureus*	0.12/0.25	0.12/0.25
Methicillin-resistant *S. aureus*	0.12/0.25	0.12/0.25
S. lugdunensis	0.06/0.12	0.06/0.12
S. pneumoniae	0.06/0.12	0.06/0.12
Penicillin resistant	0.06/0.12	0.06/0.12
Tetracycline resistant	0.06/0.12	0.06/0.12
Beta-hemolytic streptococci	0.12/0.25	0.12/0.25
S. pyogenes	0.06/0.12	0.06/0.12
S. pyogenes macrolide resistant	0.12/0.12	0.12/0.12
Viridans group streptococci	0.06/0.12	0.06/0.12
S. anginosus group	0.03/0.12	0.06/0.06
Enterococcus faecalis	0.12/0.25	0.12/0.25
Enterococcus faecium	0.06/0.12	0.06/0.12
Vancomycin nonsusceptible (MIC, ≥8 mg/liter)	0.12/0.12	0.06/0.12
H. influenzae	1/1	0.5/1
M. catarrhalis	≤0.12/0.25	≤0.12/0.25
Enterobacterales	1/8	1/8
E. coli	0.5/2	1/2
ESBL phenotype[a]	1/2	1/2
K. pneumoniae	2/4	2/8
ESBL phenotype	2/16	4/8
E. cloacae	2/4	2/4
Citrobacter spp.	1/4	1/4
P. mirabilis	16/32	16/>32
Indole-positive *Proteus* spp.	8/32	8/16
S. marcescens	4/8	4/8
A. baumannii	0.5/8	4/8
P. aeruginosa	32/>32	32/>32

[a]The extended-spectrum β-lactamase (ESBL) phenotype was defined as having a MIC value of ≥2 mg/liter for ceftazidime, ceftriaxone, or aztreonam (confirmatory testing was not performed).

streptococci ($MIC_{50/90}$, 0.12/0.25 mg/liter), regardless of species and susceptibility to penicillin, macrolides (beta-hemolytic streptococci only), or tetracycline (Table 2). All but two *S. pneumoniae* isolates (99.9%), five viridans group streptococci (99.2%), and two *Streptococcus pyogenes* isolates (99.8%) were inhibited by <0.5 mg/liter of omadacycline. Omadacycline had activity against most of the 20,028 *Enterobacterales* isolates tested ($MIC_{50/90}$, 1/8 mg/liter; 87.5% of isolates were inhibited at ≤4 mg/liter) and was most potent against *E. coli* ($MIC_{50/90}$, 0.5/2 mg/liter; 99.1% of isolates were inhibited at ≤4 mg/liter), *K. oxytoca* ($MIC_{50/90}$, 1/2 mg/liter; 97.0% of isolates were inhibited at ≤4 mg/liter), and *Citrobacter* spp. ($MIC_{50/90}$, 1/4 mg/liter; 94.9% of isolates were inhibited at ≤4 mg/liter) (Table 1). Omadacycline lacked activity against the *Enterobacterales* species *P. mirabilis* ($MIC_{50/90}$, 16/>32 mg/liter) and indole-positive *Proteus* spp. ($MIC_{50/90}$, 8/32 mg/liter) (Table 1).

Omadacycline also had potent activity against resistant subsets of *Enterobacteriaceae*, including extended-spectrum-β-lactamase-phenotype ($MIC_{50/90}$, 1/2 mg/liter [98.0% of isolates were inhibited at ≤4 mg/liter]), non-extended-spectrum-β-lactamase-phenotype ($MIC_{50/90}$, 0.5/2 mg/liter [99.4% of isolates were inhibited at ≤4 mg/liter]), and carbapenem-resistant ($MIC_{50/90}$, 1/2 mg/liter [100.0% of isolates

were inhibited at ≤4 mg/liter]) strains of *E. coli*. The extended-spectrum-β-lactamase phenotype is based on an MIC value of ≥2 mg/liter for ceftazidime, ceftriaxone, or aztreonam. Confirmatory susceptibility testing was not performed. Omadacycline was less active against extended-spectrum-β-lactamase-phenotype *K. pneumoniae* ($MIC_{50/90}$, 4/8 mg/liter [76.4% of isolates were inhibited at ≤4 mg/liter]) and carbapenem-resistant *K. pneumoniae* ($MIC_{50/90}$, 4/8 mg/liter [72.4% of isolates were inhibited at ≤4 mg/liter]) isolates than against non-extended-spectrum-β-lactamase-phenotype *K. pneumoniae* isolates ($MIC_{50/90}$, 1/4 mg/liter [94.4% of isolates were inhibited at ≤4 mg/liter]). Against ceftazidime-nonsusceptible *E. cloacae* species complex isolates (MIC, ≥8 mg/liter; AmpC-derepressed phenotype isolates), omadacycline was less active ($MIC_{50/90}$, 2/8 mg/liter; 84.9% of isolates were inhibited at ≤4 mg/liter) than it was against ceftazidime-susceptible isolates ($MIC_{50/90}$, 2/4 mg/liter; 95.5% of isolates were inhibited at ≤4 mg/liter) (Table 2).

The $MIC_{50/90}$ values for omadacycline against tetracycline-resistant strains of *E. coli* and *K. pneumoniae* were 1/4 mg/liter and 4/16 mg/liter, respectively, and 97.6% of tetracycline-resistant *E. coli* isolates and 63.2% of tetracycline-resistant *K. pneumoniae* isolates were inhibited by ≤4 mg/liter of omadacycline (data not shown). Among the tetracycline-resistant *E. cloacae* species complex isolates, 56.7% were inhibited by omadacycline at ≤4 mg/liter ($MIC_{50/90}$, 4/16 mg/liter) (data not shown). Among the tetracycline-resistant strains of *Citrobacter* spp., omadacycline activity was decreased ($MIC_{50/90}$, 4/8 mg/liter [70.0% of isolates were inhibited at ≤4 mg/liter]) (data not shown) compared to that against all *Citrobacter* isolates ($MIC_{50/90}$, 1/4 mg/liter [94.9% of isolates were inhibited at ≤4 mg/liter]) (Table 2). In contrast, tetracycline-resistant strains of *S. marcescens* remained mostly susceptible to omadacycline ($MIC_{50/90}$, 4/8 mg/liter [84.3% of isolates were inhibited at ≤4 mg/liter]) (data not shown) when their omadacycline susceptibility was compared to that of all *S. marcescens* isolates ($MIC_{50/90}$, 4/8 mg/liter [86.6% of isolates were inhibited at ≤4 mg/liter]) (Table 2).

Omadacycline ($MIC_{50/90}$, 4/8 mg/liter) inhibited 76.6% of *A. baumannii* isolates at ≤4 mg/liter (Table 2). Omadacycline retained some activity against tetracycline-resistant *A. baumannii* isolates ($MIC_{50/90}$, 4/8 mg/liter; 61.9% of isolates were inhibited at ≤4 mg/liter). Omadacycline demonstrated good *in vitro* activity against *S. maltophilia* ($MIC_{50/90}$, 4/8 mg/liter [79.6% of isolates were inhibited at ≤4 mg/liter]) and had limited to no activity at the concentrations tested against *P. aeruginosa* ($MIC_{50/90}$, 32/>32 mg/liter) (Table 2).

Omadacycline was equally active against β-lactamase-negative ($MIC_{50/90}$, 0.5/1 mg/liter) and β-lactamase-positive ($MIC_{50/90}$, 0.5/1 mg/liter) isolates of *H. influenzae* (Table 2). Omadacycline was also very active against *M. catarrhalis* isolates ($MIC_{50/90}$, ≤0.12/0.25 mg/liter) (Table 2).

Activity of omadacycline and comparators against acute bacterial skin and skin structure infection isolates. The activity of omadacycline and comparators against key pathogens from patients with acute bacterial skin and skin structure infection is shown in Table 4.

Greater than 90.0% of *S. aureus* (99.0% susceptible), *Staphylococcus lugdunensis* (98.1% susceptible), *E. faecalis* (97.4% susceptible), *S. anginosus* group (100.0% susceptible), and *S. pyogenes* (98.2% susceptible) isolates from acute bacterial skin and skin structure infection were susceptible to omadacycline at the U.S. Food and Drug Administration-assigned breakpoints (Tables 1 and 4). Notably, 94.0% of coagulase-negative staphylococci from acute bacterial skin and skin structure infection were inhibited at the *S. aureus* breakpoint of ≤0.5 mg/liter, whereas only 66.7% were inhibited at the *S. lugdunensis* breakpoint (data not shown). Notably, 94.0% of coagulase-negative staphylococci isolates from acute bacterial skin and skin structure infection were inhibited at the *S. aureus* breakpoint of ≤0.5 mg/liter, whereas only 66.7% were inhibited at the *S. lugdunensis* breakpoint of ≤0.12 mg/liter (data not shown).

Methicillin-resistant *S. aureus* accounted for 31.0% of *S. aureus* isolates from acute bacterial skin and skin structure infection, and 97.1% of those methicillin-resistant *S.*

TABLE 4 Activity of omadacycline and comparator antimicrobial agents when tested against bacterial isolates from skin and skin structure infections in the United States and Europe, SENTRY Program, 2016 to 2018

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Staphylococcus aureus (4,632)					
Omadacycline	0.12	0.25	≤0.015 to 4	99.0[b]/0.3	
Doxycycline	≤0.06	0.25	≤0.06 to 8	98.1/0.6	95.9/2.5
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	94.1/5.1	93.1/6.5
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	91.7/8.2	91.5/8.3
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—	100.0/—
Erythromycin	0.25	>8	≤0.06 to >8	61.2/34.8	61.6/36.8
Levofloxacin	0.25	>4	0.06 to >4	75.9/23.7	75.9/24.1
Linezolid	1	2	≤0.12 to >8	>99.1/<0.1	>99.1/<0.1
Oxacillin	0.5	>2	≤0.25 to >2	69.0/31.0	69.0/31.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	98.9/1.1	98.9/1.1
Vancomycin	1	1	≤0.12 to 2	100.0/—	100.0/—
Methicillin susceptible (3,194)					
Omadacycline	0.12	0.25	≤0.015 to 1	99.9[b]/0.0	
Doxycycline	≤0.06	0.12	≤0.06 to >8	99.3/0.2	97.5/1.1
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	96.2/3.2	95.3/4.5
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	97.9/2.1	97.7/2.1
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—	100.0/—
Erythromycin	0.25	>8	≤0.06 to >8	78.3/17.4	78.9/19.5
Levofloxacin	0.25	0.5	0.06 to >4	94.0/5.6	94.0/6.0
Linezolid	1	2	0.25 to 4	100.0/—	100.0/—
Oxacillin	0.5	1	≤0.25 to 2	100.0/—	100.0/—
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	99.5/0.5	99.5/0.4
Vancomycin	1	1	≤0.12 to 2	100.0/—	100.0/—
Methicillin resistant (1,438)					
Omadacycline	0.12	0.25	≤0.015 to 4	97.1[b]/0.9	
Doxycycline	≤0.06	1	≤0.06 to >8	95.3/1.6	92.3/5.6
Tetracycline	≤0.5	8	≤0.5 to >8	89.5/9.3	88.0/11.0
Clindamycin	≤0.25	>2	≤0.25 to >2	78.0/21.8	78.0/22.0
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—	100.0/—
Erythromycin	>8	>8	≤0.06 to >8	23.3/73.4	23.3/75.3
Linezolid	1	2	≤0.12 to >8	99.9/0.1	99.9/0.1
Levofloxacin	4	>4	0.12 to >4	35.5/63.7	35.5/64.5
Oxacillin	>2	>2	>2 to >2	0.0/100.0	0.0/100.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	97.4/2.6	97.4/2.5
Vancomycin	1	1	0.25 to 2	100.0/—	100.0/—
Tetracycline resistant (237)					
Omadacycline	0.12	0.5	0.06 to 2	92.8[b]/1.7	
Doxycycline	2	>8	0.12 to >8	62.4/11.8	21.9/47.7
Tetracycline	>8	>8	>8	0.0/100.0	0.0/100.0
Clindamycin	≤0.25	>2	≤0.25 to >2	65.8/34.2	65.8/34.2
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—	100.0/—
Erythromycin	>8	>8	≤0.06 to >8	41.4/52.7	41.4/56.5
Levofloxacin	0.25	>4	0.12 to >4	59.9/39.7	59.9/40.1
Linezolid	1	2	0.5 to 2	100.0/—	100.0/—
Oxacillin	>2	>2	≤0.25 to >2	43.5/56.5	43.5/56.5
Trimethoprim-sulfamethoxazole	≤0.5	1	≤0.5 to >4	94.9/5.1	94.9/5.1
Vancomycin	1	1	0.5 to 1	100.0/—	100.0/—
Coagulase-negative staphylococci[c] (348)					
Omadacycline	0.12	0.5	≤0.015 to 1		
Oxacillin	1	>2	≤0.25 to >2	54.3/45.7	55.2/44.8
Erythromycin	0.12	>8	≤0.06 to >8	53.4/45.1	53.7/45.7
Clindamycin	≤0.25	>2	≤0.25 to >2	81.3/18.4	80.7/18.7
Levofloxacin	0.25	>4	≤0.03 to >4	71.0/26.7	71.0/29.0
Linezolid	0.5	1	≤0.12 to 2	100.0/—	100.0/—
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—	100.0/—
Tetracycline	≤0.5	8	≤0.5 to >8	89.4/9.2	81.9/12.1
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	78.2/21.8	78.2/12.9
Vancomycin	1	2	≤0.12 to 4	100.0/—	100.0/—

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TABLE 4 (Continued)

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Staphylococcus lugdunensis (103)					
Omadacycline	0.06	0.12	≤0.015 to 0.5	98.1[d]/1.0	
Doxycycline	≤0.06	≤0.06	≤0.06 to 4	100.0/—	96.1/1.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.1/4.9	95.1/4.9
Oxacillin	1	1	≤0.25 to >2	98.1/1.9	98.1/1.9
Erythromycin	≤0.06	>8	≤0.06 to >8	83.5/15.5	84.5/15.5
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	95.1/4.9	95.1/4.9
Levofloxacin	0.25	0.5	≤0.03 to 1	100.0/—	100.0/—
Linezolid	0.5	1	≤0.12 to 1	100.0/—	100.0/—
Daptomycin	0.25	0.25	≤0.12 to 1	100.0/—	100.0/—
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to 4	99.0/1.0	99.0/0.0
Vancomycin	0.5	1	0.25 to 1	100.0/—	100.0/—
Beta-hemolytic streptococci[e] (960)					
Omadacycline	0.06	0.12	0.03 to 1		
Tetracycline	0.5	>4	≤0.25 to >4	61.2/37.2	60.6/38.8
Clindamycin	≤0.25	>2	≤0.25 to >2	86.0/12.7	87.3/12.7
Daptomycin	≤0.06	0.25	≤0.06 to 0.5	100.0/—	100.0/—
Erythromycin	0.03	>16	≤0.015 to >16	74.1/24.9	74.1/24.9
Levofloxacin	0.5	1	0.12 to >4	99.0/0.7	99.0/1.0
Linezolid	1	2	0.25 to 2	100.0/—	100.0/—
Penicillin	0.015	0.06	≤0.008 to 0.12	100.0/—	100.0/—
Vancomycin	0.5	0.5	0.12 to 1	100.0/—	100.0/—
Streptococcus pyogenes[f] (544)					
Omadacycline	0.06	0.12	0.03 to 0.25	98.2[d]/0.0	
Tetracycline	≤0.25	>4	≤0.25 to >4	82.1/17.5	81.8/17.9
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	95.6/3.9	96.1/3.9
Daptomycin	≤0.06	≤0.06	≤0.06 to 0.5	100.0/—	100.0/—
Erythromycin	0.03	2	≤0.015 to >16	87.3/12.2	87.3/12.2
Levofloxacin	0.5	1	0.12 to >4	99.6/0.2	99.6/0.4
Linezolid	1	2	0.5 to 2	100.0/—	100.0/—
Penicillin	≤0.008	0.015	≤0.008 to 0.03	100.0/—	100.0/—
Vancomycin	0.5	0.5	0.12 to 1	100.0/—	100.0/—
Viridans group streptococci[g] (97)					
Omadacycline	0.06	0.12	≤0.015 to 0.5		
Tetracycline	0.5	>4	≤0.25 to >4	62.5/34.4	
Ceftriaxone	0.12	0.25	≤0.015 to >2	95.9/3.1	94.8/5.2
Clindamycin	≤0.25	>2	≤0.25 to >2	83.3/11.5	88.5/11.5
Daptomycin	0.25	0.5	≤0.06 to 1	100.0/—	
Erythromycin	≤0.015	>16	≤0.015 to >16	66.7/29.2	
Levofloxacin	0.5	2	0.25 to >4	96.9/2.1	
Linezolid	1	1	≤0.12 to >4	99.0/—	
Penicillin	0.03	0.25	≤0.008 to 8	88.7/3.1	92.8/3.1
Vancomycin	0.5	1	≤0.06 to 1	100.0/—	100.0/—
Streptococcus anginosus group (67)					
Omadacycline	0.06	0.12	≤0.015 to 0.12	100.0[h]/—	
Tetracycline	0.5	>4	≤0.25 to >4	65.2/31.8	
Ceftriaxone	0.12	0.25	≤0.015 to >2	98.5/1.5	98.5/1.5
Clindamycin	≤0.25	0.5	≤0.25 to >2	87.9/7.6	92.4/7.6
Daptomycin	0.12	0.25	≤0.06 to 0.5	100.0/—	
Erythromycin	≤0.015	2	≤0.015 to >16	80.3/13.6	
Levofloxacin	0.5	0.5	0.25 to 1	100.0/—	
Linezolid	1	1	≤0.12 to 2	100.0/—	
Penicillin	0.03	0.06	≤0.008 to 4	98.5/1.5	98.5/1.5
Vancomycin	0.5	1	≤0.06 to 1	100.0/—	100.0/—
Enterococcus faecalis (382)					
Omadacycline	0.12	0.25	≤0.015 to 1	97.4[i]/0.3	
Tetracycline	>16	>16	≤0.12 to >16	25.4/73.8	
Minocycline	>8	>8	≤0.06 to >8	29.1/55.7	
Ampicillin	1	1	≤0.5 to 2	100.0/—	100.0/—
Daptomycin	0.5	1	≤0.25 to 2	100.0/—	
Erythromycin	2	>16	0.25 to >16	10.6/46.9	

(Continued on next page)

TABLE 4 (Continued)

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Linezolid	1	2	0.25 to 4	99.5/0.0	100.0/—
Levofloxacin	1	>4	≤0.03 to >4	74.1/25.4	74.6/25.4
Piperacillin-tazobactam	4	8	1 to >16		100.0/—
Vancomycin	1	2	≤0.12 to >16	99.0/1.0	99.0/1.0
Enterococcus faecium (155)					
Omadacycline	0.06	0.12	0.03 to 1		
Tetracycline	>16	>16	≤0.12 to >16	36.1/62.6	
Minocycline	8	>8	≤0.06 to >8	48.8/30.0	
Ampicillin	>16	>16	≤0.5 to >16	9.0/91.0	7.7/91.0
Daptomycin	1	2	≤0.25 to 4	100.0/—	
Erythromycin	>16	>16	≤0.12 to >16	2.7/86.7	
Linezolid	1	2	0.25 to 2	100.0/—	100.0/—
Levofloxacin	>4	>4	0.5 to >4	5.8/92.9	7.1/92.9
Piperacillin-tazobactam	>16	>16	8 to >16		8.0/90.7
Vancomycin	1	>16	0.25 to >16	63.2/36.8	63.2/36.8
Escherichia coli (978)					
Omadacycline	1	2	≤0.06 to 16		
Tetracycline	2	>16	0.5 to >16	60.5/39.1	
Doxycycline	2	>8	0.12 to >8	63.5/23.7	
Minocycline	1	8	0.12 to >32	85.7/8.9	
Ceftazidime	0.25	32	0.03 to >32	80.9/15.0	74.4/19.1
Ceftriaxone	≤0.06	>8	≤0.06 to >8	73.5/25.6	73.5/25.6
Gentamicin	1	>8	0.12 to >8	88.6/11.1	88.1/11.4
Imipenem	≤0.12	0.25	≤0.12 to 4	99.5/0.3	99.7/0.0
Levofloxacin	0.06	>4	≤0.03 to >4	65.7/32.7	65.7/32.7
Piperacillin-tazobactam	2	16	≤0.5 to >64	92.3/4.4	87.9/7.7
ESBL phenotype *E. coli*[j] (273)					
Omadacycline	1	4	0.25 to 16		
Tetracycline	>16	>16	0.5 to >16	38.8/60.8	
Doxycycline	8	>8	0.25 to >8	42.5/33.0	
Minocycline	2	16	0.25 to >32	80.6/10.2	
Ceftazidime	16	>32	0.25 to >32	31.5/53.8	8.4/68.5
Ceftriaxone	>8	>8	0.12 to >8	5.1/91.6	5.1/91.6
Gentamicin	1	>8	0.25 to >8	71.7/27.2	71.3/28.3
Imipenem	≤0.12	0.25	≤0.12 to 4	98.2/1.1	98.9/0.0
Levofloxacin	>4	>4	≤0.03 to >4	30.4/66.7	30.4/66.7
Piperacillin-tazobactam	4	64	≤0.5 to >64	84.2/9.2	72.9/15.8
Klebsiella pneumoniae (504)					
Omadacycline	2	8	0.25 to 32	89.1[k]/4.2	
Tetracycline	2	>16	0.5 to >16	65.9/28.2	
Doxycycline	2	>8	0.25 to >8	68.4/25.0	
Minocycline	2	16	0.5 to >32	76.9/14.2	
Ceftazidime	0.5	>32	0.03 to >32	63.3/34.7	61.1/36.7
Ceftriaxone	0.12	>8	≤0.06 to >8	62.1/37.5	62.1/37.5
Gentamicin	0.25	>8	≤0.12 to >8	76.9/22.1	76.5/23.1
Imipenem	≤0.12	4	≤0.12 to >8	86.3/11.9	88.1/9.1
Levofloxacin	0.06	>4	≤0.03 to >4	66.5/30.6	66.5/30.6
Piperacillin-tazobactam	4	>64	≤0.5 to >64	71.0/23.0	65.7/29.0
ESBL phenotype *K. pneumoniae*[j] (200)					
Omadacycline	4	8	0.5 to 32	78.5[k]/8.5	
Tetracycline	>16	>16	1 to >16	34.5/56.5	
Doxycycline	8	>8	0.5 to >8	38.5/47.5	
Minocycline	4	32	0.5 to >32	62.3/20.3	
Ceftazidime	>32	>32	0.5 to >32	7.5/87.5	2.0/92.5
Ceftriaxone	>8	>8	≤0.06 to >8	4.5/94.5	4.5/94.5
Gentamicin	>8	>8	0.25 to >8	43.2/54.3	42.2/56.8
Imipenem	0.25	>8	≤0.12 to >8	66.5/29.0	71.0/23.0
Levofloxacin	>4	>4	≤0.03 to >4	23.0/71.5	23.0/71.5
Piperacillin-tazobactam	>64	>64	1 to >64	32.0/55.5	25.0/68.0

(Continued on next page)

TABLE 4 (Continued)

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Enterobacter cloacae species complex[l] (407)					
Omadacycline	2	4	0.5 to 32	94.7[k]/2.8	
Tetracycline	2	16	0.5 to >16	86.0/11.1	
Doxycycline	2	8	0.5 to >8	88.5/6.9	
Minocycline	2	4	0.5 to >32	92.9/4.4	
Ceftazidime	0.5	>32	0.06 to >32	77.9/21.4	75.2/22.1
Ceftriaxone	0.25	>8	≤0.06 to >8	71.0/25.8	71.0/25.8
Gentamicin	0.25	0.5	≤0.12 to >8	93.6/6.1	92.6/6.4
Imipenem	0.25	0.5	≤0.12 to >8	97.8/1.5	98.5/0.7
Levofloxacin	≤0.03	0.5	≤0.03 to >4	90.9/6.2	90.9/6.2
Piperacillin-tazobactam	2	64	1 to >64	82.8/9.8	80.8/17.2
Serratia marcescens (167)					
Omadacycline	4	8	0.5 to >32		
Tetracycline	>16	>16	2 to >16	3.6/81.4	
Doxycycline	4	>8	1 to >8	56.3/15.6	
Minocycline	4	8	1 to 32	89.5/5.8	
Ceftazidime	0.25	0.5	0.06 to >32	99.4/0.6	97.0/0.6
Ceftriaxone	0.25	2	≤0.06 to >8	88.6/4.8	88.6/4.8
Gentamicin	0.5	1	0.25 to >8	99.4/0.6	98.2/0.6
Imipenem	0.5	1	≤0.12 to 8	95.2/1.2	98.8/1.2
Levofloxacin	0.12	1	≤0.03 to >4	89.2/5.4	89.2/5.4
Piperacillin-tazobactam	2	8	≤0.5 to >64	95.8/2.4	94.6/4.2
Acinetobacter baumannii (156)					
Omadacycline	2	8	≤0.06 to 32		
Tetracycline	8	>16	0.5 to >16	37.8/48.7	
Doxycycline	1	>8	≤0.06 to >8	71.2/26.9	
Gentamicin	8	>8	0.12 to >8	46.2/48.7	46.2/53.8
Imipenem	2	>8	≤0.12 to >8	50.0/45.5	50.0/45.5
Levofloxacin	>4	>4	0.06 to >4	37.8/60.9	35.3/62.2
Piperacillin-tazobactam	>64	>64	≤0.5 to >64	35.9/59.6	
Trimethoprim-sulfamethoxazole	2	>4	≤0.5 to >4	51.9/48.1	51.9/44.9

[a]Criteria published by the Clinical and Laboratory Standards Institute (33) and The European Committee on Antimicrobial Susceptibility Testing (34). S, susceptibility; R, resistance; —, not applicable.
[b]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for *S. aureus* (acute bacterial skin and skin structure infection) were applied (33, 35, 36).
[c]Organisms include *Staphylococcus capitis* (*n* = 15), *Staphylococcus caprae* (*n* = 7), *Staphylococcus cohnii* (*n* = 1), *Staphylococcus epidermidis* (*n* = 153), *Staphylococcus haemolyticus* (*n* = 35), *Staphylococcus hominis* (*n* = 9), *Staphylococcus lugdunensis* (*n* = 103), *Staphylococcus saprophyticus* (*n* = 4), *Staphylococcus schleiferi* (*n* = 4), *Staphylococcus simulans* (*n* = 9), and *Staphylococcus warneri* (*n* = 8).
[d]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for *S. lugdunensis* acute bacterial skin and skin structure infection) were applied (33, 35, 36).
[e]Organisms include *Streptococcus agalactiae* (*n* = 258), *Streptococcus canis* (*n* = 3), *Streptococcus dysgalactiae* (*n* = 155), and *Streptococcus pyogenes* (*n* = 544).
[f]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for *S. pyogenes* (were applied (33, 35, 36).
[g]Organisms include *Streptococcus anginosus* (*n* = 31), *S. anginosus* group (*n* = 19), *Streptococcus constellatus* (*n* = 13), *Streptococcus gallolyticus* (*n* = 4), *Streptococcus gordonii* (*n* = 2), *Staphylococcus intermedius* (*n* = 4), *Streptococcus mitis* group (*n* = 15), *Streptococcus mutans* (*n* = 1), *Streptococcus parasanguinis* (*n* = 2), *Streptococcus salivarius/Streptococcus vestibularis* (*n* = 4), and *Streptococcus sanguinis* (*n* = 2).
[h]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for the *S. anginosus* group (acute bacterial skin and skin structure infection) were applied (33, 35, 36).
[i]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for *E. faecalis* (acute bacterial skin and skin structure infection) were applied (33, 35, 36).
[j]The extended-spectrum β-lactamase (ESBL) phenotype was defined as having a MIC value of ≥2 mg/liter for ceftazidime, ceftriaxone, or aztreonam (confirmatory testing was not performed).
[k]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for the *Enterobacteriaceae* (*Enterobacter cloacae and Klebsiella pneumoniae* only; acute bacterial skin and skin structure infection) were applied (33, 35, 36).
[l]Organisms include *Enterobacter cloacae* (*n* = 227), *E. cloacae* species complex (*n* = 172), *Enterobacter asburiae* (*n* = 6), and *Enterobacter kobei* (*n* = 2).

aureus isolates were susceptible to omadacycline (Tables 1 and 4). Comparable activity was seen with linezolid (99.9% susceptible), daptomycin (100.0% susceptible), trimethoprim-sulfamethoxazole (97.4% susceptible), and vancomycin (100.0% susceptible). Erythromycin, clindamycin, levofloxacin, and tetracycline were all considerably less active against methicillin-resistant *S. aureus* than against methicillin-susceptible *S. aureus* (Table 4). Omadacycline was active against 92.8% of tetracycline-resistant *S. aureus* isolates (Table 4). Linezolid, daptomycin, and vancomycin were the most active

agents against coagulase-negative staphylococci from acute bacterial skin and skin structure infection.

Among the streptococci isolated from patients with acute bacterial skin and skin structure infection, beta-hemolytic streptococci were generally susceptible to the agents tested, with these isolates showing less than 90.0% susceptibility only to erythromycin (74.1% susceptible), clindamycin (86.0% susceptible), and tetracycline (61.2% susceptible) (Table 4). Penicillin, linezolid, daptomycin, and vancomycin were the most active agents tested against beta-hemolytic streptococci, with all isolates (100.0%) being susceptible at the Clinical and Laboratory Standards Institute (CLSI) breakpoints. Omadacycline ($MIC_{50/90}$, 0.06/0.12; 98.2% susceptible) was more active than tetracycline ($MIC_{50/90}$, ≤0.25/>4; 82.1% susceptible) against *S. pyogenes* isolates from acute bacterial skin and skin structure infection (Table 4). Omadacycline (95.9% of isolates were inhibited using the *S. anginosus* breakpoint of ≤0.12 mg/liter), ceftriaxone (95.9% susceptible), levofloxacin (96.9% susceptible), linezolid (99.0% susceptible), daptomycin (100.0% susceptible), and vancomycin (100.0% susceptible) were all very active against acute bacterial skin and skin structure infection isolates of viridans group streptococci (Table 4). Only erythromycin and tetracycline showed less than 80.0% activity against viridans group streptococci. Omadacycline ($MIC_{50/90}$, 0.06/0.12; 100.0% susceptible) was more active than tetracycline ($MIC_{50/90}$, 0.5/>4 mg/liter; 65.2% susceptible) against *S. anginosus* group isolates from acute bacterial skin and skin structure infection (Table 4).

Omadacycline was active against 97.4% of *E. faecalis* isolates from acute bacterial skin and skin structure infection (Tables 1 and 4). Similarly, 96.8% of *E. faecium* isolates from acute bacterial skin and skin structure infection were inhibited by ≤0.25 mg/liter of omadacycline. The only comparator agents with activity against *E. faecium* isolates were daptomycin (100.0% susceptible) and linezolid (100.0% susceptible) (Table 4). Among the vancomycin-nonsusceptible enterococci from acute bacterial skin and skin structure infection, only omadacycline (93.5% of isolates were inhibited at ≤0.25 mg/liter), linezolid (100.0% susceptible), and daptomycin (100.0% susceptible at an MIC of ≤4 mg/liter) retained activity (data not shown).

Omadacycline and imipenem were the most active agents tested against acute bacterial skin and skin structure infection isolates of *E. coli*, *K. pneumoniae*, and the *E. cloacae* species complex, including isolates of the extended-spectrum-β-lactamase and ceftazidime-nonsusceptible phenotypes (Table 4). Only 3.6% of *S. marcescens* isolates were susceptible to tetracycline, but 86.8% were inhibited by ≤4 mg/liter of omadacycline (Table 4). Ceftazidime (99.4% susceptible) and gentamicin (99.4% susceptible) were the most active agents tested against *S. marcescens* isolates.

A. baumannii isolates associated with acute bacterial skin and skin structure infection showed a characteristic resistance profile, with the isolates displaying a rate of susceptibility of greater than 70.0% only to doxycycline (71.2% susceptible) (Table 4). There are no interpretive criteria for omadacycline against *A. baumannii*; however, 82.1% of the 156 acute bacterial skin and skin structure infection isolates tested were inhibited at ≤4 mg/liter.

Activity of omadacycline and comparators against community-acquired bacterial pneumonia isolates. The activity of omadacycline and comparators against key pathogens from patients with community-acquired bacterial pneumonia is shown in Table 5. Using U.S. Food and Drug Administration community-acquired bacterial pneumonia susceptibility breakpoints for *S. pneumoniae* and *Haemophilus* spp. (Table 1), omadacycline was highly active against *S. pneumoniae* ($MIC_{50/90}$, 0.06/0.12 mg/liter; 98.7% susceptible; Tables 2 and 5), regardless of the penicillin-resistant (omadacycline $MIC_{50/90}$, 0.06/0.12 mg/liter; 97.9% susceptible) or tetracycline-resistant (omadacycline $MIC_{50/90}$, 0.06/0.12 mg/liter; 97.0% susceptible) phenotype (Table 4). Omadacycline activity against penicillin-resistant (MIC, ≥2 mg/liter) *S. pneumoniae* isolates ($MIC_{50/90}$, 0.06/0.12 mg/liter; 97.9% susceptible) was comparable to levofloxacin activity ($MIC_{50/90}$, 1/2 mg/liter; 97.9% susceptible) and slightly less than vancomycin activity ($MIC_{50/90}$, 0.25/0.5 mg/liter; 100.0% susceptible) and linezolid ac-

TABLE 5 Activity of omadacycline and comparator antimicrobial agents when tested against bacterial isolates from community-acquired respiratory tract infections in the United States and Europe, SENTRY Program, 2016 to 2018

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Streptococcus pneumoniae (2,626)					
Omadacycline	0.06	0.12	≤0.015 to 1	98.7[b]/0.1	
Tetracycline	0.5	>4	≤0.25 to >4	78.2/21.4	78.2/21.4
Amoxicillin-clavulanate	≤0.03	2	≤0.03 to >4	94.4/3.0	81.7/14.0
Ceftriaxone	0.03	1	≤0.015 to >2	96.5[c]/0.5	86.2/0.5
Clindamycin	≤0.25	>2	≤0.25 to >2	83.9/15.7	84.3/15.7
Erythromycin	0.03	>16	≤0.015 to >16	65.6/34.0	65.6/34.0
Levofloxacin	1	2	0.25 to >4	98.3/1.4	98.3/1.7
Linezolid	1	2	≤0.12 to 2	100.0/—	100.0/0.0
Penicillin	0.03	2	≤0.008 to >4	66.5[d]/12.5	66.5/4.5
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	72.6/17.7	77.7/17.7
Vancomycin	0.25	0.5	≤0.06 to 0.5	100.0/—	100.0/0.0
Penicillin resistant (MIC, ≥2 mg/liter) (328)					
Omadacycline	0.06	0.12	0.03 to 0.25	97.9[b]/0.0	
Tetracycline	>4	>4	≤0.25 to >4	42.7/57.0	42.7/57.0
Amoxicillin-clavulanate	2	>4	0.5 to >4	55.5/23.8	1.5/86.3
Ceftriaxone	1	2	0.25 to >2	72.3[c]/4.3	7.9/4.3
Clindamycin	≤0.25	>2	≤0.25 to >2	50.6/49.1	50.9/49.1
Erythromycin	>16	>16	≤0.015 to >16	20.1/79.6	20.1/79.6
Levofloxacin	1	2	0.5 to >4	97.9/1.5	97.9/2.1
Linezolid	1	2	0.25 to 2	100.0/—	100.0/0.0
Penicillin	2	4	2 to >4	0.0[d]/100.0	0.0/100.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12 to >4	27.7/64.0	32.9/64.0
Vancomycin	0.25	0.5	0.12 to 0.5	100.0/—	100.0/0.0
Tetracycline resistant (561)					
Omadacycline	0.06	0.12	≤0.015 to 1	97.0[b]/0.2	
Tetracycline	>4	>4	4 to >4	0.0/100.0	0.0/100.0
Amoxicillin-clavulanate	0.25	4	≤0.03 to >4	81.1/8.9	61.0/31.4
Ceftriaxone	0.25	2	≤0.015 to >2	86.5[c]/2.1	65.1/2.1
Clindamycin	>2	>2	≤0.25 to >2	33.7/65.1	34.9/65.1
Erythromycin	>16	>16	≤0.015 to >16	12.8/86.1	12.8/86.1
Levofloxacin	1	2	0.25 to >4	98.2/1.4	98.2/1.8
Linezolid	1	2	0.25 to 2	100.0/—	100.0/0.0
Penicillin	0.25	4	2 to >4	26.2[d]/33.3	26.2/73.8
Trimethoprim-sulfamethoxazole	1	>4	≤0.12 to >4	41.7/36.7	54.0/36.7
Vancomycin	0.25	0.5	≤0.06 to 0.5	100.0/—	100.0/0.0
Haemophilus influenzae (1,575)					
Omadacycline	0.5	1	≤0.12 to 16	99.6*f*/0.1	
Tetracycline	0.5	1	0.12 to >8	99.4/0.6	99.1/0.6
Amoxicillin-clavulanate	0.5	2	≤0.06 to >8	99.6/0.4	93.4/6.6
Ampicillin	0.5	>8	≤0.12 to >8	66.5/26.0	66.5/33.5
Azithromycin	1	2	≤0.12 to >8	99.0/—	99.0/—
Ceftriaxone	0.004	0.015	≤0.002 to 0.5	100.0/—	99.7/0.3
Levofloxacin	0.015	0.03	0.008 to >2	99.6/—	98.1/1.9
Haemophilus parainfluenzae (16)					
Omadacycline	1	4	0.5 to 16	87.5[e]/6.2	
Tetracycline	0.5	>8	0.25 to >8	68.8/12.5	68.8/31.2
Amoxicillin-clavulanate	0.5	2	0.12 to 4	100.0/0.0	93.8/6.2
Ampicillin	0.5	8	0.25 to >8	75.0/18.8	75.0/25.0
Azithromycin	2	4	0.25 to 8	93.8/—	93.8/—
Ceftriaxone	0.008	0.12	≤0.002 to 0.25	100.0/—	93.8/6.2
Levofloxacin	0.03	>2	0.008 to >2	87.5/—	81.2/18.8
Moraxella catarrhalis (913)					
Omadacycline	≤0.12	0.25	≤0.12 to 0.5		
Tetracycline	0.25	0.5	≤0.06 to >8	99.7/0.3	99.7/0.3
Amoxicillin-clavulanate	≤0.25	≤0.25	≤0.25 to 0.5	100.0/0.0	100.0/0.0
Azithromycin	≤0.03	≤0.03	≤0.03 to 1	99.9/—	99.9/0.1
Ceftriaxone	0.25	0.5	≤0.002 to 2	100.0/—	99.3/0.0
Levofloxacin	0.06	0.06	≤0.015 to 2	100.0/—	99.7/0.3
Penicillin	>4	>4	≤0.03 to >4		

[a]Criteria published by the Clinical and Laboratory Standards Institute (33) and The European Committee on Antimicrobial Susceptibility Testing (34). S, susceptibility; R, resistance; —, not applicable.

[b]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for *S. pneumoniae* community-acquired bacterial pneumonia were applied (35, 36).

[c]Using nonmeningitis breakpoints.

[d]Criteria published by the Clinical and Laboratory Standards Institute (2019) for penicillin (oral penicillin) (33).

[e]In the absence of Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for *Haemophilus* spp. were applied (35, 36).

tivity ($MIC_{50/90}$, 1/2 mg/liter; 100.0% susceptible). Most of the other agents tested showed suboptimal activity against penicillin-resistant *S. pneumoniae* isolates (range, 20.1 to 72.3% susceptible). Aside from *S. pneumoniae*, omadacycline was active against other pathogens frequently recovered from patients with community-acquired bacterial pneumonia, such as *H. influenzae* ($MIC_{50/90}$, 0.5/1 mg/liter; 99.6% susceptible) and *M. catarrhalis* ($MIC_{50/90}$, ≤0.12/0.25 mg/liter; 98.8% of isolates were inhibited at ≤0.25 mg/liter), regardless of β-lactamase production or geographic region (Tables 2, 3, and 5). These isolates were generally susceptible to most agents tested, as well.

Activity of omadacycline and comparators against urinary tract infection isolates. Among the Gram-positive cocci causing urinary tract infection, *S. aureus* and *Enterococcus* spp. were the most common (Table 6). Omadacycline ($MIC_{50/90}$, 0.12/0.25 mg/liter; 98.2% of isolates were inhibited at ≤0.5 mg/liter) was comparable in activity to linezolid ($MIC_{50/90}$, 1/2 mg/liter; 100.0% susceptible) and daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/liter; 100.0% susceptible) against *S. aureus* (including methicillin-resistant *S. aureus* isolates) (Table 6). Omadacycline was active against *E. faecalis* (2.2% vancomycin-resistant) and *E. faecium* (52.4% vancomycin-resistant) isolates from urinary tract infection, inhibiting 97.4% of *E. faecalis* isolates and 97.6% of *E. faecium* isolates at ≤0.25 mg/liter (Table 6). Linezolid ($MIC_{50/90}$, 1/2 mg/liter; 98.8% to 100.0% susceptible) and daptomycin ($MIC_{50/90}$, 0.5 to 1/1 to 2 mg/liter; 100.0% susceptible) were the only comparator agents with activity against >90.0% of both *E. faecalis* and *E. faecium* isolates.

Among the *E. coli* ($n = 2,872$) and *K. pneumoniae* ($n = 911$) isolates from urinary tract infections, 17.1% and 27.0%, respectively, expressed an extended-spectrum-β-lactamase phenotype (Table 6). Omadacycline ($MIC_{50/90}$, 0.5/2 mg/liter; 99.4% of isolates were inhibited at ≤4 mg/liter), imipenem ($MIC_{50/90}$, ≤0.12/≤0.12 mg/liter; 99.9% susceptible), and piperacillin-tazobactam ($MIC_{50/90}$, 2/8 mg/liter; 96.1%/93.5% susceptible [CLSI/European Committee on Antimicrobial Susceptibility Testing {EUCAST} breakpoints]) were the most active agents tested against *E. coli*, including those with an extended-spectrum-β-lactamase phenotype (98.8% of isolates were inhibited at ≤4 mg/liter, 99.4% susceptible, and 85.5% susceptible, respectively) (Table 6). Similarly, omadacycline and imipenem were the most active agents tested against *K. pneumoniae* (92.1% of isolates were inhibited at ≤4 mg/liter and 94.8% were susceptible, respectively), including those with an extended-spectrum-β-lactamase phenotype (81.3% of isolates were inhibited at ≤4 mg/liter and 81.3% were susceptible, respectively).

The most active agents against urinary tract infection isolates of the *Enterobacter cloacae* species complex were omadacycline ($MIC_{50/90}$, 2/8 mg/liter; 85.2% of isolates were inhibited at an MIC of ≤4 mg/liter), imipenem ($MIC_{50/90}$, 0.25/1 mg/liter; 96.8% susceptible), and gentamicin ($MIC_{50/90}$, 0.25/8 mg/liter; 89.7% susceptible) (Table 6). Although all tested agents showed decreased activity against ceftazidime-nonsusceptible (MIC, ≥8 mg/liter) isolates, omadacycline (74.0% of isolates were inhibited at ≤4 mg/liter [data not shown]), imipenem (93.2% susceptible), and gentamicin (75.3% susceptible) were the most active against these AmpC-derepressed-phenotype isolates (Table 6). Omadacycline inhibited 95.5% of *Citrobacter* urinary tract infection isolates at ≤4 mg/liter, activity exceeded only by that of imipenem (98.5% susceptible).

DISCUSSION

Antimicrobial resistance is a growing problem worldwide (17). Active surveillance and antimicrobial stewardship efforts are essential to combat this threat to patient safety across all health care settings (18, 19). The SENTRY Antimicrobial Surveillance Program has conducted surveillance of antimicrobial-resistant pathogens globally for more than 20 years (20) and for omadacycline-resistant pathogens since 2009 (12, 21–26). The present study documents the *in vitro* activity of omadacycline against 49,000 bacterial isolates collected in the United States and Europe during the 2016 to 2018 SENTRY survey.

Overall, omadacycline provided broad coverage against Gram-positive cocci and Gram-negative bacilli, including those isolated from patients with acute bacterial skin

TABLE 6 Activity of omadacycline and comparator antimicrobial agents when tested against bacterial isolates from urinary tract infections in the United States and Europe, SENTRY Program, 2016 to 2018

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Staphylococcus aureus (109)					
Omadacycline	0.12	025	0.03 to 1		
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	98.2/1.8	97.2/2.8
Doxycycline	≤0.06	0.12	≤0.06 to >8	99.1/0.9	98.2/0.9
Clindamycin	≤0.25	>2	≤0.25 to >2	78.9/18.3	78.9/21.1
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—	100.0/0.0
Erythromycin	0.25	>8	≤0.06 to >8	53.2/41.3	53.2/43.1
Levofloxacin	0.5	>4	0.06 to >4	52.3/47.7	52.3/47.7
Linezolid	1	2	≤0.12 to 4	100.0/0.0	100.0/0.0
Oxacillin	0.5	>2	≤0.25 to >2	58.7/41.3	58.7/41.3
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to 16	99.1/0.9	99.1/0.9
Vancomycin	1	1	0.25 to 1	100.0/0.0	100.0/0.0
Methicillin resistant (45)					
Omadacycline	0.12	0.25	0.03 to 1		
Tetracycline	≤0.5	1	≤0.5 to >8	95.6/4.4	95.6/4.4
Doxycycline	≤0.06	0.25	≤0.06 to >8	97.8/2.2	95.6/2.2
Clindamycin	≤0.25	>2	≤0.25 to >2	55.6/42.2	55.6/44.4
Daptomycin	0.25	0.5	0.25 to 1	100.0/—	100.0/0.0
Erythromycin	>8	>8	≤0.06 to >8	24.4/71.1	24.4/73.3
Linezolid	1	2	0.25 to 4	100.0/0.0	100.0/0.0
Levofloxacin	>4	>4	0.25 to >4	11.1/88.9	11.1/88.9
Oxacillin	>2	>2	>2 to >2	0.0/100.0	0.0/100.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to 16	97.8/2.2	97.8/2.2
Vancomycin	1	1	0.5 to 1	100.0/0.0	100.0/0.0
Enterococcus faecalis (312)					
Omadacycline	0.12	0.25	≤0.015 to 1		
Tetracycline	>16	>16	≤0.12 to >16	25.3/74.4	
Minocycline	>8	>8	≤0.06 to >8	33.2/53.2	
Ampicillin	1	1	≤0.5 to 2	100.0/—	100.0/—
Daptomycin	0.5	1	≤0.25 to 2	100.0/—	
Erythromycin	>16	>16	≤0.12 to >16	9.3/57.9	
Levofloxacin	1	>4	0.12 to >4	78.8/21.2	78.8/21.2
Linezolid	1	2	0.25 to 2	100.0/—	100.0/—
Piperacillin-tazobactam	4	8	2 to 16		100.0/—
Vancomycin	1	2	0.5 to >16	97.8/2.2	97.8/2.2
Enterococcus faecium (82)					
Omadacycline	0.06	0.12	0.03 to 1		
Tetracycline	>16	>16	≤0.12 to >16	34.6/65.4	
Minocycline	2	>8	≤0.06 to >8	58.3/22.9	
Ampicillin	>16	>16	≤0.5 to >16	4.9/95.1	4.9/95.1
Daptomycin	1	2	≤0.25 to 4	100.0/—	
Erythromycin	>16	>16	≤0.12 to >16	8.8/82.4	
Levofloxacin	>4	>4	1 to >4	3.7/95.1	4.9/95.1
Linezolid	1	2	0.25 to 4	98.8/0.0	100.0/—
Piperacillin-tazobactam	>16	>16	2 to 16		8.8/91.2
Vancomycin	>16	>16	0.25 to >16	45.1/52.4	45.1/54.9
Escherichia coli (2,872)					
Omadacycline	0.5	2	≤0.06 to 16		
Tetracycline	2	>16	≤0.25 to >16	66.9/32.9	
Doxycycline	1	>8	0.25 to >8	70.6/19.8	
Minocycline	1	8	0.12 to >32	86.2/8.0	
Ceftazidime	0.25	8	≤0.015 to >32	88.3/9.5	84.4/11.7
Ceftriaxone	≤0.06	>8	≤0.06 to >8	84.0/15.8	84.0/15.8
Gentamicin	1	>8	≤0.12 to >8	88.9/10.8	88.5/11.1
Imipenem	≤0.12	≤0.12	≤0.12 to >8	99.9/0.1	99.9/<0.1
Levofloxacin	≤0.03	>4	≤0.03 to >4	72.4/26.6	72.4/26.6
Piperacillin-tazobactam	2	8	≤0.5 to >64	96.1/1.6	93.5/3.9

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TABLE 6 (Continued)

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
ESBL phenotype *E. coli*[b] (491)					
Omadacycline	1	2	0.12 to 16		
Tetracycline	>16	>16	0.5 to >16	35.8/64.0	
Doxycycline	8	>8	0.25 to >8	46.2/29.1	
Minocycline	2	16	0.12 to >32	82.0/11.3	
Ceftazidime	16	>32	0.25 to >32	31.8/55.8	8.8/68.2
Ceftriaxone	>8	>8	0.12 to >8	6.3/92.5	6.3/92.5
Gentamicin	1	>8	0.25 to >8	71.8/27.6	70.1/28.2
Imipenem	≤0.12	0.25	≤0.12 to >8	99.4/0.4	99.6/0.2
Levofloxacin	>4	>4	≤0.03 to >4	23.4/75.6	23.4/75.6
Piperacillin-tazobactam	4	32	≤0.5 to >64	85.5/5.9	73.5/14.5
Klebsiella pneumoniae (911)					
Omadacycline	2	4	0.25 to >32		
Tetracycline	2	>16	0.5 to >16	72.1/24.3	
Doxycycline	2	>8	0.5 to >8	73.5/20.5	
Minocycline	2	16	0.5 to >32	80.3/13.9	
Ceftazidime	0.25	>32	0.03 to >32	75.3/22.5	73.4/24.7
Ceftriaxone	≤0.06	>8	≤0.06 to >8	74.0/25.8	74.0/25.8
Gentamicin	0.25	>8	≤0.12 to >8	85.6/13.8	84.9/14.4
Imipenem	≤0.12	0.5	≤0.12 to >8	94.8/4.5	95.5/3.4
Levofloxacin	0.06	>4	≤0.03 to >4	76.1/18.3	76.1/18.3
Piperacillin-tazobactam	4	>64	≤0.5 to >64	85.0/10.8	77.9/15.0
ESBL phenotype *K. pneumoniae*[b] (246)					
Omadacycline	2	8	0.5 to >32		
Tetracycline	>16	>16	0.5 to >16	39.4/55.3	
Doxycycline	8	>8	0.5 to >8	43.5/43.9	
Minocycline	4	>32	0.5 to >32	61.0/27.9	
Ceftazidime	32	>32	0.5 to >32	8.5/83.3	1.6/91.5
Ceftriaxone	>8	>8	0.12 to >8	3.7/95.5	3.7/95.5
Gentamicin	4	>8	≤0.12 to >8	50.0/48.0	47.6/50.0
Imipenem	≤0.12	8	≤0.12 to >8	81.3/16.7	83.3/12.6
Levofloxacin	4	>4	≤0.03 to >4	30.7/60.2	30.7/60.2
Piperacillin-tazobactam	16	>64	1 to >64	51.2/35.8	37.4/48.8
Enterobacter cloacae species complex (185)					
Omadacycline	2	8	0.25 to 32		
Tetracycline	2	>16	0.25 to >16	76.2/20.0	
Doxycycline	2	>8	0.25 to >8	79.5/14.6	
Minocycline	2	32	0.25 to >32	71.7/16.2	
Tetracycline	2	>16	0.25 to >16	76.2/20.0	
Ceftriaxone	0.5	>8	≤0.06 to >8	56.2/42.7	56.2/42.7
Ceftazidime	0.5	>32	0.12 to >32	60.5/38.4	56.2/39.5
Gentamicin	0.25	8	≤0.12 to >8	89.7/8.1	88.6/10.3
Imipenem	0.25	1	≤0.12 to 8	96.8/1.6	98.4/1.1
Levofloxacin	0.06	>4	≤0.03 to >4	76.2/20.5	76.2/20.5
Piperacillin-tazobactam	4	>64	0.25 to >64	69.2/16.8	62.2/30.8
Enterobacter cloacae species complex, ceftazidime nonsusceptible (MIC, ≥8 mg/liter) (73)					
Omadacycline	2	16	0.5 to 32		
Tetracycline	2	>16	1 to >16	60.3/37.0	
Doxycycline	2	>8	0.5 to >8	64.4/24.7	
Minocycline	8	32	2 to >32	43.2/35.1	
Ceftazidime	>32	>32	8 to >32	0.0/97.3	0.0/100.0
Ceftriaxone	>8	>8	4 to >8	0.0/100.0	0.0/100.0
Gentamicin	0.5	>8	≤0.12 to >8	75.3/20.5	72.6/24.7
Imipenem	0.25	1	≤0.12 to 8	93.2/4.1	95.9/2.7
Levofloxacin	0.5	>4	≤0.03 to >4	54.8/42.5	54.8/42.5
Piperacillin-tazobactam	64	>64	1 to >64	23.3/41.1	13.7/76.7

(Continued on next page)

TABLE 6 (Continued)

Antimicrobial agent (no. of isolates tested)	MIC (mg/liter)			% S/% R[a]	
	50%	90%	Range	CLSI	EUCAST
Citrobacter spp.[c] (198)					
Omadacycline	1	4	0.25 to 16		
Tetracycline	1	>16	0.5 to >16	84.4/12.7	
Doxycycline	1	>8	0.25 to >8	85.9/10.1	
Minocycline	2	8	0.5 to >32	87.4/9.0	
Ceftazidime	0.25	32	0.06 to >32	87.4/12.6	84.3/12.6
Ceftriaxone	0.12	>8	≤0.06 to >8	86.4/13.6	86.4/13.6
Gentamicin	0.5	1	≤0.12 to >8	93.4/5.6	93.4/6.6
Imipenem	0.25	1	≤0.12 to 4	98.5/1.0	99.0/0.0
Levofloxacin	≤0.03	1	≤0.03 to >4	89.4/6.1	89.4/6.1
Piperacillin-tazobactam	2	32	1 to >64	87.9/8.1	84.3/12.1

[a]Criteria published by the Clinical and Laboratory Standards Institute (33) and The European Committee on Antimicrobial Susceptibility Testing (34). S, susceptibility; R, resistance; —, not applicable.

[b]The extended-spectrum β-lactamase (ESBL) phenotype was defined as having a MIC value of ≥2 mg/liter for ceftazidime, ceftriaxone, or aztreonam (confirmatory testing was not performed).

[c]Organisms include *Citrobacter amalonaticus* (*n* = 1), *C. amalonaticus/Citrobacter farmeri* (*n* = 4), *Citrobacter braakii* (*n* = 1), *Citrobacter freundii* (*n* = 28), *C. freundii* species complex (*n* = 80), *Citrobacter koseri* (*n* = 83), and *Citrobacter sedlakii* (*n* = 1).

and skin structure infection, community-acquired bacterial pneumonia, and urinary tract infection (Tables 2 and 4 to 6). Omadacycline was active against methicillin-resistant *S. aureus* isolates, MR coagulase-negative staphylococci, vancomycin-resistant enterococci, viridans group streptococci, beta-hemolytic streptococci, and penicillin- and macrolide-resistant *S. pneumoniae* isolates (Table 2). Tetracycline-resistant Gram-positive strains remained susceptible to omadacycline. Omadacycline was active against extended-spectrum-β-lactamase-phenotype and carbapenem-resistant strains of *E. coli* and was less active against extended-spectrum-β-lactamase-phenotype *K. pneumoniae*, carbapenem-resistant *K. pneumoniae*, and ceftazidime-nonsusceptible *E. cloacae* strains. Tetracycline-resistant *Enterobacteriaceae* strains were slightly less susceptible to omadacycline than tetracycline-susceptible strains. Omadacycline demonstrated activity against *Acinetobacter* spp. and *S. maltophilia* as well as against respiratory isolates of *H. influenzae* and *M. catarrhalis*. Omadacycline was not active (MIC_{90}, ≥32 mg/liter) at the concentrations tested against *Proteus* spp., indole-positive *Proteus* spp., and *P. aeruginosa*.

Omadacycline was among the most active agents tested against pathogens from each of the key clinical indications, acute bacterial skin and skin structure infection, community-acquired bacterial pneumonia, and urinary tract infection. Among the most common Gram-positive cocci isolated from patients with acute bacterial skin and skin structure infection, more than 90.0% (97.4% to 100.0% susceptible) of *S. aureus*, *S. lugdunensis*, *S. pyogenes*, *S. anginosus* group, and *E. faecalis* isolates were susceptible to omadacycline at the approved U.S. Food and Drug Administration breakpoints (Table 1). Methicillin-resistant *S. aureus* isolates accounted for 31.0% of *S. aureus* isolates from acute bacterial skin and skin structure infection, and 97.1% were susceptible to omadacycline (Table 4). Comparable activity was seen with linezolid (99.9% susceptible), daptomycin (100.0% susceptible), trimethoprim-sulfamethoxazole (97.4% susceptible), and vancomycin (100.0% susceptible). In addition to omadacycline (98.2 to 100.0% susceptible), all *S. pyogenes* and *S. anginosus* group isolates from acute bacterial skin and skin structure infection were susceptible to linezolid, daptomycin, and vancomycin. Omadacycline was the most active agent by the $MIC_{50/90}$ against acute bacterial skin and skin structure infection isolates of *E. faecalis* and *E. faecium*, including vancomycin-nonsusceptible strains.

Omadacycline and imipenem were the most active agents tested against acute bacterial skin and skin structure infection isolates of *E. coli*, *K. pneumoniae*, and the *E. cloacae* species complex, including extended-spectrum-β-lactamase-phenotype and ceftazidime-nonsusceptible isolates (Table 4). Likewise, omadacycline and doxycycline

were the most active agents tested against *A. baumannii* isolates from acute bacterial skin and skin structure infection.

The major pathogens associated with community-acquired bacterial pneumonia included *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (Table 5). Omadacycline was active against these organisms, including penicillin-resistant, macrolide-resistant, and tetracycline-resistant strains of *S. pneumoniae*. Omadacycline, levofloxacin, linezolid, and vancomycin were the most active agents against *S. pneumoniae*. *H. influenzae* and *M. catarrhalis* were generally susceptible to most agents tested.

Urinary tract infections (UTIs) commonly occur in the community and health care settings (27). The microbial spectrum of uncomplicated cystitis and pyelonephritis consists mainly (75 to 95%) of *E. coli*, with occasional species of other *Enterobacterales*, such as *Klebsiella pneumoniae* and *Proteus mirabilis*, being responsible (27). Gram-positive cocci (GPC; methicillin-resistant *Staphylococcus aureus* [MRSA] and enterococci) are common in more complicated catheter-associated urinary tract infections (cUTIs) but are rarely isolated in uncomplicated urinary tract infections (uUTIs) (27). Omadacycline and imipenem were the most active agents tested against *Enterobacteriaceae* isolates from UTIs, including extended-spectrum-β-lactamase-phenotype isolates of *E. coli* and *K. pneumoniae* and ceftazidime-nonsusceptible isolates of the *E. cloacae* species complex. The Gram-positive cocci causing urinary tract infection were most often *S. aureus* and *Enterococcus* spp. (Table 6). Omadacycline, linezolid, and daptomycin were among the most active agents tested against both *S. aureus* and enterococci, including the methicillin-resistant *S. aureus* and vancomycin-resistant enterococcus subsets. In view of the broad range of activity of omadacycline against Gram-positive cocci and Gram-negative bacilli (Tables 2 and 6), it would seem to be a useful choice in treating cUTIs, in which mixed Gram-positive cocci and Gram-negative bacilli may occur and pathogens resistant to older antimicrobials are common (3, 5, 25).

It has been established that the ratio of the area under the concentration-time curve (AUC) to the MIC (AUC/MIC) is the pharmacokinetic (PK)/pharmacodynamic (PD) parameter that best correlates with antibacterial efficacy for the tetracycline class of antibiotics (28). Studies by Lepak et al. of omadacycline in *S. aureus* neutropenic mouse models of pneumonia (29) and thigh infection (30) have confirmed this to be true for omadacycline as well. Based on the MIC_{90} value of 0.25 mg/liter for omadacycline and *S. aureus*, as shown in numerous large surveillance studies, including SENTRY (10, 12, 21, 22, 24), the clinical doses of omadacycline would produce exposures that would exceed all 1-log-kill targets for epithelial lining fluid (ELF) and plasma in the pneumonia model and the plasma stasis target in the thigh infection model. Bhavnani et al. (31) used the *in vivo* PD targets for the *S. aureus* thigh infection model in Monte Carlo simulations to predict the probability of target attainment in patients with acute bacterial skin and skin structure infection. The omadacycline MIC distribution for *S. aureus* was simulated using clinical isolate data from the SENTRY Surveillance Program (MIC_{90}, 0.25 mg/liter) (25). They found that at the $MIC_{90,}$ the predicted target attainment for bacteriostasis exceeded 90% for dosing regimens of either 100 mg or 200 mg intravenously (i.v.) twice daily on day 1 followed by 100 mg i.v. once on day 2 and 300 mg orally on day 3. These data support the FDA clinical breakpoint of $\leq$0.5 mg/liter for *S. aureus* and acute bacterial skin and skin structure infection (29).

These data build upon information from the SENTRY Program beginning in 2009 (12, 21–26) and demonstrate a consistency in the spectrum of omadacycline activity over time and across geographic regions. In addition, we document the excellent activity of omadacycline against key pathogens from the U.S. Food and Drug Administration indications of acute bacterial skin and skin structure infection and community-acquired bacterial pneumonia as well as those from the indication of urinary tract infection, for which clinical trials have recently completed. Surveillance is ongoing.

MATERIALS AND METHODS

Organisms. A total of 49,000 nonduplicate bacterial isolates were collected prospectively from 73 medical centers located in the United States (33 sites [23 states and all 9 United States Census

Divisions], 24,500 isolates) and Europe (40 sites [19 countries], 24,500 isolates) for the 2016 to 2018 SENTRY Antimicrobial Surveillance Program. European isolates were obtained from Belarus (1 site), Belgium (1 site), The Czech Republic (1 site), France (5 sites), Germany (5 sites), Greece (1 site) Hungary (1 site), Ireland (2 sites), Israel (1 site), Italy (4 sites), Poland (1 site), Portugal (1 site), Romania (1 site), Russia (3 sites), Slovenia (1 site), Spain (3 sites), Sweden (3 sites), Turkey (2 sites), and the United Kingdom (3 sites). All organisms were isolated from hospitalized patients with bloodstream infections (12,758 isolates), community-acquired respiratory tract infections (5,135 isolates), hospital-associated respiratory tract infections (10,225 isolates), acute bacterial skin and skin structure infections (11,013 isolates), intra-abdominal infections (2,829 isolates), complicated urinary tract infections (5,914 isolates), and other types of infections (1,126 isolates). Isolates were identified to the species level at each participating medical center, and isolate identity was confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), using standard microbiology methods and matrix-assisted laser desorption ionization–time of flight technology mass spectrometry (Bruker, Billerica, Massachusetts, United States) when necessary.

Antimicrobial susceptibility testing. MIC values were determined using the reference Clinical and Laboratory Standards Institute broth microdilution method (32). Quality control and results interpretation were performed in accordance with the Clinical and Laboratory Standards Institute M100 document (33) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) (34) guidelines. In the absence of omadacycline Clinical and Laboratory Standards Institute breakpoints, U.S. Food and Drug Administration breakpoints for acute bacterial skin and skin structure infection and community-acquired bacterial pneumonia (Table 1) were applied (35). *E. coli* and *K. pneumoniae* were grouped as being of extended-spectrum-β-lactamase phenotype based on the Clinical and Laboratory Standards Institute screening criteria for potential extended-spectrum-β-lactamase production, i.e., a MIC of $\geq$2 mg/liter for ceftazidime, ceftriaxone, or aztreonam (33). Although other β-lactamases, such as AmpC and KPC, may also produce an extended-spectrum-β-lactamase phenotype, these strains were grouped because they demonstrate resistance to various broad-spectrum β-lactam compounds. Carbapenem-resistant *Enterobacteriaceae* were defined as having an imipenem MIC value of $\geq$4 mg/liter. *E. cloacae* species complex isolates were classified as ceftazidime susceptible (MIC, $\leq$4 mg/liter) and ceftazidime nonsusceptible (MIC, $\geq$8 mg/liter). Other isolates with resistant phenotypes tested included methicillin-resistant *S. aureus* (oxacillin MIC, $\geq$4 mg/liter, or cefoxitin MIC, $\geq$8 mg/liter); vancomycin-nonsusceptible enterococci (MIC, $\geq$8 mg/liter); tetracycline-resistant *Enterobacteriaceae*, *A. baumannii*, staphylococci, and enterococci (all MIC values, $\geq$16 mg/liter) and *S. pneumoniae* (MIC, $\geq$4 mg/liter); and macrolide-resistant beta-hemolytic streptococci (erythromycin MIC, $\geq$1 mg/liter). Quality control strains were tested concurrently and included *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. All quality control results were within published ranges.

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