Activity of Omadacycline Tested against *Streptococcus pneumoniae* from a Global Surveillance Program (2014)

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ABSTRACT

Background: Omadacycline (OMC) is a new broad spectrum aminomethylcycline in late stage clinical development for both community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections, as oral and intravenous once daily formulations. It has excellent activity against respiratory tract pathogens and tetracycline (TET) resistant organisms. In this report the activity of OMC and comparator agents were tested against *Streptococcus pneumoniae* (SPN) selected from a 2014 global surveillance program and compared to the results of a 2010 surveillance program.

Methods: Approximately 50 PEN-S, 50 PEN-I and 50 PEN-R SPN isolates from Europe (EU) and the same numbers from North America (NA) were selected for susceptibility testing. Comparator agents were tested in validated dry-form panels by broth microdilution in CA-MHB supplemented with 2.5-5% lysed horse blood following Clinical and Laboratory Standards Institute (CLSI) M07-A10 (2015) methods. QC guidelines were those of CLSI. OMC was tested in dry-form panels in 2010 and in fresh-frozen medium in 2014.

Results: The OMC $MIC_{50/90}$ for SPN collected during 2014 was 0.06/0.06 µg/mL, respectively, similar to 2010 ($MIC_{50/90}$, 0.06/0.12 µg/mL). The MIC_{90} (0.06 µg/mL) was identical for the PEN-S, -I, –R, MDR (≥3 classes), and ceftriaxone non-susceptible (CRO-NS) subgroups. Identical OMC MIC_{90} values were exhibited by NA and EU SPN and NS subgroups (0.06 µg/mL for 2014 isolates; 0.12 µg/mL for 2010). In 2010 R in NA/EU for doxycycline (DOX) was 21.9/22.2%, for erythromycin (ERY, 37.5/24.1%), and for trimethoprim-sulfamethoxazole (SXT, 23.8/16.3%). For PEN-R SPN, R to DOX and TET in NA/EU in 2010 ranged from 57.9-64.1%, ERY from 73.8-93.4%, SXT from 54.0-76.1% and CRO from 1.6-8.6%. R to these agents in 2014 PEN-R SPN isolates was also elevated.

Conclusions: OMC was active against SPN including isolates which were MDR, PEN-R, CRO-NS, TET-NS, DOX-NS, LEV-NS or SXT-NS. The activity of OMC was similar between 2010 and 2014, and between NA and EU for either period. Resistance to DOX, ERY, SXT were high and co-resistance was common. The potent activity of OMC against SPN indicates that OMC merits further study in bacterial pneumonia especially where MDR may be a concern.

INTRODUCTION

Streptococcus pneumoniae is the most common bacterial pathogen causing pneumonia. Bacterial resistance occurring in *S. pneumoniae* is a serious problem to many of the commonly used oral agents. As antimicrobial resistance among *S. pneumoniae* extends beyond the β-lactams to include macrolides and fluoroquinolones, the choice of appropriate therapies becomes limited. Further, multidrug resistance leads to increased morbidity and mortality. Thus it is important to choose the appropriate initial empiric therapy.

Omadacycline (PTK 0796; [7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline]) is a novel tetracycline antibacterial agent, which is currently under clinical development for use as both an oral and intravenous formulation against acute bacterial skin and skin structure infections, community-acquired pneumonia, and urinary tract infections. Omadacycline has broad spectrum activity against Gram-positive, Gram-negative, atypical and anaerobic bacteria, including those with multi-drug resistance (MDR).

In this report, the activity of omadacycline and comparator agents were tested against *S. pneumoniae* selected from a 2014 global surveillance program and compared to the results of a 2010 surveillance program.

MATERIALS AND METHODS

Organism collection: A total of 51 penicillin-susceptible (Pen-S), 51 Pen-I and 51 Pen-R *S. pneumoniae* (S, ≤0.06; I, 0.12-1; R, ≥2 µg/mL) isolates from 2014 global surveillance program from Europe and 50 Pen-S, 50 Pen-I and 51 Pen-R *S. pneumoniae* isolates from North America (2014 global Surveillance; n= 304) were selected for susceptibility testing. The 2014 data were compared to the results from testing 1,834 *S. pneumoniae* from a 2010 global surveillance program. MDR *S. pneumoniae* were defined as R ≥3 antimicrobial classes.

Susceptibility testing: Comparator agents were tested in validated dry-form panels manufactured by Thermo Fisher Scientific Inc. (Cleveland, Ohio, USA) by broth microdilution in cation-adjusted Mueller-Hinton broth with 2.5-5% lysed horse blood following Clinical and Laboratory Standards Institute (CLSI) methods. Omadacycline was tested in dry-form panels in 2010 and panels with fresh frozen medium made at JMI Laboratories (North Liberty, Iowa, USA) for testing 2014 isolates. Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures (M07-A10, M100-S25). The QC strain tested was *S. pneumoniae* ATCC 49619 (M100-S25). All QC results were within published ranges. Interpretive criteria used were those of CLSI (M07-A10, M100-S25) and EUCAST (2015).

RESULTS

Omadacycline activity: 2010 compared to 2014

- The MIC distributions for all *S. pneumoniae* tested in 2014 and 2010 showed that the vast majority of omadacycline MIC values were at 0.03 and 0.06 µg/mL (96.7% in 2014; 82.3% in 2010; **Table 1**).
- The majority of omadacycline MIC values for all subgroups (Pen-S, -I, -R, MDR, and ceftriaxone non-susceptible [CRO-NS]) also resided at 0.03 and 0.06 µg/mL indicating that omadacycline activity did not differ among the various subgroups. The MIC_{50} and MIC_{90} for omadacycline for *S. pneumoniae* collected during 2014 was 0.06 and 0.06 µg/mL, respectively (**Table 1**). MIC values for omadacycline for 2014 isolates ranged from ≤0.015 - 0.12 µg/mL (**Table 1**).
- The omadacycline MIC_{90} (0.06 µg/mL) for 2014 isolates was identical for the Pen-S, -I, -R, MDR, and CRO-NS subgroups (**Table 1**). The omadacycline MIC_{90} when tested against S. *pneumoniae* isolates from 2010 was 0.12 µg/mL and the MIC_{90} did not differ for the Pen-S, -I, -R, MDR, or CRO-NS subgroups (**Table 1**).

Omadacycline activity: Europe compared to North America

- Identical omadacycline MIC_{90} values were exhibited by North American and European *S. pneumoniae* and the non-susceptible (NS) subgroups listed above (0.06 µg/mL for 2014 isolates; 0.12 µg/mL for 2010; **Table 1**). The majority of omadacycline MIC values for isolates from all subgroups from Europe (**Table 1**) and North America (**Table 1**), regardless of year (2010 or 2014) were at 0.03 and 0.06 µg/mL.

Susceptibility: 2010 compared to 2014

- For the 2014 *S. pneumoniae* isolates, tigecycline susceptibility was 100.0%; for 2010 it was 99.8% (**Table 2**). Levofloxacin susceptibility was 97.4-99.3% for 2010 and 2014 (**Table 2**).
- For Pen-R *S. pneumoniae*, susceptibility to doxycycline ranged from 33.3-38.2%, erythromycin susceptibility from 12.7-15.5%, trimethoprim-sulfamethoxazole from 25.4-26.5% and CRO from 57.8-62.1 (data not shown). Levofloxacin (98.0-98.8% susceptible) and tigecycline (99.7-100.0% susceptible) exhibited a high level of susceptibility (data not shown).
- For 2010 and 2014, susceptibility to tetracycline and doxycycline was 21.4-21.9% and 20.3-22.6% in MDR *S. pneumoniae*, CRO-NS was 29.5-32.8%, erythromycin-NS was 92.7-95.6%, while levofloxacin-NS was 2.1-4.4% (**Table 2**). Levofloxacin and tigecycline exhibited a high level of susceptibility (**Table 2**).
- Levofloxacin and tigecycline exhibited a high level of susceptibility against CRO-NS *S. pneumoniae* for years 2010 and 2014 (levofloxacin, 98.4-100.0% susceptible; tigecycline, 98.4-100.0% susceptible; **Table 2**).

Susceptibility: Europe compared to North America

- Tigecycline (Europe, 99.9-100.0% susceptible; North America, 99.8-00.0% susceptible) and levofloxacin (Europe, 97.4-99.3% susceptible; North America, 97.4-99.3% susceptible) exhibited a high level of susceptibility (**Table 3**).
- For penicillin-R *S. pneumoniae*, susceptibility to doxycycline in Europe ranged from 33.3-41.3%, erythromycin susceptibility from 19.6-26.2%, trimethoprim-sulfamethoxazole from 25.5-42.9% and ceftriaxone from 60.8-70.6% (data not shown). For North America, highly compromised levels of susceptibility were noted for the above agents as well (data not shown). Levofloxacin and tigecycline exhibited a high level of susceptibility in Europe (levofloxacin, 97.6-98.0% susceptible; tigecycline,100.0% susceptible) and North America (levofloxacin, 98.0-99.5% susceptible; tigecycline, 99.5-100.0% susceptible; data not shown).
- For MDR *S. pneumoniae*, susceptibility to doxycycline in Europe ranged from 14.0-19.7%, erythromycin susceptibility from 8.5-8.9%, trimethoprim-sulfamethoxazole from 21.1-41.4% and ceftriaxone from 69.0-77.1% (non-meningitis breakpoints; **Table 3**). For North America, highly compromised levels of susceptibility were noted for the above agents (**Table 3**). Tigecycline exhibited a high level of susceptibility in Europe (100.0% susceptible; **Table 3**) and levofloxacin was somewhat compromised (94.4-96.2% susceptible). In North America, levofloxacin (97.0-98.9% susceptible) and tigecycline (99.3-100.0% susceptible) exhibited high levels of susceptibility (**Table 3**).
- For CRO-NS *S. pneumoniae*, susceptibility to doxycycline in Europe ranged from 31.8-40.5%, erythromycin susceptibility from 16.2-18.2%, and trimethoprim-sulfamethoxazole from 9.1-29.7% (**Table 3**). For North America, highly compromised levels of susceptibility were noted for the above agents as well (**Table 3**). Levofloxacin and tigecycline exhibited a high level of susceptibility in Europe (levofloxacin, 97.3-100.0% susceptible; tigecycline,100.0% susceptible; **Table 3**) and North America (levofloxacin, 98.9-100.0% susceptible; tigecycline, 97.8-100.0% susceptible; **Table 3**).

Table 3. Activity of omadacycline and comparator antimicrobial agents when tested against *S. pneumoniae* by region (2014 vs. 2010).

Organism group (no. tested)/ antimicrobial agent	North America								Europe							
	2014				2010				2014				2010			
	CLSI[a] %S	EUCAST[a] %S	$MIC_{50/90}$	MIC Range	CLSI[a] %S	EUCAST[a] %S	$MIC_{50/90}$	MIC Range	CLSI[a] %S	EUCAST[a] %S	$MIC_{50/90}$	MIC Range	CLSI[a] %S	EUCAST[a] %S	$MIC_{50/90}$	MIC Range
S. pneumoniae			(151)				(1,028)				(153)				(806)	
Omadacycline	-	-	0.06/0.06	0.015 — 0.12	-	-	0.06/0.12	≤0.015 — 0.5	-	-	0.06/0.06	0.015 — 0.12	-	-	0.03/0.12	≤0.015 — 0.5
Tigecycline	100.0[b]	-	0.03/0.03	≤0.015 — 0.06	99.8[b]	-	≤0.03/0.06	≤0.03 — 0.12	100.0[b]	-	0.03/0.06	≤0.015 — 0.06	99.9[b]	-	≤0.03/≤0.03	≤0.03 — 0.12
Doxycycline	64.9	65.6	0.12/8	≤0.06 — >8	75.4	78.5	0.25/8	≤0.06 — >8	60.1	60.8	0.12/8	≤0.06 — >8	75.6	78.4	0.12/8	≤0.06 — >8
Tetracycline	66.2	66.2	0.25/>16	0.12 — >16	78.5	78.5	0.5/>8	≤0.25 — >8	60.1	60.1	0.25/>16	0.12 — >16	77.2	77.2	0.5/>8	≤0.25 — >8
Amoxicillin-clavulanate	70.2[c]	-	≤1/8	≤1 — >8	84.2[c]	-	≤1/8	≤1 — >8	81.7[c]	-	≤1/8	≤1 — >8	93.5[c]	-	≤1/2	≤1 — 8
Ceftriaxone	57.6[d]	57.6	0.25/2	≤0.06 — 4	79.6[d]	79.6	≤0.06/1	≤0.06 — 8	58.8[d]	58.8	0.25/2	≤0.06 — 8	82.8[d]	82.8	≤0.06/1	≤0.06 — 4
	84.8[c]	-			91.1[c]	-			85.6[c]	-			95.4[c]	-		
Clindamycin	68.9	69.5	≤0.25/>2	≤0.25 — >2	80.8	81.2	≤0.25/>1	≤0.25 — >1	63.4	65.4	≤0.25/>2	≤0.25 — >2	82.4	83.1	≤0.25/>1	≤0.25 — >1
Erythromycin	38.4	38.4	4/>16	≤0.12 — >16	61.6	61.6	≤0.06/>8	≤0.06 — >8	53.6	53.6	≤0.12/>16	≤0.12 — >16	75.6	75.6	≤0.06/>8	≤0.06 — >8
Levofloxacin	97.4	97.4	1/1	0.5 — >4	99.3	99.3	1/1	≤0.5 — >4	97.4	97.4	1/1	0.5 — >4	99.3	99.3	1/1	≤0.5 — >4
Penicillin	33.1[e]	33.1[d]	0.25/4	≤0.06 — 8	59.4[e]	59.4[d]	≤0.03/4	≤0.03 — >4	33.3[e]	33.3[d]	0.25/2	≤0.06 — 8	73.9[e]	73.9[d]	≤0.03/2	≤0.03 — >4
	33.1[f]	33.1[c]			59.4[f]	59.4[c]			33.3[f]	33.3[c]			73.9[f]	73.9[c]		
	81.5[g]	-			86.8[g]	-			90.8[g]	-			94.7[g]	-		
TMP/SMX[h]	57.0	63.6	≤0.5/>4	≤0.5 — >4	68.3	72.7	≤0.5/>4	≤0.5 — >4	49.7	54.2	1/>4	≤0.5 — >4	77.0	82.3	≤0.5/4	≤0.5 — >4
MDR			(66)				(277)				(71)				(157)	
Omadacycline	-	-	0.06/0.06	0.015 — 0.12	-	-	0.06/0.12	≤0.015 — 0.25	-	-	0.06/0.06	0.03 — 0.12	-	-	0.06/0.12	≤0.015 — 0.5
Tigecycline	100.0	-	0.03/0.06	≤0.015 — 0.06	99.3	-	≤0.03/0.06	≤0.03 — 0.12	100.0	-	0.03/0.06	≤0.015 — 0.06	100.0	-	≤0.03/0.06	≤0.03 — 0.06
Doxycycline	24.2	25.8	4/>8	≤0.06 — >8	23.8	25.6	4/>8	≤0.06 — >8	19.7	19.7	8/>8	0.12 — >8	14.0	15.9	4/>8	≤0.06 — >8
Tetracycline	25.8	25.8	>16/>16	0.12 — >16	25.3	25.3	>8/>8	≤0.25 — >8	18.3	18.3	>16/>16	0.12 — >16	14.6	14.6	>8/>8	≤0.25 — >8
Amoxicillin-clavulanate	42.4[c]	-	4/8	≤1 — >8	47.7[c]	-	4/8	≤1 — >8	64.8[c]	-	2/8	≤1 — >8	73.9[c]	-	2/8	≤1 — 8
Ceftriaxone	27.3[d]	27.3	1/2	≤0.06 — 4	40.1[d]	40.1	1/2	≤0.06 — 8	25.4[d]	25.4	1/2	≤0.06 — 8	33.1[d]	33.1	1/2	≤0.06 — 4
	65.2[c]	-			66.8[c]	-			69.0[c]	-			77.1	-		
Clindamycin	34.8	34.8	>2/>2	≤0.25 — >2	33.6	34.7	>1/>1	≤0.25 — >1	22.5	26.8	>2/>2	≤0.25 — >2	28.0	30.6	>1/>1	≤0.25 — >1
Erythromycin	1.5	1.5	>16/>16	0.25 — >16	0.7	0.7	>8/>8	≤0.06 — >8	8.5	8.5	>16/>16	≤0.12 — >16	8.9	8.9	>8/>8	≤0.06 — >8
Levofloxacin	97.0	97.0	1/1	0.5 — >4	98.9	98.9	1/1	≤0.5 — >4	94.4	94.4	1/1	0.5 — >4	96.2	96.2	1/1	≤0.5 — >4
Penicillin	1.5[e]	1.5[d]	2/4	≤0.06 — 8	0.0[e]	0.0[d]	2/4	0.12 — >4	4.2[e]	4.2[d]	2/4	≤0.06 — 8	7.0[e]	7.0[d]	2/4	≤0.03 — >4
	1.5[f]	1.5[c]			0.0[f]	0.0[c]			4.2[f]	4.2[c]			7.0[f]	7.0[c]		
	57.6[g]	-			52.0[g]	-			80.3[g]	-			74.5[g]	-		
TMP/SMX[h]	16.7	22.7	4/>4	≤0.5 — >4	13.4	19.9	4/>4	≤0.5 — >4	21.1	29.6	4/>4	≤0.5 — >4	27.4	41.4	4/>4	≤0.5 — >4
Ceftriaxone-NS (MIC, ≥ 2µg/mL)			(23)				(92)				(22)				(37)	
Omadacycline	-	-	0.06/0.06	0.03 — 0.06	-	-	0.06/0.12	≤0.015 — 0.25	-	-	0.06/0.06	0.03 — 0.06	-	-	0.06/0.12	0.03 — 0.25
Tigecycline	100.0	-	0.03/0.06	≤0.015 — 0.06	97.8	-	≤0.03/≤0.03	≤0.03 — 0.12	100.0	-	0.03/0.06	≤0.015 — 0.06	100.0	-	≤0.03/0.06	≤0.03 — 0.06
Doxycycline	17.4	17.4	4/8	0.12 — 8	15.2	16.3	4/8	≤0.06 — >8	31.8	31.8	4/8	0.12 — >8	37.8	40.5	4/8	0.12 — 8
Tetracycline	17.4	17.4	>16/>16	0.25 — >16	17.4	17.4	>8/>8	≤0.25 — >8	31.8	31.8	>16/>16	0.25 — >16	40.5	40.5	>8/>8	≤0.25 — >8
Amoxicillin-clavulanate	0.0[c]	-	8/8	4 — 8	4.3[c]	-	8/8	≤1 — >8	36.4[c]	-	8/>8	≤1 — >8	54.[c]	-	2/8	2 — 8
Ceftriaxone	0.0[c]	0.0	2/2	2 — 4	0.0[c]	0.0	2/8	2 — 8	0.0[c]	0.0	2/8	2 — 8	0.0[c]	0.0	2/2	2 — 4
	0.0[d]	-			0.0[d]	-			0.0[d]	-			0.0[d]	-		
Clindamycin	17.4	17.4	>2/>2	≤0.25 — >2	16.3	17.4	>1/>1	≤0.25 — >1	18.2	18.2	>2/>2	≤0.25 — >2	35.1	35.1	>/>1	≤0.25 — >1
Erythromycin	0.0	0.0	>16/>16	2 — >16	0.0	0.0	>8/>8	4 — >8	18.2	18.2	>16/>16	≤0.12 — >16	16.2	16.2	>8/>8	≤0.06 — >8
Levofloxacin	100.0	100.0	1/1	1 — 1	98.9	98.9	1/1	≤0.5 — 4	100.0	100.0	1/1	0.5 — 1	97.3	97.3	1/1	≤0.5 — >4
Penicillin	0.0[e]	0.0[d]	4/4	2 — 8	0.0[e]	0.0[d]	4/4	0.25 — >4	0.0[e]	0.0[d]	2/4	1 — 8	0.0[e]	0.0[d]	4/4	2 — >4
	0.0[f]	0.0[c]			0.0[f]	0.0[c]			0.0[f]	0.0[c]			0.0[f]	0.0[c]		
	13.0[g]	-			3.3[g]	-			50.0[g]	-			32.4[g]	-		
TMP/SMX	0.0	0.0	4/>4	4 — >4	1.1	1.1	4/>4	≤0.5 — >4	9.1	13.6	>4/>4	≤0.5 — >4	16.2	29.7	4/>4	≤0.5 — >4

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Breakpoints from FDA Package Insert revised 12/2014.
c. Using Non Meningitis breakpoints.
d. Using Meningitis breakpoints.
e. Using oral breakpoints.
f. Using Parenteral, Meningitis breakpoints.
g. Using Parenteral, Non Meningitis breakpoints.
h. Trimethoprim-sulfamethoxazole.

Table 1. Cumulative frequency distribution of omadacycline MIC results for *S. pneumoniae* isolates.

Organism/region	Year	No. of Isolates	MIC in µg/mL: ≤0.015	0.03	0.06	0.12	0.25	0.5	MIC_{50}	MIC_{90}
S. pneumoniae										
NA + EU	2014	304	6 (2.0)	123 (42.4)	171 (98.7)	4 (100.0)	--	--	0.06	0.06
NA + EU	2010	1834	77 (4.2)	795 (47.5)	715 (86.5)	182 (96.5)	51 (99.2)	14 (100.0)	0.06	0.12
NA	2014	151	4 (2.6)	60 (42.4)	85 (98.7)	2 (100.0)	--	--	0.06	0.06
NA	2010	1028	34 (3.3)	400 (42.2)	482 (89.1)	84 (97.3)	25 (99.7)	3 (100.0)	0.06	0.12
EU	2014	153	2 (1.3)	63 (42.5)	86 (98.7)	2 (100.0)	--	--	0.06	0.06
EU	2010	806	43 (5.3)	395 (54.3)	233 (83.3)	98 (95.4)	26 (98.6)	11 (100.0)	0.03	0.12
Penicillin-S										
NA + EU	2014	101	3 (3.0)	59 (61.4)	38 (99.0)	1 (100.0)	--	--	0.03	0.06
NA + EU	2010	1207	61 (5.1)	588 (53.8)	422 (88.7)	96 (96.7)	31 (99.3)	9 (100.0)	0.03	0.12
NA	2014	50	2 (4.0)	27 (58.0)	20 (98.0)	1 (100.0)	--	--	0.03	0.06
NA	2010	611	25 (4.1)	268 (48.0)	263 (91.0)	38 (97.2)	14 (99.5)	3 (100.0)	0.06	0.06
EU	2014	51	1 (2.0)	32 (64.7)	18 (100.0)	--	--	--	0.03	0.06
EU	2010	596	36 (6.0)	320 (59.7)	159 (86.4)	58 (96.1)	17 (99.0)	6 (100.0)	0.03	0.12
Penicillin-I										
NA + EU	2014	101	3 (3.0)	38 (40.6)	58 (98.0)	2 (100.0)	--	--	0.06	0.06
NA + EU	2010	292	7 (2.4)	114 (41.4)	126 (84.6)	36 (96.9)	8 (99.7)	1 (100.0)	0.06	0.12
NA	2014	50	2 (4.0)	20 (44.0)	28 (100.0)	--	--	--	0.06	0.06
NA	2010	208	5 (2.4)	76 (38.9)	99 (86.5)	24 (98.1)	4 (100.0)	--	0.06	0.12
EU	2014	51	1 (2.0)	18 (37.3)	30 (96.1)	2 (100.0)	--	--	0.06	0.06
EU	2010	84	2 (2.4)	38 (47.6)	27 (79.8)	12 (94.0)	4 (98.8)	1 (100.0)	0.06	0.12
Penicillin-R										
NA + EU	2014	102	--	26 (25.5)	75 (99.0)	1 (100.0)	--	--	0.06	0.06
NA + EU	2010	335	9 (2.7)	93 (30.4)	167 (80.3)	50 (95.2)	12 (98.8)	4 (100.0)	0.06	0.12
NA	2014	51	--	13 (25.5)	37 (98.0)	1 (100.0)	--	--	0.06	0.06
NA	2010	209	4 (1.9)	56 (28.7)	120 (86.1)	22 (96.7)	7 (100.0)	--	0.06	0.12
EU	2014	51	--	13 (25.5)	38 (100.0)	--	--	--	0.06	0.06
EU	2010	126	5 (4.0)	37 (33.3)	47 (70.6)	28 (92.9)	5 (96.8)	4 (100.0)	0.06	0.12
MDR										
NA + EU	2014	137	2 (1.5)	31 (24.1)	101 (97.8)	3 (100.0)	--	--	0.06	0.06
NA + EU	2010	434	13 (3.0)	130 (32.9)	206 (80.4)	66 (95.6)	16 (99.3)	3 (100.0)	0.06	0.12
NA	2014	66	2 (3.0)	13 (22.7)	50 (98.5)	1 (100.0)	--	--	0.06	0.06
NA	2010	277	6 (2.2)	83 (32.1)	146 (84.8)	33 (96.8)	9 (100.0)	--	0.06	0.12
EU	2014	71	--	18 (25.4)	51 (97.2)	2 (100.0)	--	--	0.06	0.06
EU	2010	157	7 (4.5)	47 (34.4)	60 (72.6)	33 (93.6)	7 (98.1)	3 (100.0)	0.06	0.12
Ceftriaxone-NS (MIC, ≥2 µg/mL)										
NA + EU	2014	45	--	11 (24.4)	34 (100.0)	--	--	--	0.06	0.06
NA + EU	2010	129	2 (1.6)	38 (31.0)	70 (85.3)	14 (96.1)	5 (100.0)	--	0.06	0.12
NA	2014	23	0 (0.0)	6 (26.1)	17 (100.0)	--	--	--	0.06	0.06
NA	2010	92	2 (2.2)	29 (33.7)	51 (89.1)	7 (96.7)	3 (100.0)	--	0.06	0.12
EU	2014	22	--	5 (22.7)	17 (100.0)	--	--	--	0.06	0.06
EU	2010	37	--	9 (24.3)	19 (75.7)	7 (94.6)	2 (100.0)	--	0.06	0.12

Abbreviations: NA = North America; EU = Europe; S = susceptible; I = intermediate; R = resistant; NS = non-susceptible.

Table 2. Activity of omadacycline and comparator antimicrobial agents when tested against combined *S. pneumoniae* (2014 vs. 2010).

Organism group (no. tested)/ antimicrobial agent	2014						2010					
	CLSI[a]		EUCAST[a]		µg/mL		CLSI[a]		EUCAST[a]		µg/mL	
	%S	%R	%S	%R	$MIC_{50/90}$	MIC range	%S	%R	%S	%R	$MIC_{50/90}$	MIC range
S. pneumoniae				(304)						(1,834)		
Omadacycline	-	-	-	-	0.06/0.06	0.015 — 0.12	-	-	-	-	0.06/0.12	≤0.015 — 0.5
Tigecycline	100.0	-[b]	-	-	0.03/0.06	≤0.015 — 0.06	99.8	-[b]	-	-	≤0.03/≤0.03	≤0.03 — 0.12
Doxycycline	62.5	37.2	63.2	35.5	0.12/8	≤0.06 — >8	75.5	22.0	78.5	20.3	0.25/8	≤0.06 — >8
Tetracycline	63.2	36.5	63.2	36.5	0.25/>16	0.12 — >16	77.9	22.0	77.9	22.0	0.5/>8	≤0.25 — >8
Amoxicillin-clavulanate	76.0	15.8[c]	-	-	≤1/8	≤1 — >8	88.3	8.4[c]	-	-	≤1/4	≤1 — >8
Ceftriaxone	58.2	14.8[d]	58.2	2.0	0.25/2	≤0.06 — 8	81.0	7.0[d]	81.0	1.1	≤0.06/1	≤0.06 — 8
	85.2	2.0[c]	-	-			93.0	1.1[c]	-	-		
Clindamycin	66.1	32.6	67.4	32.6	≤0.25/>2	≤0.25 — >2	81.5	17.9	82.1	17.9	≤0.25/>1	≤0.25 — >1
Erythromycin	46.1	52.3	46.1	52.3	2/>16	≤0.12 — >16	67.7	31.6	67.7	31.6	≤0.06/>8	≤0.06 — >8
Levofloxacin	97.4	2.3	97.4	2.6	1/1	0.5 — >4	99.3	0.7	99.3	0.7	1/1	≤0.5 — >4
Penicillin	33.2	33.6[e]	33.2	66.8[d]	0.25/4	≤0.06 — 8	65.8	18.3[e]	65.8	34.2[d]	≤0.03/2	≤0.03 — >4
	33.2	66.8[f]	33.2	13.8[c]			65.8	34.2[f]	65.8	9.8[c]		
	86.2	1.0[g]	-	-			90.2	0.4[g]	-	-		
TMP/SMX[h]	53.3	38.5	58.9	38.5	≤0.5/>4	≤0.5 — >4	72.1	20.5	76.9	20.5	≤0.5/4	≤0.5 — >4
MDR				(137)						(434)		
Omadacycline	-	-	-	-	0.06/0.06	0.015 — 0.12	-	-	-	-	0.06/0.12	≤0.015 — 0.5
Tigecycline	100.0	-[b]	-	-	0.03/0.06	≤0.015 — 0.06	99.5	-[b]	-	-	≤0.03/0.06	≤0.03 — 0.12
Doxycycline	21.9	78.1	22.6	75.9	8/>8	≤0.06 — >8	20.3	78.6	22.1	75.6	4/>8	≤0.06 — >8
Tetracycline	21.9	77.4	21.9	77.4	>16/>16	0.12 — >16	21.4	78.1	21.4	78.1	>8/>8	≤0.25 — >8
Amoxicillin-clavulanate	54.0	33.6[c]	-	-	2/8	≤1 — >8	57.1	34.6[c]	-	-	2/8	≤1 — >8
Ceftriaxone	26.3	32.8[d]	26.3	4.4	1/2	≤0.06 — 8	37.6	29.5[d]	37.6	4.6	1/2	≤0.06 — 8
	67.2	4.4[c]	-	-			70.5	4.6[c]	-	-		
Clindamycin	28.5	69.3	30.7	69.3	>2/>2	≤0.25 — >2	31.6	66.8	33.2	66.8	>1/>1	≤0.25 — >1
Erythromycin	5.1	92.7	5.1	92.7	>16/>16	≤0.12 — >16	3.7	95.6	3.7	95.6	>8/>8	≤0.06 — >8
Levofloxacin	95.6	4.4	95.6	4.4	1/1	0.5 — >4	97.9	2.1	97.9	2.1	1/1	≤0.5 — >4
Penicillin	2.9	61.3[e]	2.9	97.1[d]	2/4	≤0.06 — 8	2.5	61.3[e]	2.5	97.5[d]	2/4	≤0.03 — >4
	2.9	97.1[f]	2.9	30.7[c]			2.5	97.5[f]	2.5	39.9[c]		
	69.3	2.2[g]	-	-			60.1	1.6[g]	-	-		
TMP/SMX	19.0	81.0	26.3	69.3	4/>4	≤0.5 — >4	18.4	81.6	27.6	66.6	4/>4	≤0.5 — >4
Ceftriaxone-NS (MIC, ≥2 µg/mL)				(45)						(129)		
Omadacycline	-	-	-	-	0.06/0.06	0.03 — 0.06	-	-	-	-	0.06/0.12	≤0.015 — 0.25
Tigecycline	100.0	-[b]	-	-	0.03/0.06	≤0.015 — 0.06	98.4	-[b]	-	-	≤0.03/0.06	≤0.03 — 0.12
Doxycycline	24.4	75.6	24.4	75.6	4/8	0.12 — >8	21.7	76.7	23.3	73.6	4/8	≤0.06 — >8
Tetracycline	24.4	75.6	24.4	75.6	>16/>16	0.25 — >16	24.0	76.0	24.0	76.0	>8/>8	≤0.25 — >8
Amoxicillin-clavulanate	17.8	73.3[c]	-	-	8/8	≤1 — >8	18.6	75.2[c]	-	-	8	≤1 — >8
Ceftriaxone	0.0	100.0[d]	0.0	13.3	2/4	2 — 8	0.0	100.0[d]	0.0	16.3	2/4	2 — 8
	0.0	13.3[c]	-	-			0.0	16.3[c]	-	-		
Clindamycin	17.8	82.2	17.8	82.2	>2/>2	≤0.25 — >2	21.7	77.5	22.5	77.5	>1/>1	≤0.25 — >1
Erythromycin	8.9	91.1	8.9	91.1	>16/>16	≤0.12 — >16	4.7	95.3	4.7	95.3	>8/>8	≤0.06 — >8
Levofloxacin	100.0	0.0	100.0	0.0	1/1	0.5 — 1	98.4	0.8	98.4	1.6	1/1	≤0.5 — >4
Penicillin	0.0	95.6[e]	0.0	100.0[d]	4/4	1 — 8	0.0	98.4[e]	0.0	100.0[d]	4/4	0.25 — >4
	0.0	100.0[f]	0.0	68.9[c]			0.0	100.0[f]	0.0	88.4[c]		
	31.1	6.7[g]	-	-			11.6	5.4[g]	-	-		
TMP/SMX	4.4	93.3	6.7	93.3	>4/>4	≤0.5 — >4	5.4	89.9	9.3	89.9	4/>4	≤0.5 — >4

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Breakpoints from FDA Package Insert revised 12/2014.
c. Using Non Meningitis breakpoints.
d. Using Meningitis breakpoints.
e. Using oral breakpoints.
f. Using Parenteral, Meningitis breakpoints.
g. Using Parenteral, Non Meningitis breakpoints.
h. Trimethoprim-sulfamethoxazole.

CONCLUSIONS

- Omadacycline was highly active against *S. pneumoniae* (MIC_{90}, 0.06-0.12 µg/mL).
- The activity of omadacycline was similar for the North American and European regions in both 2014 and 2010.
- Omadacycline was highly active against ceftriaxone non-susceptible, Pen-R, macrolide-R, quinolone-R and MDR subgroups of *S. pneumoniae*.
- *S. pneumoniae* resistance rates to doxycycline, azithromycin, and TMP/SMX continue to be high for both North America and Europe.

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