Antimicrobial Activity of PTK 0796 (Omadacycline) and Comparator Agents Against Contemporary Pathogens Commonly Associated with Community-Acquired Respiratory Tract Infections Collected During 2011 from the European Union

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Abstract

Objectives: To determine the activity of PTK 0796 (omadacycline) and comparator agents against recent (2011) *Streptococcus pneumoniae* (SPN), *Haemophilus influenzae* (HI), and *Moraxella catarrhalis* (MCAT) isolated in the European Union (EU). PTK 0796 is a novel aminomethylcycline which is currently under clinical development for both intravenous and oral formulations. It has excellent activity against pathogens from the respiratory tract and overcomes tetracycline resistance.

Methods: Susceptibility (S) testing for omadacycline and commonly used antimicrobials was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology on a total of 1,024 isolates in 2011 from medical centers in the SENTRY Antimicrobial Surveillance Program platform in the EU. S interpretations were performed using CLSI and EUCAST guidelines.

Results: PTK 0796 was very active against SPN independent of S to penicillin (PEN; $MIC_{50/90}$, 0.06/0.06 mg/L for PEN-S and -resistant [R] strains). PTK 0796 was 16-fold more active than levofloxacin ($MIC_{50/90}$, 1/1 mg/L) and ceftriaxone (MIC_{90}, 1 mg/L) against SPN. SPN showed high R rates to erythromycin (S, 60.8%) and tetracycline (S, 69.3% CLSI/68.8% EUCAST) even though all isolates had PTK 0796 MIC values ≤0.25 mg/L. PTK 0796 against HI (13.9% beta-lactamase positive) and MCAT (98.5% beta-lactamase positive) exhibited low MIC values (Table) independent of beta-lactamase production.

Agent		Organism (no. tested) SPN (600)	HI (359)	MCAT (65)
PTK 0796	$MIC_{50/90}$[a]	0.06 / 0.06	0.5 / 1	0.12 / 0.12
Ceftriaxone	$MIC_{50/90}$[a]	≤0.06 / 1	≤0.06 / ≤0.06	0.25 / 0.5
	%S[b]	92.0 (73.3)	100.0 (100.0)	100.0 (98.5)
Erythromycin	$MIC_{50/90}$[a]	≤0.12 / >16	NT[e]	NT[e]
	%S[b]	60.8 (60.8)	NT[e]	NT[e]
Levofloxacin	$MIC_{50/90}$[a]	1 / 1	≤0.12 / ≤0.12	≤0.12 / ≤0.12
	%S[b]	98.7 (98.7)	100.0 (100.0)	100.0 (100.0)
Tigecycline	$MIC_{50/90}$[a]	≤0.03/0.06	0.25/0.5	0.06/0.06
	%S[c]	99.7 (IE)[d]	87.7 (IE)[d]	- (IE)[d]

a. MIC values in mg/L.
b. Categorized by CLSI breakpoints and in parentheses by EUCAST breakpoints.
c. Categorized by USA drug package insert breakpoints and in parentheses by EUCAST breakpoints.
d. IE= insufficient evidence to determine breakpoint.
e. NT= not tested.

Conclusions: PTK 0796 was very active against SPN, regardless of PEN-S status, with $MIC_{50/90}$ value of 0.06/0.06 mg/L and no MIC value greater than 0.25 mg/L. PTK 0796 was also very active against *M. catarrhalis* ($MIC_{50/90}$, 0.12/0.12 mg/L) and *H. influenzae* ($MIC_{50/90}$, 0.5/1 mg/L) with activity independent of beta-lactamase status.

Introduction

PTK 0796 (omadacycline) is a novel antibacterial agent of the tetracycline family, which is currently under clinical development as both intravenous and oral formulations. This new tetracycline has shown broad-spectrum activity against a wide range of bacteria, including Gram-positive and -negative strains. It has excellent activity against pathogens from respiratory tract infections and overcomes tetracycline resistance in these bacteria.

The aims of this study were to evaluate the *in vitro* activity of PTK 0796 tested against recent (2011) *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* clinical isolates collected from the European Union (EU) countries, Turkey, and Israel; and to monitor the activity of PTK 0796 and comparator agents tested against contemporary clinical isolates from this region as part of an international surveillance testing program.

Materials and Methods

Bacterial isolates. A total of 1,024 clinical isolates were collected during 2011 from 22 medical centers located in 9 European countries, Turkey and Israel. The number of isolates, percent of total collection, and the number of medical centers monitored in each country were: Belgium (38; 3.6%; one medical center), France (370; 35.2%; five medical centers), Germany (51; 4.9%; two medical centers), Greece (9; 0.9%; one medical center), Ireland (142; 13.5%; two medical centers), Israel (9; 0.9%; one medical center), Italy (40; 3.8%; two medical centers), Spain (82, 7.8%; two medical centers), Sweden (157; 14.9%; two medical centers), Turkey (92; 8.8%; two medical centers), and the United Kingdom (UK; 61; 5.8%; two medical centers). The collection of clinical isolates consisted of 600 *S. pneumoniae*, 359 *H. influenzae*, and 65 *M. catarrhalis*.

Susceptibility testing. Susceptibility testing was performed by reference broth microdilution method per Clinical and Laboratory Standards Institute (CLSI; M07-A9; 2012) using validated dry-form panels produced by ThermoFisher Inc, formerly TREK Diagnostics (Cleveland, Ohio, USA) for *S. pneumoniae;* frozen-form reference panels were used for *H. influenzae* and *M. catarrhalis*. Media used were cation-adjusted Mueller-Hinton broth with 2.5-5% lysed horse blood supplement for testing of streptococci, and *Haemophilus* Test Medium (HTM) for testing *H. influenzae*. HTM medium for the frozen-form panels was fresh; frozen <12 hours after preparation. Interpretive breakpoint criteria for comparator agents were those published in CLSI (M100-S22; 2012) and EUCAST (2012), except for tigecycline where the USA Food and Drug Administration (USA-FDA) breakpoints were applied (Tygacil Package Insert, 2010).

Methods-continued

Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S22, 2012) quality control (QC) strains: *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247. MIC ranges for PTK 0796 and comparator agents tested against ATCC QC strains were those published in the CLSI M100-S22 (2012). Susceptibility testing as described above was performed by JMI Laboratories (North Liberty, Iowa, USA) using current CLSI (M07-A9; 2012) and Good Laboratory Practice (GLP) quality assurance practices.

Results

- 1,024 respiratory isolates (600 *S. pneumoniae,* 359, *H. influenzae,* and 65 *M. catarrhalis*) were collected from 22 medical centers in 11 countries during 2011.
- PTK 0796 demonstrated potent activity against *S. pneumoniae* ($MIC_{50/90}$, 0.06/0.06 mg/L) including penicillin-intermediate and penicillin-resistant subgroups (Table 1).
- Total of 94.3/99.5% of 600 *S. pneumoniae* had PTK 0796 MIC values of ≤0.06/0.12 mg/L, respectively with the highest PTK 0796 MIC value observed at 0.25 mg/L (Table 1).
- PTK 0796 was 16-fold more active than levofloxacin ($MIC_{50/90}$, 1/1 mg/L) and ceftriaxone (MIC_{90}, 1 mg/L; Table 2) against *S. pneumoniae.*
- *S. pneumoniae* exhibited high rates of resistance against erythromycin (39.0% resistant) and tetracycline (30.2/30.7% resistant) based on CLSI and EUCAST interpretive criteria.
- PTK had potent activity against *H. influenzae* with MIC_{90} values at 1 mg/L for *H. influenzae,* and the β-lactamase-positive and-negative subgroups (Table 1 and 3).
- There was little tetracycline resistance, (1.1/1.4% resistant by CLSI/EUCAST interpretive criteria; Table 3). The agent demonstrating the highest level of resistance among *H. influenzae* was trimethoprim/sulfamethoxazole (26.2/29.5% resistant; CLSI/EUCAST interpretive criteria, respectively).
- All agents were very active against *M. catarrhalis* (Table 3). The PTK 0796 $MIC_{50/90}$ values were 0.12/0.12 mg/L, respectively, only one β-lactamase-negative *M. catarrhalis* isolate (PTK 0796 MIC, ≤0.06 mg/L) was detected.

Table 2. Comparison of in vitro activity of PTK 0796 (omadacycline) and other selected antimicrobial agents tested against *S. pneumoniae* (600 isolates) from Europe.

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Streptococcus pneumoniae (600)					
PTK 0796	0.06	0.06	≤0.015 – 0.25	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	99.7 / -	- / -
Doxycycline	0.25	8	≤0.06 – >8	- / -	69.8 / 29.3
Tetracycline	0.5	>8	≤0.25 – >8	69.3 / 30.2	68.8 / 30.7
Penicillin[c]	≤0.06	2	≤0.06 – 8	91.8 / 1.3	- / -
Penicillin[d]	≤0.06	2	≤0.06 – 8	63.5 / 23.8	63.5 / 8.2
Amoxicillin/clavulanate	≤1	4	≤1 – >8	89.2 / 4.8	- / -
Ceftriaxone	≤0.06	1	≤0.06 – 4	92.0 / 1.3	73.3 / 1.3
Erythromycin	≤0.12	>16	≤0.12 – >16	60.8 / 39.0	60.8 / 39.0
Clindamycin	≤0.25	>2	≤0.25 – >2	72.0 / 27.8	72.2 / 27.8
Levofloxacin	1	1	≤0.12 – >4	98.7 / 1.0	98.7 / 1.3
TMP/SMX[e]	≤0.5	4	≤0.5 – >4	72.3 / 15.7	82.5 / 15.7
Penicillin-susceptible (MIC, ≤0.06 mg/L; 381)					
PTK 0796	0.06	0.06	≤0.015 – 0.25	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	99.5 / -	- / -
Doxycycline	0.12	0.25	≤0.06 – >8	- / -	91.3 / 8.1
Tetracycline	≤0.25	1	≤0.25 – >8	91.1 / 8.7	90.6 / 8.9
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.12	8	≤0.12 – >16	86.1 / 13.6	86.1 / 13.6
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.4 / 7.6	92.4 / 7.6
Levofloxacin	1	1	≤0.12 – >4	99.0 / 0.5	99.0 / 1.0
TMP/SMX[e]	≤0.5	1	≤0.5 – >4	89.8 / 5.8	92.9 / 5.8
Penicillin-intermediate (MIC, 0.12-1 mg/L; 76)					
PTK 0796	0.06	0.06	≤0.015 – 0.12	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	- / -
Doxycycline	2	>8	≤0.06 – >8	- / -	48.7 / 50.0
Tetracycline	8	>8	≤0.25 – >8	48.7 / 51.3	48.7 / 51.3
Amoxicillin/clavulanate	≤1	2	≤1 – 4	98.7 / 0.0	- / -
Ceftriaxone	0.25	1	≤0.06 – 2	98.7 / 0.0	68.4 / 0.0
Erythromycin	>16	>16	≤0.12 – >16	25.0 / 75.0	25.0 / 75.0
Clindamycin	1	>2	≤0.25 – >2	48.7 / 51.3	48.7 / 51.3
Levofloxacin	1	1	≤0.12 – >4	97.3 / 2.7	97.3 / 2.7
TMP/SMX[e]	≤0.5	>4	≤0.5 – >4	63.2 / 21.1	77.6 / 21.1
Penicillin-resistant (MIC, ≥2 mg/L; 143)					
PTK 0796	0.06	0.06	≤0.015 – 0.25	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	- / -
Doxycycline	8	8	0.12 – >8	- / -	23.8 / 74.8
Tetracycline	>8	>8	≤0.25 – >8	22.4 / 76.2	21.7 / 77.6
Penicillin[c]	2	4	2 – 8	65.7 / 5.6	- / -
Amoxicillin/clavulanate	2	8	≤1 – >8	55.2 / 20.3	- / -
Ceftriaxone	1	2	0.25 – 4	67.1 / 5.6	4.9 / 5.6
Erythromycin	>16	>16	≤0.12 – >16	12.6 / 87.4	12.6 / 87.4
Clindamycin	>2	>2	≤0.25 – >2	30.1 / 69.2	30.8 / 69.2
Levofloxacin	1	1	0.5 – >4	98.6 / 1.4	98.6 / 1.4
TMP/SMX[e]	1	>4	≤0.5 – >4	30.8 / 39.2	57.3 / 39.2

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].
c. Criteria as published by the CLSI [2012] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2012] for 'Penicillin (oral penicillin V)'.
e. Trimethoprim/sulfamethoxazole .

Table 3. Comparison of in vitro activity of PTK 0796 (omadacycline) and other selected antimicrobial agents tested against the Gram-negative fastidious pathogens *H. influenzae* (359 isolates) and *M. catarrhalis* (65 isolates) from Europe.

Antimicrobial agent (no. tested)	MIC (mg/L) MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
H. influenzae (359)					
PTK 0796	0.5	1	0.25 – 8	- / -	- / -
Tigecycline[b]	0.25	0.5	0.06 – 2	87.7/ -	- / -
Tetracycline	0.5	0.5	≤0.12 – 16	98.6 / 1.1	98.1 / 1.4
Ampicillin	0.25	>8	≤0.12 – >8	83.3 / 13.9	83.3 / 16.7
Amoxicillin/clavulanate	≤1	2	≤1 – 8	99.7 / 0.3	88.3 / 11.7
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Azithromycin	1	2	0.06 – >4	99.2 / -	1.1 / 0.8
Levofloxacin	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -	100.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -	100.0 / 0.0
TMP/SMX[c]	≤0.5	>4	≤0.5 – >4	68.8 / 26.2	68.8 / 29.5
β-lactamase positive (50)					
PTK 0796	1	1	0.25 – 4	- / -	- / -
Tigecycline[b]	0.25	0.5	0.12 – 1	86.0/ -	- / -
Tetracycline	0.5	1	≤0.12 – 16	90.0 / 8.0	90.0 / 10.0
Ampicillin	>8	>8	2 – >8	0.0 / 98.0	0.0 / 100.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	90.0 / 10.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Azithromycin	1	2	0.12 – 4	100.0 / -	2.0 / 0.0
Levofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -	100.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	≤0.12	100.0 / -	100.0 / 0.0
TMP/SMX[c]	≤0.5	>4	≤0.5 – >4	68.0 / 30.0	68.0 / 32.0
β-lactamase negative (309)					
PTK 0796	0.5	1	0.25 – 8	- / -	- / -
Tigecycline[b]	0.25	0.5	0.06 – 2	88.0/ -	- / -
Tetracycline	0.5	0.5	≤0.12 – 2	100.0 / 0.0	99.4 / 0.0
Ampicillin	0.25	1	≤0.12 – 4	96.8 / 0.3	96.8 / 3.2
Amoxicillin/clavulanate	≤1	2	≤1 – 8	99.7 / 0.3	88.0 / 12.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Azithromycin	1	2	0.06 – >4	99.0 / -	1.0 / 1.0
Levofloxacin	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -	100.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	≤0.12 – 0.25	100.0 / -	100.0 / 0.0
TMP/SMX[c]	≤0.5	>4	≤0.5 – >4	68.9 / 25.6	68.9 / 29.1
M. catarrhalis (65)					
PTK 0796	0.12	0.12	≤0.06 – 0.5	- / -	- / -
Tigecycline[b]	0.06	0.06	0.03 – 0.25	- / -	- / -
Tetracycline	0.25	0.25	≤0.12 – 2	100.0 / 0.0	98.5 / 0.0
Penicillin	>2	>2	≤0.03 – >2	- / -	- / -
Amoxicillin/clavulanate	≤1	≤1	≤1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	0.25	0.5	≤0.06 – 2	100.0 / -	98.5 / 0.0
Azithromycin	≤0.03	≤0.03	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -	100.0 / 0.0
Moxifloxacin	≤0.12	≤0.12	≤0.12	- / -	100.0 / 0.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – 2	95.4 / 0.0	95.4 / 1.5

a. Criteria as published by the CLSI [2012] and EUCAST [2012].
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].
c. Trimethoprim/sulfamethoxazole.

Conclusions

- PTK 0796 (omadacycline) demonstrated potent activity against the key bacterial respiratory pathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis)*.
- PTK 0796 activity was unaffected by penicillin or tetracycline susceptibility patterns.
- PTK 0796, which is currently undergoing clinical development for acute bacterial skin and skin structure infections, exhibited activity against key bacterial respiratory pathogens and merits further studies in this clinical indication.

References

1. Bowser T, Bhatia B, Chen J, Ismail M, McIntyre L, Mechiche R, Nelson M, Ohemeng K, Verma A (2003). PTK 0796 and other novel tetracycline derivatives exhibiting potent in vitro and in vivo activities against antibiotic resistant Gram-positive bacteria. Abstr. F-755. *43rd ICAAC, September 11-14, 2003,* Chicago, Illinois, USA.
2. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition.* Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement.* Wayne, PA: CLSI.
4. European Committee on Antimicrobial Susceptibility Testing (2012). Breakpoint tables for interpretation of MICs and zone diameters. Version 2.0, January 2012. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 1, 2012.
5. Macone A, Donatelli J, Dumont T, Levy SB, Tanaka SK, Levy SB (2003). In vitro activity of PTK 0796 against Gram-positive and Gram-negative organisms. Abstr. F-754. *43rd ICAAC, September 11-14, 2003,* Chicago, Illinois, USA.
6. McKenney D, Quinn JM, Jackson CL, Guilment JL, Landry JA, Tanak SK, Cannon EP (2003). Evaluation of PTK 0796 in experimental models of infections caused by Gram-positive and Gram-negative pathogens. Abstr. F-757. *43rd ICAAC, September 11-14, 2003,* Chicago, Illinois, USA.
7. McKenney D, Quinn JM, Jackson CL, Guilment JL, Landry JA, Tanaka SK, Cannon EP (2003). The efficacy of PTK 0796 in murine models of *Streptococcus pneumoniae* infections. Abstr. F-758. *43rd ICAAC, September 11-14, 2003,* Chicago, Illinois, USA.
8. Sader HS, Mendes RE, Biedenbach DJ, Jones RN (2010). Antimicrobial activity of PTK796 tested against Gram-positive organisms causing bloodstream infections in 2009. Abstr. E-1588. *50th ICAAC, September 12-15, 2010,* Boston, Massachusetts, USA.
9. Traczewski MM, Brown SD (2003). PTK 0796: In vitro potency and spectrum of activity compared to ten other antimicrobial compounds. Abstr. F-753. *43rd ICAAC, September 11-14, 2003,* Chicago, Illinois, USA.
10. Tygacil Package Insert (2010). Available at www.tygacil.com. Accessed October, 2010.
11. Weir S, Macone A, Donatelli J, Trieber C, Taylor DE, Tanaka SK, Levy SB (2003). The mechanism of action of PTK 0796. Abstr. F-751. *43rd ICAAC, September 11-14, 2003,* Chicago, Illinois, USA.

Table 1. MIC frequency and cumulative percent inhibited distributions of PTK 0796 (omadacycline) for EU respiratory pathogens.

Organism/Subgroup (no. tested)	Number of isolates (cumulative %) inhibited at PTK 0796 MIC(mg/L) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (600)	9 (1.5)	173 (30.3)	384 (94.3)	31 (99.5)	3 (100.0)	-	-	-	-	-	0.06	0.06
penicillin-susceptible (381)	7 (1.8)	122 (33.9)	236 (95.8)	14 (99.5)	2 (100.0)	-	-	-	-	-	0.06	0.06
penicillin-intermediate (76)	1 (1.3)	27 (36.8)	43 (93.4)	5 (100.0)	-	-	-	-	-	-	0.06	0.06
penicillin-resistant (143)	1 (0.7)	24 (17.5)	105 (90.9)	12 (99.3)	1 (100.0)	-	-	-	-	-	0.06	0.06
Haemophilus influenzae (359)	-	-	-	-	15 (4.2)	173 (52.4)	146 (93.0)	22 (99.2)	2 (99.7)	1 (100.0)	0.5	1
β-lactamase-negative (309)	-	-	-	-	14 (4.5)	153 (54.1)	120 (92.9)	20 (99.4)	1 (99.7)	1 (100.0)	0.5	1
β-lactamase-positive (50)	-	-	-	-	1 (2.0)	20 (42.0)	26 (94.0)	2 (98.0)	1 (100.0)	-	1	1
Moraxella catarrhalis (172)	-	-	12 (18.5)[a]	49 (93.9)	3 (98.5)	1 (100.0)	-	-	-	-	0.12	0.12

a. 12 *M. catarrhalis* isolates MIC values were ≤0.06 mg/L