Comparison of Omadacycline and Tigecycline Pharmacodynamics in the Plasma, Epithelial Lining Fluid, and Alveolar Macrophages in Healthy Subjects

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Disclosures

- This study was funded by Paratek Pharmaceuticals
- KAR has been a consultant to Paratek Pharmaceuticals
- JNS, SV, ET, LGR, SC, AM, and SKT are employees of Paratek Pharmaceuticals

Introduction

- **Omadacycline (PTK 0796) is a first-in-class aminomethylcycline antibiotic**
- **Chemical structure overcomes efflux pump and ribosomal protection mechanisms of tetracycline resistance**
- ***In vitro* activity against respiratory pathogens including:**
  - **Methicillin-resistant *Staphylococcus aureus* (MRSA)**
  - **Multidrug-resistant *Streptococcus pneumoniae***
  - ***Haemophilus influenzae*, *Moraxella catarrhalis***
  - ***Legionella pneumophila*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae***
- **Omadacycline was recently shown to be noninferior to moxifloxacin in a Phase 3 clinical trial for community-acquired bacterial pneumonia (CABP) [NCT02531438]**

***Future Microbiol.* 2016; 11: 1421-34**

Intrapulmonary Sites and Pharmacodynamics

- **Epithelial lining fluid (ELF) and alveolar cells (AC) have been advocated as important infection sites for common extracellular and intracellular respiratory pathogens, respectively**
- **Ratio of $AUC_{0\text{-}24}$ to MIC ($AUC_{0\text{-}24}$/MIC) has been the pharmacokinetic-pharmacodynamic parameter that best correlates with antibacterial efficacy for the tetracycline class of antibiotics**
  - **Lepak et al. recently confirmed this for omadacycline against isolates of *Streptococcus pneumoniae* in a neutropenic mouse pneumonia model**
  - **Typical ranges of ELF $AUC_{0\text{-}24}$/MIC ratios associated with a net bacterial stasis and a 1-log and 2-log CFU reduction from baseline were 14.18 to 17.80, 6.00 to 17.61, and 17.26 to 47.27, respectively**

Clin Pharmacokinet 2011; 50: 637-64
Antimicrob Agents Chemother 2017 Feb 13. pii: AAC.02368-16

Objectives

- To determine concentrations of omadacycline and tigecycline in epithelial lining fluid (ELF) and alveolar cells (AC) and define the time course of pulmonary distribution with concurrent plasma sampling of omadacycline and tigecycline in healthy adult subjects
- To determine and compare the pharmacokinetics of omadacycline and tigecycline in plasma and pulmonary compartments in healthy adult subjects
- Compare $AUC_{0\text{-}24}$/MIC ratios for omadacycline and tigecycline against common respiratory pathogens in the plasma, ELF, and AC

Methods

- **Single center, multiple dose, open label study in healthy subjects**
  - **18-55 years old**
  - **No significant past medical history**
  - **No concomitant medications**
  - **Non-smokers**
- **Randomized to omadacycline or tigecycline**
- **Conducted according to Good Clinical Practice and Good Laboratory Practice guidelines**

Methods

Omadacycline (OMC)

- 100 mg intravenously q12h x 2 doses, then 100 mg q24h x 3 doses
- Plasma: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h after the start of the 5th dose
- 42 subjects randomized to 1 BAL time following the 5th dose: 0.5, 1, 2, 4, 8, 12, or 24 h

Tigecycline (TGC)

- 100 mg intravenously x 1 dose, then 50 mg q12h x 6 doses[a]
- Plasma: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h after the start of the 7th dose
- 21 subjects randomized to 1 BAL time following the 7th dose: 2, 4, 6, 12 h

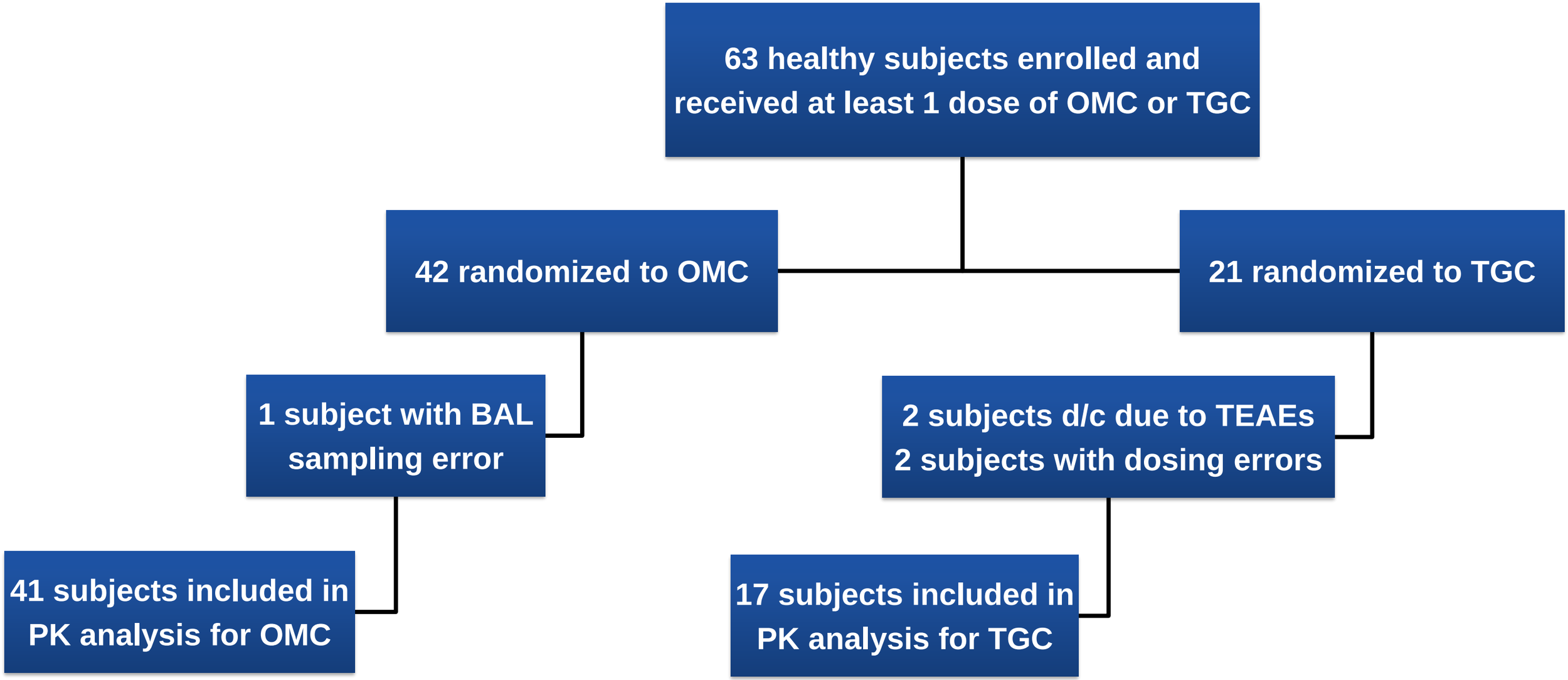
Plasma and BAL samples were assayed for urea concentration and OMC or TGC concentrations (in plasma, BAL fluid, and cell pellet) using LC/MS/MS

[a] Conte JE Jr, et al. *Int J Antimicrob Agents* 2005;25:523-529

Methods

- Noncompartmental analysis of omadacycline and tigecycline in the plasma was performed using Phoenix WinNonlin, version 7.0 (Pharsight Corp., Cary, North Carolina)
- Plasma pharmacokinetic parameters were calculated using serial plasma concentration-time data obtained after the 5^{th} dose of omadacycline and 7^{th} dose of tigecycline
- $AUC_{0\text{-}24}$ for omadacycline and $AUC_{0\text{-}12}$ for tigecycline reported for plasma, ELF, and AC using linear-log trapezoidal method
- Calculations of the volume of ELF and drug concentration were determined with the urea dilution method
- Calculations of drug concentration in AC determined from measured concentration of drug and volume of AC in cell suspension

Results – Enrollment



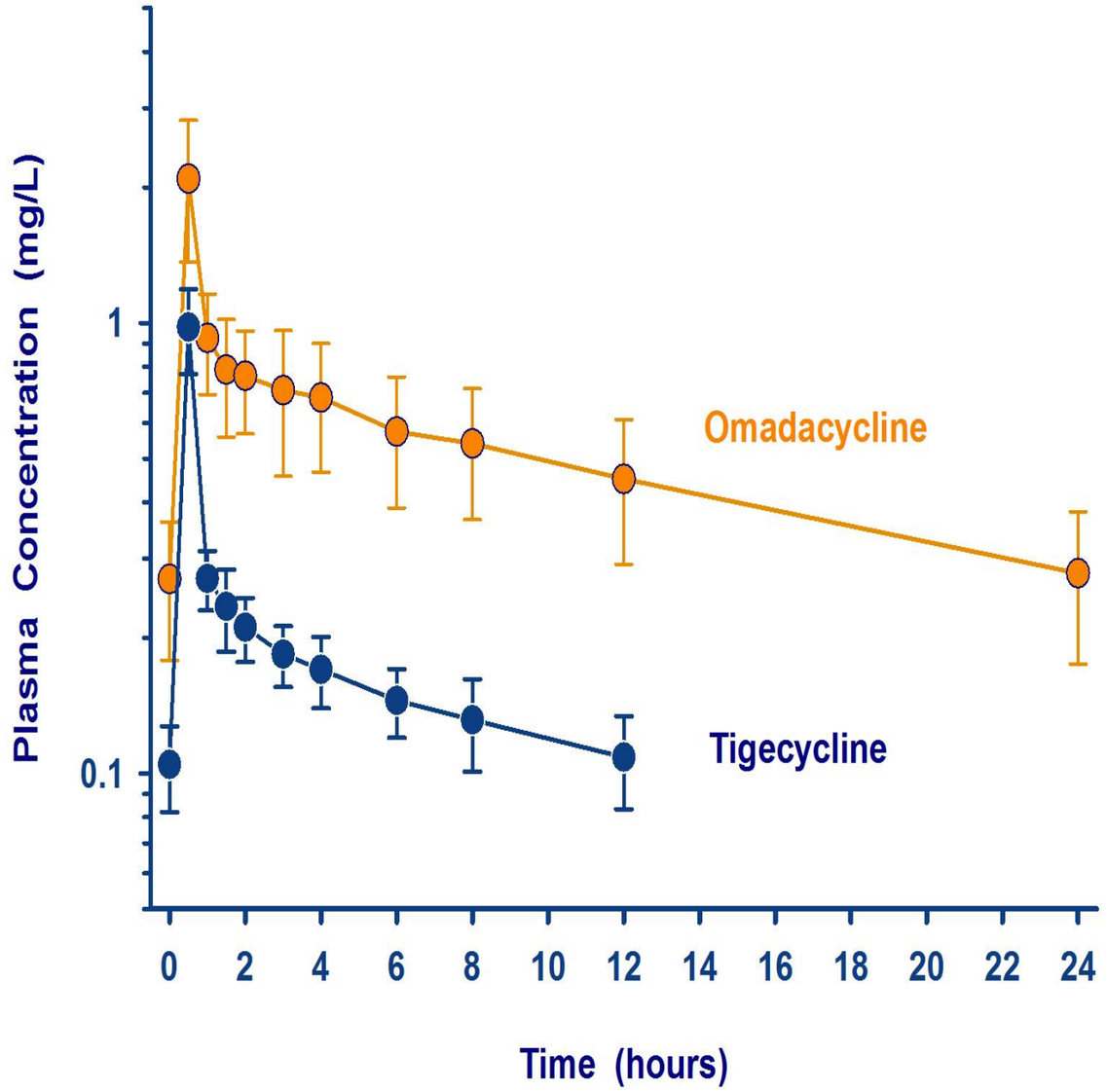
Characteristics of Healthy Subjects Receiving Omadacycline and Tigecycline[a]

Treatment	Sex (n)	Age (yr)	Height (cm)	Weight (kg)	CL_{CR}[b] (mL/min)	BAL total cell count (cells/mm^3)	Macrophages (%)
Omadacycline	M (28) F (13)	38 ± 10	173 ± 10	78.0 ± 12.4	110 ± 21	128 ± 93	82 ± 17
Tigecycline	M (13) F (4)	40 ± 10	174 ± 10	78.6 ± 12.4	109 ± 26	154 ± 89	91 ± 5

[a] Data expressed as mean ± SD except for sex (M = male, F = female)

[b] CL_{CR} calculated creatinine clearance using the Cockcroft-Gault formula

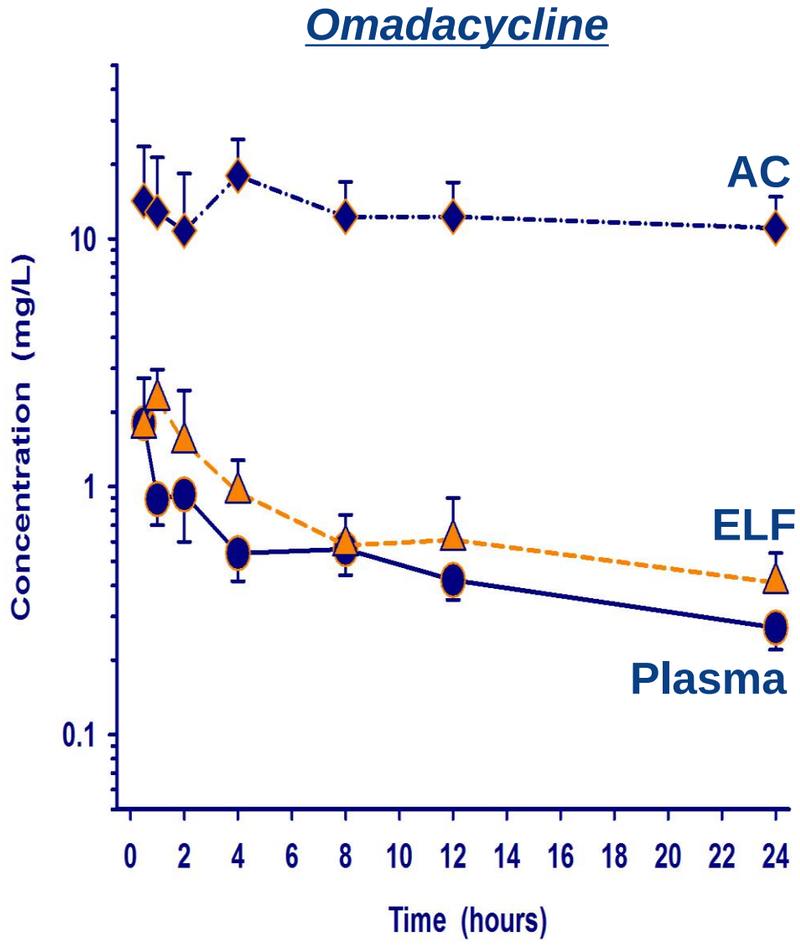
Plasma Pharmacokinetics

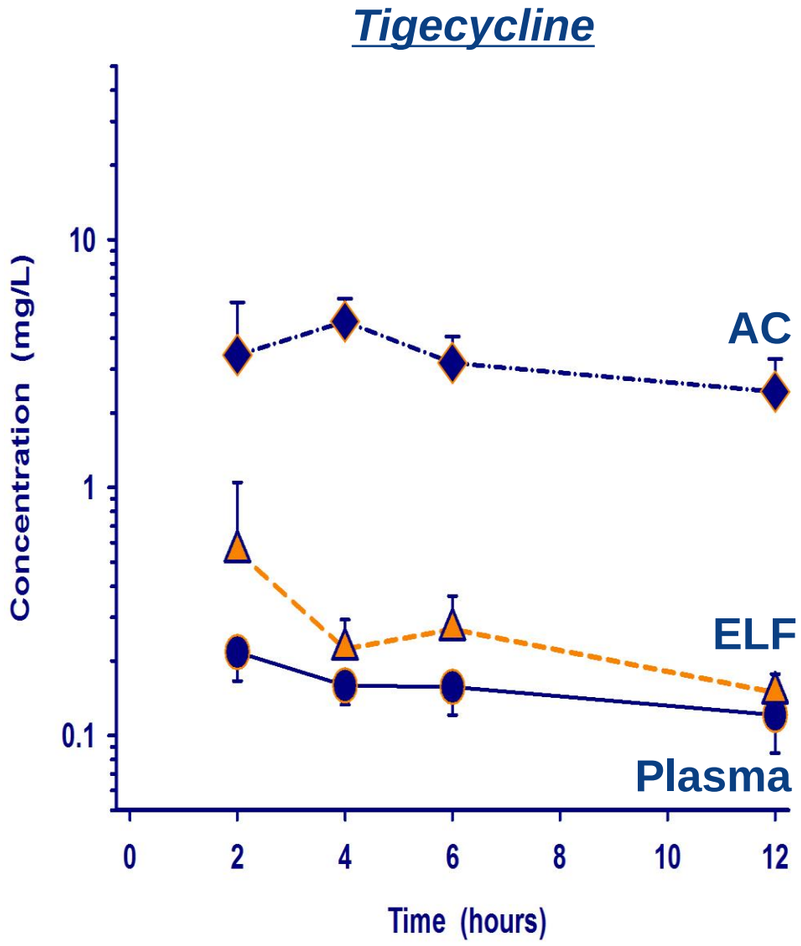


Parameter[a]	Omadacycline	Tigecycline
C_{max} (mg/L)	2.12 ± 0.68	0.98 ± 0.21
C_{min} (mg/L)	0.28 ± 0.10	0.11 ± 0.03
$AUC_{0-\tau}$ (mg•h/L)	12.14 ± 3.22	2.20 ± 0.42
V_{ss} (L)	190 ± 53	315 ± 67
CL (L/h)	8.79 ± 2.21	23.1 ± 4.1
$t_{1/2}$ (h)	16.0 ± 3.5	11.4 ± 2.6

[a] Data expressed as mean ± SD

Mean (± SD) Total Plasma, ELF, and AC Concentrations During the BAL Sampling Times for Omadacycline and Tigecycline





Site	$AUC_{0-\tau}$ (mg•h/L)	
	Omadacycline	Tigecycline
Plasma	11.73	1.83
ELF	17.23	3.16
AC	302	38.5

Site	AUC Ratios: Site-to-Plasma	
	Omadacycline	Tigecycline
Total P		
ELF:P	1.47	1.73
AC:P	25.8	21.0
Unbound P		
ELF:P	1.84	6.17
AC:P	32.2	75.1

Plasma (P) protein binding: Omadacyclilne ~20%[a]
Tigecycline ~ 72%[b]

[a] Villano S, et al. Poster 518. ASM Microbe 2016.
[b] Mukker JK, et al. *J Pharm Sci* 2014;103:1013-1019

$AUC_{0\text{-}24}$ / MIC_{90} for ELF for Omadacycline and Tigecycline Against Extracellular Respiratory Tract Pathogens

Pathogen	MIC_{90} (mg/L)[a]		$AUC_{0\text{-}24}$ / MIC_{90}[b]	
	Omadacycline	Tigecycline	Omadacycline	Tigecycline
Streptococcus pneumoniae	0.12	0.06	144	105
Staphylococcus aureus				
MSSA	0.25	0.25	69	25
MRSA	0.5	0.25	34	25
Moraxella catarrhalis	0.25	0.12	69	53
Haemophilus influenzae	2	0.5	8.6	13

[a] JMI 2016 Surveillance Data (on file, Paratek)

[b] Based on mean $AUC_{0\text{-}24}$ in ELF: Omadacycline = 17.23 mg•h/L; Tigecycline = 6.32 mg•h/L ($2 \times AUC_{0\text{-}12}$)

$AUC_{0\text{-}24}$ / MIC_{90} for AC for Omadacycline and Tigecycline Against Intracellular Respiratory Tract Pathogens

Pathogen	MIC_{90} (mg/L)[a]		$AUC_{0\text{-}24}$ / MIC_{90}[b]	
	Omadacycline	Tigecycline	Omadacycline	Tigecycline
Legionella pneumophila	0.25	8	1208	9.6
Chlamydophila pneumoniae	0.25	0.12	1208	642
Mycoplasma pneumoniae	0.12	0.12[c]	2517	642

[a] Dubois J et al. Poster 1992, ICAAC 2015; Edelstein PH et al. *Antimicrob Agents Chemother* 2003;47:533-540; JMI 2016 Surveillance Data (on file, Paratek)

[b] Based on mean $AUC_{0\text{-}24}$ in AC: Omadacycline = 302 mg•h/L; Tigecycline = 77 mg•h/L (2 × $AUC_{0\text{-}12}$)

[c] Range <0.015 to 0.12 (only 8 strains)

Safety

		Omadacycline (N=42)	Tigecycline (N=21)
Subjects with any TEAE	n (%)	12 (28.6)	11 (52.4)
TEAEs reported in > 1 subject: Headache		5 (11.9)	3 (14.3)
TEAEs reported in > 1 subject: Epistaxis		2 (4.8)	2 (9.5)
TEAEs reported in > 1 subject: Nausea		1 (2.4)	10 (47.6)
TEAEs reported in > 1 subject: Vomiting		0	3 (14.3)
TEAEs reported in > 1 subject: Decreased appetite		0	2 (9.5)
Subjects with any TEAE leading to study drug discontinuation		0	2 (9.5)
Nausea		0	2 (9.5)
Subjects with any serious TEAE		0	0

There were no clinically significant findings in clinical laboratory results, vital signs or ECGs

Further details were previously presented: Poster P1257, ECCMID 2017

Summary

- A similar pattern and time course of omadacycline and tigecycline was observed in plasma (total), ELF, and AC concentrations
- Despite having similar penetration ratios, the magnitude of systemic exposure (based of $AUC_{0\text{-}24}$ values) of omadacycline was approximately ~3-fold higher than tigecycline in plasma (total), ELF, and AC concentrations
- Higher concentrations allow for similar or greater $AUC_{0\text{-}24}$/MIC at all sites evaluated for both extracellular and intracellular respiratory pathogens
- The intrapulmonary pharmacokinetics of omadacycline in healthy subjects suggests adequate target-site penetration for the current intravenous dosing regimen used in the clinical trial for community-acquired bacterial pneumonia
- Further analysis using larger omadacycline concentration-time and MIC datasets, population pharmacokinetic modeling, and Monte Carlo simulations are planned