REVIEW

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Future MICROBIOLOGY

Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections

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Omadacycline is a first-in-class aminomethylcycline antibiotic that circumvents common tetracycline resistance mechanisms. *In vitro* omadacycline has potent activity against Gram-positive aerobic bacteria including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus* spp. It is also active against common Gram-negative aerobes, some anaerobes and atypical bacteria including *Legionella* spp. and *Chlamydia* spp. Ongoing Phase III clinical trials with omadacycline are investigating once daily doses of 100 mg intravenously followed by once daily doses of 300 mg orally for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. This paper provides an overview of the microbiology, nonclinical evaluations, clinical pharmacology and initial clinical experience with omadacycline.

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- aminomethylcycline
- bacterial infection
- omadacycline
- tetracyclines

Background

The tetracycline family of therapeutic agents has been in commercial use since the late 1940s, although there is evidence that they may have provided antibiotic protection (through ingestion of grain contaminated by *Streptomyces* bacteria) even in ancient times (Cook *et al.*, 1989) [1]. While the tetracyclines have represented a mainstay of broad-spectrum antibiotics for many years, but the increasing incidence of bacterial resistance has relegated older tetracyclines to a limited role for treating common infectious diseases [2,3]. Growing resistance to tetracyclines encouraged research into mechanisms of resistance and discovery of new generations of tetracycline. Tigecycline, a glycylcycline tetracycline, was introduced in the past decade and has been successfully used clinically, in part, because it circumvents the common tetracycline resistance mechanisms. However, tigecycline is only available as an intravenous (iv.) formulation, and is associated with a high incidence of dose-related nausea and vomiting, and safety concerns including increased all-cause mortality [4]. Thus, alternatives are needed for treating common community- and hospital-acquired infections.

Omadacycline is a first-in-class aminomethylcycline antibiotic that overcomes the most common mechanisms of tetracycline [5,6]. Omadacycline is active *in vitro* against Gram-positive aerobes, many Gram-negative aerobes regardless of ESBL phenotype, some anaerobes and atypical bacteria including *Legionella* spp. and *Chlamydia* spp. [7]. In addition, omadacycline is active *in vitro* against many resistant Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococcus [7].

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Omadacycline is undergoing clinical development as once daily oral and intravenous monotherapy for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). This review provides an overview of the microbiology, nonclinical data, clinical pharmacology and initial clinical experience with omadacycline.

Chemistry

As with other members of the tetracycline class, omadacycline binds to the tetracycline binding site on the 30S subunit of the bacterial ribosome and inhibits bacterial protein synthesis [6,8]. Omadacycline differs from tetracycline by modifications at both the C7 and presence of an aminomethyl group at the C9 position **(Figure 1)** [5]. Modifications at the C7 position were added to overcome the tetracycline efflux mechanism of resistance, and modifications at the C9 position were added to overcome ribosome protection mechanism of resistance [7]. Omadacycline is prepared by chemical modification of minocycline, and is a stable, well-characterized crystalline drug substance [5]. Omadacycline is administered as the tosylate salt for the intravenous formulation.

Microbiology

Omadacycline demonstrates antimicrobial activity *in vitro* against a range of Gram-positive and Gram-negative aerobes and some anaerobic bacteria that are commonly associated with ABSSSI and CABP [7,9–10].

Against *S. aureus*, omadacycline demonstrated an MIC_{90} for all isolates collected of ≤0.25 mcg/ml [Paratek Pharmaceuticals, data on file]. Importantly, omadacycline was active *in vitro* against MRSA, penicillin-resistant *Streptococcus pneumoniae*, multidrug-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococcus with an MIC_{90} of ≤0.12 mcg/ml **(Tables 1, 2 & 3)** [11,12]. Additionally, omadacycline retained activity against tetracycline-resistant isolates **(Table 4)** [Paratek Pharmaceuticals, data on file].

Against Gram-negative pathogens, the MIC_{90} of omadacycline for *Haemophilus influenzae* was 2 mcg/ml and for *Moraxella catarrhalis* was 0.25 mcg/ml [13]. *In vitro*, omadacycline also demonstrated activity with a MIC_{90} at ≤4.0 mcg/ml against many *Escherichia coli, Enterobacter aerogenes, Enterobacter cloacae, Serratia marcescens, Salmonella* spp., *Shigella* spp. and *Stenotrophomonas maltophilia* **(Table 5)** [14]. *In vitro*, omadacycline demonstrates no notable activity (MIC_{90} values >16 mcg/ml) against *Proteus* spp., *Providencia* spp., *Pseudomonas* spp. and *Morganella* spp.

In vitro activity with omadacycline was demonstrated against atypical bacteria including *Legionella pneumophila* **(Table 6)** and *Chlamydia* spp. (MIC_{90} of 0.25 mcg/ml) [15]. *In vitro*, omadacycline exhibits the following activity against the anaerobes tested: *Bacteroides fragilis* (MIC_{90} = 2 mcg/ml), *Clostridium difficile* (MIC_{90} = 0.12 mcg/ml), *Clostridium perfringens* (MIC_{90} = 4 mcg/ml) and anaerobic Gram-positive cocci (MIC_{90} = 0.5 mcg/ml) [Paratek Pharmaceuticals, data on file].

Two mechanisms, efflux pump and ribosomal protection, account for much of the resistance to tetracycline antibiotics [3,6]. While omadacycline is known to inhibit protein synthesis with a greater potency than tetracycline, definitive experiments performed with functional assays and macromolecular synthesis demonstrated that omadacycline inhibited protein synthesis in tetracycline-resistant bacterial strains that expressed both the efflux pump and ribosomal protection mechanisms [3,6,7]. Using a cell-free *in vitro* protein synthesis model, protein synthesis inhibition activity of omadacycline was investigated in both the presence and absence of the Tet(O), a ribosome protection protein. Omadacycline inhibited protein synthesis in a cell-free system regardless of whether Tet(O) was present or not. Importantly, omadacycline was able to overcome tetracycline resistance mechanisms and also was not affected by resistance mechanisms of other antibiotics [6]. Surveillance data from 2015 demonstrate that omadacycline retains activity (MIC_{90} value 0.25 mcg/ml) against tetracycline resistant strains of *S. aureus, E. faecalis* and *S. pneumoniae* **(Table 4)** [Paratek Pharmaceuticals, data on file].

Additionally, the potential for the emergence of resistance to omadacycline was assessed by both single and multistep pressure selection. Resistance to omadacycline was not observed either following a single exposure to drug or after serial passage at sub-MIC concentrations for any of the strains [Paratek Pharmaecuticals, data on file].

Nonclinical evaluations

• Metabolism

The potential for enzymatic metabolism of omadacycline was evaluated *in vitro* using either

pooled human liver microsome preparations, S9, liver cytosol or recombinant flavin monooxygenases (FMO1, FMO3, FMO5) [16]. CYP450 isozymes evaluated included CYP 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4/5. Omadacycline did not induce CYP isozymes and no or minimal (<40% of maximal positive control response) induction of their mRNAs was observed. Omadacycline exhibited no significant inhibition of CYP isozyme activity and demonstrated no significant binding to human microsomes. These results indicate a low potential for drug–drug interactions via enzymatic metabolism.

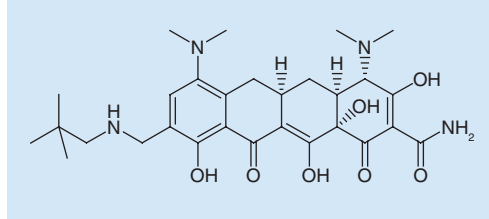

Figure 1. Chemical structure of omadacycline. Adapted with permission from [4].

• Transporter effects

Transport of [14C]omadacycline was determined in human embryonic kidney 293 cells stably expressing human organic anion transporters 1 or 3 (hOAT1 or hOAT3), human organic cation transporter 2 (hOCT2) and human organic anion transport polypeptide transporters OATP1B1 and OATP1B3 as well as P-gp, MRP2 and Breast Cancer Resistance Protein [17]. No difference was observed for accumulation of [14C]omadacycline into cells expressing hOAT1, hOAT3, hOCT2, OATP1B1 or OATP1B3. Omadacycline appeared to be a substrate for P-gp but not Breast Cancer Resistance Protein or MRP-2. Omadacycline did not inhibit hOAT3 function but inhibited hOAT1 by approximately 32.1% at 25 µM. Transport of probes for OATP1B1 and OATP1B3 was reduced by 10.1% with omadacycline 100 µM. Omadacycline did not inhibit P-gp, BRCP or MRP-2 and did not induce P-gp or MRP-2 mRNA. Overall, the potential for omadacycline drug–drug interactions via transporter effects appears to be minimal.

• Nonclinical cardiovascular effects

The cardiovascular risk potential for omadacycline was evaluated through a series of *in vitro* and *in vivo* studies, including mammalian pharmacologic receptor binding; human ether-à-go-go-Related Gene (hERG) channel binding; effects on rabbit *ex vivo* sinoatrial node activity; and *in vivo* effects on cardiovascular function in the cynomolgus monkey [18]. No significant binding to the hERG channel, β-adrenergic receptor or any other receptors was observed that could result in a direct stimulatory effect on heart rates. Omadacycline binds *in vitro* to the muscarinic-2 (M_2) receptor subtype but not the M_1, M_3 or M_4 receptor subtypes and exhibited a concentration-dependent antagonism of the effect carbamylcholine (a muscarinic receptor agonist), which resulted in an increase in heart rate in the *ex vivo* sinoatrial node model that reached a peak at 4.5 h after the dose. Omadacycline exhibited no effect on hERG channel activity

Table 1. *In vitro* activity of omadacycline and comparators against methicillin-resistant *Staphylococcus aureus* strains isolated in 2014 (n = 402).

Organism group (number tested) antimicrobial agent	MIC_{50}	MIC_{90}	MIC range
Omadacycline	0.12	0.12	0.03–1
Tigecycline	0.06	0.12	≤0.015–0.25
Doxycycline	0.12	1	≤0.06–>8
Tetracycline	0.12	16	≤0.03–>16
Clindamycin	≤0.25	>2	≤0.25–>2
Daptomycin	0.25	0.5	0.12–2
Erythromycin	>16	>16	≤0.12–>16
Gentamicin	≤1	>8	≤1–>8
Levofloxacin	>4	>4	≤0.12–>4
Linezolid	1	1	≤0.12–2
Trimethoprim–sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4
Vancomycin	1	1	0.25–2

Adapted with permission from Flamm *et al.* (2015) [10].

Table 2. Susceptibility of bacterial strains to omadacycline.

Organism	Number of isolates	MIC_{50}	MIC_{90}
Gram-positive pathogens			
Staphylococcus aureus (MSSA)	52	0.25	0.25
Enterococcus faecalis (VSE)	107	0.25	0.5
Enterococcus faecalis (VRE)	47	0.12	0.25
Enterococcus faecium (VSE)	56	0.12	0.12
Enterococcus faecium (VRE)	100	0.12	0.12
Streptococcus pyogenes	104	0.12	0.12
Streptococcus agalactiae	53	0.12	0.25
Staphylococcus saprophyticus (MR)	8	–	0.12–1
Gram-negative pathogens			
Haemophilus influenza	105	0.5	1
Moraxella catarrhalis	105	0.25	0.25
Citrobacter freundii	51	2	2
Enterobacter cloacae	62	2	16
Salmonella spp.	52	2	8
Serratia marcescens	51	4	8
Shigella spp.	51	1	2
Acinetobacter baumannii	53	0.25	4
Burkholderia cepacia	29	2	64
Stentrophomonas maltophilia	52	2	8
Anaerobic pathogens			
Bacteroides fragilis	100	1	2
Bacteroides thetaiotaomicron	100	0.5	8
Clostridium difficile	27	0.12	0.12
Clostridium perfringens	100	1	4
Anaerobic Gram-positive cocci	101	0.25	0.5

[Paratek Pharmaceuticals, data on file]

at a concentration of 100 ug/ml. In addition, omadacycline at doses up to 40 mg/kg had no effect on the QTc interval in conscious monkeys. Overall these nonclinical findings showed that omadacycline had a vagolytic effect on heart rate but had a low potential for cardiac arrhythmia or clinically significant cardiovascular toxicity.

Clinical pharmacokinetics & pharmacodynamics

The human pharmacokinetic profile of omadacycline was characterized in healthy subjects. Pharmacokinetic parameters are shown from a bioavailability study that compared single intravenous and oral administration using the formulations and doses being evaluated in ongoing Phase III studies **(Table 7)**.

• Absorption, distribution, metabolism & excretion

In a mass balance study, six healthy male subjects received a single oral 300 mg dose of [14C] omadacycline (mean radioactivity 36.6 µCi) under fasting conditions [20]. Mean recovery of the radioactive dose was 95.5% after 7 days. In plasma, omadacycline and its C-4 epimer (which is formed spontaneously upon standing) accounted for 100% of the AUC. No enzymatically formed metabolites were detected. Based on radioactivity measurements, the main routes of elimination were fecal (81.1%) and urinary (14.4%). Given on an oral bioavailability of 35% for the tablet formulation, approximately 40% of the absorbed dose should be eliminated in the urine [20]. In a separate experiment, *in vitro* determination of protein binding in human plasma found no dose dependency over concentrations ranging from 0.1 to 10 mcg/ml, and the mean bound protein fraction was 21% [21].

• Intravenous dosing

After single intravenous doses of omadacycline from 25 to 600 mg, mean $AUC_{0\text{-inf}}$ was linear and ranged from 1.3 to 36.0 mcg*h/ml [19]. For single doses from 25 to 200 mg (0.5 mg/ml infused over

30 min), mean C_{max} was 0.3–2.0 mcg/ml; for single doses ranging from 300 to 600 mg (1.0 mg/ml infused over 60 min), mean C_{max} was 2.5–4.5 mcg/ml. Omadacycline demonstrated accumulation following multiple-dose administration of 200 mg iv. once daily for 7 days. Between Days 1 and 7 mean C_{max} increased from 2.8 to 3.4 mcg/ml, and mean AUC_{0-24} increased from 11.2 to 17.4 mcg*h/ml. Therefore, based on AUC omadacycline accumulated by approximately 50% from Day 1 to steady-state.

• Oral dosing

The earliest clinical studies of oral omadacycline were conducted with simple capsule formulations. Subsequently, various oral formulations have been evaluated in an effort to improve bioavailability and tolerability. The bioavailability of different oral formulations of omadacycline relative to an intravenous dose was investigated in an open-label, randomized, crossover study in healthy subjects [22]. Subjects received omadacycline 100 mg iv., two 300-mg tablet formulations

Table 3. *In vitro* activity of omadacycline and comparators against *Streptococcus pneumoniae* strains isolated in 2014.

Organism group (number tested) antimicrobial agent	MIC_{50}	MIC_{90}	MIC range
Streptococcus pneumoniae *(1834)*			
Omadacycline	0.06	0.06	0.015–0.12
Tigecycline	0.03	0.06	≤0.015–0.06
Doxycycline	0.12	8	≤0.06–>8
Tetracycline	0.25	>16	0.12–>16
Amoxicillin-clavulanate	≤1	8	≤1–>8
Ceftriaxone	0.25	2	≤0.06–8
Clindamycin	≤0.25	>2	≤0.25–>2
Erythromycin	2	>16	≤0.12–>16
Levofloxacin	1	1	0.5–>4
Penicillin	0.25	4	≤0.06–8
Trimethoprim–sulfamethoxazole	≤0.5	>4	≤0.5–>4
MDR (434)			
Omadacycline	0.06	0.06	0.015–0.12
Tigecycline	0.03	0.06	≤0.015–0.06
Doxycycline	8	>8	≤0.06–>8
Tetracycline	>16	>16	0.12–>16
Amoxicillin-clavulanate	2	8	≤1–>8
Ceftriaxone	1	2	≤0.06–8
Clindamycin	>2	>2	≤0.25–>2
Erythromycin	>16	>16	≤0.12–>16
Levofloxacin	1	1	0.5–>4
Penicillin	2	4	≤0.06–8
Trimethoprim–sulfamethoxazole	4	>4	≤0.5–>4
Ceftriaxone-NS (MIC ≥2 μg/ml) (129)			
Omadacycline	0.06	0.06	0.03–0.06
Tigecycline	0.03	0.06	≤0.015–0.06
Doxycycline	4	8	0.12–>8
Tetracycline	>16	>16	0.25–>16
Amoxicillin-clavulanate	8	8	≤1–>8
Ceftriaxone	2	4	2–8
Clindamycin	>2	>2	≤0.25–>2
Erythromycin	>16	>16	≤0.12–>16
Levofloxacin	1	1	0.5–1
Penicillin	4	4	1–8
Trimethoprim–sulfamethoxazole	>4	>4	≤0.5–>4

MDR: Multidrug resistant; MIC: Minimum inhibitory concentration; NS: Not specified.
Adapted with permission from Flamm *et al.* (2015) [11].

Table 4. *In vitro* activity of omadacycline against tetracycline-resistant strains isolated in 2015.

Organism	n	MIC_{50}	MIC_{90}	MIC range
Staphylococcus aureus	77	0.12	0.25	0.015–2
Enterococcus faecalis	472	0.12	0.25	0.015–2
Streptococcus pneumoniae	200	0.12	0.25	0.015–0.25

[Paratek Pharmaceuticals, data on file]

with different dissolution profiles and a 300 mg oral solution. Equivalent total exposure relative to the 100 mg iv. dose was observed with both 300 mg tablet formulations with geometric mean ratios (90% CI) for $AUC_{0\text{-inf}}$ of 1.00 (0.93,1.07) and 0.96 (0.90,1.03), respectively. The coefficients of variation for $AUC_{0\text{-inf}}$ for all studied formulations ranged from 16 to 24%. The absolute bioavailability of the tablet formulation selected for use in Phase III studies was approximately 35%. Thus, a 300 mg oral dose of the Phase III tablet formulation produced omadacycline exposure equivalent to that of a 100 mg iv. dose.

With respect to pharmacodynamic assessments, animal models had identified AUC/MIC as the index that is most important for the efficacy of omadacycline [23]. In humans, the serum concentrations achieved following a 100 mg iv. or 300 mg oral dose are associated with AUC values **(Table 7)** that are expected to provide clinical activity against the bacteria commonly associated with ABSSSI and CABP.

• Food effect

A Phase I, random-sequence, open-label, 4-period crossover study evaluated the effects of food on the pharmacokinetics of omadacycline in healthy subjects (Tzanis *et al.*, 2016) [24]. In each period subjects received a single 300 mg oral dose of omadacycline but the meal time varied relative to dosing: A) ≥6-h fast before dosing, B) standard, high fat, non-dairy meal 4 h before dosing, C) standard, high fat, non-dairy meal 2 h before dosing, and D) standard, high fat meal containing dairy 2 h before dosing. Compared with a fast of at least 6 h, omadacycline exposure (AUC and C_{max}) was reduced by 15–17% for the meal 4 h before dosing, 40–42% for the meal 2 h before dosing, and 59–63% for the meal with dairy 2 h before dosing. Thus, the food effect was more pronounced when a meal was consumed closer to oral dosing, with an even greater effect when dairy was included in the meal. The latter findings are consistent with the known tetracycline characteristic of binding to calcium as well as other multivalent cations. Accordingly, in general it is recommended that oral omadacycline should be administered in a fasted state, with avoidance of concomitant oral products containing calcium or other multivalent cations (e.g., dairy products, antacids, or multivitamins).

• Effect of gender & age

Two Phase I studies were undertaken to evaluate the effect of age and gender on the PK of omadacycline after oral and intravenous administration in healthy volunteers [25]. Both were double-blind and placebo-controlled studies of single doses of omadacycline. Study 1 included four groups: young males; young females; elderly males; and elderly females – all of whom received omadacycline 200 mg oral or placebo. Study 2 included healthy young male and female subjects who received a single 200 mg oral or 100 mg iv. dose of omadacycline or placebo. In Study 1, no effect of age on omadacycline absorption and PK profile was observed, but exposure (C_{max} and AUC_{inf}) was at least 30% higher among females versus males in both age groups. In contrast, in study 2 omadacycline exposure based on $AUCi_{nf}$ was similar for both genders after the oral dose, but was approximately 30% higher among females versus males after the intravenous dose. Therefore, female subjects tended to have higher omadacycline exposure than male subjects, though this was not observed consistently in the two studies. In a population PK analysis of subjects across 10 different Phase I studies of omadacycline, the proportion of female subjects was low (19%), but the model showed that gender did not affect omadacycline clearance (the only subject characteristic that did so was renal function) [26]. Overall, no dosage adjustment for omadacycline is necessary on the basis of patient age or gender.

• ECG QT evaluation

The effect of single therapeutic and supratherapeutic intravenous doses of omadacycline on ventricular repolarization and the relationship between plasma concentrations of omadacycline and QTc intervals was evaluated [27]. In this double-dummy, randomized, crossover study, healthy subjects were randomized to omadacycline

100 mg iv., omadacycline 300 mg iv., moxifloxacin 400 mg or placebo. Mean AUC_{0-24} and C_{max} were dose proportional for omadacycline 100 mg and 300 mg. ECG results showed that omadacycline did not increase QTc; the largest one-sided upper 95% confidence bound (95% CB) on the difference between and omadacycline and placebo (ddQTcF) was 1.53 ms for omadacycline 100 mg and 0.83 ms for omadacycline 300 mg. Further, no relationship was observed between omadacycline plasma concentrations and ddQTcF. Assay sensitivity was confirmed with a >10 ms increase in ddQTcF with moxifloxacin. Within 1 h after dosing, mean peak increases in heart rate were observed for omadacycline (17 bpm for 100 mg iv. and 24 bpm for 300 mg iv.) versus 3 bpm

Table 5. *In vitro* activity of omadacycline and comparators against Gram-negative pathogens isolated in 2014.

Organism group (number tested) antimicrobial agent	MIC_{50}	MIC_{90}	MIC range
Enterobacteriaceae (301)			
Omadacycline	2	≥8	0.25–≥8
Tigecycline	0.12	1	≤0.015–4
Doxycycline	2	≥16	0.25–≥16
Tetracycline	2	≥32	0.5–≥32
Amoxicillin-clavulanate	8	≥16	≤1–≥16
Aztreonam	≤0.12	16	≤0.12–≥32
Ceftazidime	0.25	16	0.03–>32
Ceftriaxone	≤0.06	≥16	≤0.06–≥16
Gentamicin	≤1	≥16	≤1–≥16
Imipenem	≤0.12	1	≤0.12–4
Levofloxacin	≤0.12	≥8	≤0.12–≥8
Trimethoprim–sulfamethoxazole	≤0.5	≥8	≤0.5–≥8
Escherichia coli *(138)*			
Omadacycline	1	2	0.25–≥8
Tigecycline	0.06	0.12	≤0.015–1
Doxycycline	2	≥16	0.25–≥16
Tetracycline	2	≥32	0.5–≥32
Amoxicillin-clavulanate	4	≥16	≤1–≥16
Aztreonam	≤0.12	16	≤0.12–≥32
Ceftazidime	0.25	4	0.03–>32
Ceftriaxone	≤0.06	≥16	≤0.06–≥16
Gentamicin	≤1	≥16	≤1–≥16
Imipenem	≤0.12	≤0.12	≤0.12–0.5
Levofloxacin	≤0.12	≥8	≤0.12–≥8
Trimethoprim–sulfamethoxazole	≤0.5	≥8	≤0.5–≥8
Klebsiella *spp. (60)*[†]			
Omadacycline	2	4	0.5–≥8
Tigecycline	0.25	0.5	≤0.015–2
Doxycycline	2	≥16	0.5–≥16
Tetracycline	1	≥32	0.5–≥32
Amoxicillin-clavulanate	2	≥16	≤1–≥16
Aztreonam	≤0.12	≥32	≤0.12–≥32
Ceftazidime	0.12	>32	0.06–>32
Ceftriaxone	≤0.06	≥16	≤0.06–≥16
Gentamicin	≤1	≥16	≤1–≥16
Imipenem	≤0.12	0.25	≤0.12–4
Levofloxacin	≤0.12	≥8	≤0.12–≥8
Trimethoprim–sulfamethoxazole	≤0.5	≥8	≤0.5–≥8

[†]Organisms include: *K. oxytoca* (8), *K. pneumoniae* (52).
Adapted with permission from Flamm *et al.* (2015) [12].

Table 6. Susceptibility of *Legionella pneumophila* for all serogroups and for serogroup 1 collected from 1995 to 2014.

Organism group (number tested) antimicrobial agent	MIC_{50}	MIC_{90}	MIC range
Legionella pneumophila, *all serogroups (100 strains)*			
Omadacycline	0.25	0.25	0.06–1
Doxycycline	1	1	0.5–1
Telithromycin	0.03	0.06	0.016–0.12
Azithromycin	0.12	0.5	0.008–0.5
Erythromycin	0.25	1	0.06–2
Levofloxacin	0.016	0.016	≤0.004–0.03
Moxifloxacin	0.008	0.016	≤0.004–0.06
Legionella pneumophila, *serogroup 1 (45 strains)*			
Omadacycline	0.25	0.25	0.06–0.5
Doxycycline	1	1	0.5–1
Telithromycin	0.03	0.06	0.016–0.12
Azithromycin	0.12	0.5	0.016–0.5
Erythromycin	0.25	1	0.06–2
Levofloxacin	0.016	0.016	≤0.004–0.03
Moxifloxacin	0.016	0.016	≤0.004–0.06

Adapted with permission from Dubois *et al.* (2015) [14].

for placebo and 5 bpm for moxifloxacin. These changes were asymptomatic, not associated with changes in blood pressure, and were comparable across all groups by 12–24 h after dosing. Overall, this study is consistent with the results of preclinical studies demonstrating a low potential for adverse cardiac effects with omadacycline.

• Hepatic impairment

The PK of omadacycline was evaluated in subjects with varying degrees of hepatic impairment (mild, moderate and severe as determined by Child–Pugh classes A, B and C, respectively) and matched healthy subjects [28]. Both intravenous and oral doses of omadacycline were evaluated in these subjects. Results showed no effect of any degree of hepatic impairment on the PK of oral or intravenous omadacycline; geometric mean ratios for C_{max} and AUC ranged from 0.89 to 1.37. Further, pooled analysis of dose-normalized PK parameters demonstrated no clear relationship between exposure parameters and the severity of hepatic impairment. Thus, no dose adjustment for omadacycline is warranted in patients with hepatic impairment.

Clinical efficacy for treatment of skin infections

Two randomized, double-blind, multicenter studies (a Phase II study started in 2007 and a truncated Phase III study started in 2009) have been completed with omadacycline in patients with skin infections [29,30]. At the time that these studies were conducted, these infections were classified as 'complicated skin and skin structure infections' (cSSSI). In the Phase II study, adult patients with cSSSI received omadacycline 100 mg iv. once daily followed by the option to switch to 200 mg oral once daily, or linezolid 600 mg iv. twice daily with the option to switch to 600 mg oral twice daily. Aztreonam 2 g iv. twice daily could be added to linezolid if an infection due to a Gram-negative pathogen was suspected. Treatment was administered for up to 14 days. A total of 219 patients were treated (111 omadacycline, 108 linezolid) for an average of 10 days in both treatment groups [29]. The primary efficacy assessment was performed at the test of cure (TOC) visit, which was to occur 10–17 days after the last dose of study drug. Clinical success at that timepoint was defined (in abbreviated terms) as resolution of infection such that no additional antibiotics were needed for the skin infection at that time or used at any time between the end of study drug treatment and the TOC evaluation, and no antibiotics were given for another indication up to that time in the study. Clinical response in the intent-to-treat population was 88.3% with omadacycline and 75.9% with linezolid, and both drugs also were effective in patients known to be infected with MRSA.

In the truncated Phase III study, enrollment was stopped early because of a decision by the US FDA to change the primary end point in studies of

the treatment of bacterial skin infection. However, patients who had been enrolled up to that point were followed as originally planned [30]. In the study, adult patients with cSSSI received omadacycline 100 mg iv. once daily followed by the option to switch to 300 mg oral once daily, or linezolid using same dosing regimen as the Phase II study. Moxifloxacin (IV or oral) could be added to linezolid if an infection due to a Gram-negative pathogen was suspected. Treatment was administered for up to 14 days. A total of 140 patients with cSSSI were treated (68 omadacycline, 72 linezolid) for an average of 10 days in both treatment groups [30]. Clinical success was defined similarly to that in the Phase II study. Clinical response at the TOC visit in the intent-to-treat population was comparable for omadacycline and linezolid (85 vs 89%), and again both drugs were effective in the patients known to be infected with MRSA.

Clinical safety & tolerability

In Phase I studies, single doses of omadacycline have been administered across a wide dose range (25–600 mg iv., and 50–600 mg oral). Multiple doses of up 200 mg iv. once daily (7 days) and 300 mg oral once daily (10 days) also have been investigated. Both the intravenous and oral formulations have been generally well tolerated in these studies. In the intravenous administration studies, modest and reversible alanine aminotransferase increases were seen most notably with intravenous doses of 300 mg or greater. Following oral administration of omadacycline, mild nausea was observed most commonly at oral doses of 400 mg or greater. However, the different oral formulations evaluated in early studies (e.g., capsule vs tablet) may have influenced the gastrointestinal profile.

In both oral and intravenous Phase I studies, dose-dependent, transient increases in heart rate were observed for several hours following administration of omadacycline. The increases in heart rate were rarely reported as adverse events (palpitations) and were not associated with any ECG changes or other cardiac findings. Receptor binding studies suggest that omadacycline binds to the M2 subtype of the muscarinic receptor of the vagus nerve and this results in a short-lived nonadrenergic, vagolytic effect on heart rate, which is likely to be most notable in healthy volunteer subjects with relatively high vagal tone and lower resting heart rates (see the 'Nonclinical cardiovascular effects' section). Importantly, omadacycline did not increase ECG QTc intervals (see the 'Electrocardiogram QT evaluation' section).

In the Phase II and truncated Phase III studies in cSSSI, the incidence and type of adverse event (AE) was comparable between omadacycline and linezolid **(Table 8)** [29,30]. In the Phase II study, gastrointestinal AEs were most common overall (19% omadacycline, 17% linezolid). Premature discontinuation of treatment due to an AE was very infrequent in both groups (1% omadacycline, 2% linezolid). There was no pattern of adverse changes in laboratory safety parameters among patients treated with omadacycline; linezolid patients showed a modest decrease in platelet count, which is a known potential effect of that drug. Increased serum transaminases were reported as AEs in 3% of omadacycline patients and 7% of linezolid patients. Measurement of

Table 7. Summary of pharmacokinetic parameters for omadacycline after single intravenous and oral doses.

Parameters	100 mg iv. (n = 21)	300 mg oral tablet (n = 21)
AUC_{last} (h*mcg/ml)	8.8 ± 1.4	8.8 ± 2.0
%CV	15.6	22.4
AUC_{inf} (h**mcg/ml)	10.0 ± 1.5	10.3 ± 2.5
%CV	15.5	24.3
C_{max} (mcg/ml)	1.8 ± 0.7	0.5 ± 0.1
%CV	36.8	19.8
T_{max} (h)	0.5	2.8
%CV	19.8	25.8
$T_{1/2}$ (h)	16.8 ± 1.6	16.8 ± 1.7
%CV	9.3	10.1
CL (for iv.) or CL/F (for oral), (L/h)	10.3 ± 1.8	30.7 ± 6.5
%CV	17.3	21.0

Values are mean ± standard deviation, except for T_{max}, which is median.
AUC: Area under the concentration-time curve; CL: Clearance; CV: Coefficient of variation; CL/F: Total clearance after oral administration; iv.: Intravenous.
Data taken from Sun *et al.* (2011) [19].

Table 8. Incidence (%) of adverse events occurring in >3% of patients in either treatment group from Phase II and III studies in complicated skin and skin structure infections.

Adverse event	Patients n (%)	
	Omadacycline (n = 179)	Linezolid (n = 180)
Nausea	31 (17.3)	27 (15.0)
Headache	23 (12.9)	14 (7.8)
Constipation	11 (6.2)	4 (2.2)
Dizziness	11 (6.2)	11 (6.1)
Vomiting	11 (6.2)	15 (8.3)
CPK increased	10 (5.6)	3 (1.7)
Fatigue	8 (4.5)	5 (2.8)
Diarrhea	6 (3.4)	19 (10.6)
Rash	6 (3.4)	6 (3.3)
ALT increased	5 (2.8)	11 (6.1)
AST increased	4 (2.2)	7 (3.9)
Insomnia	4 (2.2)	8 (4.4)
Decreased appetite	2 (1.1)	6 (3.3)
Dysgeusia	1 (0.6)	6 (3.3)

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase.
Adapted with permission from [27,28].

vital signs was performed less frequently than in the Phase I studies, but changes from baseline in heart rate and blood pressure at the end of the course of treatment were clinically insignificant and similar between the treatment groups. Three omadacycline patients (3%) had AEs of tachycardia and one other patient reported palpitations; all of these AEs were mild in intensity, were assessed as unrelated to study drug, and none resulted in discontinuation.

In the truncated Phase III study, gastrointestinal AEs again were most common overall (44% omadacycline, 40% linezolid) [28]. Premature discontinuation of treatment due to an AE was infrequent (3% omadacycline, 0% linezolid). Among laboratory-related events, creatine phosphokinase elevation (with no clinical manifestations) was reported in 9% of omadacycline patients compared with 3% for linezolid. Increased alanine aminotransferase was reported as an AE in one omadacycline patient (2%) and four linezolid patients (6%). Tachycardia was reported as an AE in two omadacycline patients (3%) and four linezolid patients (6%).

Overall, the target therapeutic doses of omadacycline were very well tolerated in both oral and intravenous formulations. There were no serious AEs that were related to study drug in any of the completed clinical studies. Across both of the studies in cSSSI patients, nausea was the most common AE; all such events were of mild or moderate intensity and did not lead to treatment discontinuation in any of the completed studies. In contrast, dose-limiting nausea and vomiting occurs with intravenous tigecycline and with both intravenous and oral administration of eravacycline [31–36]. Because it is well tolerated, especially with regard to GI effects of nausea and vomiting that are common with many antibiotics, omadacycline may be particularly well suited for treatment of community-acquired bacterial infections, whether they are managed in hospital or as outpatients.

Discussion

Omadacycline is being evaluated in two Phase III randomized, double-blind studies in ABSSSI and CABP. The primary objective of these studies is to demonstrate the noninferiority of omadacycline to active comparators. The ABSSSI study is expected enroll approximately 650 patients with skin infections known or suspected to be due to Gram-positive pathogens. This study will evaluate the following two regimens, each of which is to be administered for 7–14 days:

- Omadacycline 100 mg iv. every 12 h for two doses and then 100 mg iv. every 24 h through at least Day 3, then an option to switch to 300 mg PO every 24 h;
- Linezolid 600 mg iv. every 12 h through at least Day 3, then an option to switch to 600 mg PO every 12 h.

EXECUTIVE SUMMARY

Mechanism of action

- Omadacycline exerts its primary effect by binding to the 30S subunit of the bacterial ribosome and inhibiting protein synthesis.
- Omadacycline is active against bacterial strains expressing efflux and ribosomal protection, which are the two main forms of tetracycline resistance.

Microbiology

- Omadacycline demonstrates antimicrobial activity *in vitro* against a wide range of Gram-positive and Gram-negative pathogens.
- Omadacycline is active against methicillin-resistant *Staphylococcus aureus*, penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococcus.
- Omadacycline exhibits *in vitro* activity against anerobes including *Bacteroides fragilis, Clostridium difficile, Clostridium perfringens* and anaerobic Gram-positive cocci.
- Omadacycline is active against atypical bacteria including *Legionella pneumophila* and *Chlamydia* spp.

Pharmacokinetics

- Following intravenous (iv.) administration, omadacycline exhibits a linear pharmacokinetic profile over the dose range of 25–600 mg.
- The oral tablet formulation is 35% bioavailable; a 300 mg oral dose is bioequivalent to a 100 mg iv. dose.
- Omadacycline has low plasma protein binding (21%) and no active metabolites have been identified; *in vitro* studies indicate a low potential for drug–drug interactions.
- Omadacycline is eliminated predominantly by fecal elimination of parent drug; approximately 40% of an absorbed dose is excreted in the urine.

Clinical efficacy

- In both a Phase II and a truncated Phase III clinical study in patients with complicated skin and skin structure infections, the efficacy of omadacycline was noninferior to linezolid.

Safety & tolerability

- In the completed studies in patients with complicated skin and skin structure infections, the target therapeutic doses of omadacycline were well tolerated in both oral and intravenous formulations. In these studies the adverse event (AE) profile of omadacycline was comparable to linezolid; the most common AE was nausea, which occurred at similar rates for both omadacycline and linezolid and did not lead to any treatment discontinuations.
- Transient increases in heart rate (due to a vagolytic effect) were observed most notably in healthy volunteers with lower resting heart rates; there were no associated changes in blood pressure or other cardiac findings. Omadacycline does not prolong QTc intervals.
- Reversible increases in liver enzymes have been observed at relatively high doses.

Dosage & administration

- For the indications of treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, omadacycline is being evaluated as once-daily doses of 100 mg iv. followed by once daily doses of 300 mg orally.
- Oral omadacycline should be administered in a fasted state.
- Among adults, no dosage adjustment is required for age, gender, or hepatic impairment.

The CABP study is expected to enroll approximately 750 patients with known or suspected bacterial pneumonia classified as Patient Outcomes Research Team (PORT) Risk Class II–IV. This study will evaluate the following two regimens, each of which is to be administered for 7–14 days:

- Omadacycline 100 mg iv. every 12 h for two doses and then 100 mg iv. every 24 h through at least Day 3, then an option to switch to 300 mg PO every 24 h;
- Moxifloxacin 400 mg iv. every 24 h through at least Day 3, then an option to switch to 400 mg PO every 24 h.

In addition to the Phase III studies described above, additional clinical pharmacology studies of omadacycline are ongoing to quantify lung penetration and urinary excretion, to evaluate the PK of omadacycline in subjects with renal impairment, and to assess the safety profile of multiple doses higher than those being used in the ongoing Phase III studies. These evaluations will inform decisions about potential development of omadacycline for indications beyond ABSSSI and CABP.

Conclusion & future perspective

Omadacycline may represent a novel antibiotic with a broad spectrum of activity against community-associated bacterial pathogens, once daily oral and intravenous dosing, favorably pharmacokinetics, low plasma protein binding, low potential for drug–drug interactions, and early evidence of efficacy and tolerability. Ongoing and future clinical studies with both oral and intravenous formulations will help define the place of omadacycline in the armamentarium for treating common, serious bacterial infectious diseases originating in the community.

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