Discovery, pharmacology, and clinical profile of omadacycline, a novel aminomethylcycline antibiotic

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ABSTRACT

Omadacycline is novel, aminomethyl tetracycline antibiotic being developed for oral and intravenous (IV) administration for the treatment of community-acquired bacterial infections. Omadacycline is characterized by an aminomethyl substituent at the C9 position of the core 6-member ring. Modifications at this position result in an improved spectrum of antimicrobial activity by overcoming resistance known to affect older generation tetracyclines via ribosomal protection proteins and efflux pump mechanisms. In vitro, omadacycline has activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical pathogens including *Legionella* and *Chlamydia* spp. Omadacycline offers once daily oral and IV dosing and a clinical tolerability and safety profile that compares favorably with contemporary antibiotics used across serious community-acquired infections where resistance has rendered many less effective. In studies in patients with complicated skin and skin structure infections, including those with MRSA infections, omadacycline exhibited an efficacy and tolerability profile that was comparable to linezolid. Ongoing and planned clinical studies are evaluating omadacycline as monotherapy for treating serious community-acquired bacterial infections including Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP). This review provides an overview of the discovery, microbiology, nonclinical data, and available clinical safety and efficacy data for omadacycline, with reference to other contemporary tetracycline-derived antibiotics.

1. Introduction

Omadacycline is a novel aminomethylcycline antibiotic being developed for once daily oral and intravenous (IV) administration for the treatment of community-acquired bacterial infections.[1] Omadacycline is being developed because of an increasing incidence of resistance to earlier tetracyclines including doxycycline and minocycline and the resistance faced by other classes of antibiotics.[2] Omadacycline differs from earlier generation tetracyclines because it overcomes the two primary tetracycline resistance mechanisms of ribosomal protection and efflux,[3] thus restoring the historical broad-spectrum efficacy of earlier generation tetracyclines.

Extensive results from in vitro studies have demonstrated antibacterial activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical pathogens including *Legionella* and *Chlamydia* spp.[4] Based on this profile, omadacycline was advanced into phase 2 and 3 studies for complicated skin and skin structure infections (cSSSI) where it showed efficacy and

tolerability comparable to linezolid.[5,6] Omadacycline is currently undergoing development in phase 3 clinical studies for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP).

2. Discovery of omadacycline

2.1. Structure–activity relationship

Omadacycline is a stable, well-characterized crystalline drug substance that differs from other tetracyclines because of a novel modification at the C9 position.[1] Omadacycline is an aminomethylcycline antibiotic that is characterized by an aminomethyl group at the C9 position on the tetracycline structure.[1] Modifications at the C9 position result in improved antimicrobial potency for these new generation tetracyclines attributed to stability to ribosomal protection proteins and efflux pump mechanisms.[7,8]

A series of aminomethylcyclines with potent in vitro activity (minimum inhibitory concentration [MIC] $\leqslant$ 0.06–2.0 mcg/mL) were evaluated in vitro against Gram-positive bacteria possessing different tetracycline resistance mechanisms of ribosomal protection (Tet (M)) in *Staphylococcus aureus*, *Enterococcus faecalis*, and

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Streptococcus pneumoniae and efflux (Tet (K) in *S. aureus* and Tet (L) in *E. faecalis*).[1] Omadacycline was identified as one of the lead aminomethylcyclines in that series by classical structure–activity relationship determinations, which now represent a novel class of tetracycline-derived antibiotics with potent in vitro activity against tetracycline-resistant Gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE).

Omadacycline differs from the glycylcycline tetracyclines, tigecycline (9-*t*-butylglycylamido) and eravacycline (TP-434, 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline) by the presence of an aminomethyl group at the C9 position (Fig. 1).[9,10] Modifications at the C9 position result in improved antimicrobial potency for these new generation tetracyclines attributed to stability to ribosomal protection proteins and efflux pump mechanisms.[7,8] Omadacycline has other absorption, distribution, metabolism, and excretion (ADME) attributes that further distinguish it from the glycylcycline class of tetracyclines. These differences will be discussed further below under Pharmacology.

2.2. Omadacycline mechanism of action

In vitro macromolecular synthesis assays with radiolabeled substrates demonstrated that omadacycline inhibits protein synthesis while having no significant effect on RNA, DNA and peptidoglycan synthesis. Further, omadacycline binds to the tetracycline binding site on the 30S subunit of the bacterial ribosome[3,11] with enhanced binding similar to tigecycline based on additional molecular interactions.[12]

2.3. Overcoming tetracycline resistance

There are two basic and clinically important mechanisms of tetracycline resistance: tetracycline efflux[2] and ribosome protection.[2] Tetracycline efflux proteins are membrane-associated proteins that recognize and export tetracycline from the cell, thus reducing the intracellular drug concentration. They are found in both Gram-positive and Gram-negative bacteria. Ribosomal protection proteins are cytoplasmic proteins that bind the ribosome, causing an alteration in ribosomal conformation that prevents tetracycline from binding.[13]

The majority of efflux proteins result in bacterial resistance to tetracyclines but not to minocycline, aminomethylcyclines or glycylcyclines.[2,3] However, the Gram-negative *tet*(B) gene produces an efflux protein, which produces bacterial resistance to both tetracycline and minocycline but not aminomethylcyclines and glycylcyclines.[2,3] Ribosomal protection proteins produce broad resistance to tetracyclines that exceeds that observed with bacteria that carry efflux proteins that impact doxycycline and minocycline.[2] Of the 10 or more ribosomal protection proteins, the Tet (M) and Tet(O) proteins have been most closely characterized and both omadacycline and tigecycline retain activity against both types.[2,3]

The in vitro activity of omadacycline and other aminomethylcyclines was tested against Gram-positive bacteria that possessed the primary tetracycline resistance mechanisms of ribosomal protection and efflux.[3,14] Omadacycline exhibited excellent activity against clinical bacterial isolates possessing a variety of tetracycline resistance mechanisms. Furthermore, the ability of omadacycline to inhibit whole-cell protein synthesis was not affected in whole-cell assays by the presence of either tetracycline efflux (Tet(K)) or ribosome protection (Tet(O)).[3,14] Omadacycline also demonstrates potent in vitro activity against TET-resistant Gram-positive bacteria that were resistant to other antibiotics including quinolones and glycopeptides as well as tetracyclines.[15]

The ability to select resistance in vitro is often used to indicate the potential for bacteria to become resistant to an antibiotic either during therapy (often as a single mutational event) or over the lifetime of the antibiotic (often due to a series of mutations). Bacteria that carry any of the classic tetracycline resistance genes conferring either ribosomal protection or a tetracycline efflux pump have remained susceptible to omadacycline. No Gram-positive clinical isolates with reduced susceptibility to omadacycline (MIC ⩾ 4 mcg/mL) have been identified including strains that are resistant to currently available antibiotics, such as methicillin, vancomycin, and doxycycline.[4,16] Selection of single-step resistant mutants in *S. aureus* strains, including those carrying tetracycline resistance determinants *tet*(M) and *tet*(K), was not observed with omadacycline. Further, in multiple step passage studies conducted over 10 days, no selection for multi-step resistant mutants in tetracycline sensitive and tetracycline-resistant strains of *S. aureus* was observed with omadacycline.[3,14] Compared to MICs in susceptible strains (MIC range: ⩽0.06–0.5 mcg/mL), MICs were not significantly affected by the presence of Tet(M) (MIC range: 0.125–0.5 mcg/mL) or Tet(L) or Tet(K) (MIC range: 0.125–0.25 mcg/mL) in resistant strains. Therefore, target-based resistance to omadacycline or resistance based on mutational changes to tetracycline efflux or ribosome protection are unlikely to arise quickly.

3. In vitro microbiology

The in vitro activity of omadacycline has been evaluated in numerous studies against a broad range of Gram-positive and Gram-negative aerobic bacteria as well as many anaerobes and atypical pathogens.[4,16–19] In particular, in vitro activity has been demonstrated against tetracycline-resistant pathogens including MRSA, PRSP, and VRE.[4,16]

3.1. Gram-positive bacteria

Gram-positive pathogens including drug-resistant strains are highly sensitive in vitro to omadacycline (data on file).[16,19–22] A comparison of in vitro activity for various antibiotics against *S. aureus* found that the MIC_{90} for all isolates collected during
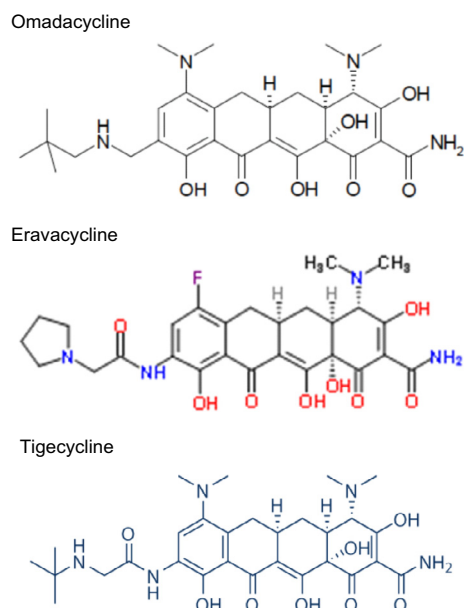
Figure 1. Chemical structures of new generation tetracyclines, omadacycline, eravacycline, and tigecycline.[3,9,10]

2014 was 0.12 mcg/mL (data on file), and the MIC data were similar for all MRSA as well as hospital-associated and community-associated MRSA (Tables 1 and 3). Similar results were reported in a separate analysis of in vitro activity of methicillin-sensitive and resistant *S. aureus*, where the MIC_{90} for omadacycline was ⩽2 mcg/mL for all isolates, but was ⩽0.5 mcg/mL for the majority of isolates.[20]

A similar comparison of in vitro activity of antibiotics against *Streptococcus pneumoniae* collected during 2014 reported an omadacycline MIC_{90} of 0.06 mcg/mL for all isolates, which was similar to the results for isolates tested in 2010.[16] The MIC_{90} for omadacycline remained at 0.06 mcg/mL for the penicillin-sensitive, multidrug-resistant, and ceftriaxone non-susceptible isolates (Tables 2 and 3).

The in vitro activity of omadacycline was evaluated against isolates of methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), vancomycin-sensitive and -resistant *E. faecium* (VRE), *E. faecalis*, penicillin-sensitive (SPN) and -resistant *S. pneumoniae* (PRSP), and Groups A and B beta-hemolytic streptococci in a series of studies.[19,21,22] Omadacycline demonstrated consistent in vitro activity spanning a time period from 2003 to 2012 with a maximum omadacycline MIC_{90} ranging from ⩽0.5 to 1.0 mcg/mL, but the MIC_{90} was ⩽0.5 mcg/mL.

3.2. Gram-negative bacteria

The in vitro activity of omadacycline against Gram-negative bacteria has been evaluated in a number of studies.[17,21–23] Omadacycline demonstrated in vitro activity against *Haemophilus influenzae* and *Moraxella catarrhalis* with a MIC_{90} of 2 and 0.25 mcg/mL, respectively.[22] Omadacycline also demonstrated activity against many Gram-negative species including *Escherichia coli*, *Enterobacter aerogenes*, *E. cloacae*, *Serratia marcescens*, *Salmonella* spp., *Shigella* spp., and *Stenotrophomonas maltophilia* with a MIC_{90} at <4.0 mcg/mL.[22] Other Gram-negative pathogens including *Pseudomonas aeruginosa*, *Proteus* spp., and *Providencia* spp. exhibited a higher (>16 mcg/mL) MIC_{90} for omadacycline. In another study, omadacycline demonstrated in vitro activity against *E. coli*, *Klebsiella pneumoniae*, and *H. influenzae* with MIC_{90} of 2–4 mcg/mL.[4] The in vitro activity of various antibiotics was tested against Enterobacteriaceae causing urinary tract infections from surveillance data collected during 2014 and compared with isolates collected in 2010.[17] For 2014 the omadacycline MIC_{90} for *E. coli* was ⩽4 mcg/mL and for Enterobacteriaceae was ⩾8 mcg/mL (Tables 3 and 4). Additionally, the MIC distributions were similar for *E. coli* and *K. pneumoniae* regardless of ESBL phenotype (Table 4). No MIC_{90} drift was observed between 2010 and 2014 isolates tested.

3.3. Anaerobic bacteria

Omadacycline exhibits in vitro activity against anaerobes including *Bacteroides fragilis*, *Clostridium difficile*, *Clostridium perfringens*, and anaerobic Gram-positive cocci with a MIC_{90} of 0.12–4 mcg/mL (data on file).[24] Against *C. difficile*, the in vitro activity of omadacycline was evaluated using both broth and agar microdilution methods.[24] The MIC_{90} for omadacycline was 0.06 for broth microdilution and 0.12 mcg/mL for agar microdilution, which was comparable to other antibiotics tested including doxycycline and metronidazole and was superior to clindamycin, imipenem, and cefotaxime.

3.4. Atypical bacteria

Omadacycline demonstrates in vitro activity against the atypical pathogens *Legionella pneumophila*.[18] The in vitro activity of omadacycline against *L. pneumophila* isolated from 1995 to 2005

and from 2006 to 2014 was examined to determine changes in susceptibility over time.[18] No change in the in vitro activity of omadacycline against all tested *L. pneumophila* or against serogroup 1 was identified over the time period from 1995 to 2014. The MIC_{90} for omadacycline was 0.25 mcg/mL, which was comparable to other tested antibiotics (Table 5). Further, omadacycline has been shown to inhibit and kill *L. pneumophila* within macrophages, an important characteristic necessary for the treatment of pneumonia caused by *Legionella*.[25]

3.5. Bactericidal vs. bacteriostatic activity

In a study of 85 strains of different bacteria, in vitro bactericidal activity was observed against streptococci, *M. catarrhalis,* and *H. influenzae*, while bacteriostatic activity was observed against enterococci, *S. aureus*, and *E. coli*.[26] Time-kill studies generally confirmed the mean bactericidal concentration (MBC) data.[26] In static time-kill studies of *H. influenzae*, omadacycline concentrations of 1× the MIC were required for a ⩾3 Log_{10} CFU reduction from baseline.[27] Thus, omadacycline demonstrated potent in vitro bactericidal activity against *H. influenzae* at concentrations that were up to twice the MIC of 0.5–2 mcg/mL. Notably, omadacycline was rapidly bactericidal against *H. influenzae* and *S. pneumoniae*, with bactericidal activity comparable to tigecycline. Against tetracycline-sensitive and -resistant strains of *S. aureus*, omadacycline exhibited improved early killing compared to doxycycline although neither achieved 3 log_{10} reduction in viable counts at clinically relevant concentrations within 24 h.[14]

3.6. Postantibiotic effect

The postantibiotic effect (PAE) of omadacycline compared with tigecycline and linezolid was evaluated against target pathogens to better evaluate pharmacodynamics properties.[28] MICs were determined against clinical isolates of *S. aureus*, *E. faecalis*, *E. faecium*, *S. pneumoniae*, and *E. coli*. PAE was determined after initial exposure of log-phase bacteria to 5X the MIC of each antibiotic for 1 h alongside an unexposed control. PAE was calculated as the time for bacteria to grow 1-log after initial exposure and drug washout relative to unexposed controls. Overall, the PAE of omadacycline was similar to that of tigecycline with the exception of enterococci (for which the PAE was slightly longer with tigecycline). Relative to linezolid, omadacycline and tigecycline exhibited prolonged PAE. This prolonged PAE with omadacycline and tigecycline suggests an added benefit in the treatment of serious community-acquired bacterial infections.

3.7. Efficacy in animal models

The in vivo efficacy of omadacycline was demonstrated against Gram-positive and Gram-negative pathogens using several different murine models of infection (Table 6).[4]

In a series of experiments (data on file), the in vivo efficacy of omadacycline was studied in non-neutropenic models of *S. aureus* thigh wound infection, *S. pneumoniae* lethal pneumonia infection, and *H. influenzae* pneumonia (Table 7a–c). Against *S. aureus* and *S. pneumoniae*, omadacycline and tigecycline exhibited efficacy at comparable doses and both were generally more potent than the other antibiotics tested. Relatively higher doses of omadacycline were required to achieve efficacy against *H. influenzae*.

Consistent with its in vitro activity against *C. difficile*, omadacycline has been shown to be effective against *C. difficile* infection in the hamster colitis model.[24] The MIC_{90} for omadacycline was 0.06 mcg/mL, and omadacycline was as active as tigecycline, metronidazole, and vancomycin in the hamster model. Median survival was 12 days for omadacycline vs. 2 days for vancomycin and

Table 1
Activity of omadacycline and other antimicrobial agents tested against North American and European MRSA, hospital-acquired MRSA, and community-acquired MRSA for 2014 vs. 2010 (data on file)

Organism (no. tested) Antimicrobial agent	North America				Europe			
	2014		2010		2014		2010	
	MIC$_{50/90}$	MIC range	MIC$_{50/90}$	MIC range	MIC$_{50/90}$	MIC range	MIC$_{50/90}$	MIC range
MRSA	200		2508		202		750	
Omadacycline	**0.06/0.12**	**0.03–1**	**0.12/0.5**	**0.03–4**	**0.12/0.12**	**0.03–1**	**0.12/0.5**	**0.03–2**
Tigecycline	0.06/0.12	0.03–0.25	0.12/0.25	⩽0.03–1	0.06/0.12	⩽0.015–0.25	0.12/0.25	⩽0.03–0.5
Doxycycline	0.12/0.5	⩽0.06–>8	0.12/0.5	⩽0.06–>8	0.12/2	⩽0.06–>8	⩽0.25/2	⩽0.06–>8
Tetracycline	0.12/1	⩽0.03–>16	⩽0.25/1	⩽0.25–>8	0.12/16	⩽0.03–>16	0.25/>8	⩽0.25–>8
Clindamycin	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2
Daptomycin	0.25/0.5	0.12–2	0.25/0.5	⩽0.06–2	0.25/0.5	0.12–1	0.250.5	0.12–2
Erythromycin	>16/>16	0.25–>16	>4/>4	⩽0.25–>4	>16/>16	⩽0.12–>16	>4/>4	⩽0.25–>4
Gentamicin	⩽1/⩽1	⩽1–>8	⩽1/⩽1	⩽1–>8	⩽1/>8	⩽1–>8	⩽1/>8	⩽1–>8
Levofloxacin	4/>4	⩽0.12–>4	4/>4	⩽0.5–>4	>4/>4	⩽0.12–>4	>4/>4	⩽0.5–>4
Linezolid	1/1	0.5–1	1/1	⩽0.12–8	1/1	⩽0.12–2	1/1	0.25–2
TMP-SMX	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5–>4	0.12/0.25	⩽0.5–>4
Vancomycin	1/1	0.25–2	1/1	0.25–2	1/1	0.25–2	0.12/0.25	⩽0.12–2
Hospital-acquired MRSA	101		497		102		379	
Omadacycline	**0.12/0.5**	**0.06–1**	**0.12/0.5**	**0.06–4**	**0.12/0.12**	**0.03–1**	**0.12/0.25**	**0.03–2**
Tigecycline	0.06/0.12	0.03–0.25	0.12/0.25	⩽0.03–0.5	0.06/0.12	⩽0.015–0.25	0.12/0.25	⩽0.03–0.5
Doxycycline	0.12/0.5	⩽0.06–8	0.12/1	⩽0.06–>8	0.12/2	⩽0.06–>8	0.12/4	⩽0.06–>8
Tetracycline	0.12/1	0.06–>16	⩽0.25/2	⩽0.25–>8	0.12/>16	⩽0.03–>16	⩽0.25/>8	⩽0.25–>8
Clindamycin	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2
Daptomycin	0.250.5	0.12–1	0.25/0.5	0.12–1	0.25/0.5	0.12–1	0.25/0.5	0.12–2
Erythromycin	>16/>16	0.25–>16	>4/>4	⩽0.25–>4	>16/>16	⩽0.12–>16	>4/>4	⩽0.25–>4
Gentamicin	⩽1/⩽1	⩽1–>8	⩽1/⩽1	⩽1–>8	⩽1/>8	⩽1–>8	⩽1/>8	⩽1–>8
Levofloxacin	>4/>4	⩽0.12–>4	>4/>4	⩽0.5–>4	>4/>4	⩽0.12–>4	>4/>4	⩽0.5–>4
Linezolid	1/1	0.5–1	1/1	0.25–8	1/1	⩽0.12–2	1/1	0.25–2
TMP-SMX	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5–>4
Vancomycin	1/1	0.5–2	1/1	0.5–2	1/1	0.25–2	1/1	⩽0.12–2
Community-acquired MRSA	99		1461		100		233	
Omadacycline	**0.06/0.12**	**0.03–1**	**0.12/0.25**	**0.03–4**	**0.12/0.12**	**0.12**	**0.12/0.25**	**0.03–1**
Tigecycline	0.06/0.12	0.03–0.12	0.12/0.25	⩽0.03–0.5	0.06/0.12	0.12	0.12/0.25	⩽0.03–0.5
Doxycycline	⩽0.06/0.5	⩽0.06–>8	0.12/0.25	⩽0.06–>8	0.12/1	1	0.12/1	⩽0.06–>8
Tetracycline	0.12/1	⩽0.03–>16	⩽0.25/0.5	⩽0.25–>8	0.12/16	16	⩽0.25/>8	⩽0.25–>8
Clindamycin	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	⩽0.25–>2	⩽0.25/>2	>2	⩽0.25/>2	⩽0.25–>2
Daptomycin	0.25/0.5	0.12–2	0.25/0.5	⩽0.06–2	0.25/0.5	0.5	0.25/0.5	0.12–1
Erythromycin	>16/>16	0.25–>16	>4/>4	⩽0.25–>4	>16/>16	>16	>4/>4	⩽0.25–>4
Gentamicin	⩽1/⩽1	⩽1–>8	⩽1/⩽1	⩽1–>8	⩽1/>8	>8	⩽1/>8	⩽1–>8
Levofloxacin	4/>4	⩽0.12–>4	4/>4	⩽0.5–>4	>4/>4	>4	>4/>4	⩽0.5–>4
Linezolid	1/1	0.5–1	1/1	⩽0.12–2	1/1	1	1/1	0.25–2
TMP-SMX	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5–>4	⩽0.5/⩽0.5	⩽0.5	⩽0.5/⩽0.5	⩽0.5–>4
Vancomycin	1/1	0.25–2	1/1	0.25–2	1/1	1	1/1	0.25–2

4 days for clindamycin.[24] Thus, omadacycline demonstrates potential efficacy for the treatment of *C. difficile* Infections.

4. In vivo pharmacology

4.1. Non-clinical pharmacology

4.1.1. In vitro stability and drug–drug interaction potential of omadacycline

The stability of omadacycline (4.8 and 48 μM) was assessed in human microsomes and hepatocytes.[38] After 30 min incubation of omadacycline in human microsomes, >90% of omadacycline was recovered intact. Similarly, after incubation of omadacycline up to 24 h in human hepatocytes, >86% was recovered intact. These results indicate that omadacycline is not metabolized to any significant extent.

The potential for drug-drug-interactions with omadacycline was assessed using either pooled human liver microsome preparations, S9, liver cytosol, or recombinant flavin monooxygenases (FMO1, FMO3, FMO5).[38] Induction of CYP450 isozymes was evaluated in primary human hepatocytes incubated with omadacycline 1–100 μM and a substrate probe for 24 and 48 h. Inhibition of CYP450 isozymes was evaluated with pooled human microsomes at omadacycline concentrations of 1–50 μM and isozyme specific substrates at concentrations approximating the Km of each substrate. 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 demonstrated no significant inhibition of CYP isozyme activity. In addition, there was no time-dependent inhibition of omadacycline or its possible metabolites for CYP1A2 2C9, 2D6 or 3A4/5.

4.1.2. Transporter effects

Human drug transporter proteins were used to evaluate the in vitro potential for drug–drug interactions with omadacycline.[39] The effects of [14C]omadacycline to induce or inhibit were evaluated against cells stably expressing human organic anion transporters 1 or 3 (hOAT1 or hOAT3), organic cation transporter 2 (hOCT2), and organic anion transport polypeptide transporters OATP1B1 and OATP1B3. The effect of P-glycoprotein (P-gp), multidrug resistance-associated protein 2 (MRP2), and Breast Cancer Resistance Protein (BCRP) on omadacycline transport was evaluated in Caco-2 cells. The inhibitory effect of omadacycline on hOAT1, hOAT3, hOCT2, OATP1B1, and OATP1B3 was determined in HEK293 cells, and inhibition of BRCP, P-gp, and MRP2 by omadacycline was determined in T8, T0.3, and MDCKII cell lines. Assessment of mRNA levels in human hepatocytes was used to determine induction of P-gp and MRP2 by omadacycline.

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Table 2
Activity of omadacycline and other antimicrobial agents against *S. pneumoniae* by region for 2014 vs. 2010[16]

Organism (no. tested) Antimicrobial agent	North America				Europe			
	2014		2010		2014		2010	
	MIC$_{50/90}$	MIC Range	MIC$_{50/90}$	MIC Range	MIC$_{50/90}$	MIC Range	MIC$_{50/90}$	MIC Range
S. pneumoniae penicillin-sensitive	151		1028		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	0.03/0.03	⩽0.015–0.06	⩽0.03/0.06	⩽0.03–0.12	0.03/0.06	⩽0.015–0.06	⩽0.03/⩽0.03	⩽0.03–0.12
Doxycycline	0.12/8	⩽0.06–>8	0.25/8	⩽0.06–>8	0.12/8	⩽0.06–>8	0.12/8	⩽0.06–>8
Amoxicillin-clavulanate	⩽1/8	⩽1–>8	⩽1/8	⩽1–>8	⩽1/8	⩽1–>8	⩽1/2	⩽1–8
Tetracycline	0.25/16	0.12–>16	0.5/>8	⩽0.25–>8	0.25/16	0.12–>16	0.5/>8	⩽0.25–>8
Ceftriaxone	0.25/2	⩽0.06–4	⩽0.06/1	⩽0.06–8	0.25/2	⩽0.06–8	⩽0.06/1	⩽0.06–4
Clindamycin	⩽0.25/>2	⩽0.25–>2	⩽0.25/>1	⩽0.25–>1	⩽0.25/>2	⩽0.25–>2	⩽0.25/>1	⩽0.25–>1
Erythromycin	4/>16	⩽0.12–>16	⩽0.06/>8	⩽0.06–>8	⩽0.12/>16	⩽0.12–>16	⩽0.06/>8	⩽0.06–>8
Levofloxacin	1/1	0.5–>4	1/1	⩽0.5–>4	1/1	0.5–>4	1/1	⩽0.5–>4
Penicillin	0.25/4	⩽0.06–8	⩽0.03/4	⩽0.03–>4	0.25/2	⩽0.06–8	⩽0.03/2	⩽0.03–>4
TMP-SMX	⩽0.5/>4	⩽0.5–>4	⩽0.5/>4	⩽0.5–>4	1/>4	⩽0.5–>4	⩽0.5/4	⩽0.5–>4
Multi-drug resistant	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	0.03/0.06	⩽0.015–0.06	⩽0.03/0.06	⩽0.03–0.12	0.03/0.06	⩽0.015–0.06	⩽0.03/0.06	⩽0.03–0.06
Doxycycline	4/>8	⩽0.06–>8	4/>8	⩽0.06–>8	8/>8	0.12–>8	4/>8	⩽0.06–>8
Tetracycline	>16/>16	0.12–>16	>8/>8	⩽0.25–>8	>16/>16	0.12–>16	>8/>8	⩽0.25–>8
Amoxicillin-clavulanate	4/8	⩽1–>8	4/8	⩽1–>8	2/8	⩽1–>8	2/8	⩽1–8
Ceftriaxone	1/2	⩽0.06–4	½	⩽0.06–8	1/2	⩽0.06–8	1/2	⩽0.06–4
Clindamycin	>2/>2	⩽0.25–>2	>1/>1	⩽0.25–>1	>2/>2	⩽0.25–>2	>1/>1	⩽0.25–>1
Erythromycin	>16/>16	0.25–>16	>8/>8	⩽0.06–>8	>16/>16	⩽0.12–>16	>8/>8	⩽0.06–>8
Levofloxacin	1/1	0.5–>4	1/1	⩽0.5–>4	1/1	0.5–>4	1/1	⩽0.5–>4
Penicillin	2/4	⩽0.06–8	2/4	0.12–>4	2/4	⩽0.06–8	2/4	⩽0.03–>4
TMP-SMX	4/>4	⩽0.5–>4	4/>4	⩽0.5–>4	4/>4	⩽0.5–>4	4/>4	⩽0.5–>4
Ceftriaxone-NS (MIC, ⩾2 µg/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	0.03/0.06	⩽0.015–0.06	⩽0.03/⩽0.03	⩽0.03–0.12	0.03/0.06	⩽0.015–0.06	⩽0.03/0.06	⩽0.03–0.06
Doxycycline	4/8	0.12–8	4/8	⩽0.06–>8	4/8	0.12–>8	4/8	0.12–8
Tetracycline	>16/>16	0.25–>16	>8/>8	⩽0.25–>8	>16/>16	0.25–>16	>8/>8	⩽0.25–>8
Amoxicillin-clavulanate	8/8	4–8	8/8	⩽1–>8	8/>8	⩽1–>8	2/8	2–8
Ceftriaxone	2/2	2–4	2/8	2–8	2/8	2–8	2/2	2–4
Clindamycin	>2/>2	⩽0.25–>2	>1/>1	⩽0.25–>1	>2/>2	⩽0.25–>2	>/>1	⩽0.25–>1
Erythromycin	>16/>16	2–>16	>8/>8	4–>8	>16/>16	⩽0.12–>16	>8/>8	⩽0.06–>8
Levofloxacin	1/1	1–1	1/1	⩽0.5–4	1/1	0.5–1	1/1	⩽0.5–>4
Penicillin	4/4	2–8	4/4	0.25–>4	2/4	1–8	4/4	2–>4
TMP-SMX	4/>4	4–>4	4/>4	⩽0.5–>4	>4/>4	⩽0.5–>4	4/>4	⩽0.5–>4

Table 3
MIC distribution for omadacycline against key pathogen (Europe 2010–2011)[17]

Organism	No.	Omadacycline MIC in mg/L[a]											
		⩽0.03	0.06	0.12	0.25	0.5	1	2	4	8	⩾16	MIC$_{50}$	MIC$_{90}$
Staphylococcus aureus	5,533	42 (0.8)	619 (11.9)	3762 (79.9)	**943** (**97.0**)	149 (99.7)	13 (>99.9)	5 (100.0)	—	—	—	0.12	0.25
MSSA	3,994	29 (0.7)	475 (12.6)	2802 (82.8)	**589** (**97.5**)	94 (99.9)	4 (>99.9)	1 (100.0)	—	—	—	0.12	0.25
MRSA	1,539	13 (0.8)	144 (10.2)	960 (72.6)	**354** (**95.6**)	55 (99.2)	9 (99.7)	4 (100.0)	—	—	—	0.12	0.25
Streptococcus pneumoniae	2,233	1004 (45.0)	**1027** (**91.0**)	162 (98.2)	29 (99.5)	11 (100.0)	—	—	—	—	—	0.06	0.06
Pen-R	404	121 (30.0)	224 (85.4)	**49** (**97.5**)	6 (99.0)	4 (100.0)	—	—	—	—	—	0.06	0.12
Escherichia coli	3,757	—	—	6 (0.2)	255 (6.9)	1635 (50.5)	1085 (79.3)	**559** (**94.2**)	178 (99.0)	33 (99.8)	6 (100.0)	0.5	2
ESBL-negative	3,087	—	—	3 (0.1)	232 (7.6)	1444 (54.4)	875 (82.7)	**390** (**95.4**)	118 (99.2)	21 (99.9)	4 (100.0)	0.5	2
ESBL phenotype	670	—	—	3 (0.4)	23 (3.9)	191 (32.4)	210 (63.7)	169 (89.0)	**60** (**97.9**)	12 (99.7)	2 (100.0)	1	4
Klebsiella pneumoniae	1,250	—	—	—	5 (0.4)	30 (2.8)	289 (25.9)	567 (71.3)	194 (86.8)	**96** (**94.5**)	69 (100.0)	2	8
ESBL-negative	739	—	—	—	—	20 (2.7)	222 (32.7)	366 (82.3)	**77** (**92.7**)	27 (96.3)	27 (100.0)	2	4
ESBL phenotype	511	—	—	—	5 (1.0)	10 (2.9)	67 (16.0)	201 (55.4)	117 (78.3)	**69** (**91.8**)	42 (100.0)	2	8
Klebsiella oxytoca	313	—	—	—	1 (0.3)	9 (3.2)	180 (60.7)	89 (89.1)	**15** (**93.9**)	16 (99.0)	3 (100.0)	1	4
Enterobacter cloacae	636	—	—	—	—	7 (1.1)	111 (18.6)	349 (73.4)	**110** (**90.7**)	29 (95.3)	30 (100.0)	2	4
Acinetobacter baumannii	502	—	4 (0.8)	39 (8.6)	32 (14.9)	56 (26.1)	79 (41.8)	118 (65.3)	**145** (**94.2**)	23 (98.8)	6 (100.0)	2	4

Table 4
In vitro activity of omadacycline and other antimicrobial agents against North American and European urinary tract isolates from surveillance data for 2014 vs. 2010[17]

Organism (no. tested) Antimicrobial agent	North America				Europe			
	2014		2010		2014		2010	
	MIC$_{50/90}$	MIC range	MIC$_{50/90}$	MIC range	MIC$_{50/90}$	MIC Range	MIC$_{50/90}$	MIC range
Enterobacteriaceae	150		377		151		449	
Omadacycline	**2/⩾8**	**0.5–⩾8**	**1/4**	**0.25–>32**	**2/⩾8**	**0.25–⩾8**	**1/8**	**0.25–>32**
Tigecycline	0.12/1	⩽0.015–4	0.12/0.5	0.06–4	0.12/1	⩽0.015–4	0.12/0.5	⩽0.03–4
Doxycycline	2/⩾16	0.5–⩾16	1/⩾16	0.25–⩾16	2/⩾16	0.25–⩾16	2/⩾16	⩽0.06–⩾16
Tetracycline	2/⩾32	0.5–>32	1/⩾16	0.5–⩾16	2/⩾32	0.5–⩾32	2/⩾16	⩽0.25–⩾16
Amoxicillin-clavulanate	4/⩾16	⩽1–⩾16	4/⩾16	⩽1–⩾16	8/⩾16	⩽1–⩾16	8/⩾16	⩽1–⩾16
Aztreonam	⩽0.12/4	⩽0.12–⩾32	⩽0.12/0.25	⩽0.12–⩾32	⩽0.12/⩾32	⩽0.12–⩾32	⩽0.12/8	⩽0.12–⩾32
Ceftazidime	0.12/2	0.03–>32	0.12/0.5	0.03–>32	0.25/16	0.03–>32	0.12/4	0.03–>32
Ceftriaxone	⩽0.06/4	⩽0.06–⩾16	⩽0.06/0.25	⩽0.06–⩾16	⩽0.06/⩾16	⩽0.06–⩾16	⩽0.06/⩾16	⩽0.06–⩾16
Gentamicin	⩽1/4	⩽1–⩾16	⩽1/⩽1	⩽1–⩾16	⩽1/⩾16	⩽1–⩾16	⩽1/⩾16	⩽1–⩾16
Imipenem	⩽0.12/1	⩽0.12–4	⩽0.12/0.5	⩽0.12–4	⩽0.12/1	⩽0.12–4	⩽0.12/0.5	⩽0.12–⩾16
Levofloxacin	⩽0.12/⩾8	⩽0.12–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.12/⩾8	⩽0.12–⩾8	⩽0.5/⩾8	⩽0.5–⩾8
TMP-SMX	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8
E. coli	59		224		79		319	
Omadacycline	**0.5/2**	**0.5–4**	**0.5/1**	**0.25–4**	**1/4**	**0.25–⩾8**	**0.5/2**	**0.25–8**
Tigecycline	0.06/0.12	0.06–0.25	0.12/0.25	0.06–0.5	0.06/0.12	⩽0.015–1	0.12/0.25	⩽0.03–1
Doxycycline	1/⩾16	0.5–⩾16	1/⩾16	0.25–⩾16	2/⩾16	0.25–⩾16	1/⩾16	⩽0.06–⩾16
Tetracycline	2/⩾32	0.5–>32	1/⩾16	0.5–⩾16	2/⩾32	0.5–⩾32	2/⩾16	⩽0.25–⩾16
Amoxicillin-clavulanate	4/⩾16	⩽1–⩾16	8/⩾16	⩽1–⩾16	8/⩾16	⩽1–⩾16	4/⩾16	⩽1–⩾16
Aztreonam	⩽0.12/16	⩽0.12–⩾32	⩽0.12/0.5	⩽0.12–⩾32	⩽0.12/16	⩽0.12–⩾32	⩽0.12/0.5	⩽0.12–⩾32
Ceftazidime	0.25/4	0.06–32	0.12/0.5	0.03–32	0.25/4	0.03–32	0.12/0.5	0.03–>32
Ceftriaxone	⩽0.06/⩾16	⩽0.06–⩾16	⩽0.06/0.25	⩽0.06–⩾16	⩽0.06/⩾16/⩾16	⩽0.06–⩾16	⩽0.06/0.25	⩽0.06–⩾16
Gentamicin	⩽1/⩾16	⩽1–⩾16	⩽1/2	⩽1–⩾16	⩽1	⩽1–⩾16	⩽1/2	⩽1–⩾16
Imipenem	⩽0.12/⩽0.12	⩽0.12–0.5	⩽0.12/⩽0.12	⩽0.12–0.5	⩽0.12/⩽0.12	⩽0.12–0.25	⩽0.12/⩽0.12	⩽0.12–1
Levofloxacin	⩽0.12/⩾8	⩽0.12–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.12/⩾8	⩽0.12–⩾8	⩽0.5/⩾8	⩽0.5–⩾8
TMP-SMX	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8
Klebsiella spp.	31		103		29		52	
Omadacycline	**2/2**	**0.5–⩾8**	**2/4**	**0.5–32**	**2/⩾8**	**1–⩾8**	**2/8**	**8**
Tigecycline	0.25/0.25	⩽0.015–2	0.25/0.5	0.06–2	0.25/1	0.12–2	0.25/0.5	0.5
Doxycycline	2/⩾16	0.5–⩾16	1/⩾16	0.25–⩾16	2/⩾16	0.5–⩾16	2/⩾16	⩾16
Tetracycline	1/16	0.5–>32	1/⩾16	0.5–⩾16	2/⩾32	0.5–⩾32	2/⩾16	⩾16
Amoxicillin-clavulanate	2/4	⩽1–⩾16	2/8	⩽1–⩾16	8/⩾16	⩽1–⩾16	2/⩾16	⩾16
Aztreonam	⩽0.12/0.25	⩽0.12–⩾32	⩽0.12/0.25	⩽0.12–⩾32	0.25/⩾32	⩽0.12–⩾32	⩽0.12/⩾32	⩾32
Ceftazidime	0.12/0.25	0.06–>32	0.12/0.5	0.03–>32	0.25/>32	0.06–>32	0.12/32	32
Ceftriaxone	⩽0.06/0.12	⩽0.06–⩾16	⩽0.06/0.25	⩽0.06–⩾16	0.25/⩾16	⩽0.06–⩾16	⩽0.06/⩾16	⩾16
Gentamicin	⩽1/⩽1	⩽1–⩾16	⩽1/⩽1	⩽1–⩾16	⩽1/⩾16	⩽1–⩾16	⩽1/⩾16	⩾16
Imipenem	⩽0.12/0.25	⩽0.12–4	⩽0.12/0.25	⩽0.12–1	⩽0.12/0.5	⩽0.12–4	⩽0.12/0.5	0.5
Levofloxacin	⩽0.12/⩽0.12	⩽0.12–⩾8	⩽0.5/⩽0.5	⩽0.5–⩾8	0.5/⩾8	⩽0.12–⩾8	⩽0.5/⩾8	⩾8
TMP-SMX	⩽0.5/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩽0.5–⩾8	⩾8/⩾8	⩽0.5–⩾8	⩽0.5/⩾8	⩾8

Omadacycline did not inhibit P-gp, BRCP or MRP-2 nor induce P-gp or MRP-2 mRNA. While omadacycline was a weak substrate for P-gp (but not MRP-2 or BCRP), omadacycline was neither an inhibitor nor an inducer of P-gp, MRP-2 or BCRP. No difference was observed for accumulation of [14C]omadacycline into cells expressing hOAT1, hOAT3, hOCT2, OATP1B1 or OATP1B3. No inhibition of hOAT3 function and ~32.1% inhibition of hOAT1 was observed with omadacycline 25 μM. Transport of probes for OATP1B1 and OATP1B3 was reduced by ±10.1% with omadacycline 100 μM (~57 mcg/mL). Overall, these results indicated that omadacycline does not interact in vitro with human transporters and is unlikely to act as either an inhibitor or an inducer of P-gp. Thus, the potential for drug-drug interactions appears to be minimal with co-administration of omadacycline and human drug transporters.

4.1.3. Nonclinical cardiovascular effects

A series of in vitro and in vivo studies were conducted to evaluate the effects of omadacycline on the cardiovascular system.[40] Studies evaluated mammalian pharmacologic receptor binding (including the beta-adrenergic receptor); human ether-a-go-go-related gene (hERG) channel binding; effects on rabbit ex vivo sinoatrial (SA) node activity; and in vivo effects on cardiovascular function in the cynomolgus monkey. No significant binding to the hERG channel, beta-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 and exhibited a concentration-dependent antagonism of the effect carbamylcholine (a muscarinic receptor agonist), which produced an increase in heart rate in the ex vivo SA node model. Omadacycline exhibited no effect on human ether-à-go-go-Related

Table 5
Susceptibility of *Legionella pneumophila* tested from 1995 to 2014[18]

Organism (no. tested)	Collection date	Antibiotic	Range	MIC$_{50}$ (mcg/mL)	MIC$_{90}$ (mcg/mL)
All serogroups (100 strains)	1995–2014	Omadacycline	0.06–1	0.25	0.25
		Doxycycline	0.5–1	1	1
		Telithromycin	0.016–2	0.03	0.06
		Azithromycin	0.008–0.5	0.12	0.5
		Erythromycin	0.06–2	0.25	1
		Levofloxacin	⩽0.004–0.03	0.016	0.016
		Moxifloxacin	⩽0.004–0.06	0.008	0.016
Serogroup 1 (90 strains)	1995–2014	Omadacycline	0.06–0.5	0.25	0.25
		Doxycycline	0.5–1	1	1
		Telithromycin	0.016–0.12	0.03	0.06
		Azithromycin	0.016–0.5	0.12	0.5
		Erythromycin	0.06–2	0.25	1
		Levofloxacin	⩽0.004–0.03	0.016	0.016
		Moxifloxacin	⩽0.004–0.06	0.016	0.016
Serogroup 1 (45 strains)	1995–2005	Omadacycline	0.06–0.5	0.25	0.25
		Doxycycline	0.5–1	1	1
		Telithromycin	0.016–0.12	0.03	0.06
		Azithromycin	0.016–0.5	0.12	0.5
		Erythromycin	0.06–2	0.12	1
		Levofloxacin	0.008–0.03	0.016	0.016
		Moxifloxacin	⩽0.004–0.06	0.008	0.016
Serogroup 1 (45 strains)	2006–2014	Omadacycline	0.06–0.5	0.25	0.25
		Doxycycline	0.5–1	1	1
		Telithromycin	0.016–0.06	0.03	0.06
		Azithromycin	0.016–0.5	0.12	0.5
		Erythromycin	0.06–2	0.25	1
		Levofloxacin	⩽0.004–0.06	0.016	0.016
		Moxifloxacin	⩽0.004–0.06	0.008	0.016

Table 6
Summary of the efficacy of omadacycline in mouse models of infection

Reference	Model	Bacterial strain	Author conclusions
Endermann et al[29]	Subcutaneous pouch	*B. fragilis*	OMC more potent than metronidazole
	Septicaemia	*VRE*	OMC more potent than vancomycin, linezolid
	Caecal ligation	Polymicrobial	OMC more potent than imipenem, linezolid
Ladel et al[30]	Abscess	*S. aureus*	OMC more potent than linezolid, vancomycin
	Neutropenic thigh wound	*S. aureus*	OMC more potent than linezolid, as potent as vancomycin
Broetz-Oesterhelt et al,[31]	Systemic infection	MSSA, MRSA	OMC more potent than vancomycin or linezolid
Endermann et al[32]	Pneumonia	*S. pneumoniae*	OMC as potent as vancomycin and more potent that linezolid
Bhatia et al.[15]	Systemic infection	*S. pneumoniae*	OMC more potent than other aminomethycylines or doxycycline
McKenney et al,[33]	Systemic infection	*S. aureus*	OMC more potent than linezolid and as potent as vancomycin
	Neutropenic thigh wound	*MRSA*	OMC more potent than linezolid, vancomycin
	Renal infection	*E. faecalis*	OMC more potent than linezolid, vancomycin
	Renal infection	*E. coli*	OMC as potent as minocycline and less potent than ciprofloxacin
McKenney et al.[34,35]	Systemic infection	*S. pneumoniae* tet-sensitive	OMC more potent than minocycline, linezolid, vancomycin
	Systemic infection	*S. pneumoniae* tet-resistant	OMC more potent than minocycline, linezolid, as potent as vancomycin
	Pneumonia	*S. pneumoniae* tet-sensitive	OMC more potent than minocycline, linezolid, comparable to vancomycin
	Pneumonia	*S. pneumoniae* tet-resistant	OMC more potent than minocycline and linezolid, less potent than vancomycin
	Chronic lung infection	*S. pneumoniae* tet-sensitive	OMC more potent than minocycline, linezolid, vancomycin
	Neutropenic thigh wound	*S. pneumoniae* tet-sensitive	OMC more potent than minocycline, linezolid, vancomycin
	Neutropenic thigh wound	*S. pneumoniae* tet-resistant	OMC more potent than minocycline, linezolid, vancomycin
Craig et al.[36]	Neutropenic and non-neutropenic thigh model	*S. pneumoniae S. aureus, E. coli,* and *K. pneumoniae*	The pharmacodynamic driver of efficacy for OMC is AUC. The AUC required for efficacy is much lower for non-neutropenic animals. OMC was slightly more potent than tigecycline against gram negative pathogens
Tessier et al.[37]	Pneumonia	*S. pneumoniae*	The pharmacodynamic driver of efficacy is AUC

AUC = area under the concentration curve.

Gene (hERG) channel activity at a concentration of 100 mcg/mL and the inhibitory concentration (IC$_{25}$) was 166 mcg/mL. In addition, omadacycline at doses up to 40 mg/kg had no effect on the QTc interval in conscious monkeys, which indicates a low potential for hERG-related effects on cardiac repolarization in humans. Based on these results, omadacycline modified the parasympathetic effect on heart rate but had a low potential for cardiac arrhythmia or clinically significant cardiovascular toxicity.

Table 7a
Efficacy of omadacycline and tigecycline in non-neutropenic community-acquired *Staphylococcus aureus* murine thigh wound infections[*]

Strain	Drug	MIC (µg/mL)	Static dose ED$_{50}$ mg/kg
S. aureus USA300	Omadacycline	0.25	0.40
	Tigecycline	0.125	0.45
S. aureus USA400	Omadacycline	0.5	0.68
	Tigecycline	0.06	0.46

[*] *S. aureus* USA300 or USA400 was grown overnight in a 37 °C shaker at 180 rpm in Mueller Hinton Broth (Northeast Labs, Waterville, Maine) and diluted in sterile PBS (Fisher Scientific, Boston, MA) to 1×10^8 CFU/mL. Mice were lightly anesthetized by 3% isoflurane in oxygen, and a volume of 100 µL diluted culture was injected into the underside of the left thigh of each mouse. Two hours post-infection, groups of mice (n = 4-8/group) were treated with a single intravenous dose of omadacycline or tigecycline, dissolved in sterile saline for injection at a volume of 10 mg/mL. Two groups of untreated mice served as controls. One group was sacrificed at the start of therapy (2 h PI), and the other group was sacrificed at the end of the experiment (24 h PI). Mice were sacrificed by isoflurane or CO_2 narcoses followed by cervical dislocation at 24 h PI. Thigh muscles were removed aseptically, placed in 10 mL of ice cold sterile PBS and homogenized, diluted and plated onto Trypticase Soy Agar II plates with 5% sheep's blood (Northeast Labs, Waterville, Maine) to determine the bacterial load per thigh. The Static Dose was calculated based on the bacterial load at the time of treatment and was the dose of drug required to prevent further increase during the 24 h post treatment.

4.2. Human pharmacokinetics

The pharmacokinetic profile of IV omadacycline, administered as the HCl salt, was linear over the dose range of 25–600 mg.[41] Omadacycline IV pharmacokinetic parameters can be compared to other tetracyclines (Table 8).

The peak omadacycline concentration (C_{max}) was impacted by the duration of infusion (30 min vs. 60 min); however, C_{max} was approximately dose-linear for doses infused over the same duration.[41] The mean terminal elimination half-life was approximately 17 h, ranging from 11.7 to 26 h across the dose levels. The mean systemic clearance of omadacycline was 17.1 L/h, and was independent of dose, while the volume of distribution was large and ranged from 333 L to 640 L, indicating a large degree of tissue distribution. Pharmacokinetic data after daily 200 mg IV doses for 7 days were predictable from single dose pharmacokinetics. At Day 7, the steady-state AUC$_{0-24}$ was approximately 50% higher than the Day 1 AUC$_{0-24}$. After daily IV dosing with 200 mg of omadacycline, an approximate 20% increase in C_{max} was observed at Day 7, and steady-state was reached by Day 4.

During the development process, oral omadacycline formulations have evolved from free base in a capsule through a series of tablet and salt formulations in order to optimize oral bioavailability while improving tolerability. The current phase 3 tablet formulation is the tosylate salt of omadacycline. Following the administration of the phase 3 tablet formulation (300 mg administered as 2×150 mg tablets) in 20 subjects, the median T_{max} was 3.0 h, mean half-life was 17 h, and mean Cmax was 0.54 ± 0.11 mcg/mL.[44] These subjects also were administered a 100 mg IV dose of omadacycline in order to evaluate absolute bioavailability. The absolute bioavailability for the phase 3 tablet formulation was 34.5%. The 300 mg oral dose using the phase 3 tablet formulation was bioequivalent to the 100 mg IV dose with a geometric mean ratio of 0.96 for AUC$_{inf}$.

Food intake taken less than 6 h prior to oral dosing decreased the absorption of omadacycline; therefore, subjects should be fasted for 6 h before dosing and only drink water and eat no food for 2 h after taking oral omadacycline.[45] Slightly higher exposure to omadacycline was observed after both oral and IV administration in female subjects, who had a 20–35% higher AUC as compared to male subjects. There was no effect of age on the pharmacokinetics of oral omadacycline. In addition, there was no effect of hepatic impairment (Child-Pugh classes A, B and C) on the pharmacokinetics of oral or IV omadacycline.[46]

A mass balance study, using a single oral 300 mg dose of [14C] omadacycline (36.6 µCi), was evaluated in six healthy males.[47] Peak plasma radioactivity concentrations occurred from 1 to 4 h and the mean terminal radioactive half-life was 17.6 h. In plasma, omadacycline and its C-4 epimer accounted for 100% of the AUC. The C-4 epimer is formed spontaneously (non-enzymatically) from omadacycline upon standing. No enzymatically formed metabolites were detected. Radioactivity was collected and measured in feces and urine up to 168 h following dose administration. The majority of the omadacycline radioactivity excreted was in the feces (81.1% of the dose). This 81.1% represents the sum of biliary excretion of omadacycline and the C-4 epimer and unabsorbed dose (~65% of the dose). In urine, the mean total radioactivity was 14.4% (all omadacycline and its C-4 epimer) of the administered dose, which was approximately 40% of the absorbed dose.[47] Total radioactive recovery was 95.5%.

Table 7b
Omadacycline and comparators in non-neutropenic acute lethal *Streptococcus pneumoniae* murine pneumonia model following a single IV treatment[*]

Drug	MIC mcg/mL	7 day PD$_{50}$mg/kg
Omadacycline	0.125	1.50
Tigecycline	0.125	0.91
Ceftriaxone	0.015	0.37
Minocycline	0.25	3.44
Doxycycline	0.125	10.26
Linezolid	1	38.81
Vancomycin	0.5	3.30
Levofloxacin	0.25	>18
Azithromycin	0.03	3.31
Daptomycin	0.25	>100

[*] *S. pneumoniae* PBS 1339 was grown on Trypticase Soy Agar (TSA) II with 5% sheep's blood agar plates (Northeast Laboratory Services, Winslow, ME). Following the overnight incubation, the colonies were aseptically collected from 2 to 3 agar plates and resuspended in 3 mL of sterile PBS (Mediatech, Inc, Manassas, VA) to approximately 1.0×10^9 CFU/mL then diluted 1:10 in sterile PBS. Mice were lightly anesthetized with isoflurane and infected (n = 5 mice/group) by intranasal inoculation with 50 µL of the 1.0×10^8 CFU/mL suspension (final inoculum was ~5 × 10^6 CFU/mouse). At 2 h PI, mice were treated with a single intravenous injection of omadacycline or comparator in sterile saline for injection (Baxter Healthcare Corp., Deerfield, IL), or saline alone. Mice were observed daily for 7 days PI, and signs of morbidity and mortality were recorded. All saline-treated control animals were dead by 96 h post-infection. The Protective Dose was calculated based on survival at 7 days post infection.

Table 7c
Comparison of a single IV dose of omadacycline versus comparators in a non-neutropenic *Haemophilus influenzae* murine pneumonia model[*]

	MIC (mcg/mL)	Static ED$_{50}$ (mg/kg)
Omadacycline	1	6.47 ± 3.27
Tigecycline	0.25	2.31 (1.36, 3.27)
Levofloxacin	<0.06	2.40 (0.10, 3.89)
Ciprofloxacin	<0.06	1.16 (0.36, 1.96)
Ceftriaxone	<0.06	0.10 (0.08, 0.12)

[*] *H. influenzae* PBS 981 was streaked out on Chocolate agar plates and incubated overnight in a CO_2 enriched environment at 37 °C. Following the overnight incubation (Day 0), colonies were aseptically collected from approximately 1 confluent plate and resuspended in 5 mL of sterile Phosphate Buffered Saline (PBS) to approximately 1.5×10^6 CFU/mL. CD-1 male mice were lightly anesthetized with isoflurane and infected intranasally with 50 µL containing 2.93–16.7 × 10^4 CFU (mean 7.60×10^4 CFU). Groups of mice (n = 5/group) were treated at 2 h PI with intravenous omadacycline or comparator in sterile saline for injection, or saline alone. At 24 h PI, mice were euthanized via CO_2 or isoflurane narcoses followed by cervical dislocation. Lungs were aseptically collected, weighed, and placed in cold sterile PBS, homogenized and serially diluted in sterile PBS and plated on Chocolate agar plates, incubated overnight at 37 °C on a CO_2 enriched environment at to enumerate the CFU/g of each lung. The Static Dose was calculated based on the bacterial load at the time of treatment and was the dose of drug required to prevent further increase during the 24 h post treatment.

Table 8
Comparison of the single dose PK profile of eravacycline, omadacycline, and tigecycline (Tygacil Package Insert; data on file).[42,43]

	Omadacycline	Eravacycline	Tigecycline
Dose for PK data shown	100 mg IV	1.5 mg/kg q24 h IV	50 mg q12 h IV
	300 mg oral	100 mg q12 h oral	
C_{max} (mcg/mL)	1.8 IV	1.9 IV	0.87
	0.7 oral	0.16 oral	
AUC_{0-24} (mcg h/L)	8.8 IV	7.9 IV	4.7
	5.9 oral	3.1 oral	
Clearance (L/h)	17.1	17.8	23.8
Half-life (h)	17	10–14	37–66
Protein binding (%)	21%	79–87%	69–87%
	Dose-independent	Atypical nonlinear	Atypical nonlinear
Oral bioavailability (%)	34.5	28.0	Not orally available
Clinical dosing regimen	[anticipated]	[anticipated]	[approved prescribing information]
	IV: 200 mg IV loading dose, then 100 mg q24 h Oral: 300 mg q24	IV: 1.0–1.5 mg/kg q12 h or q24 h Oral: 200 mg q12 h	IV: 100 mg loading dose, then 50 mg q12 h

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%.[48]

5. Clinical profile of omadacycline

5.1. Efficacy for treatment of skin infections

Two randomized, double-blind, multi-center studies (a phase 2 and a truncated phase 3 study) were completed with omadacycline in patients with complicated skin and skin structure infections (cSSSI).[5,6] In these studies, adult patients with cSSSI received omadacycline 100 mg IV once daily followed by the option to switch to 200 mg oral once daily (phase 2) or 300 mg oral once daily (phase 3). In both studies the comparator was linezolid 600 mg IV with the option to switch to 600 mg oral twice daily. Treatment was administered for up to 14 days.

In the phase 2 study, 219 patients were treated (111 omadacycline, 108 linezolid) for an average of 10 days.[5] Clinical response at the test of cure (TOC) visit 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 (Fig. 2). In the truncated phase 3 study, enrollment was stopped early because of a decision by the U.S. Food and Drug Administration (FDA) to change the primary endpoint in studies of the treatment of bacterial skin infection.[6] In the study, a total of 140

patients were treated (68 omadacycline, 72 linezolid) for an average of 10 days in both treatment groups.[6] 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 (Fig. 2).

5.2. Safety and tolerability

In the phase 2 and truncated 3 phase studies in cSSSI, the incidence and type of AEs was comparable between omadacycline and linezolid.[5,6] In the phase 2 study, the overall incidence of AEs was 41% for omadacycline and 51% for linezolid.[5] Gastrointestinal AEs were most common occurring in 19% of omadacycline patients and 17% of linezolid patients. Nausea and vomiting were reported in 12% and 5%, respectively, of omadacycline patients primarily during oral treatment, compared to 7% and 4%, respectively, of linezolid patients. Premature discontinuation of treatment due to an adverse event (AE) was very infrequent in both groups (1% omadacycline, 2% linezolid).

In the truncated phase 3 study, the overall incidence of AEs was 82% for omadacycline and 81% for linezolid.[6] Gastrointestinal AEs were most common occurring in 44% of omadacycline patients and 40% of linezolid patients. The most commonly reported GI AEs were nausea (27% omadacycline, 26% linezolid), vomiting (9% omadacycline, 15% linezolid), constipation (9% omadacycline, 3% linezolid, and diarrhea (4% omadacycline, 18% linezolid). Premature discontinuation of treatment due to an AE was infrequent (3% omadacycline, 0 linezolid).

Overall, the target therapeutic doses of omadacycline were very well tolerated in both oral and IV 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, and nausea also was observed in some early phase 1 studies of oral formulations (most notably at oral doses of 400 mg or greater). However, all nausea 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 IV tigecycline and with both IV and oral administration of eravacycline.[42,43,49–52] Passarell and colleagues[51] evaluated the relationship between nausea and vomiting and drug exposure in 136 healthy volunteers who were treated with IV tigecycline in phase 1 studies. Across a dosage range from 12.5 to 300 mg IV, nausea occurred in 38% and 24% of events were severe; vomiting occurred in 18% and 36% of events were severe. For each 1 mg h/L increase in AUC_{0-24}, the incidence of nausea/vomiting increased by 18.6%. An analysis of the incidence of nausea and vomiting in patients from phase 3 trials deter-
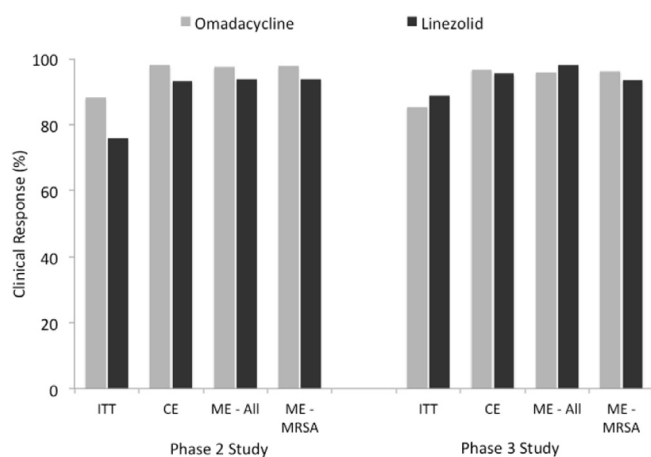
Figure 2. Clinical response with omadacycline and linezolid at the test of cure visit in a phase 2 and a truncated phase 3 study of patients with cSSSI.[5,6] ITT = intent-to-treat; CE = clinically evaluable; ME = microbiologically evaluable.

mined that the pharmacodynamic driver of nausea/vomiting for tigecycline was an AUC threshold that is lower than the AUC required for efficacy; each one unit increase in the tigecycline AUC was associated with a 17–18% increase in the incidence of nausea/vomiting with tigecycline.[52]

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.

6. Summary and conclusions

Omadacycline represents a novel, aminomethyl tetracycline discovered on the basis of improved microbiologic characteristics compared with older tetracyclines. The primary characteristics of the 9-aminomethylcyclines include broad-spectrum activity, including atypical pathogens, and overcoming the two primary mechanisms of tetracycline resistance, efflux and ribosome protection. In addition, the pharmacologic nature of omadacycline afforded two additional benefits: oral bioavailability and lack of glycylcycline-induced dose-limiting nausea and vomiting. Further, the pharmacokinetic and pharmacodynamic properties of omadacycline (long-half life, absence of metabolism, low protein-binding, and low potential for drug–drug interactions via the CYP pathway) support its potential clinical efficacy and ease of use, which will be elucidated further in phase 3 registration studies. Thus, omadacycline is a well-tolerated, once daily, oral and IV antibiotic, with potential for the treatment of community-acquired infections including those caused by antibiotic-resistant pathogens. Ongoing and planned clinical studies are evaluating omadacycline as monotherapy for treating common bacterial infections including ABSSSI and CABP, and potentially other bacterial infections including urinary tract infections, sinusitis or other common infectious diseases.

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