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# Omadacycline: A Novel Oral and Intravenous Aminomethylcycline Antibiotic Agent

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## Abstract

Omadacycline is a novel aminomethylcycline antibiotic developed as a once-daily, intravenous and oral treatment for acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP). Omadacycline, a derivative of minocycline, has a chemical structure similar to tigecycline with an alkylaminomethyl group replacing the glyclamido group at the C-9 position of the D-ring of the tetracycline core. Similar to other tetracyclines, omadacycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Omadacycline possesses broad-spectrum antibacterial activity against Gram-positive and Gram-negative aerobic, anaerobic, and atypical bacteria. Omadacycline remains active against bacterial isolates possessing common tetracycline resistance mechanisms such as efflux pumps (e.g., TetK) and ribosomal protection proteins (e.g., TetM) as well as in the presence of resistance mechanisms to other antibiotic classes. The pharmacokinetics of omadacycline are best described by a linear, three-compartment model following a zero-order intravenous infusion or first-order oral administration with transit compartments to account for delayed absorption. Omadacycline has a volume of distribution ( $V_d$ ) ranging from 190 to 204 L, a terminal elimination half-life ( $t_{1/2}$ ) of 13.5–17.1 h, total clearance ( $CL_T$ ) of 8.8–10.6 L/h, and protein binding of 21.3% in healthy subjects. Oral bioavailability of omadacycline is estimated to be 34.5%. A single oral dose of 300 mg (bioequivalent to 100 mg IV) of omadacycline administered to fasted subjects achieved a maximum plasma concentration ( $C_{max}$ ) of 0.5–0.6 mg/L and an area under the plasma concentration–time curve from 0 to infinity ( $AUC_{0-\infty}$ ) of 9.6–11.9 mg h/L. The free plasma area under concentration–time curve divided by the minimum inhibitory concentration (i.e.,  $fAUC_{24h}/MIC$ ), has been established as the pharmacodynamic parameter predictive of omadacycline antibacterial efficacy. Several animal models including neutropenic murine lung infection, thigh infection, and intraperitoneal challenge model have documented the in vivo antibacterial efficacy of omadacycline. A phase II clinical trial on complicated skin and skin structure infection (cSSSI) and three phase III clinical trials on ABSSSI and CABP demonstrated the safety and efficacy of omadacycline. The phase III trials, OASIS-1 (ABSSSI), OASIS-2 (ABSSSI), and OPTIC (CABP), established non-inferiority of omadacycline to linezolid (OASIS-1, OASIS-2) and moxifloxacin (OPTIC), respectively. Omadacycline is currently approved by the FDA for use in treatment of ABSSSI and CABP. Phase II clinical trials involving patients with acute cystitis and acute pyelonephritis are in progress. Mild, transient gastrointestinal events are the predominant adverse effects associated with use of omadacycline. Based on clinical trial data to date, the adverse effect profile of omadacycline is similar to studied comparators, linezolid and moxifloxacin. Unlike tigecycline and eravacycline, omadacycline has an oral formulation that allows for step-down therapy from the intravenous formulation, potentially facilitating earlier hospital discharge, outpatient therapy, and cost savings. Omadacycline has a potential role as part of an antimicrobial stewardship program in the treatment of patients with infections caused by antibiotic-resistant and multidrug-resistant Gram-positive [including methicillin-resistant *Staphylococcus aureus* (MRSA)] and Gram-negative pathogens.

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## Key Points

Omadacycline is the first intravenous and oral aminomethylcycline antibiotic approved (2018) by the US Food and Drug Administration (FDA) for clinical use in patients experiencing acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP).

Omadacycline possesses broad-spectrum antibacterial activity against Gram-positive and Gram-negative, aerobic, anaerobic, and atypical bacteria. It remains active against isolates possessing common tetracycline resistance mechanisms such as efflux pumps (e.g., TetK) and ribosomal protection proteins (e.g., TetM) and in the presence of other resistance mechanisms to other antibiotic classes.

Omadacycline has a potential role in decreasing the duration of patient hospitalization and in treatment of infections caused by antibiotic-resistant and multidrug-resistant pathogens.

## 1 Introduction

The clinical use of a tetracycline was first reported in 1948, when chlortetracycline was administered to a patient after the patient failed treatment with  $\beta$ -lactam therapy [1]. Chlortetracycline was initially isolated from a species of the spore-forming bacteria *Streptomyces* during soil screening studies [1, 2]. Many other naturally occurring tetracycline antibiotics were also identified in the 1950s and 1960s and tetracycline antibiotics were sought after because they were ‘broad-spectrum antibiotics’ with potent activity against various pathogens, including Gram-positive, Gram-negative, and atypical bacteria [1, 3]. Their broad-spectrum activity was shown to be the result of their inhibition of the bacterial 30S ribosomal subunit and protein translation [4, 5].

In the late 1960s, semi-synthetic processes led to the development of the second-generation tetracyclines, minocycline and doxycycline, which demonstrated a similar mechanism of action but with improved pharmacological properties and spectrum of activity [2, 6]. The advances in chemical synthesis methods, a relatively well-tolerated adverse effect profile, and low production costs have driven the widespread use of tetracyclines, not only in human and animal infections, but also as prophylaxis and/or growth promotion in animal feeds [7–9]. This extensive use resulted in the emergence and widespread dissemination of

tetracycline-resistant bacterial genes and strains and limited their clinical efficacy [2].

More recently, chemical modification to C-7 and C-9 groups in the D ring of the tetracycline core lead to the identification and development of the glycylcycline class (tigecycline, eravacycline). These new glycylcyclines restored activity against bacteria carrying the major mechanisms of tetracycline resistance (efflux pumps and ribosomal protection proteins) [4, 10, 11] and are frequently used clinically to treat patients with multidrug-resistant (MDR), and severe and complicated infections [3, 5, 6, 12].

Omadacycline (NUZYRA®/PTK 0796) is a new aminomethylcycline developed by Paratek Pharmaceuticals (Boston, MA, USA). It is an intravenous and oral antibiotic therapy, approved (2018) by the US Food and Drug Administration (FDA), for clinical use in acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) [13–15]. Recent microbiological data demonstrate omadacycline’s in vitro activity against multiple pathogens including methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*,  $\beta$ -hemolytic streptococci, vancomycin-resistant *Enterococcus* (VRE), *Enterobacteriales*, *Legionella pneumophila*, *Mycoplasma* spp., *Ureaplasma* spp., *Bacteroides* spp., and *Clostridioides difficile* [16, 17]. Omadacycline is currently in clinical development for the treatment of urinary tract infections including acute pyelonephritis (NCT03757234) and cystitis (NCT03425396).

This paper reviews the existing published data on omadacycline, including relevant chemistry, mechanism of action, mechanism of resistance, microbiology, pharmacokinetics, pharmacodynamics, animal models, clinical trials, adverse effects, drug interactions, and its place in therapy. We conducted a comprehensive search of PubMed and Scopus using the search terms ‘omadacycline’ and ‘PTK-0796’ (up to July 2019) to identify references for this paper. Recent conference proceedings (2017–2019) and publications related to omadacycline were also obtained directly from Paratek Pharmaceuticals.

## 2 Chemistry

The chemical structures of omadacycline, tigecycline, and eravacycline are depicted in Fig. 1. The basic core structure of tetracyclines consists of four rings (labelled A, B, C, and D, Fig. 2) that form a naphthacene ring system that appears to have a half planar and half bent 3-D structure [1, 2, 12, 16]. Generally, any changes in the lower unit of tetracycline (C-1, C-2, C-3, C-4, C-10, C-11, C-11a, C-12, and C-12a) will result in a decrease in antibacterial

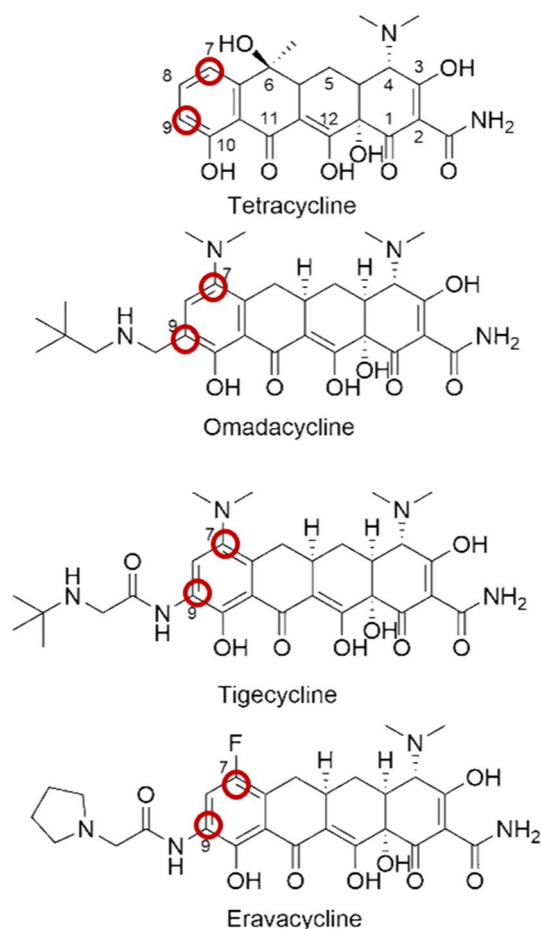


**Fig. 1** Chemical structures of tetracycline, omadacycline, eravacycline, and tigecycline

activity [12, 18]. Substitutions in the upper unit (positions C-7 to C-9) of the tetracycline core were discovered to overcome tetracycline resistance mechanisms and increase antibacterial activity [10, 12].

Tigecycline and eravacycline are both synthetic tetracycline analogs that contain a glycylamido substituent at the C-9 position. Tigecycline is formed by the addition of a *t*-butylglycylamido group at this position, while in eravacycline, this is replaced by a pyrrolidinoacetamido group [12, 19]. The C-7 position is amenable to substitution with strong electron withdrawing groups or electron donating groups [12] and eravacycline contains a fluorine atom at this position, while tigecycline contains a dimethylamino group [12, 19]. Omadacycline (7-dimethylamino-9-neopentylaminomethyl-6-demethyl-6-deoxytetracycline) is similar in structure to tigecycline at the C-7 position with a dimethylamino group, but replaces the glycylamido group at C-9 with an alkylaminomethyl group [10] (Fig. 1).

Omadacycline is the first aminomethylcycline, and represents a novel class of substituted minocyclines, to

be approved for clinical use [4, 11]. The C-9 substitution with an aminomethyl provided some benefits in contrast to maintaining the glycylamido substitution that is present in tigecycline and eravacycline. The aminomethyl substitution in the C-9 position provided a molecule with increased bioavailability [10].

Honeyman et al. [10] initially synthesized 7-dimethylamino-9-aminomethyl-6-demethyl-6-deoxytetracycline, which contained an unsubstituted aminomethyl group at the C-9 position. The free amine of this side chain provided a scaffold from which a variety of analogs were synthesized. An initial set of molecules was produced, consisting of alkylamine, amide, carbamate, urea, heterocyclic, and aryl- or heteroaryl-amine substitutions. Lipophilic or benzylic substitutions to the aminomethyl side chain resulted in the most potent antibacterial activity, against ribosomal alteration and efflux producing tetracycline-resistant strains. Moreover, analogs with increased polarity or charged moieties were found to decrease the antibacterial activity significantly. Acyl derivatives of the aminomethyl side chain had reduced activity against tetracycline-resistant organisms, although the addition of larger alkyl substituents such as a *t*-butyl group led to compounds that demonstrated modest activity (MIC 2–32 mg/L). Alkyl substituted aminomethyl derivatives were chosen for further optimization and screening. In addition, it was discovered that alkyl groups extending at least three carbons from the aminomethyl side chain were most preferred, and branched alkyl chains as well as piperidine analogs displayed superior activity. Branching at the 1-position of the alkyl side chain had a negative steric impact on activity due to steric effects, and introduction of two methyl groups at the 2-position led to a significant improvement in activity. Alkyl side chains containing more than five carbons as well as piperidine derivatives were found to display significantly lower activity in the presence of plasma, indicating high plasma protein binding. More lipophilic derivatives were also found to be less orally bioavailable. Overall, omadacycline, which contains a neopentyl group alkylated to the aminomethyl side chain, was found to display potent antibacterial activity, low serum protein binding, and good bioavailability [10].

### 3 Mechanism of Action

In Gram-negative bacteria, tetracyclines are reported to cross the outer membrane of the cell wall as a tetracycline-magnesium complex using outer membrane porins, OmpF and OmpC [2, 3, 9]. Once inside the periplasm, tetracyclines dissociate from magnesium becoming lipophilic enough to diffuse across the cytoplasmic membrane by passive diffusion [3, 9]. In Gram-positive bacteria, uncharged tetracycline molecules have been reported to enter the cytoplasm via

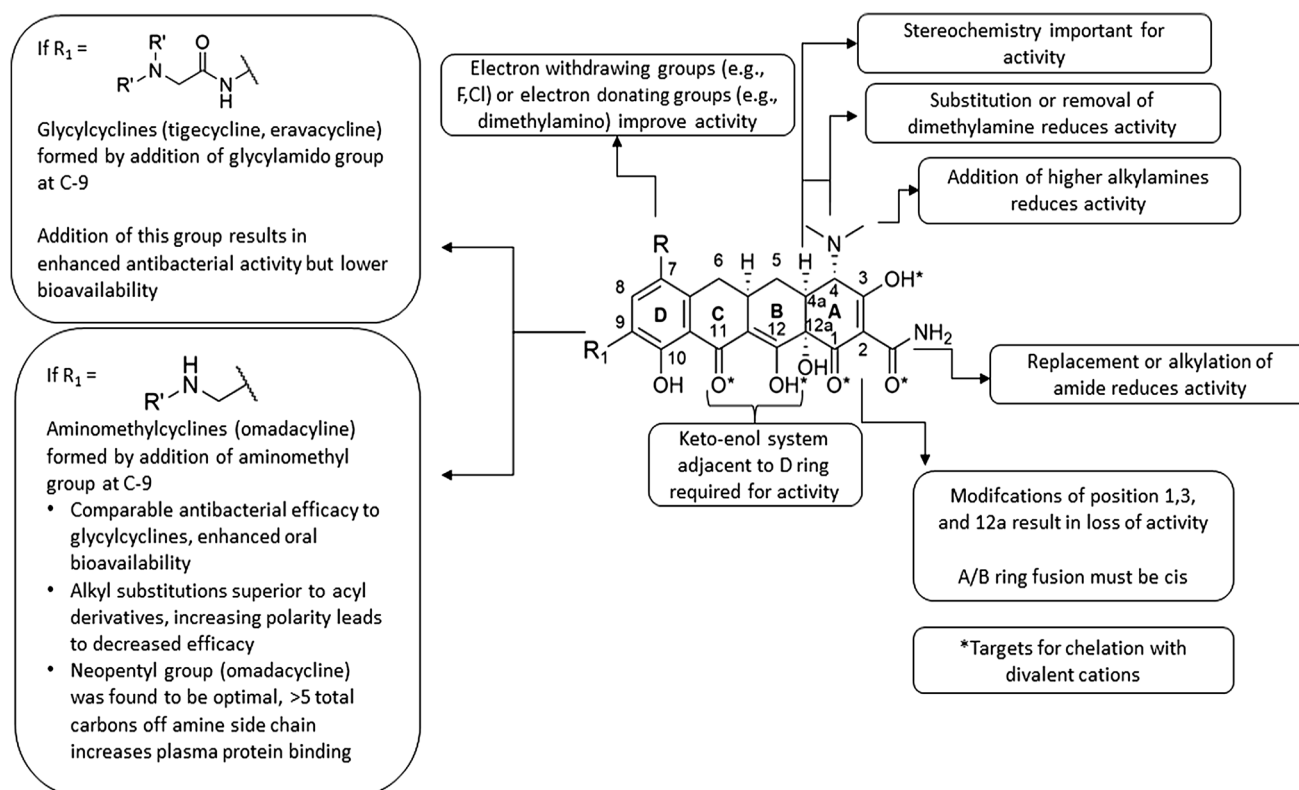


Fig. 2 General structure–activity relationships for tetracyclines (adapted from Refs. [1, 10, 12])

passive diffusion and/or active transport [3, 9]. Within the cytoplasm, tetracyclines remain chelated and likely inhibit the ribosome while in complex with magnesium [3, 9]. This is supported by X-ray crystal structures of tetracycline in complex with the *Thermus thermophilus* 30S subunit [20]. Divalent ions are vital in the transport and binding of tetracyclines to their target [2].

During translation, tetracyclines bind to the 16S rRNA component of the 30S subunit, effectively blocking the access of aminoacyl-tRNA to the acceptor site (A-site) of the ribosome [2]. This competitive inhibition is reversible and accounts for the bacteriostatic activity of tetracycline, minocycline, doxycycline, tigecycline, eravacycline, and omadacycline [3, 9]. The primary binding site on the 30S subunit is known as Tet1 [8]. Omadacycline has a twofold higher affinity for the 30S ribosome than tetracycline [20]. Minocycline binds analogously to tetracycline and inhibits in vitro translation two- to seven-fold more efficiently than tetracycline [20]. Ribosomal competition assays using [ $^3$ H]-tetracycline report an  $IC_{50}$  (the concentration of agent inhibiting 50% of ribosomes) of  $1.63 \pm 0.01 \mu M$  for minocycline and  $1.96 \pm 0.01 \mu M$  for omadacycline [4]. The comparable  $IC_{50}$  values indicate a similarity in binding site and affinity of minocycline and omadacycline in outcompeting tetracycline at the Tet1 site [4].

The inhibitory activity of omadacycline and tetracycline in protein synthesis, versus tetracycline-susceptible and -resistant *S. aureus* isolates was investigated in a whole cell assay by Draper et al. [4]. They reported an  $IC_{50}$  of omadacycline in the presence of TetK (an efflux pump in *S. aureus* RN4250) to be 0.08 mg/L; this value is considerably lower than the  $IC_{50}$  of tetracycline, which was 13.8 mg/L [4]. In the presence of TetM (a ribosomal protein protection in *S. aureus* MRSA5), the  $IC_{50}$  of omadacycline was 0.11 mg/L (with an MIC of 0.125 mg/L) compared with > 64 mg/L for tetracycline [4]. In a tetracycline-susceptible wild-type isolate, *S. aureus* RN450, the  $IC_{50}$  values of omadacycline and tetracycline were calculated to be < 0.03 mg/L and 0.04 mg/L, respectively [4]. In the same study, Draper et al. [4] isolated 70S ribosomes from *Escherichia coli* MRE600 and used them in cell-free Poly(U)-dependent Poly (Phe) synthesis (in vitro translation) to determine the ability of omadacycline to inhibit protein synthesis in the presence and absence of ribosomal protection protein, TetO [4]. In contrast with tetracycline, omadacycline had similar activity in the presence and absence of TetO [4]. These data indicate that omadacycline remains active and relatively unaffected by the presence of tetracycline efflux pumps (TetK) and ribosomal protection proteins (TetM) [4].

## 4 Mechanism of Resistance

Resistance to tetracyclines may result from increased production of efflux pumps, ribosomal protection proteins (RPPs), drug degradation, and rRNA mutations [2, 9, 12, 21]. The first two mechanisms, efflux pumps and RPPs, currently predominate in clinical settings [2] yet do not affect the antimicrobial activity of omadacycline [22]. In general, tetracycline resistance mechanisms are acquired and determined by the presence of *tet* genes summarized in Table 1 [2, 9, 12, 22–25].

Efflux pumps may be present in both Gram-positive and Gram-negative bacteria and have been divided into various families/groups based on sequence homology [2, 9, 12]. TetA, part of the largest group of efflux pumps (the major facilitator family), use protons (H<sup>+</sup>) to pump tetracycline out of the cell against its concentration gradient [12, 20, 21]. Macone et al. [11] investigated the effects of efflux pumps on the activity of omadacycline. These researchers reported that omadacycline obtained lower MICs than tetracycline against *S. aureus* with Tet(K) efflux gene and *Enterococcus faecalis* with Tet(L) efflux gene, and *E. coli* with Tet(A) efflux gene and various species of *Enterobacteriaceae* (referred to subsequently as *Enterobacterales*) with the Tet(B) efflux gene [11, 21, 24]. Similar to tigecycline, omadacycline appears to circumvent this mechanism of resistance [4, 19]. The presence of the C-7 functional group has been attributed to omadacycline's ability to inhibit protein synthesis effectively despite the presence of this mechanism of resistance [25].

In contrast to efflux pumps, the exact mechanism of RPPs is not fully understood [4]. However, studies have suggested that these proteins alter ribosomal conformation and cause the release of the drug from its active site [2, 4]. Unlike tetracycline and minocycline, which are susceptible to RPPs, the inhibitory effects of omadacycline remain relatively unaffected because the drug either binds to the ribosome in a unique way or has additional sites of interaction with the ribosome [4, 23]. The modification in

C-9 position of the tetracycline D ring has been associated with this ability to evade RPPs [25]. Additional studies are underway to further identify this mechanism of resistance [4].

Drug degradation can inactivate tetracyclines but only occurs for aerobic organisms [20]. FAD-requiring monooxygenase, encoded by *tetX* and *tet37* determinants, hydroxylates the C-11a position in between rings B and C of the tetracycline core [20, 23]. This disturbs the magnesium coordination properties and affects the binding affinity of the drug to the ribosome. Moreover, the hydroxylated version of the drug degrades without the need of enzymes [20]. This mechanism of resistance impairs the activity of glycylcyclines and omadacycline [20].

Mutation in rRNA reduces the activity of omadacycline by decreasing the affinity of the drug to the ribosome [8, 20]. Heidrich et al. [8] determined the MICs of tetracycline, tigecycline, and omadacycline in the presence of two known 16Ss rRNA mutations, G1055C and G996U. G1055C was identified in *Cutibacterium acnes* and *Brachyspira hydrophila* and G996U was found in *Helicobacter pylori* [8]. *E. coli* was used as plasmid host [8]. The MICs of all three drugs in both mutants demonstrated an increase of four- to eight-fold, indicating all were susceptible to mutations in rRNA regardless of their affinity for the ribosome [8].

In the presence of other drug-resistance mechanisms, Dubois et al. [26] evaluated the minimum inhibitory concentrations (MICs) of omadacycline compared with other agents including tigecycline, doxycycline, and azithromycin. Omadacycline demonstrated potent in vitro activity (MIC<sub>90</sub> ≤ 0.25 mg/L) against MRSA, macrolide-resistant *S. aureus* (*ermA*, *ermB*, *ermC*), and ciprofloxacin-resistant *S. aureus* (*gyrA*, *parC*) [26], demonstrating that it was not affected by these various resistance mechanisms.

**Table 1** Tetracycline-specific resistance mechanisms and associated resistance genes

| Tetracycline resistance mechanism | Tetracycline resistance gene                                                                                                                                                              |                                                                                                                                                                                                                                                                                |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   | Gram-positive bacteria                                                                                                                                                                    | Gram-negative bacteria                                                                                                                                                                                                                                                         |
| Efflux pump                       | <i>tetK</i> , <i>tetL</i> , <i>terV</i> , <i>terZ</i> , <i>tetAP</i> , <i>tetAB</i> , <i>tet33</i> , <i>tet38</i> , <i>tet40</i> , <i>tet45</i> , <i>otrB</i> , <i>otrC</i> , <i>tcr3</i> | <i>tetA</i> , <i>tetB</i> , <i>tetC</i> , <i>tetD</i> , <i>tetE</i> , <i>tetG</i> , <i>tetH</i> , <i>tetI</i> , <i>tetJ</i> , <i>tetK</i> , <i>tetL</i> , <i>tetY</i> , <i>tet30</i> , <i>tet31</i> , <i>tet34</i> , <i>tet35</i> , <i>tet39</i> , <i>tet41</i> , <i>tet42</i> |
| Ribosomal protection protein      | <i>tetM</i> , <i>tetO</i> , <i>tetP</i> , <i>tetQ</i> , <i>tetS</i> , <i>tetT</i> , <i>tetW</i> , <i>tetZ</i> , <i>tetB(P)</i> , <i>tet32</i> , <i>tet36</i> , <i>otrA</i>                | <i>tetM</i> , <i>tetO</i> , <i>tetQ</i> , <i>tetS</i> , <i>tetW</i> , <i>tet36</i> , <i>tet44</i>                                                                                                                                                                              |
| Drug degradation                  |                                                                                                                                                                                           | <i>tetX</i> , <i>tet34</i> , <i>tet37</i>                                                                                                                                                                                                                                      |
| rRNA mutations                    | G1058C                                                                                                                                                                                    | A926T, G927T, A928C, ΔG942, G966U                                                                                                                                                                                                                                              |

Adapted from Refs. [2, 9, 12, 22–25]; see also Roberts—<http://faculty.washington.edu/marilyn/> [22]

## 5 Microbiology

Published data reporting MICs for omadacycline tested against Gram-positive and Gram-negative aerobic, anaerobic, and atypical bacteria are summarized in Tables 2, 3, 4 and 5 [3, 11, 12, 15–17, 19, 26–66]. The MIC values of the comparator drugs tetracycline and tigecycline were pooled from comparative studies evaluating omadacycline as well as studies that did not evaluate omadacycline [3, 12, 19, 32, 36, 51–55, 57, 64, 67]. In general, omadacycline MICs were comparable to MICs for tigecycline and were lower than MICs for tetracycline [16, 65].

Table 2 [3, 12, 16, 17, 19, 27–29, 31, 46, 64–66, 68] presents the in vitro activity of omadacycline against Gram-positive aerobic bacteria including isolates with common resistance phenotypes. Omadacycline is active against most isolates of staphylococci, streptococci, and enterococci regardless of resistance phenotype and maintains its activity against tetracycline-resistant Gram-positive cocci with MIC<sub>90</sub> ≤ 0.25 mg/L [64, 65] as well as against Gram-positive cocci resistant to other antimicrobial classes including macrolides, β-lactams, and vancomycin [16, 17, 65].

The in vitro activity of omadacycline against Gram-negative aerobic bacteria, including isolates with various resistance phenotypes, is displayed in Table 3 [3, 12, 16, 17, 19, 27–31, 38, 46, 63–66, 68]. In general, omadacycline was more active than tetracycline against Gram-negative aerobic bacteria. It maintained its activity against tetracycline-resistant isolates but was less active than tigecycline against Gram-negative aerobic bacteria. Omadacycline has in vitro activity against most species of *Enterobacterales* including *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Citrobacter* spp. as well as *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria* spp., and some isolates of *Acinetobacter* spp. Omadacycline, like other tetracyclines, including tigecycline and eravacycline, is inactive against *P. aeruginosa*, *Proteus* spp., and *Providencia* spp. Tigecycline is also inactive against *Morganella morganii*. Omadacycline has been shown to not induce planktonic adhesion (bacterial biofilm formation in biofilm assays) at sub-MIC concentrations, unlike tetracycline [16, 60, 69].

There are currently limited data examining the in vitro activity of omadacycline against anaerobes (Table 4) [16, 39, 44, 46]. Omadacycline demonstrates anti-anaerobic activity similar to tigecycline and greater than tetracycline, and remains active against tetracycline-resistant anaerobes. The in vitro activity of omadacycline against atypical bacteria is shown in Table 5 [45, 47–49, 56, 58]. Omadacycline's activity against atypical bacteria listed in Table 5 is similar to tigecycline and greater than

tetracycline, and it remains active against tetracycline-resistant organisms. Although omadacycline is less active against *Ureaplasma* spp. than *Mycoplasma* spp., it demonstrated MICs of 0.25–2 mg/L against two isolates demonstrating high-level macrolide resistance (azithromycin MIC 16–32 mg/L), four isolates demonstrating high-level tetracycline resistance (MIC 8–16 mg/L), and two isolates that were fluoroquinolone resistant [49]. Omadacycline has also been shown to possess activity versus biothreat pathogens *B. anthracis* (MIC<sub>90</sub> 0.06 mg/L) and *Y. pestis* (MIC<sub>90</sub> 1 mg/L) [47].

## 6 Pharmacokinetics

Pharmacokinetic (PK) studies of oral and intravenous omadacycline published to date are summarized in Table 6 [70–74] and Table 7 [70, 73, 75, 76], respectively. In a study by Sun et al., the oral bioavailability of omadacycline was 34.5% when administered in tablet form to fasted subjects [70]. Similar concentration profiles were achieved with different formulations including regular tablets, slow dissolution tablets, and an oral solution. Tzanis et al. showed that omadacycline absorption was significantly affected by food, especially when dairy-containing food was consumed within 4 h prior to the dose. Specifically, the relative bioavailability of a single dose of omadacycline was reduced by 17%, 42%, and 63% when administered 4 h after a high-fat meal, 2 h after a high-fat meal, and 2 h after a high-fat and dairy-containing meal, respectively [71]. The relatively low oral absorption of omadacycline results in significant elimination of unchanged drug in the feces. Flarakos et al. studied the metabolism and excretion of a single 300-mg oral dose of omadacycline in six subjects [77]. Most of the drug (81.1% ± 2.3%) was recovered in the feces; 14.4% ± 2.3% was excreted in the urine. Omadacycline was not metabolized. It did not induce or inhibit major cytochrome P450 (CYP) enzymes [13]. Verapamil, a P-glycoprotein inhibitor, administered 2 h prior to a single 300-mg oral dose of omadacycline, increased omadacycline AUC by approximately 25% and C<sub>max</sub> by approximately 9% [13].

In PK studies of intravenous omadacycline, the mean volume of distribution (V<sub>d</sub>) was 204 L and 190 L in healthy subjects [75, 76] and 168 L in women with cystitis, respectively [73]. As detailed in Tables 6 and 8, the terminal half-life (t<sub>1/2</sub>) of omadacycline was 13.5–17.1 h in healthy adults and 11.4 h in women with cystitis. The total drug clearance (CL<sub>T</sub>) ranged from 8.8 to 10.6 L/h, with a renal clearance (CL<sub>R</sub>) of 2.4–3.1 L/h [70, 73, 75, 76]. Approximately 20% of the intravenous dose of omadacycline was excreted unchanged in the urine over 24 h and 27% was excreted over 72 h [73, 75].

**Table 2** In vitro activity (MIC, mg/L) of omadacycline and comparators against Gram-positive aerobic bacteria

| Bacteria                                      | Omadacycline                   |                                |             | Tetracycline                   |                                | Tigecycline                    |                                |
|-----------------------------------------------|--------------------------------|--------------------------------|-------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                                               | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC range   | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> |
| <i>Staphylococcus aureus</i> (all)            | 0.12                           | 0.25                           | ≤0.015–8    | 0.12                           | ≤0.5                           | 0.12                           | 0.25                           |
| <i>S. aureus</i> (MSSA) <sup>c</sup>          | 0.12                           | 0.25                           | ≤0.015–2    | ≤0.5                           | 0.12                           | 0.12                           | 0.12                           |
| <i>S. aureus</i> (MRSA) <sup>c</sup>          | 0.12                           | 0.25                           | ≤0.015–8    | ≤0.5                           | 4                              | 0.12                           | 0.25                           |
| <i>S. aureus</i> (CA-MRSA) <sup>c</sup>       | 0.12                           | 0.25                           | 0.03–1      | ≤0.25                          | 0.5                            | 0.12                           | 0.5                            |
| <i>S. aureus</i> (HA-MRSA) <sup>c</sup>       | 0.12                           | 0.5                            | 0.06–1      | 0.12                           | 0.5                            | 0.12                           | 0.5                            |
| <i>S. aureus</i> (TR) <sup>d</sup>            | 0.12                           | 0.5                            | 0.03–2      | 16                             | 16                             | 0.12                           | 0.25                           |
| <i>Staphylococcus epidermidis</i> (all)       | 0.06                           | 0.25                           | ≤0.015–0.5  | 0.25                           | 0.5                            | 0.25                           | 0.5                            |
| Coagulase-negative Staphylococci (all)        | 0.12                           | 1                              | ≤0.015–2    | 0.12                           | 16                             | 0.25                           | 0.25                           |
| CoNS (MS) <sup>e</sup>                        | 0.12                           | 0.5                            | ≤0.015–2    | 0.25                           | 4                              | 0.12                           | 0.25                           |
| CoNS (MR) <sup>e</sup>                        | 0.25                           | 1                              | ≤0.015–2    | 0.25                           | > 8                            | 0.12                           | 0.5                            |
| CoNS (TR) <sup>d</sup>                        | 0.25                           | 0.5                            | 0.03–2      | ≥ 16                           | ≥ 16                           | 0.12                           | 0.25                           |
| <i>Staphylococcus lugdunensis</i>             | 0.06                           | 0.12                           | ≤0.03–0.12  | –                              | –                              | –                              | –                              |
| <i>Staphylococcus pseudintermedius</i>        | 0.12                           | –                              | 0.12–0.12   | 0.12                           | –                              | 0.06                           | –                              |
| <i>Enterococcus</i> spp. (all)                | 0.06                           | 0.25                           | ≤0.015–4    | 0.5                            | > 32                           | 0.12                           | 0.25                           |
| <i>Enterococcus</i> spp. (VS) <sup>f</sup>    | 0.12                           | 0.25                           | ≤0.015–4    | –                              | –                              | –                              | –                              |
| <i>Enterococcus</i> spp. (VR) <sup>f</sup>    | 0.06                           | 0.25                           | ≤0.015–1    | –                              | –                              | –                              | –                              |
| <i>Enterococcus faecalis</i> (all)            | 0.12                           | 0.25                           | ≤0.015–4    | > 16                           | > 16                           | 0.06                           | 0.12                           |
| <i>E. faecalis</i> (VS) <sup>f</sup>          | 0.12                           | 0.25                           | ≤0.015–4    | > 16                           | > 16                           | 0.06                           | 0.12                           |
| <i>E. faecalis</i> (VR) <sup>f</sup>          | 0.12                           | 0.25                           | ≤0.015–1    | > 16                           | > 16                           | 0.06                           | 0.12                           |
| <i>E. faecalis</i> (TR) <sup>d</sup>          | 0.12                           | 0.25                           | ≤0.015–2    | ≥ 16                           | ≥ 16                           | 0.06                           | 0.12                           |
| <i>Enterococcus faecium</i> (all)             | 0.06                           | 0.12                           | ≤0.015–8    | 16                             | > 16                           | 0.12                           | 0.25                           |
| <i>E. faecium</i> (VS) <sup>f</sup>           | 0.06                           | 0.12                           | ≤0.015–1    | 16                             | > 16                           | 0.03                           | 0.06                           |
| <i>E. faecium</i> (VR) <sup>f</sup>           | 0.12                           | 0.5                            | ≤0.015–8    | > 16                           | > 16                           | 0.03                           | 0.06                           |
| <i>E. faecium</i> (TR) <sup>d</sup>           | 0.12                           | 0.25                           | ≤0.015–8    | ≥ 16                           | ≥ 16                           | 0.06                           | 0.06                           |
| Other <i>Enterococcus</i> spp.                | 0.06                           | 0.12                           | ≤0.015–0.5  | –                              | –                              | 0.12                           | 0.25                           |
| <i>Streptococcus pneumoniae</i> (all)         | 0.06                           | 0.12                           | ≤0.015–1    | ≤0.25                          | > 8                            | 0.03                           | 0.06                           |
| <i>S. pneumoniae</i> (PS) <sup>g</sup>        | 0.03                           | 0.06                           | ≤0.015–0.5  | ≤0.25                          | 0.5                            | 0.03                           | 0.06                           |
| <i>S. pneumoniae</i> (PI) <sup>g</sup>        | 0.06                           | 0.06                           | ≤0.015–1    | 0.5                            | > 8                            | 0.03                           | 0.06                           |
| <i>S. pneumoniae</i> (PR) <sup>g</sup>        | 0.06                           | 0.12                           | ≤0.015–0.5  | 32                             | 32                             | 0.06                           | 0.06                           |
| <i>Streptococcus anginosus</i> group (all)    | 0.06                           | 0.12                           | ≤0.015–0.12 | 0.5                            | > 8                            | 0.03                           | 0.03                           |
| <i>S. anginosus</i> group (TR) <sup>d</sup>   | 0.06                           | 0.12                           | ≤0.015–0.12 | ≥ 16                           | ≥ 16                           | 0.06                           | 0.12                           |
| Viridans group streptococci (all)             | 0.06                           | 0.12                           | ≤0.015–2    | 0.5                            | > 8                            | ≤0.03                          | 0.12                           |
| Viridans group streptococci (PS) <sup>g</sup> | 0.06                           | 0.12                           | ≤0.03–2     | –                              | –                              | 0.06                           | 0.25                           |
| Viridans group streptococci (PR) <sup>g</sup> | 0.12                           | –                              | ≤0.03–0.25  | –                              | –                              | 0.03                           | 0.06                           |
| Viridans group streptococci (TR) <sup>d</sup> | 0.12                           | 0.25                           | ≤0.015–2    | ≥ 16                           | ≥ 16                           | 0.06                           | 0.12                           |
| β-hemolytic streptococci (all)                | 0.06                           | 0.12                           | ≤0.015–0.5  | 0.5                            | > 8                            | 0.06                           | 0.06                           |
| β-hemolytic streptococci (TR) <sup>d</sup>    | 0.12                           | 0.25                           | 0.03–1      | ≥ 16                           | ≥ 16                           | 0.06                           | 0.06                           |
| β-hemolytic streptococci (MR) <sup>e</sup>    | 0.12                           | 0.25                           | 0.03–0.5    | > 8                            | > 8                            | 0.06                           | 0.06                           |
| <i>Streptococcus pyogenes</i> (all)           | 0.06                           | 0.12                           | ≤0.015–0.5  | ≤0.06                          | 64                             | 0.03                           | 0.06                           |
| <i>S. pyogenes</i> (MR) <sup>e</sup>          | 0.12                           | 0.25                           | 0.06–0.25   | –                              | –                              | –                              | –                              |
| <i>S. pyogenes</i> (TR) <sup>d</sup>          | 0.12                           | 0.25                           | 0.06–0.5    | ≥ 16                           | ≥ 16                           | –                              | –                              |
| <i>Streptococcus agalactiae</i> (all)         | 0.06                           | 0.12                           | ≤0.015–0.5  | 32                             | 64                             | 0.06                           | 0.06                           |
| <i>S. agalactiae</i> (MR) <sup>e</sup>        | 0.12                           | 0.25                           | 0.06–0.5    | –                              | –                              | –                              | –                              |
| <i>S. agalactiae</i> (TR) <sup>d</sup>        | 0.12                           | 0.12                           | 0.03–0.5    | ≥ 16                           | ≥ 16                           | –                              | –                              |
| <i>Corynebacterium</i> spp.                   | 0.25                           | 0.5                            | ≤0.06–0.5   | 0.12                           | 1                              | –                              | –                              |
| <i>Bacillus anthracis</i>                     | 0.03                           | 0.06                           | <0.03–0.06  | <0.03                          | 0.12                           | –                              | –                              |
| <i>Listeria monocytogenes</i>                 | 0.5                            | 0.5                            | 0.5         | 4                              | 4                              | 0.25                           | 0.5                            |

**Table 2** (continued)

Adapted from Refs. [3, 12, 16, 17, 19, 27–29, 31, 46, 64–66, 68]

– No data

<sup>a</sup>MIC<sub>50</sub>, minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

<sup>b</sup>MIC<sub>90</sub>, minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

<sup>c</sup>MSSA methicillin-susceptible *S. aureus*; MRSA methicillin-resistant *S. aureus* (oxacillin MIC,  $\geq 4$  mg/L or cefoxitin MIC,  $\geq 8$  mg/L); CA-MRSA community-associated methicillin-resistant *S. aureus*; HA-MRSA healthcare-associated methicillin-resistant *S. aureus*

<sup>d</sup>TR tetracycline resistant (MIC,  $\geq 16$  mg/L)

<sup>e</sup>MS macrolide-susceptible (azithromycin MIC,  $< 16$  mg/L); *S. pyogenes* MR and  $\beta$ -hemolytic streptococci MR, macrolide-resistant (erythromycin MIC,  $\geq 1$  mg/L); *S. pneumoniae* MR, macrolide-resistant (erythromycin MIC,  $\geq 1$  mg/L and azithromycin MIC,  $\geq 2$  mg/L)

<sup>f</sup>VS vancomycin-susceptible (MIC,  $\leq 4$  mg/L); VR vancomycin-resistant (MIC,  $\geq 32$  mg/L)

<sup>g</sup>PS penicillin-susceptible; PI penicillin-intermediate; PR penicillin-resistant (MIC,  $\geq 2$  mg/L)

The maximum plasma concentration ( $C_{\max}$ ) of omadacycline for a single 100-mg intravenous dose (30-min infusion) was 1.8–2.1 mg/L in healthy subjects [70, 75, 76]. The mean areas under the concentration–time curve ( $AUC_{0-\infty}$ ) were 9.8 mg h/L to 10 mg h/L [70, 75]. For oral omadacycline in fasted subjects, the  $C_{\max}$  at 2.5–3 h was 0.5–0.6 mg/L for a single 300-mg dose compared with 0.8–1.1 mg/L for a multiple-dose regimen [70–73]. The  $AUC_{0-\infty}$  for a single 300-mg oral dose (various formulations tested) ranged from 9.6 to 11.9 mg h/L, which was comparable to a 100-mg IV dose and consistent with a bioavailability of 34.5% [70, 71]. AUC targets were used to develop the recommended oral dosing regimen for ABSSSIs, that is, 450 mg daily for 2 days ( $AUC_{0-24h} = 9.0$  mg h/L) followed by 300 mg daily ( $AUC_{24h} = 9.3$  mg h/L) [13, 72].

In a study by Lin et al., the protein binding of omadacycline in human plasma was 21.3% compared with 15.3%, 26.1%, and 21.2% in mouse, rat, and monkey plasma, respectively [78]. Such protein binding is relatively low compared with that of other tetracyclines including 60–95% for doxycycline, 55–96% for minocycline, 79–90% for eravacycline, and 71–89% for tigecycline [12, 19]. Unlike eravacycline and tigecycline, omadacycline did not exhibit concentration-dependent protein binding over a range of 10–10,000 ng/mL.

In a study by Gotfried et al., the intrapulmonary PK of omadacycline was investigated in 41 healthy adults who received 100 mg of intravenous omadacycline at 0, 12, 24, 48, and 72 h [76]. Intrapulmonary penetration was characterized by the ratio of  $AUC_{24h}$  in epithelial lining fluid (ELF) or alveolar cells to the free (unbound)  $AUC_{24h}$  in plasma. The  $AUC_{24h}$  values in ELF and alveolar cells were 17.2 mg h/L and 302.5 mg h/L, respectively, whereas the  $AUC_{24h}$  ratios relative to the free  $AUC_{24h}$  in plasma were 1.5 and 25.8.

In a population-PK study by Lakota et al., the concentration profile of omadacycline was best described by a linear, three-compartment model with zero-order intravenous infusion or first-order oral administration [79]. PK data was used from 14 phase I ( $n = 433$ ) and three phase III studies of CABP and ABSSSIs ( $n = 180$ ). Subjects were

71% male with a mean age of  $39 \pm 15$  years, weight of  $78.4 \pm 14.6$  kg, and creatinine clearance of  $99.8 \pm 28.1$  mL/min/ $1.73$  m<sup>2</sup>. In the final model, the mean volumes in the central, first peripheral, and second peripheral compartments were 21.1 L, 79.9 L, and 129 L, respectively. Gender was a significant covariate for omadacycline CL with final estimates of 10.3 L/h in males and 8.7 L/h in females.

The PK of omadacycline has been studied in patients with renal and hepatic impairment [75, 80]. Berg et al. studied the PK of omadacycline in subjects undergoing chronic hemodialysis (HD) ( $n = 8$ ) compared with healthy subjects matched for age, gender, and weight ( $n = 8$ ) [75]. A single 100-mg intravenous dose produced an  $AUC_{0-\infty}$  of 9.8 mg h/L in the control group compared with 10.3 mg h/L when administered post-HD and 10.2 mg h/L when administered pre-HD to those with end-stage renal disease. Only 7.9% of the pre-HD dose was recovered in dialysate. Ting et al. described the PK of omadacycline in patients with mild ( $n = 6$ ), moderate ( $n = 6$ ), and severe ( $n = 6$ ) hepatic impairment (Child–Turcotte–Pugh class A, B, C) compared with matched subjects ( $n = 12$ ) [81]. The mean  $AUC_{0-\infty}$  ratio (90% confidence interval) for a 100-mg intravenous dose in subjects with mild hepatic impairment compared with controls was 0.89 (0.7–1.1), whereas ratios for a 50-mg intravenous dose in those with moderate and severe hepatic impairment versus controls was 0.80 (0.6–1.0) and 0.97 (0.8–1.2), respectively. The conclusions of these studies were that dosage adjustments would not be required for patients with renal or hepatic impairment [75, 80].

Lakota et al. investigated the impact of comorbidities and other factors on the CL of omadacycline. After adjusting for gender, there were no significant differences in total drug CL in patients with a history of chronic lung disease, coronary artery disease, diabetes mellitus, heart failure, or hypertension [80]. Although there was a statistically significant difference in CL between smokers and non-smokers (i.e., 11.2 L/h vs 10.0 L/h), it was not considered clinically significant.

**Table 3** In vitro activity (MIC, mg/L) of omadacycline and comparators against Gram-negative aerobes

| Bacteria                                                | Omadacycline                   |                                |           | Tetracycline      |                   | Tigecycline       |                   |
|---------------------------------------------------------|--------------------------------|--------------------------------|-----------|-------------------|-------------------|-------------------|-------------------|
|                                                         | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC range | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>Enterobacteriaceae</i> (all)                         | 1                              | 8                              | 0.06–> 32 | 2                 | > 16              | 0.25              | 1                 |
| <i>Enterobacteriaceae</i> (CNS) <sup>c</sup>            | 2                              | 8                              | 0.12–> 32 | 16                | > 16              | 0.25              | 1                 |
| <i>Enterobacteriaceae</i> (TR) <sup>d</sup>             | 2                              | 16                             | 0.12–> 32 | ≥ 16              | ≥ 16              | 0.5               | 2                 |
| <i>Escherichia coli</i> (all)                           | 0.5                            | 2                              | 0.12–32   | 2                 | > 16              | 0.12              | 0.25              |
| <i>E. coli</i> (CS) <sup>c</sup>                        | 0.5                            | 2                              | 0.12–32   | 2                 | > 16              | 0.12              | 0.25              |
| <i>E. coli</i> (CNS) <sup>c</sup>                       | 1                              | 2                              | 0.12–32   | > 16              | > 16              | 0.12              | 0.25              |
| <i>E. coli</i> (TR) <sup>d</sup>                        | 1                              | 4                              | 0.12–32   | > 64              | ≥ 64              | 0.12              | 0.25              |
| <i>E. coli</i> (ESBL) <sup>h</sup>                      | 1                              | 4                              | 0.12–> 32 | > 8               | > 8               | 0.25              | 1                 |
| <i>Klebsiella pneumoniae</i> (all)                      | 2                              | 8                              | 0.12–> 32 | 2                 | > 16              | 0.25              | 1                 |
| <i>K. pneumoniae</i> (CS) <sup>c</sup>                  | 1                              | 4                              | 0.25–> 32 | 1                 | > 16              | 0.25              | 0.5               |
| <i>K. pneumoniae</i> (CNS) <sup>c</sup>                 | 2                              | 8                              | 0.25–> 32 | 16                | > 16              | 0.25              | 0.5               |
| <i>K. pneumoniae</i> (TR) <sup>d</sup>                  | 4                              | 16                             | 0.5–> 32  | ≥ 16              | ≥ 16              | 0.5               | 2                 |
| <i>K. pneumoniae</i> (ESBL) <sup>h</sup>                | 2                              | 8                              | 0.25–> 32 | > 8               | > 8               | 1                 | 4                 |
| <i>Klebsiella oxytoca</i> (all)                         | 1                              | 4                              | 0.25–32   | 1                 | 8                 | 0.25              | 0.5               |
| <i>K. oxytoca</i> (TR) <sup>d</sup>                     | 2                              | 8                              | 0.25–> 32 | ≥ 16              | ≥ 16              | 0.5               | 1                 |
| <i>Enterobacter cloacae</i> species complex (all)       | 2                              | 4                              | 0.25–> 32 | 2                 | 16                | 0.5               | 2                 |
| <i>E. cloacae</i> spp. complex (CS) <sup>c</sup>        | 2                              | 4                              | 0.25–> 32 | 2                 | 4                 | 0.25              | 0.5               |
| <i>E. cloacae</i> spp. complex (CNS) <sup>c</sup>       | 2                              | 8                              | 0.25–> 32 | 2                 | > 16              | 0.5               | 1                 |
| <i>E. cloacae</i> spp. complex (TR) <sup>d</sup>        | 4                              | 16                             | 1–32      | ≥ 16              | ≥ 16              | 0.5               | 2                 |
| Other <i>Enterobacter</i> spp. (all)                    | 2                              | 4                              | 0.06–> 32 | 1                 | 4                 | 0.25              | 0.5               |
| Other <i>Enterobacter</i> spp. (TR) <sup>d</sup>        | 16                             | 16                             | 2–16      | ≥ 16              | ≥ 16              | 2                 | 2                 |
| <i>Citrobacter</i> spp. (all)                           | 1                              | 4                              | 0.25–> 32 | 1                 | 4                 | 0.25              | 0.5               |
| <i>Citrobacter</i> spp. (TR) <sup>d</sup>               | 4                              | 8                              | 0.5–8     | ≥ 16              | ≥ 16              | 0.5               | 1                 |
| <i>Citrobacter freundii</i>                             | 1                              | 4                              | 0.5–16    | 1                 | > 16              | 0.5               | 2                 |
| <i>Citrobacter freundii</i> (TR) <sup>d</sup>           | 4                              | 8                              | 0.25–16   | ≥ 16              | ≥ 16              | 0.5               | 1                 |
| <i>Proteus mirabilis</i> (all)                          | 16                             | > 32                           | 1–> 32    | > 16              | > 16              | 4                 | 4                 |
| <i>P. mirabilis</i> (TR) <sup>d</sup>                   | 16                             | > 32                           | 2–> 32    | ≥ 16              | ≥ 16              | 2                 | 4                 |
| <i>Proteus</i> spp. (IP) <sup>f</sup>                   | 8                              | 32                             | 0.5–> 32  | 16                | > 16              | 1                 | 2                 |
| <i>Proteus</i> spp. (IP <sup>f</sup> , TR) <sup>d</sup> | 8                              | 32                             | 0.5–> 32  | ≥ 16              | ≥ 16              | 1                 | 2                 |
| <i>Salmonella</i> spp.                                  | 2                              | 4                              | 0.12–16   | 2                 | 32                | 0.5               | 0.5               |
| <i>Serratia marcescens</i>                              | 4                              | 8                              | 0.5–> 32  | > 8               | > 8               | 1                 | 1                 |
| <i>S. marcescens</i> (TR) <sup>d</sup>                  | 4                              | 8                              | 0.5–> 32  | ≥ 16              | ≥ 16              | 1                 | 2                 |
| Other <i>Serratia</i> spp.                              | 2                              | 4                              | 0.25–16   | –                 | –                 | –                 | –                 |
| <i>Shigella</i> spp.                                    | 1                              | 2                              | –         | 128               | 128               | 0.25              | 0.5               |
| <i>Yersinia pestis</i>                                  | 1                              | 1                              | 0.12–2    | 0.5               | 2                 | –                 | –                 |
| <i>Pseudomonas aeruginosa</i>                           | 32                             | 128                            | 1–128     | 8                 | > 32              | 8                 | 16                |
| <i>Acinetobacter baumannii</i> (all)                    | 2                              | 8                              | 0.06–> 32 | > 16              | > 16              | 0.5               | 2                 |
| <i>A. baumannii</i> (TR) <sup>d</sup>                   | 4                              | 8                              | 0.25–> 32 | ≥ 16              | ≥ 16              | 2                 | 8                 |
| <i>Stenotrophomonas maltophilia</i>                     | 2                              | 8                              | 0.25–> 32 | 16                | 32                | 1                 | 2                 |
| <i>Burkholderia cepacia</i>                             | 2                              | 64                             | –         | 32                | 32                | 1                 | 16                |
| <i>Haemophilus influenzae</i> (all)                     | 1                              | 1                              | 0.12–16   | 0.5               | 1                 | 0.12              | 0.25              |
| <i>H. influenzae</i> (BLP) <sup>i</sup>                 | 1                              | 1                              | 0.25–4    | 0.5               | 0.5               | 0.12              | 0.25              |
| <i>H. influenzae</i> (BLN) <sup>i</sup>                 | 1                              | 1                              | 0.12–16   | 0.5               | 1                 | 0.12              | 0.25              |
| <i>Moraxella catarrhalis</i> (all)                      | 0.12                           | 0.25                           | 0.06–1    | 0.25              | 0.5               | 0.06              | 0.06              |
| <i>Pasteurella canis</i>                                | 0.25                           | 0.25                           | 0.12–0.25 | 0.12              | 0.25              | 0.06              | 0.06              |
| <i>Pasteurella multocida</i> subsp. <i>multocida</i>    | 0.25                           | 0.25                           | 0.12–0.25 | 0.12              | 0.25              | 0.03              | 0.12              |
| <i>Pasteurella multocida</i> subsp. <i>septica</i>      | 0.25                           | 0.25                           | 0.12–0.25 | 0.12              | 0.25              | 0.06              | 0.06              |
| <i>Eikenella corrodens</i>                              | 8                              | 16                             | 4–16      | 4                 | 4                 | 4                 | 8                 |

**Table 3** (continued)

| Bacteria                                  | Omadacycline                   |                                |             | Tetracycline      |                   | Tigecycline       |                   |
|-------------------------------------------|--------------------------------|--------------------------------|-------------|-------------------|-------------------|-------------------|-------------------|
|                                           | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC range   | MIC <sub>50</sub> | MIC <sub>90</sub> | MIC <sub>50</sub> | MIC <sub>90</sub> |
| <i>Bergeyella zoohelcum</i>               | 0.06                           | 0.12                           | ≤0.015–0.25 | 0.25              | 0.25              | 0.06              | 0.06              |
| <i>Neisseria gonorrhoeae</i> (all)        | 2                              | 4                              | 0.25–4      | 1                 | ≥32               | 0.5               | 1                 |
| <i>N. gonorrhoeae</i> (CIPS) <sup>c</sup> | 1                              | 2                              | 0.25–2      | 2                 | 4                 | 0.5               | 0.5               |
| <i>N. gonorrhoeae</i> (CIPR) <sup>c</sup> | 4                              | 4                              | 1–4         | 32                | 64                | 0.5               | 0.5               |
| <i>Neisseria weaveri</i>                  | 0.25                           | 0.25                           | 0.12–0.5    | 0.12              | 0.25              | 0.06              | 0.6               |
| <i>Neisseria zoodegmatis</i>              | 0.25                           | 0.5                            | 0.12–0.5    | 0.12              | 0.12              | 0.06              | 0.06              |

Adapted from Refs. [3, 12, 16, 17, 19, 27–31, 38, 46, 63, 65, 66, 68]

– No data

<sup>a</sup>MIC<sub>50</sub> minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

<sup>b</sup>MIC<sub>90</sub> minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

<sup>c</sup>CNS ceftazidime non-susceptible; CS ceftazidime-susceptible

<sup>d</sup>TR tetracycline-resistant (MIC, ≥16 mg/L)

<sup>e</sup>CIPS ciprofloxacin-susceptible, CIPR ciprofloxacin-resistant

<sup>f</sup>IP indole positive

<sup>g</sup>PS penicillin-susceptible; PI penicillin-intermediate; PR penicillin-resistant (MIC, ≥2 mg/L)

<sup>h</sup>ESBL extended-spectrum β-lactamase or ceftazidime resistant (MIC, >4 mg/L)

<sup>i</sup>BLN β-lactamase-negative; BLP β-lactamase-positive

**Table 4** In vitro activity (MIC, mg/L) of omadacycline and comparators against anaerobic bacteria

| Bacteria                          | Omadacycline                   |                                |           | Tetracycline                   |                                | Tigecycline                    |                                |
|-----------------------------------|--------------------------------|--------------------------------|-----------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                                   | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | Range     | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> |
| <i>Clostridioides difficile</i>   | 0.25                           | 0.5                            | 0.12–8    | 0.06                           | >256                           | 0.25                           | 0.25                           |
| <i>Clostridium perfringens</i>    | 4                              | 16                             | 0.12–16   | –                              | –                              | 8                              | >16                            |
| <i>Peptostreptococcus</i> spp.    | 0.12                           | 1                              | 0.06–2    | 0.5                            | 16                             | 0.12                           | 2                              |
| <i>P. asaccharolytica</i>         | 0.25                           | 0.5                            | 0.06–2    | NA                             | NA                             | 0.25                           | 0.5                            |
| <i>Bacteroides fragilis</i>       | 0.5                            | 4                              | 0.25–16   | 8                              | 32                             | 2                              | 8                              |
| <i>Bacteroides ovatus</i>         | 0.5                            | 8                              | 0.06–>16  | –                              | –                              | 0.5                            | 16                             |
| <i>Bacteroides thetaioamicron</i> | 1                              | 4                              | 0.12–16   | –                              | –                              | 1                              | 8                              |
| <i>Bacteroides vulgatus</i>       | 0.12                           | 1                              | 0.06–2    | –                              | –                              | 0.25                           | 1                              |
| <i>Bacteroides pyogenes</i>       | 0.25                           | 0.25                           | 0.06–0.25 | 0.25                           | 16                             | 0.25                           | 0.5                            |
| <i>Fusobacterium</i> spp.         | 0.25                           | 0.25                           | 0.25–1    | 0.12                           | 0.5                            | 0.03                           | 0.06                           |
| <i>Porphyromonas</i> spp.         | 0.06                           | 0.06                           | 0.06–0.5  | 0.06                           | 0.12                           | ≤0.03                          | ≤0.03                          |
| <i>Prevotella heparinolytica</i>  | 0.12                           | 0.12                           | 0.12–0.12 | 0.12                           | 8                              | 0.06                           | 0.12                           |
| <i>Prevotella</i> spp.            | 0.5                            | 2                              | 0.12–8    | 0.25                           | 16                             | 0.25                           | 0.25                           |

Adapted from Refs. [39, 44, 46]

– No data

<sup>a</sup>MIC<sub>50</sub> minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates

<sup>b</sup>MIC<sub>90</sub> minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates

## 7 Pharmacodynamics

Consistent with the tetracycline class of antibiotics, the activity of omadacycline has been associated with the pharmacodynamic (PD) index, free AUC divided by the

MIC ( $fAUC_{24h}/MIC$ ) [12, 19, 82–84]. In a study by Lepak et al., the in vivo activity of omadacycline was tested against two penicillin-sensitive (omadacycline MICs of 0.06 and 0.125 mg/L) and two penicillin-resistant (omadacycline MICs 0.03 and 0.06 mg/L) isolates of *S. pneumoniae* in a pneumonia model in neutropenic mice

**Table 5** In vitro activity (MIC, mg/L) of omadacycline and comparators against atypical bacteria

| Bacteria                        | Omadacycline                   |                                |             | Tetracycline                   |                                | Tigecycline                    |                                |
|---------------------------------|--------------------------------|--------------------------------|-------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                                 | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC range   | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub> <sup>a</sup> | MIC <sub>90</sub> <sup>b</sup> |
| <i>Mycoplasma hominis</i>       | 0.03                           | 0.06                           | 0.016–0.125 | 0.06                           | 2                              | 0.25                           | 0.5                            |
| <i>Mycoplasma pneumoniae</i>    | 0.125                          | 0.25                           | 0.125–0.25  | 0.25                           | 0.5                            | 0.12                           | 0.25                           |
| <i>Ureaplasma spp.</i>          | 1                              | 2                              | 0.25–2      | 1                              | 4                              | 4                              | 8                              |
| <i>Legionella pneumophila</i>   | 0.25                           | 0.25                           | 0.06–0.5    | 1                              | 1                              | 1                              | 1                              |
| <i>Chlamydophila pneumoniae</i> | 0.06                           | 0.25                           | 0.03–0.5    | 0.125 <sup>c</sup>             | 0.125 <sup>c</sup>             | 0.125                          | 0.125                          |
| <i>Mycobacterium abscessus</i>  | 1                              | 2                              | 0.06–8      | > 64 <sup>c</sup>              | > 64 <sup>c</sup>              | 1                              | 2                              |
| <i>Mycobacterium chelonae</i>   | 0.125                          | 0.25                           | 0.015–0.25  | 32 <sup>c</sup>                | 64 <sup>c</sup>                | 0.06                           | 0.25                           |
| <i>Mycobacterium fortuitum</i>  | 0.125                          | 0.5                            | 0.03–1      | 8 <sup>c</sup>                 | 64 <sup>c</sup>                | 0.25                           | 0.5                            |

Adapted from Refs. [45, 47–49, 56, 58, 62]

– No data

<sup>a</sup>MIC<sub>50</sub> minimum inhibitory concentration (mg/L) inhibiting growth of 50% of isolates<sup>b</sup>MIC<sub>90</sub> minimum inhibitory concentration (mg/L) inhibiting growth of 90% of isolates<sup>c</sup>Doxycycline MIC values

[83]. Two hours after inoculation, mice were treated with omadacycline doses ranging from 0.5 to 32 mg/kg every 12 h for 24 h, and total concentrations were measured in plasma and ELF. Although plasma AUC<sub>24h</sub>/MIC correlated with antibacterial activity ( $r^2 = 0.74$ ), there was significant inter-isolate variability not explained by omadacycline MIC or the presence of penicillin resistance. A total plasma AUC<sub>24h</sub>/MIC of 15.8 and 19.8 was associated with bacteriostasis against two isolates, whereas values ranging from 6.1 to 180 were observed for  $1 - \log_{10}$  bacterial kill ( $n = 4$ ). For three isolates, AUC<sub>24h</sub>/MIC thresholds of 18.7–56.2 were reported for  $2 - \log_{10}$  bacterial kill. Similar AUC<sub>24h</sub>/MIC thresholds were identified in plasma and ELF.

Lepak et al. also studied the in vivo activity of omadacycline against four MSSA and six MRSA in a thigh infection model in neutropenic mice [82]. Two hours after inoculation, mice were treated with omadacycline doses ranging from 0.25 to 64 mg/kg every 12 h for 24 h. The antibacterial activity of omadacycline was associated with total plasma AUC<sub>24h</sub>/MIC ( $r^2 = 0.93$ ) where median values of 21.9 (range 13.8–51.1) and 57.7 (range 32.2–302.5) corresponded to bacteriostasis and  $1 - \log_{10}$  bacterial kill, respectively. No significant differences in PD thresholds were evident for MSSA versus MRSA isolates.

The in vivo PD targets for *S. aureus* infection [82] were used in Monte Carlo simulations to predict the probability of target attainment in patients with ABSSSI [84]. Three omadacycline dosing regimens were investigated: (1) 100 mg intravenously twice daily on day 1 and once daily on day 2, then 300 mg orally once daily on day 3; (2) 200 mg intravenously once daily on day 1, 100 mg

intravenously once daily on day 2, then 300 mg orally once daily on day 3; and (3) 450 mg orally once daily on days 1 and 2, then 300 mg orally once daily on day 3. Free plasma concentration-time profiles were simulated using the previously described population-PK model [79]. A log-normal distribution of the  $fAUC_{24h}$  target for bacteriostasis was modeled using a median  $fAUC_{24h}$  of 21.9 (range 13.8–51.1) [82]. An omadacycline MIC distribution for *S. aureus* was simulated using clinical isolate data from the SENTRY surveillance program (MIC<sub>90</sub> = 0.25 mg/L) [66]. At the MIC<sub>90</sub>, the predicted target attainment for bacteriostasis was 91.3%, 92.6%, and 60.8% for regimens 1, 2, and 3, respectively.

Bhavnani et al. [84] also investigated the clinical PD of omadacycline in the treatment of ABSSSI using data from two phase III studies of omadacycline (OASIS-1 and OASIS-2) [85]. Only patients with microbiologically confirmed *S. aureus* infection, measured omadacycline concentrations, and clinical outcome data were included in the analysis ( $n = 125$ ). Average  $fAUC_{24h}$  from 0 to 48 h was simulated for each patient using their measured concentrations and the previously described population-PK model [79]. Logistic regression analysis was used to describe the PD relationship between  $fAUC_{24h}$ /MIC and early clinical response (ECR) at 48–72 h, defined as at least 20% reduction in lesion size without the need for rescue antibacterial therapy. The omadacycline dosing regimens were tested using Monte Carlo simulations where early clinical success with dosing regimens 1, 2, and 3 (described above) and an MIC of 0.5 mg/L was predicted in 91.9%, 92.1%, and 89.3% of cases, respectively.

**Table 6** Pharmacokinetics of oral omadacycline

| Study                      | Subjects                                              | n (M/F) | Dosing regimen <sup>a</sup>                                                | F <sub>fasted</sub> (%) | Ratio of AUC <sub>fed</sub> /AUC <sub>fasted</sub> <sup>b</sup> | C <sub>max</sub> (mg/L) <sup>c</sup> | AUC (mg h/L) <sup>d</sup> | CL <sub>T</sub> /F (L/h) | CL <sub>R</sub> (L/h) | t <sub>1/2</sub> (h) |
|----------------------------|-------------------------------------------------------|---------|----------------------------------------------------------------------------|-------------------------|-----------------------------------------------------------------|--------------------------------------|---------------------------|--------------------------|-----------------------|----------------------|
| <b>Single-dose studies</b> |                                                       |         |                                                                            |                         |                                                                 |                                      |                           |                          |                       |                      |
| Sun et al. [70, 74]        | Healthy adults<br>36 years (18–50), 76 kg<br>(52–96)  | 21      | 300 mg PO tablet for 1 dose                                                | 34.5                    |                                                                 | 0.5 ± 0.1                            | 10.3 ± 2.5                | 30.7 ± 6.5               |                       | 16.8 ± 1.7           |
|                            |                                                       | 22      | 300 mg PO slow dissolution tablet for 1 dose                               |                         |                                                                 | 0.5 ± 0.1                            | 9.6 ± 2.3                 | 33.0 ± 8.0               |                       | 16.7 ± 1.5           |
| Tzanis et al. [71]         | Healthy adults<br>32 years (21–50),<br>72 ± 13 kg     | 22      | 300 mg PO solution for 1 dose                                              |                         |                                                                 | 0.6 ± 0.2                            | 11.9 ± 2.8                | 26.5 ± 6.3               |                       | 16.7 ± 1.8           |
|                            |                                                       | 15/16   | 300 mg PO tablet for 1 dose                                                |                         |                                                                 | 0.6 ± 0.2                            | 10.2 ± 2.8                |                          |                       | 13.8 ± 1.4           |
|                            |                                                       |         | 300 mg PO tablet for 1 dose<br>(4 h after high-fat meal)                   |                         | 0.85 [0.76–0.95]                                                | 0.6 ± 0.2                            | 8.8 ± 2.6                 |                          |                       | 13.6 ± 1.7           |
|                            |                                                       |         | 300 mg PO tablet for 1 dose<br>(2 h after high-fat meal)                   |                         | 0.58 [0.52–0.65]                                                | 0.4 ± 0.1                            | 6.0 ± 1.5                 |                          |                       | 13.6 ± 1.7           |
| Multiple-dose studies      | Healthy adults<br>36 years (21–55), 79 kg<br>(63–101) |         | 300 mg PO tablet for 1 dose<br>(2 h after high-fat and dairy meal)         |                         | 0.38 [0.34–0.42]                                                | 0.3 ± 0.1                            | 4.0 ± 1.8                 |                          |                       | 13.5 ± 2.0           |
|                            |                                                       | 23      | 300 mg PO tablet q24h × 5 doses <sup>e</sup>                               |                         |                                                                 | 0.8 ± 0.2                            | 9.3 ± 2.5                 |                          |                       | 15.5 ± 1.7           |
|                            |                                                       | 24      | 450 mg PO tablet q24h × 5 doses <sup>e</sup>                               |                         |                                                                 | 1.1 ± 0.3                            | 13.4 ± 3.5                |                          |                       | 16.8 ± 1.4           |
|                            |                                                       | 23      | 600 mg PO tablet q24h × 5 doses <sup>e</sup>                               |                         |                                                                 | 1.3 ± 0.3                            | 16.4 ± 4.4                |                          |                       | 16.8 ± 1.1           |
| Overcash et al. [73]       | Cystitis 51 years (20–60),<br>72 kg (47–95)           | 0/10    | 200 mg IV for 1 dose, then<br>300 mg PO tablet q24h × 4 doses <sup>e</sup> |                         |                                                                 | 1.1 ± 0.7                            | 13.2 ± 7.9                |                          | 2.4 ± 0.9             |                      |
|                            |                                                       | 0/10    | 300 mg PO tablet q12h for 2 doses, then q24h × 4 doses <sup>e</sup>        |                         |                                                                 | 1.1 ± 0.4                            | 13.5 ± 4.5                |                          | 2.7 ± 1.0             |                      |
|                            |                                                       | 0/10    | 450 mg PO tablet q12h for 2 doses, then q24h × 4 doses <sup>e</sup>        |                         |                                                                 | 1.5 ± 0.5                            | 19.8 ± 6.1                |                          | 2.8 ± 2.3             |                      |

Adapted from Refs. [70–74]

Data presented as mean (range), mean ± standard deviation, or geometric mean [90% confidence interval]

AUC area under the concentration-time curve, CL<sub>R</sub> renal clearance, CL<sub>T</sub>/F total drug clearance/bioavailability, C<sub>max</sub> maximum plasma concentration, F oral bioavailability, IV intravenously, PO orally, q12h every 12 h, q24h every 24 h, t<sub>1/2</sub> elimination half-life

<sup>a</sup>> 6 h fasting unless otherwise indicated

<sup>b</sup>Ratio of AUC<sub>0–∞</sub> when administered with food and AUC<sub>0–∞</sub> when administered to fasted subjects

<sup>c</sup>2.5–3 h post dose

<sup>d</sup>AUC<sub>0–∞</sub> for single-dose and AUC<sub>0–24h</sub> for multiple-dose studies

<sup>e</sup>Pharmacokinetics on day 5

**Table 7** Pharmacokinetics of intravenous omadacycline

| Study                        | Subjects                                           | n (M/F) | Dosing regimen <sup>a</sup>                                                  | C <sub>max</sub> (mg/L) | AUC (mg h/L) <sup>b</sup> | V <sub>ss</sub> (L) | CL <sub>T</sub> (L/h) | CL <sub>R</sub> (L/h) | fe <sub>u</sub> (%) <sup>c</sup> | t <sub>1/2</sub> (h) |
|------------------------------|----------------------------------------------------|---------|------------------------------------------------------------------------------|-------------------------|---------------------------|---------------------|-----------------------|-----------------------|----------------------------------|----------------------|
| <b>Single-dose studies</b>   |                                                    |         |                                                                              |                         |                           |                     |                       |                       |                                  |                      |
| Berg et al. [75]             | Healthy adults<br>57 years (45–67), 92 kg (61–129) | 6/2     | 100 mg IV for 1 dose                                                         | 1.9 ± 0.4               | 9.8 ± 1.8                 | 204 ± 48            | 10.6 ± 2.0            | 3.1 ± 0.7             | 27.0 ± 3.5                       | 17.1 ± 2.6           |
| Sun et al. [70]              | Healthy adults<br>36 years (18–50), 76 kg (52–96)  | 21      | 100 mg IV for 1 dose                                                         | 1.8 ± 0.7               | 10.0 ± 1.5                |                     | 10.3 ± 1.8            |                       |                                  | 16.8 ± 1.6           |
| <b>Multiple-dose studies</b> |                                                    |         |                                                                              |                         |                           |                     |                       |                       |                                  |                      |
| Overcash et al. [73]         | Cystitis<br>51 years (20–60), 72 kg (47–95)        | 0/11    | 200 mg IV for 1 dose,<br>then 300 mg orally<br>q24h for 4 doses <sup>c</sup> | 2.2 ± 1.3               | 16.0 ± 4.6                | 168 ± 30            | 10.3 ± 1.6            | 2.6 ± 1.2             | 20.4                             | 11.4 ± 1.5           |
| Gotfried et al. [76]         | Healthy adults<br>38 ± 10 years, 78 ± 12 kg        | 28/13   | 100 mg IV q12h for 2<br>doses, then q24h for<br>3 doses <sup>d</sup>         | 2.1 ± 0.7               | 12.1 ± 3.2                | 190 ± 53            | 8.8 ± 2.2             |                       |                                  | 16.0 ± 3.5           |

Adapted from Refs. [70, 73, 75, 76]

Data presented as mean (range), mean ± standard deviation, or median [range]

AUC area under the concentration–time curve, C<sub>max</sub> maximum plasma concentration, CL<sub>R</sub> renal clearance, CL<sub>T</sub> total drug clearance, fe<sub>u</sub> fraction of dose excreted in urine, IV intravenously, q12h every 12 h, q24h every 24 h, t<sub>1/2</sub> elimination half-life, V<sub>ss</sub> volume of distribution at steady state

<sup>a</sup>0.5 h IV infusions

<sup>b</sup>AUC<sub>0–∞</sub> and fe<sub>u</sub> over 72 h for single-dose, and AUC<sub>24h</sub> and fe<sub>u</sub> over 24 h for multiple-dose studies

<sup>c</sup>Pharmacokinetics on day 1

<sup>d</sup>Pharmacokinetics on day 4

**Table 8** Animal model studies involving omadacycline

| Study             | Animal model                                        | Number of animals tested     | Antimicrobial agent | Dose                                       | Number of doses | Bacterial strain (resistant gene)             | Results <sup>a,b</sup>                            |
|-------------------|-----------------------------------------------------|------------------------------|---------------------|--------------------------------------------|-----------------|-----------------------------------------------|---------------------------------------------------|
| Lepak et al. [83] | Neutropenic murine pneumonia infection model        | Twelve neutropenic mice      | Omadacycline        | 0.5, 2, 8, 32 mg/kg SC                     | 1               | <i>S. pneumoniae</i> 1293 PR ( <i>erm</i> )   | 1 log kill: 18.24 mg/kg<br>2 log kill: NA         |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 10813 PS            | 1 log kill: 1.26 mg/kg<br>2 log kill: 1.81 mg/kg  |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> 140 PS                   | 1 log kill: 0.71 mg/kg<br>2 log kill: 3.06 mg/kg  |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 49619 PR            | 1 log kill: 0.45 mg/kg<br>2 log kill: 2.12 mg/kg  |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> ATCC 29213 MSSA              | 1 log kill: 24.21 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> SMITH MSSA                   | 1 log kill: 128.11 mg/kg                          |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> MW2 MRSA                     | 1 log kill: 44.07 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> R2527 MRSA                   | 1 log kill: 52.32 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> 6538P MSSA                   | 1 log kill: 19.94 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> ATCC 25923 MSSA              | 1 log kill: 25.40 mg/kg                           |
| Lepak et al. [82] | Neutropenic murine thigh infection model            | Four mouse thighs per strain | Omadacycline        | 0.25–64 mg/kg/12 h in 4-fold increments SC | 2               | <i>S. aureus</i> WIS-1 MRSA                   | 1 log kill: 47.62 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> LIS 1848 MRSA                | 1 log kill: 35.45 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> 307109 MRSA                  | 1 log kill: 53.00 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 10813               | 1 log kill: 26.57 mg/kg                           |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 49619               | Maximal killing: 5.24 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 1020 ( <i>tetR</i> ) | Maximal killing: 3.37 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 1199 ( <i>tetR</i> ) | Maximal killing: 3.77 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 1293 ( <i>tetR</i> ) | Maximal killing: 3.92 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 1329                 | Maximal killing: 3.95 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 1396 ( <i>tetR</i> ) | Maximal killing: 3.61 log <sub>10</sub> CFU/thigh |
| Craig et al. [86] | Normal and neutropenic murine thigh infection model | N/A                          | Omadacycline        | 0.312, 1.25, 5 mg/kg SC                    | 1               | <i>S. pneumoniae</i> CDC 146                  | Maximal killing: 2.54 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 673                  | Maximal killing: 5.31 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> CDC 1325 ( <i>tetR</i> ) | Maximal killing: 4.22 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 6301                | Maximal killing: 5.16 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 6303                | Maximal killing: 4.00 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. pneumoniae</i> ATCC 29213               | Maximal killing: 2.93 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> ATCC 29213                   | Maximal killing: 0.79 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> ATCC Smith                   | Maximal killing: 0.61 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> ATCC 33591                   | Maximal killing: 0.86 log <sub>10</sub> CFU/thigh |
|                   |                                                     |                              |                     |                                            |                 | <i>S. aureus</i> CAMRSA MW2                   | Maximal killing: 1.19 log <sub>10</sub> CFU/thigh |

Table 8 (Continued)

| Study              | Animal model                           | Number of animals tested | Antimicrobial agent | Dose                         | Number of doses | Bacterial strain (resistant gene)             | Results <sup>a,b</sup>                               |
|--------------------|----------------------------------------|--------------------------|---------------------|------------------------------|-----------------|-----------------------------------------------|------------------------------------------------------|
| Macone et al. [11] | Murine intraperitoneal challenge model | N/A                      |                     |                              |                 | <i>S. aureus</i> CAMRSA R2527 ( <i>tetR</i> ) | Maximal killing: 1.68 log <sub>10</sub> CFU/thigh    |
|                    |                                        |                          |                     |                              |                 | <i>E. coli</i> ATCC 25922                     | Maximal killing: 2.13 log <sub>10</sub> CFU/thigh    |
|                    |                                        |                          |                     |                              |                 | <i>E. coli</i> 1-741 ( <i>tetR</i> )          | Maximal killing: 1.61 log <sub>10</sub> CFU/thigh    |
|                    |                                        |                          |                     |                              |                 | <i>E. coli</i> 1-894 ( <i>tetR</i> )          | Maximal killing: 1.32 log <sub>10</sub> CFU/thigh    |
|                    |                                        |                          |                     |                              |                 | <i>K. pneumoniae</i> ATCC 43816               | Maximal killing: 0.25 log <sub>10</sub> CFU/thigh    |
|                    |                                        |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. pneumoniae</i> PBS1339                  | ED <sub>50</sub> (mg/kg): 3.34 ± 1.56                |
|                    |                                        |                          | Ceftriaxone         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 1.1 (95% CI 1.08–1.12)     |
|                    |                                        |                          | Daptomycin          |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 1.43 (95% CI 1.24–1.62)    |
|                    |                                        |                          | Doxycycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 14.23 (95% CI 11.72–16.74) |
|                    |                                        |                          | Levofloxacin        |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 19.35 (95% CI 9.15–29.56)  |
|                    |                                        |                          | Linezolid           |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 24.47 (95% CI 13.70–35.23) |
|                    |                                        |                          | Tigecycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 4.13 (95% CI 2.46–5.79)    |
|                    |                                        |                          | Vancomycin          |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 15.70 (95% CI 9.26–22.14)  |
|                    |                                        |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. pneumoniae</i> 700905                   | ED <sub>50</sub> (mg/kg): 0.45 (95% CI 0.32–0.58)    |
|                    |                                        |                          | Vancomycin          |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 0.91 (95% CI 0.73–1.09)    |
|                    |                                        |                          | Doxycycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): > 54                       |
|                    |                                        |                          | Tigecycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 1.72 (95% CI 0.6–2.82)     |
|                    |                                        |                          | Linezolid           |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 13.88 (95% CI 3.20–24.56)  |
|                    |                                        |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. pneumoniae</i> 157E-2                   | ED <sub>50</sub> (mg/kg): 1.10 (95% CI 1.08–1.12)    |
|                    |                                        |                          | Vancomycin          |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 12.32 (95% CI 6.83–17.81)  |
|                    |                                        |                          | Doxycycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 1.55 (95% CI 0.85–2.25)    |
|                    |                                        |                          | Tigecycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 1.72 (95% CI 0.06–3.37)    |
|                    |                                        |                          | Linezolid           |                              |                 |                                               | ED <sub>50</sub> (mg/kg): > 27                       |
|                    |                                        |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. aureus</i> 29213                        | ED <sub>50</sub> (mg/kg): 1.74 (95% CI 0.91–2.58)    |
|                    |                                        |                          | Vancomycin          |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 6.09 (95% CI 3.62–8.56)    |
|                    |                                        |                          | Doxycycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 0.91 (95% CI 0.89–0.92)    |
|                    |                                        |                          | Tigecycline         |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 0.73 (95% CI 0.69–0.76)    |
|                    |                                        |                          | Linezolid           |                              |                 |                                               | ED <sub>50</sub> (mg/kg): 9.91 (95% CI 7.94–11.87)   |

Table 8 (Continued)

| Study | Animal model | Number of animals tested | Antimicrobial agent | Dose                         | Number of doses | Bacterial strain (resistant gene) | Results <sup>a,b</sup>                               |
|-------|--------------|--------------------------|---------------------|------------------------------|-----------------|-----------------------------------|------------------------------------------------------|
|       |              |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. aureus</i> USA300           | ED <sub>50</sub> (mg/kg): 0.90 (95% CI 0.33–1.46)    |
|       |              |                          | Vancomycin          |                              |                 |                                   | ED <sub>50</sub> (mg/kg): > 18                       |
|       |              |                          | Doxycycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 4.13 (95% CI 3.88–4.38)    |
|       |              |                          | Tigecycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 0.58 (95% CI 0.40–0.75)    |
|       |              |                          | Linezolid           |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 8.18 (95% CI 8.05–8.31)    |
|       |              |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. aureus</i> USA400           | ED <sub>50</sub> (mg/kg): 0.45 (95% CI 0.43–0.48)    |
|       |              |                          | Vancomycin          |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 3.29 (95% CI 0.42–6.16)    |
|       |              |                          | Doxycycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 1.12 (95% CI 0.88–1.35)    |
|       |              |                          | Tigecycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 1.09 (95% CI 0.49–1.69)    |
|       |              |                          | Linezolid           |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 8.12 (95% CI 3.07–13.17)   |
|       |              |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>S. aureus</i> MRSA5            | ED <sub>50</sub> (mg/kg): 0.30 (95% CI 0.295–0.305)  |
|       |              |                          | Vancomycin          |                              |                 |                                   | ED <sub>50</sub> (mg/kg): > 18                       |
|       |              |                          | Doxycycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): > 54                       |
|       |              |                          | Tigecycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 1.74 (95% CI 0.91–2.57)    |
|       |              |                          | Linezolid           |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 24.53 (95% CI 16.13–32.94) |
|       |              |                          | Omadacycline        | 0.11–18 mg/kg body weight IV | 1               | <i>E. coli</i> PBS1478            | ED <sub>50</sub> (mg/kg): 2.02 (95% CI 1.09–2.96)    |
|       |              |                          | Ciprofloxacin       |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 0.07 (95% CI 0.05–0.09)    |
|       |              |                          | Doxycycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 17.46 (95% CI 13.51–21.42) |
|       |              |                          | Tigecycline         |                              |                 |                                   | ED <sub>50</sub> (mg/kg): 1.75 (95% CI 1.12–2.38)    |
|       |              |                          |                     |                              |                 |                                   |                                                      |

Adapted from Refs. [11, 82, 83, 86]

*erm* erythromycin ribosomal methylase, *IV* intravenously, *NA* data not available, *PR* penicillin-resistant, *PS* penicillin-susceptible, *SC* subcutaneously

<sup>a</sup>ED<sub>50</sub> (mg/kg) is 50% maximal point effect

<sup>b</sup>95% CI is 95% confidence interval

## 8 Animal Models

The in vivo antibacterial activity of omadacycline has been evaluated in various animal models and is summarized in Table 8 [11, 78, 82, 83, 86].

Lepak et al. [83] studied the in vivo activity of omadacycline against four strains of *S. pneumoniae* (1293, ATCC 10813, 140, ATCC 49619) using neutropenic murine lung pneumonia infection model. Six-week-old female ICR/Swiss neutropenic anaesthetized mice were infected with  $6.3 \pm 0.3 \log_{10}$  CFU/both lungs (colony forming units/lung) at the start of the therapy. At 2 h post-infection, omadacycline dose ranging from 0.5 to 32 mg/kg was administered subcutaneously as a single dose. For the four strains, the  $1 - \log_{10}$  kill and  $2 - \log_{10}$  kill was achieved at a dose ranging from 0.45 to 18.2 mg/kg ( $AUC_{24}/MIC$  6.1–180) and 1.8 to 3.1 mg/kg ( $AUC_{24}/MIC$  18.7–56.2), respectively [83]. Another study by Lepak et al. [82] determined the efficacy of omadacycline against four MSSA and six MRSA in a neutropenic murine thigh infection model. The mice were treated with cyclophosphamide to achieve a neutropenic state before they were infected in the thigh with  $6.5 \pm 0.1 \log_{10}$  CFU. At 2 h post-infection, 0.25–64 mg/kg of omadacycline was administered every 12 h (q12h) subcutaneously for a duration of 24 h. The mice had  $7.1 \pm 0.4 \log_{10}$  CFU/thigh at the beginning of therapy and it increased to  $9.4 \pm 0.4 \log_{10}$  CFU/thigh in the control/untreated group. The median  $1 - \log_{10}$  kill dose over 24 h of the mice treated with omadacycline was determined to be 57.7 mg/kg ( $AUC_{24}/MIC \sim 58$ ) [82].

Craig et al. [86] evaluated both normal and neutropenic murine thigh-infection models to assess the efficacy of omadacycline against various Gram-positive and Gram-negative bacteria. Normal and neutropenic Swiss ICR mice were infected with  $1 \times 10^{5.9-7.8}$  CFU/thigh of one of the 21 bacterial strains studied (Table 8). At 2 h post-infection, single doses of 0.312, 1.25, and 5 mg/kg of omadacycline were administered. Macone et al. [11] used the systemic intraperitoneal challenge model to evaluate omadacycline efficacy against antibiotic comparators (ceftriaxone, daptomycin, doxycycline, levofloxacin, linezolid, tigecycline, vancomycin, and ciprofloxacin) as depicted in Table 8.

In summary, several animal models including neutropenic murine lung infection, thigh infection, and intraperitoneal challenge models have documented the in vivo antibacterial efficacy of omadacycline. Omadacycline has also been shown to be effective for the treatment of infections caused by biothreat agents in animal models. In mouse models of inhalational *B. anthracis* and *Y. pestis* infections, Steenbergen et al. demonstrated that omadacycline was highly effective as a post-exposure treatment for *B. anthracis* in doses  $> 5$  mg/kg [47]. However, omadacycline

was less effective than ciprofloxacin in preventing *Y. pestis* infection.

## 9 Clinical Trials

Omadacycline has been investigated in several completed clinical trials (two phase II trials and three phase III trials) for treatment of various clinical conditions (clinicaltrials.gov) [73–75]. The clinical success rates of one completed phase II trial on complicated skin and skin structure infection (cSSSI, NCT03716024) and three phase III clinical trials on ABSSSI and CABP on omadacycline are summarized in Table 9 [87] and Table 10 [88–90]. The phase III trials, OASIS-1 (Omadacycline for Acute Skin and Skin Structure Infections Study, NCT02378480), OASIS-2 (NCT02877927), and OPTIC (Omadacycline for Pneumonia Treatment in the Community, NCT02531438), established non-inferiority of omadacycline to linezolid (OASIS-1, OASIS-2) and moxifloxacin (OPTIC), respectively [88–90]. Limited data are available on the completed phase II trial on cystitis. Currently, two phase II clinical trials on acute cystitis and acute pyelonephritis are underway and recruiting patients (clinicaltrials.gov).

In the phase II trial [87], patients with cSSSI were evaluated in a randomized, double-blinded manner during intravenous treatment, and evaluators were blinded during oral treatment to determine the safety and efficacy of omadacycline compared with linezolid (Table 9). There were 219 patients randomized (1:1) and enrolled between July 2007 and January 2008 from 11 different sites in the United States. Omadacycline patients ( $n = 111$ ) received a 100-mg dose intravenously once daily with an option to transition to 200 mg orally once daily [87]. Linezolid patients ( $n = 108$ ) received 600 mg intravenously twice daily with an option to transition to 600 mg orally twice daily [87]. Linezolid patients could receive intravenous aztreonam if a Gram-negative pathogen was suspected or documented. Patients had to be  $\geq 18$  years of age, have met criteria for one of the four categories of cSSSI (wound infection, major abscess, infected ulcers in a lower extremity, or cellulitis), and could not have received  $\geq 48$  h of antibiotic therapy prior to enrollment unless a resistant pathogen was identified. Patients with diabetes mellitus or documented vascular insufficiency must not have had a wound present for  $> 3$  months and patients with cellulitis alone were only eligible if they had diabetes mellitus or vascular insufficiency or had received immunosuppressive therapy within a period of 3 months prior to developing cellulitis [87]. Excluded from the trial were patients with erysipelas, cellulitis but were otherwise healthy, decubitus ulcers, infections considered life-threatening or requiring surgical intervention, infections

potentially involving bone, and patients who were pregnant and/or breastfeeding [87].

The primary endpoint was to compare the safety of omadacycline versus linezolid in the treatment of cSSSI [87]. The mean treatment durations of the omadacycline and linezolid groups were  $10.0 \pm 3.9$  and  $9.6 \pm 4.4$  days, respectively. The percentage of subjects who experienced one or more treatment-emergent adverse effects (TEAEs) related to omadacycline and linezolid were 41.4% (46/111) and 50.9% (55/108) of subjects, respectively. Gastrointestinal events were the most frequently reported adverse effects for both omadacycline [ $n = 21$  (18.9%)] and linezolid [ $n = 18$  (16.7%)] treatment groups [87]. The second endpoint of the trial was the evaluation of clinical efficacy in microbiologically evaluable (ME), clinically evaluable (CE), intent-to-treat (ITT), and modified intent-to-treat (mITT) populations [87]. In all four analyses, omadacycline exhibited numerically higher clinical response rates than linezolid (Table 9) [87].

The OASIS-1 trial [88] was a phase III, multicenter, double-blind, double-dummy, randomized (1:1) clinical investigation on the efficacy and safety of omadacycline versus linezolid in the treatment of adults with ABSSSI [85, 88]. A total of 655 randomized patients from 55 sites in multiple countries were enrolled from June 2015 through May 2016. The omadacycline treatment group ( $n = 323$ ) received 100 mg intravenously q12h for two doses then 100 mg intravenously for 24 h with an option to transition to 300 mg orally q24h after  $\geq 3$  days (Table 10) [88]. The linezolid treatment group ( $n = 322$ ) was administered 600 mg intravenously q12h, with the option to transition to 600 mg orally q12h after  $\geq 3$  days [88]. Patients enrolled were  $\geq 18$  years of age, and had a qualifying skin infection within one of three categories (wound infection, cellulitis/erysipelas, and major abscess) [88]. Patients were excluded from the trial if they had infections expected to require  $> 14$  days of treatment, if the infection was chronic ( $> 3$  months), if the patient had renal or liver insufficiency, or if they were immunocompromised [88].

The primary endpoint of the OASIS-1 trial was survival with at least 20% reduction in lesion size without rescue antibacterial therapy in the ECR evaluation (48–72 h post-initial dose) [88]. The mITT population revealed the ECR of omadacycline treatment regimens [84.8% (268/316)] were non-inferior to the ECR of linezolid treatment regimens [85.5% (266/311)] [88]. The secondary endpoint of the OASIS-1 was survival with resolution or improvement in signs and symptoms of the infection without rescue antibacterial therapy in the post-treatment evaluation (PTE, 7–14 days post-treatment) [88]. In the mITT population, the investigators assessed clinical response at PTE and reported clinical success for omadacycline and linezolid to be 86.1% (272/316) and 83.6% (260/311), respectively [88]. The

investigator-assessed clinical responses (IACR) for omadacycline and linezolid in the clinically evaluable population were 96.3% (259/269) and 93.5% (243/260), respectively (Table 10) [88]. PTE results confirmed omadacycline non-inferiority to linezolid for the treatment of ABSSSI with relation to the 10% margin for non-inferiority [74].

The OASIS-2 trial was a phase III, multicenter, double-blind, randomized (1:1), controlled, clinical investigation on the efficacy and safety of omadacycline versus linezolid in the treatment of adults with ABSSSI with oral-only regimens [89]. OASIS-2, like OASIS-1, was a non-inferiority trial with the same primary endpoint of ECR based on objective reduction in lesion size at 48–72 h following the first dose. A total of 735 randomized patients from 33 sites in the United States only (unlike OASIS-1) were enrolled from August 2016 through June 2017. The omadacycline treatment group ( $n = 368$ ) received two 450-mg once-daily doses over 48 h, then 300 mg once daily in the outpatient setting for a total of 7–14 days (Table 10) [89]. The linezolid treatment group ( $n = 367$ ) was administered 600 mg twice daily in the outpatient setting for 7–14 days [89]. As in OASIS-1, patients enrolled were  $\geq 18$  years of age, and had a qualifying skin infection within one of three categories (wound infection, cellulitis/erysipelas and major abscess) [89]. Patients were excluded from the trial if they had infections expected to require more than 14 days of treatment, if the infection was chronic ( $> 3$  months), if the patient had renal or liver insufficiency, or if they were immunocompromised [89]. The majority of patients in OASIS-2 were intravenous drug users, which may not be representative of the general population of patients with ABSSSIs or of other countries.

OASIS-2 confirmed the results of OASIS-1, showing that omadacycline was non-inferior to linezolid for all primary endpoints [89]. As in OASIS-1, there were two primary endpoints in the OASIS-2 trial. First was ECR in the mITT population, which was defined as survival with at least 20% reduction in lesion size without rescue antibacterial therapy in the ECR evaluation (48–72 h post-initial dose) [89]. The second primary endpoint was clinical response at the PTE in the mITT and CE populations. The mITT population revealed the ECR of the omadacycline treatment regimen [87.5% (315/360)] was non-inferior to the ECR of the linezolid treatment regimen [82.5% (297/360)] [89]. At the PTE, omadacycline was successful in 84.2% (303/360) mITT patients and 97.9% (278/284) CE patients compared with 80.8% (291/360) and 95.5% (279/292) for linezolid, respectively [89]. PTE results confirmed omadacycline non-inferiority to linezolid as a treatment for ABSSSI with relation to the 10% margin for non-inferiority [89].

The OPTIC trial [90] was a phase III, multicenter, double-blind, randomized (1:1) study to compare the efficacy and safety of omadacycline against moxifloxacin for the treatment of CABP [90, 91]. A total of 774 patients received

either omadacycline ( $n = 386$ ) 100 mg intravenously q12h for the first 24 h, then 100 mg intravenously q24h and after 3 days had the option to transition to omadacycline 300 mg orally once daily for a total of 7–14 days, or moxifloxacin ( $n = 388$ ) 400 mg intravenously once a day, with the option to transition after  $\geq 3$  days to 400 mg orally q24h for a total of 7–14 days (Table 10) [90]. Patients enrolled were  $\geq 18$  years of age, had shown three of four more common CABP symptoms (cough, purulent sputum production, dyspnea, pleuritic chest pain), had at least two abnormal vital sign measurements (fever, hypothermia, hypotension, and  $> 20$  breaths/min respiratory rate), had at least one laboratory finding associated with CABP (hypoxemia, physical pulmonary consolidation, elevated total white blood cells/neutrophils), had radiologically confirmed pneumonia, and were characterized as Pneumonia Severity Index (PSI) risk class II, III, or IV [90]. Patients were excluded if the onset of signs and symptoms were  $\geq 48$  h after hospitalization, if they had any suspected hepatic or renal impairment, or were immunosuppressed, pregnant, or breastfeeding [90].

The primary endpoint of the trial was to determine non-inferiority (margin 10%) based on ECR of omadacycline versus moxifloxacin in the treatment of CABP [90]. The rate of clinical success at ECR (72–120 h after first dose) in the ITT population was 81.1% and 82.7% for omadacycline and moxifloxacin, respectively, with the calculated statistical difference of  $-1.6\%$  (95% CI  $-7.1$  to  $3.8$ ) [90]. The clinical success rate at PTE in the ITT population was 87.6% and 85.1% for omadacycline and moxifloxacin, respectively, with the calculated statistical difference of  $2.5\%$  (95% CI  $-2.4$  to  $7.4$ ) [90].

## 10 Adverse Effects

The safety and tolerability of omadacycline was investigated in phase I, II, and III clinical trials. The adverse effects for omadacycline reported in non-comparative studies are summarized in Table 11 [72, 73, 75, 92] and for comparative studies in Table 12 [87, 88, 90, 92].

The safety of omadacycline was investigated in a non-comparative phase I trial in subjects with renal impairment [75]. Healthy subjects ( $n = 8$ ) and subjects with end-stage renal disease on stable HD ( $n = 8$ ) were administered a single dose of 100 mg intravenous omadacycline [75]. Five subjects reported at least one TEAE (Table 11) [75]. In all groups, a transient increase in heart rate was reported and peaked 2 h after administration [75]. The largest reported increase in heart rate was 9.5 beats/min [75]. No serious adverse events or deaths occurred [75].

Another phase I non-comparative clinical trial assessed the safety of multiple doses of omadacycline in women with

cystitis over 5 days [73]. Subjects received various regimens of omadacycline in three groups, where group 1 received 200 mg intravenously on day 1, then 300 mg orally q24h; group 2 received 300 mg orally q12h on day 1, then 300 mg orally q24h; and group 3 received 450 mg orally q12h on day 1, then 450 mg orally q24h. Gastrointestinal events were the most frequent TEAE but were reported as mild and transient, where 60–73% of patients reported nausea, 20–40% vomiting, and 0–20% diarrhea (Table 11) [73]. Seven subjects received ondansetron to prevent nausea and vomiting. Subjects in group 1 had an asymptomatic elevation of heart rate (20 beats/min) 1–3 h post-dose [73]. The elevation in heart rate in groups 2 and 3 was approximately 15 beats/min [73]. Serum alanine aminotransferase (ALT) in groups 1, 2, and 3 increased by a median of  $\leq 6.0$  U/L,  $\leq 6.0$  U/L, and 18 U/L, respectively [73]. No subjects required discontinuation of the study drug [73].

Another phase I non-comparative study determined the safety of single 300-, 450-, and 600-mg oral doses of omadacycline in 26 healthy adults [72]. This study reported an increased occurrence of adverse effects for the 600-mg oral dose. Gastrointestinal events such as nausea, vomiting, and diarrhea were consistently the most frequent TEAE (Table 11) [72]. Nausea was reported in  $\leq 7.7\%$  of subjects after a 300-mg and 450-mg dose and 16.7% after 600 mg [72]. ALT increased in one subject receiving a 450-mg dose and one subject receiving a 600-mg dose [72]. Four subjects discontinued the study due to TEAEs, three who received the drug and one who received placebo [72]. There were no serious TEAEs or deaths during the study [72]. No significant change in vital signs, physical examination, electrocardiogram (ECG), hematology, or urinalysis were reported [72].

In a phase II comparative clinical trial on cSSSI, the safety of omadacycline ( $n = 111$ ) was evaluated and compared with that of linezolid with or without aztreonam [87]. Subjects received omadacycline 100 mg intravenously q24h, with an option to step down to 200 mg orally q24h [87]. Forty-six (41.4%) subjects receiving omadacycline experienced at least one TEAE, mostly gastrointestinal (18.9%) [87]. In comparison, 55 (50.9%) subjects who received linezolid (with or without aztreonam) reported at least one TEAE, with 18 (16.7%) subjects experiencing a gastrointestinal event (Table 12) [87].

Three phase III comparative clinical trials, OASIS-1, OASIS-2, and OPTIC, determined the safety and tolerability of omadacycline [88–90].

In the OASIS-1 trial, omadacycline was compared with linezolid. Omadacycline was administered to 323 adults for 7–14 days starting with 100 mg intravenously q12h for two doses, then 100 mg intravenously q24h, then an optional step down to a 300-mg oral dose q24h after day 3 [88]. Of

**Table 9** Phase II clinical trial of omadacycline (ClinicalTrials.gov registration number NCT03716024)

| Trial description                                                                                                                                                              | Number of patients randomized | Treatment regimens                                                                                                                                        | Clinical response (%) in patients at TOC |               |               |              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|---------------|---------------|--------------|
|                                                                                                                                                                                |                               |                                                                                                                                                           | ME                                       | CE            | ITT           | mITT         |
| Randomized, multicenter, double-blinded during intravenous treatment, evaluator-blinded during oral treatment for complicated skin and skin structure infection in adults [87] | 219                           | Omadacycline: 100 mg IV once daily with an option to transition to 200 mg orally once daily for 10.0 ± 3.9 days ( <i>n</i> = 111)                         | 97.4 (75/77)                             | 98.0 (98/100) | 88.3 (98/111) | 89.3 (75/84) |
|                                                                                                                                                                                |                               | Linezolid: 600 mg IV twice daily with an option to transition to 600 mg orally twice daily for 9.6 ± 4.4 days ( <i>n</i> = 108) (option to add aztreonam) | 93.7 (59/63)                             | 93.2 (82/88)  | 75.9 (82/108) | 75.6 (59/78) |

Adapted from Refs. [87]

Data are presented as rate of clinical response [% (no. successful/total no.)] in patients given

Intent-to-treat (*ITT*) defined as all enrolled subjects receiving ≥ 1 dose of study medications. Modified intent-to-treat (*mITT*) defined as *ITT* with baseline pathogen. Clinically evaluable (*CE*) defined as all subjects in the *ITT* population who had a protocol-defined qualifying infection, received the study drug for ≥ 5 days, had all the protocol-defined qualifying evaluations, had not received rescue antibiotics. Microbiologically evaluable (*ME*) defined as *CE* with baseline pathogens

IV intravenously, *TOC* test-of-cure visit

the subjects who received omadacycline, 48.3% experienced at least one adverse effect, most frequently nausea (12.4%) and vomiting (5.3%) (Table 12) [88]. Comparatively, 45.7% of the linezolid group experienced at least one TEAE, again most often nausea (9.9%) and vomiting (5.0%) (Table 12) [88]. One subject in each treatment group discontinued the study due a gastrointestinal TEAE [88]. One subject died due to an opiate overdose, unrelated to the study drug [88].

The OASIS-2 trial compared oral regimens of omadacycline and linezolid [89]. Nausea and vomiting were more frequent in the omadacycline group compared with the linezolid group, which was attributed to the higher dose of omadacycline during the first 2 days of treatment (450 mg once daily). Rates of other adverse effects were similar between the omadacycline and linezolid groups (Table 12). Moderate nausea and vomiting was reported as the reason for omadacycline discontinuation in one patient [89].

The OPTIC trial compared omadacycline (*n* = 382) with moxifloxacin [90]. Subjects received omadacycline 100 mg intravenously q12h for two doses, then 100 mg intravenously q24h, then an optional step down to 300 mg orally q24h after day 3. The TEAE subject rates after omadacycline (41.1%) and moxifloxacin (48.5%) administration are summarized in Table 12 [90]. In each treatment group, two subjects discontinued the study due to gastrointestinal side effects. There was a difference in the incidence of diarrhea between the moxifloxacin (8.0%) and omadacycline treatment groups (1.0%) [no statistics calculated]. *C. difficile* infection was reported in 2.1% of subjects in the moxifloxacin group, while there were no cases reported in the omadacycline group. No drug-induced liver injuries (i.e., Hy's law cases) were identified [90]. There were eight deaths in the omadacycline group and four in moxifloxacin group during the study. The subjects who died in the omadacycline treatment group were all inpatients, ≥ 65 years old, and their cause of death was due to "progression of underlying pneumonia or respiratory compromise, hospital-acquired pneumonia, cardiac or vascular events, or cancer" [90].

In conclusion, both non-comparative and comparative studies have documented gastrointestinal events as the predominant adverse effects associated with omadacycline administration. These adverse effects were commonly considered mild and transient. Based on clinical trial data to date, the adverse effect profile of omadacycline is similar to the comparator agents studied, linezolid [87–89] and moxifloxacin [90]. Limited safety data warrants further investigation to fully describe the adverse effect profile of omadacycline.

As omadacycline is a tetracycline, it is expected that it would have the typical tetracycline adverse effects. All tetracyclines are deposited in teeth and bone during calcification, which can lead to dental staining and inhibition of bone growth in children [3]. Children may be affected if

**Table 10** Phase III clinical trials of omadacycline

| Trial description                                                                                                                                                       | Number of patients randomized | Treatment regimens                                                                                                                                                                                                                                                                               | Clinical response rate (%) |                |                |                |                |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------|----------------|----------------|----------------|----------------|
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  | mITT                       |                |                | CE             |                |                |
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  | ECR                        | IACR-PTE       | IACR-PTE       | ECR            | IACR-PTE       | ME             |
| Phase III OASIS-1 <sup>a</sup><br>NCT02378480<br>Randomized, double-blinded, IV transition to oral treatment for acute bacterial skin and skin structure infection [88] | 655                           | Omadacycline: Day 1: 100 mg IV q12h for first 24h, then 100 mg IV q24h. After 3 days, transition to 300 mg orally once daily for 7–14 days ( <i>n</i> = 323)<br><br>Linezolid: 600 mg IV twice daily, then after 3 days, transition to 600 mg orally twice daily for 7–14 days ( <i>n</i> = 322) | 84.8 (268/316)             | 86.1 (272/316) | 86.1 (272/316) | 92.6 (276/298) | 96.3 (259/269) | 98.5 (192/195) |
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  | 85.5 (266/311)             | 83.6 (260/311) | 83.6 (260/311) | 94.6 (278/294) | 93.5 (243/260) | 96.5 (191/198) |
| Phase III OASIS-2 <sup>a</sup><br>NCT02877927<br>Randomized, double-blinded, oral only, multicenter, controlled non-inferiority trial [89]                              | 735                           | Omadacycline: 450 mg orally once daily for 2 days, then 300 mg once daily for 7–14 days ( <i>n</i> = 368)<br><br>Linezolid: 600 mg orally twice daily for 7–14 days ( <i>n</i> = 367)                                                                                                            | 87.5 (315/360)             | 84.2 (303/360) | 84.2 (303/360) | 93.5 (315/337) | 97.9 (278/284) | 98.3 (229/233) |
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  | 82.5 (297/360)             | 80.8 (291/360) | 80.8 (291/360) | 91.4 (297/360) | 95.5 (279/292) | 97.8 (224/229) |
| Phase III OPTIC <sup>b</sup><br>NCT02531438<br>Randomized, multicenter, double-blinded IV to oral treatment for community-acquired bacterial pneumonia in adults [90]   | 774                           | Omadacycline: Day 1: 100 mg IV q12h for the first 24 h, then 100 mg IV q24h. After 3 days, transition to 300 mg orally once daily for 7–14 days ( <i>n</i> = 386)<br><br>Moxifloxacin: 400 mg IV once a day, then after 3 days, transition to 400 mg orally q24h for 7–14 days ( <i>n</i> = 388) | ITT                        |                |                | 86.5 (308/356) | 92.9 (316/340) | 93.3 (180/193) |
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  | 81.1 (313/386)             | 87.6 (338/386) | 87.6 (338/386) |                |                | 92.0 (173/188) |
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  | 82.7 (321/388)             | 85.1 (330/388) | 85.1 (330/388) | 87.2 (314/360) | 90.4 (312/345) | 94.2 (162/172) |
|                                                                                                                                                                         |                               |                                                                                                                                                                                                                                                                                                  |                            |                |                |                |                | 90.5 (153/169) |

Adapted from Refs. [88–90]

Data are presented as rate of clinical response [% (no. successful/total no.)] in patients given

ABSSSI acute bacterial skin and skin structure infection, EOT end of treatment, IV intravenously, PTE post treatment evaluation, q12h every 12 h, q24h every 24 h

<sup>a</sup>Modified intent-to-treat analysis (mITT) consist of all randomized subjects without a sole Gram-negative causative pathogen at screening. Clinically evaluable (CE) consists of all mITT subjects who received test article, have a qualifying ABSSSI, an assessment outcome, and met all other evaluability criteria in the statistical analysis plan. Microbiologically evaluable (ME) included subjects in the CE population who had at least one Gram-positive pathogen at screening. Early clinical response (ECR) within 48–72 h after first dose is defined as survival with a ≥ 20% reduction of lesion size. Investigator's assessment of clinical response post-treatment evaluation (IACR-PTE) is defined as survival after completion of a test article regimen, resolution, or improvement without further antibacterial therapy necessary

<sup>b</sup>Intent-to-treat (ITT) population consists of all randomized subjects. Modified intent-to-treat (mITT) consists of subjects in the ITT population who had at least one causative pathogen identified at screening from a culture of a respiratory specimen, culture of blood, or from a culture-independent method. Clinically evaluable (CE) consist of all ITT subjects who received test article, have qualifying community-acquired bacterial pneumonia (CABP), an assessment of outcome, and meet all other evaluability criteria detailed in the statistical analysis plan. Microbiologically evaluable (ME) include subjects in the CE population who have at least 1 causative pathogen identified at screening. Early clinical response (ECR) within 72–120 h after first dose is defined as survival with improvement in at least two of four subject symptoms (cough, sputum production, pleuritic chest pain, dyspnea), as assessed by the investigator without deterioration in any of these four symptoms. Investigator's assessment of clinical response post-treatment evaluation (IACR-PTE) defined as survival after completion of a test article regimen, with resolution of signs and symptoms of the infection to the extent that further antibacterial therapy is not necessary

**Table 11** Adverse effects associated with omadacycline in non-comparative phase I clinical trials

| Study                | Treatment dose                                                       | Number (%) of patients with adverse event | Adverse events                          |
|----------------------|----------------------------------------------------------------------|-------------------------------------------|-----------------------------------------|
| Berg et al. [75]     | Omadacycline 100 mg IV, 1 dose                                       | 2/5 (40.0)                                | Upper respiratory tract infection       |
|                      |                                                                      | 1/5 (20.0)                                | Viral upper respiratory tract infection |
|                      |                                                                      | 1/5 (20.0)                                | Bronchospasm                            |
|                      |                                                                      | 1/5 (20.0)                                | Dizziness                               |
|                      |                                                                      | 1/5 (20.0)                                | Headache                                |
|                      |                                                                      | 1/5 (20.0)                                | Infusion-site erythema                  |
|                      |                                                                      | 1/5 (20.0)                                | Papular rash                            |
| Overcash et al. [73] | Omadacycline 200 mg IV on day 1, then 300 mg orally q24h on days 2–5 | 8/9 (88.9)                                | Nausea                                  |
|                      |                                                                      | 4/9 (44.4)                                | Vomiting                                |
|                      |                                                                      | 3/9 (33.3)                                | Headache                                |
|                      |                                                                      | 2/9 (22.2)                                | Pruritus                                |
|                      |                                                                      | 1/9 (11.1)                                | Gastroesophageal reflux disease         |
|                      |                                                                      | 1/9 (11.1)                                | Vulvovaginal mycotic infection          |
|                      |                                                                      |                                           |                                         |
|                      | Omadacycline 300 mg orally daily for 5 days                          | 6/9 (66.7)                                | Nausea                                  |
|                      |                                                                      | 4/9 (44.4)                                | Vomiting                                |
|                      |                                                                      | 3/9 (33.3)                                | Amylase increased                       |
|                      |                                                                      | 2/9 (22.2)                                | Headache                                |
|                      |                                                                      | 2/9 (22.2)                                | Diarrhea                                |
|                      |                                                                      | 1/9 (11.1)                                | Vulvovaginal mycotic infection          |
|                      |                                                                      |                                           |                                         |
|                      | Omadacycline 450 mg orally daily for 5 days                          | 6/8 (75)                                  | Nausea                                  |
|                      |                                                                      | 2/8 (25)                                  | Vomiting                                |
|                      |                                                                      | 2/8 (25)                                  | Vulvovaginal mycotic infection          |
|                      |                                                                      | 1/8 (12.5)                                | Headache                                |
|                      |                                                                      | 1/8 (12.5)                                | Amylase increase                        |
|                      |                                                                      | 1/8 (12.5)                                | Diarrhea                                |
|                      |                                                                      | 1/8 (12.5)                                | Gastroesophageal reflux disease         |
| Bundrant et al. [72] | Omadacycline 300 mg orally, 1 dose                                   | 2/5 (40)                                  | Nausea                                  |
|                      |                                                                      | 2/5 (40)                                  | Vomiting                                |
|                      |                                                                      | 2/5 (40)                                  | Dizziness                               |
|                      | Omadacycline 450 mg orally, 1 dose                                   | 1/3 (33.3)                                | Nausea                                  |
|                      |                                                                      | 1/3 (33.3)                                | Alanine aminotransferase increased      |
|                      | Omadacycline 600 mg orally, 1 dose                                   | 4/6 (66.7)                                | Nausea                                  |
|                      |                                                                      | 2/6 (33.3)                                | Diarrhea                                |
|                      |                                                                      | 1/6 (16.7)                                | Vomiting                                |
|                      |                                                                      | 1/6 (16.7)                                | Dizziness                               |
|                      |                                                                      | 1/6 (16.7)                                | Alanine aminotransferase increased      |

Adapted from Refs. [72, 73, 75]

IV intravenous, q12h every 12 h, q24h every 24 h

their mother receives a tetracycline during pregnancy (most affected if antibiotic taken after the fifth month), or if the child receives single or multiple courses of tetracyclines during early childhood [3]. Dental staining occurs primarily in second dentition and, although it may be cosmetically disconcerting, the clinical significance is minor [3]. To prevent tooth discoloration and bone growth inhibition, tetracyclines

should ideally be avoided in pregnancy, lactation, and children < 8 years of age.

Finally, it is well known that tigecycline has a black box warning stating that an increase in all-cause mortality has been observed in a meta-analysis of phase III and IV clinical trials in tigecycline-treated patients versus comparator-treated patients. In the omadacycline clinical trial program and listed in the warnings and precautions section

**Table 12** Adverse effects associated with omadacycline in comparative phase II and III clinical trials

| Study                 | Treatment dose                                                                                                                                     | Number (%) of patients with adverse event | Adverse events                       |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------|
| Noel et al. [87]      | Omadacycline 100 mg IV daily, with an option to switch to 200 mg oral daily for 10.0 ± 3.9 days                                                    | 13/46 (28.3)                              | Nausea                               |
|                       |                                                                                                                                                    | 7/46 (15.2)                               | Headache                             |
|                       |                                                                                                                                                    | 5/46 (10.9)                               | Vomiting                             |
|                       |                                                                                                                                                    | 5/46 (10.9)                               | Constipation                         |
|                       |                                                                                                                                                    | 5/46 (10.9)                               | Fatigue                              |
|                       |                                                                                                                                                    | 5/46 (10.9)                               | Rash                                 |
|                       |                                                                                                                                                    | 4/46 (8.7)                                | Dizziness                            |
|                       |                                                                                                                                                    | 3/46 (6.5)                                | Alanine aminotransferase increase    |
|                       |                                                                                                                                                    | 3/46 (6.5)                                | Aspartate aminotransferase increase  |
|                       | Comparator: Linezolid 600 mg IV twice daily with an option to transition to 600 mg orally twice daily for 9.6 ± 4.4 days (± aztreonam 2 g IV q12h) | 9/55 (16.4)                               | Headache                             |
|                       |                                                                                                                                                    | 8/55 (14.5)                               | Nausea                               |
|                       |                                                                                                                                                    | 7/55 (12.7)                               | Alanine aminotransferase increase    |
|                       |                                                                                                                                                    | 6/55 (10.9)                               | Diarrhea                             |
|                       |                                                                                                                                                    | 5/55 (9.1)                                | Aspartate aminotransferase increase  |
|                       |                                                                                                                                                    | 5/55 (9.1)                                | Dizziness                            |
|                       |                                                                                                                                                    | 4/55 (7.2)                                | Vomiting                             |
|                       |                                                                                                                                                    | 2/55 (3.6)                                | Constipation                         |
|                       |                                                                                                                                                    | 2/55 (3.6)                                | Fatigue                              |
|                       |                                                                                                                                                    | 2/55 (3.6)                                | Rash                                 |
| O’Riordan et al. [88] | Omadacycline 100 mg IV twice daily × 2 doses, then 100 mg IV daily. After day 3, option to switch to 300 mg oral daily for 7–14 days               | 40/156 (25.6)                             | Nausea                               |
|                       |                                                                                                                                                    | 28/156 (17.9)                             | Infusion-site extravasation          |
|                       |                                                                                                                                                    | 17/156 (10.9)                             | Subcutaneous abscess                 |
|                       |                                                                                                                                                    | 17/156 (10.9)                             | Vomiting                             |
|                       |                                                                                                                                                    | 15/156 (9.6)                              | Cellulitis                           |
|                       |                                                                                                                                                    | 10/156 (6.4)                              | Headache                             |
|                       |                                                                                                                                                    | 9/156 (5.8)                               | Alanine aminotransferase increased   |
|                       |                                                                                                                                                    | 8/156 (5.1)                               | Aspartate aminotransferase increased |
|                       |                                                                                                                                                    | 8/156 (5.1)                               | Wound infection                      |
|                       |                                                                                                                                                    | 7/156 (4.5)                               | Diarrhea                             |
|                       | Comparator: Linezolid 600 mg IV twice daily × 3 days, then after day 3 option to switch 600 mg orally twice daily for 7–14 days                    | 7/156 (4.5)                               | Pruritus                             |
|                       |                                                                                                                                                    | 32/147 (21.8)                             | Nausea                               |
|                       |                                                                                                                                                    | 19/147 (12.9)                             | Infusion-site extravasation          |
|                       |                                                                                                                                                    | 19/147 (12.9)                             | Subcutaneous abscess                 |
|                       |                                                                                                                                                    | 16/147 (10.9)                             | Vomiting                             |
|                       |                                                                                                                                                    | 15/147 (10.2)                             | Cellulitis                           |
|                       |                                                                                                                                                    | 14/147 (9.5)                              | Alanine aminotransferase increased   |
|                       |                                                                                                                                                    | 13/147 (8.8)                              | Headache                             |
|                       |                                                                                                                                                    | 12/147 (8.2)                              | Aspartate aminotransferase increased |
|                       |                                                                                                                                                    | 10/147 (6.8)                              | Diarrhea                             |
|                       |                                                                                                                                                    | 5/147 (3.4)                               | Wound infection                      |

**Table 12** (continued)

| Study                 | Treatment dose                                                                                                                        | Number (%) of patients with adverse event | Adverse events                          |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------|
| O’Riordan et al. [89] | Omadacycline 450 mg orally twice daily for 2 days, then 300 mg once daily for 7–14 days                                               | 111/368 (30)                              | Nausea                                  |
|                       |                                                                                                                                       | 62/368 (17)                               | Vomiting                                |
|                       |                                                                                                                                       | 22/368 (6)                                | Wound infection                         |
|                       |                                                                                                                                       | 19/368 (5)                                | Alanine aminotransferase increased      |
|                       |                                                                                                                                       | 17/368 (5)                                | Aspartate aminotransferase increased    |
|                       |                                                                                                                                       | 15/368 (4)                                | Diarrhea                                |
|                       |                                                                                                                                       | 13/368 (4)                                | Headache                                |
|                       |                                                                                                                                       | 12/368 (3)                                | Cellulitis                              |
|                       |                                                                                                                                       | 10/368 (3)                                | Abdominal pain, upper                   |
|                       |                                                                                                                                       | 6/368 (2)                                 | Subcutaneous abscess                    |
|                       | Comparator: Linezolid 600 mg twice daily for 7–14 days                                                                                | 28/367 (8)                                | Nausea                                  |
|                       |                                                                                                                                       | 17/367 (5)                                | Wound infection                         |
|                       |                                                                                                                                       | 12/367 (3)                                | Aspartate aminotransferase increased    |
|                       |                                                                                                                                       | 11/367 (3)                                | Vomiting                                |
|                       |                                                                                                                                       | 11/367 (3)                                | Alanine aminotransferase increased      |
|                       |                                                                                                                                       | 10/367 (3)                                | Diarrhea                                |
|                       |                                                                                                                                       | 9/367 (3)                                 | Cellulitis                              |
|                       |                                                                                                                                       | 8/367 (2)                                 | Headache                                |
|                       |                                                                                                                                       | 8/367 (2)                                 | Subcutaneous abscess                    |
|                       |                                                                                                                                       | 4/367 (1)                                 | Abdominal pain, upper                   |
| Stets et al. [90]     | Omadacycline 100 mg IV twice daily for 1 day, then 100 mg IV daily. After 3 days, option to switch to 300 mg oral daily for 7–14 days | 14/157 (8.9)                              | Alanine aminotransferase increased      |
|                       |                                                                                                                                       | 13/157 (8.3)                              | Hypertension                            |
|                       |                                                                                                                                       | 10/157 (6.4)                              | $\gamma$ -Glutamyltransferase increased |
|                       |                                                                                                                                       | 10/157 (6.4)                              | Insomnia                                |
|                       |                                                                                                                                       | 10/157 (6.4)                              | Vomiting                                |
|                       |                                                                                                                                       | 9/157 (5.7)                               | Constipation                            |
|                       |                                                                                                                                       | 9/157 (5.7)                               | Nausea                                  |
|                       |                                                                                                                                       | 8/157 (5.1)                               | Aspartate aminotransferase increased    |
|                       |                                                                                                                                       | 8/157 (5.1)                               | Headache                                |
|                       |                                                                                                                                       | 4/157 (2.5)                               | Diarrhea                                |
|                       | Comparator: Moxifloxacin 400 mg IV daily. After 3 days, option to switch to 400 mg oral daily for 7–14 days                           | 31/188 (16.4)                             | Diarrhea                                |
|                       |                                                                                                                                       | 21/188 (11.2)                             | Nausea                                  |
|                       |                                                                                                                                       | 18/188 (9.6)                              | Alanine aminotransferase increased      |
|                       |                                                                                                                                       | 14/188 (7.4)                              | Aspartate aminotransferase increased    |
|                       |                                                                                                                                       | 11/188 (5.9)                              | Hypertension                            |
|                       |                                                                                                                                       | 8/188 (4.3)                               | $\gamma$ -Glutamyltransferase increased |
|                       |                                                                                                                                       | 8/188 (4.3)                               | Insomnia                                |
|                       |                                                                                                                                       | 6/188 (3.2)                               | Vomiting                                |
|                       |                                                                                                                                       | 6/188 (3.2)                               | Constipation                            |
|                       |                                                                                                                                       | 5/188 (2.7)                               | Headache                                |

Adapted from references [87–90]

IV intravenous, *q12h* every 12 h, *q24h* every 24 h

of the label, there was a mortality imbalance in patients with CABP (2% in the omadacycline arm and 1% in the moxifloxacin-treated patients). As the cause of the mortality imbalance was not established, patients with CABP on omadacycline, particularly those at higher risk for mortality, should be closely monitored. The US FDA has required a postmarketing commitment of Paratek pharmaceuticals to conduct an active-controlled safety study in pediatric patients (8–17 years of age) with CABP to further define omadacycline's safety and efficacy in patients with CABP. The European Medicines Agency (EMA) requested a second study in CABP to meet the regulatory standards of two phase III studies. Paratek has since withdrawn its EMA application for oral and intravenous omadacycline.

## 11 Drug Interactions

Currently, there is limited information available on drugs that may interact with omadacycline. This section will briefly summarize available data on drug interactions for omadacycline and tetracycline.

As previously discussed, the absorption of oral omadacycline is significantly reduced (17–63%) when administered 2–4 h after the consumption of food and dairy products [71, 93]. Consistent with the other members of the tetracycline family, omadacycline characteristically binds with cations forming a non-absorbable chelation complex [12, 71]. Various products such as antacids, multivitamins, and bismuth subsalicylate may contain one or more multivalent cations (calcium, magnesium, aluminum, iron, bismuth, zinc) expected to chelate with tetracyclines [94–96]. Oral iron salts should be administered 2 h before or 4 h after a tetracycline dose; taking antacids, especially those containing calcium, with tetracyclines should be avoided; and bismuth subsalicylate should be taken at least 2 h before or 6 h after tetracycline administration to minimize interaction [94–96].

An *in vitro* study utilizing radioactive omadacycline revealed that omadacycline is not a substrate, inducer, or inhibitor of the major CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) and had no significant interactions with various membrane transporters (hOAT1, hOAT3, OATP1B1, OATP1B3, and hOCT2) [77]. Omadacycline was not a substrate of BCRP or MRP2 [77]. However, omadacycline was found to be a substrate of P-glycoprotein but did not induce or inhibit its activity [77]. Verapamil, administered 2 h prior to a single 300-mg oral dose of omadacycline, increased omadacycline AUC by approximately 25% and  $C_{\max}$  by approximately 9% [13].

These data suggest that there is low potential for drug interactions with omadacycline involving these enzymes and transporters [77, 93].

Tetracycline class antibiotics may enhance the anti-coagulant effect of warfarin [3, 12, 97]. There have been some reports of increased hypothermic effects and bleeding in some patients on warfarin after starting doxycycline or tetracycline therapy [97]. The mechanism of this interaction is unknown [97]. It is recommended to monitor patients' international normalized ratio (INR) or prothrombin time more frequently and adjust dosage accordingly [3, 12, 19, 93]. The use of oral tetracycline with digoxin may increase serum digoxin concentrations [3, 12, 98]. Tetracycline likely alters the gastrointestinal flora that converts digoxin to its inactive metabolites [98]. Dose spacing does not seem to decrease the interaction, but administration of intravenous digoxin is expected to bypass this interaction [98]. The use of tetracycline and penicillin together should be avoided because tetracycline may interfere with the bactericidal activity of penicillin [3, 99]. If both medications are needed, it is recommended to administer the penicillin 2 h before the administration of tetracycline [99]. The use of tetracycline may decrease the effectiveness of oral contraceptive therapy [100]. The drug interaction between oral contraceptives and antibiotics remains controversial due to limited information [101]. The recommendation to patients is to use back-up contraceptive methods during tetracycline therapy [100, 101].

## 12 Place of Omadacycline Therapy

Omadacycline is a novel aminomethylcycline antibiotic available in intravenous and oral dose formulations and intended for once-daily use in patients. Microbiological studies document its broad-spectrum activity against Gram-positive and Gram-negative aerobic, anaerobic, and atypical bacteria. Omadacycline displays potent *in vitro* activity against tetracycline-, macrolide-,  $\beta$ -lactam-, and vancomycin-resistant isolates as well as against Gram-positive and Gram-negative isolates with MDR phenotypes. Completed phase I, II, and III clinical trials have demonstrated the safety and tolerability of intravenous and oral omadacycline. Omadacycline is currently approved by the FDA for use in the treatment of ABSSSI and CABP in adults. Safety and efficacy results from ongoing clinical trials in patients with urinary tract infection are awaited. Unlike tigecycline and eravacycline, omadacycline has an oral formulation that allows for step-down from intravenous therapy, potentially facilitating early hospital discharge and outpatient therapy, which may reduce costs associated with hospitalization. However, more data are needed to fully assess the efficacy and safety profile of omadacycline. Omadacycline, which is not currently first-line for any clinical indication, will be used as part of antimicrobial stewardship programs and has a potential role in the treatment of patients with infections

caused by antibiotic-resistant and MDR Gram-positive (including MRSA) and Gram-negative pathogens.

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## Compliance and Ethical Standards

**Conflict of interest** No conflicts are declared for Jenine Esquivel, Sheryl Zelenitsky, Courtney K. Lawrence, Heather J. Adam, Alyssa Golden, Rachel Hink, Liam Berry, Frank Schweizer, Michael A. Zhanel, Denise Bay, Philippe R. S. Lagacé-Wiens, Andrew J. Walkty, Joseph P. Lynch III and James A. Karlowksy. Dr Zhanel has received research grants from Paratek Pharmaceuticals (omadacycline), Pfizer (tigecycline), and Tetrphase (eravacycline).

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