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ADISINSIGHT REPORT

Omadacycline: First Global Approval

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Abstract
Paratek Pharmaceuticals are developing omadacycline (NUZYRA™), a first-in-class orally active aminomethylcycline antibacterial, as a treatment for various bacterial infections. The drug, which is available in intravenous and oral formulations, has a broad spectrum of antibacterial activity and was recently approved in the USA as a treatment for the treatment of community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults. This article summarizes the milestones in the development of omadacycline leading to this first global approval for the treatment of CABP and ABSSSI.

1 Introduction

Omadacycline (NUZYRA™), a first-in-class, orally active, aminomethylcycline antibacterial agent, is being developed by Paratek Pharmaceuticals as a treatment for various bacterial infections, and recently received approval in the USA for the treatment of community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults [1] Omadacycline is also under evaluation in the EU for the same indications [2]. The drug has demonstrated activity against Gram-positive, Gram-negative and atypical bacteria and is active against tetracycline-resistant bacterial pathogens expressing either ribosomal protection or efflux resistance genes, the two most common forms of tetracycline resistance [3, 4].

The recommended dosage of omadacycline, which is available in both intravenous (IV) and oral formulations, is a 200 mg IV loading dose on day 1 (either as a single 200 mg dose or two 100 mg doses) followed by a once daily 100 mg IV or 300 mg oral maintenance dose for 7 to 14 days. The option of commencing treatment with a 450 mg oral dose on day 1 is available for patients with ABSSSI [5].

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through preclinical and clinical studies to market launch and beyond.

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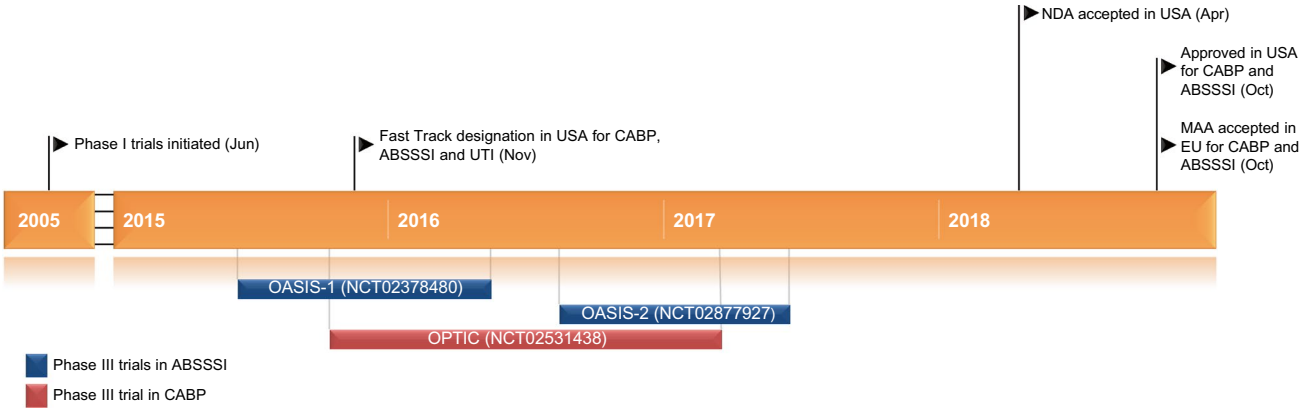
1.1 Company Agreements

In February 1997 Paratek Pharmaceuticals entered into a license agreement with Tufts University, granting Paratek an exclusive licence to patent applications and other intellectual property belonging to Tufts related to drug resistance, for the purpose of developing and commercialising products for the treatment or prevention of microbial infections. In return Tufts received shares in Paratek and the right to milestone payments of up to $US0.3 million upon the achievement of specified development and regulatory approval outcomes, as well as a minimum royalty payment of $US25,000 per year. In addition, Paratek agreed to pay Tufts royalties based on gross sales of products and a percentage in the single digits of any sublicense fee received in relation to its license agreement with Tufts.

In October 2016, Paratek entered into a cooperative agreement with the U.S. Army Medical Research Institute of Infectious Diseases to investigate the use of omadacycline as a defence to potential bioweapons, including *Yersinia pestis* and *Bacillus anthracis* [6].

In April 2017 Paratek entered into a collaboration agreement with Zai Lab, with the latter obtaining exclusive rights to develop, manufacture and commercialise omadacycline in China, Hong Kong, Macau, and Taiwan. In return, Paratek received an upfront payment of $US7.5 million and is eligible to receive additional milestone payments related to development, regulatory, and commercial milestones as well as royalty payments on net sales in the territories covered by the agreement [7].

Paratek has also entered into collaboration agreements with Bayer (in 2003) [8], Merck (in 2006) [9] and Novartis (in 2009) [10] to develop omadacycline, all of which were subsequently terminated.



Key milestones in the development of omadacycline for the treatment of CABP and ABSSSI, focussing on phase III trials. *ABSSSI* acute bacterial skin and skin structure infections, *CABP* community-acquired bacterial pneumonia, *MAA* Marketing Authorization Application, *NDA* New Drug Application, *UTI* urinary tract infections

1.2 Patent Information

The patent portfolio of omadacycline, directed to cover composition of matter, formulations, salts and polymorphs, manufacturing methods and methods of use, are owned by Paratek Pharmaceuticals. In some corresponding foreign patents and patent applications, omadacycline is covered along with other compounds in patents and patent applications that are owned jointly by Paratek and Tufts University, subject to a license agreement. The issued composition of matter patent in the United States (US patent no. 7 553 828) is expected to expire in 2023.

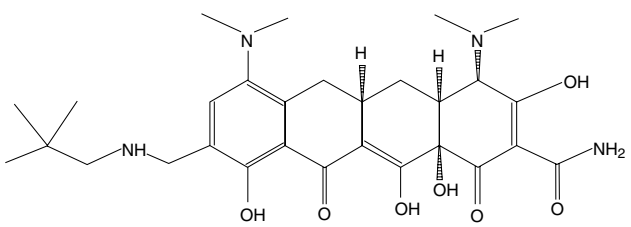
2 Scientific Summary

2.1 Pharmacodynamics

Omadacycline is semisynthetic aminomethylcycline, characterized by an aminomethyl group at the C9 position of the core tetracyclic *D* ring. Like other tetracyclines, the antibacterial action of omadacycline is due to binding to the bacterial ribosomal 30S subunit, thereby disrupting bacterial protein synthesis. Modification at position C9 is thought to overcome common tetracycline resistance mechanisms [5, 11]. In vitro, omadacycline is active against tetracycline-resistant Gram-positive bacteria expressing either ribosomal protection proteins (*tet M*) or active efflux pumps (*tet K* and *tet L*) and against Enterobacteriaceae that carry the *tet B* efflux gene. Like other tetracyclines, omadacycline is bacteriostatic; however, bactericidal activity against some *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates has been demonstrated [5].

Omadacycline effectively inhibited bacterial protein synthesis in vitro. In contrast to tetracycline, the inhibitory effect of omadacycline was not affected by the presence of the ribosomal protection protein Tet(O) and the drug efficiently competed with tritium-labelled tetracycline for binding to 70S ribosomes in vitro. Tetracycline resistant [minimum inhibitory concentration (MIC) 32 to > 64 μg/mL] strains of *Staphylococcus aureus* (MRSA5 and RN4250 with ribosomal and efflux tetracycline resistance mechanisms, respectively) and *S. pneumoniae* (PBS382, ribosomal protection) were susceptible to omadacycline in vitro with MICs of < 0.06 to 0.25 μg/L [12].

Omadacycline has also been tested against Gram-positive and Gram-negative isolates collected in the USA and Europe as part of the 2017 SENTRY antimicrobial surveillance program (14,000 clinical isolates) [3]. The drug had potent in vitro activity against *S. aureus*, including methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) isolates (overall MIC_{90} 0.25 μg/mL, 2684 strains), coagulase-negative staphylococci, including MRSA isolates (overall MIC_{90} 0.5 μg/mL, 373 strains), *S. pneumoniae*, including penicillin-resistant isolates (overall MIC_{90} 0.12 μg/mL, 968 strains), β-haemolytic streptococci, including *S. agalactiae* (MIC_{90} 0.25 μg/mL, 261 strains) and *S. pyogenes* (overall MIC_{90} 0.12 μg/mL, 299 strains), viridans group streptococci (MIC_{90} 0.12 μg/mL, 132 strains), *Enterococcus faecalis,* including vancomycin-resistant isolates (overall MIC_{90} 0.25 μg/mL, 427 strains), *E. faecium*, including vancomycin-resistant isolates (overall MIC_{90} 0.12 μg/mL, 218 strains), *H. influenzae* (MIC_{90} 1 μg/mL, 556 strains) and *Moraxella catarrhalis* (MIC_{90} 0.25 μg/mL, 313 strains).



Chemical structure of omadacycline

Omadacycline has activity against most Enterobacteriaceae strains (MIC_{90} 8 µg/mL with 87% of isolates susceptible at ≤ 4 µg/mL, 5993 strains), including *Escherichia coli* [overall MIC_{90} 2 µg/mL, 2581 strains, including extended-spectrum β-lactamase (ESBL) producing isolates] and *Klebsiella pneumoniae*, (overall MIC_{90} 8 µg/mL, 1269 strains including ESBL producing isolates) [3].

The US FDA identified MIC breakpoints for omadacycline for pathogens associated with ABSSSI are: *S. aureus* (includes MRSA isolates) susceptible ≤ 0.05 µg/mL, resistant ≥ 2 µg/mL; *E. faecalis* susceptible ≤ 0.25 µg/mL, resistant ≥ 1 µg/mL; *S. lugdunensis, S. anginosus* group and *S. pyogenes* susceptible ≤ 0.12 µg/mL, resistant ≥ 0.5 µg/mL; Enterobacteriaceae (*K. pneumoniae* and *E. cloacae)* susceptible ≤ 4 µg/mL, resistant ≥ 16 µg/mL. Those for pathogens associated with CABP are: *S. aureus* (MSSA only) susceptible ≤ 0.25 µg/mL, resistant ≥ 1 µg/mL; *S. pneumoniae* susceptible ≤ 0.12 µg/mL, resistant ≥ 0.5 µg/mL; *Haemophilus spp.* susceptible ≤ 2 µg/mL, resistant ≥ 8 µg/mL; Enterobacteriaceae (*K. pneumoniae*) susceptible ≤ 4 µg/mL, resistant ≥ 16 µg/mL [13].

The in vitro activity of omadacycline has also been tested against clinical isolates of various anaerobic bacteria, including *Bacteroides fragilis* (MIC_{90} 4 µg/mL, 21 isolates), *B. thetaiotaomicron* (MIC_{90} 4 µg/mL, 21 isolates), *B. vulgatus* (MIC_{90} 1 µg/mL, 21 isolates), *B. ovatus* (MIC_{90} 8 µg/mL, 15 isolates), Prevotella spp. (MIC_{90} 2 µg/mL, 22 isolates) and *P. asaccharolytica* (MIC_{90} 0.5 µg/mL, 21 isolates) [4]. Omadacycline has potent in vitro activity against the biothreat pathogens *Y. pestis* (MIC_{90} 1 µg/mL, 30 strains) and *B. anthracis* (MIC_{90} 0.06 µg/mL, 30 strains) [14].

As well as showing in vitro activity against tetracycline-resistant Gram-positive bacteria and Enterobacteriaceae, omadacycline was active against certain *S. aureus, S. pneumoniae* and *H. influenzae* strains carrying macrolide resistance genes (*erm* A, B and/or C) or ciprofloxacin resistance genes (*gyr*A and *par*C) and against β-lactamase positive *H. influenzae* [5]. Omadacycline showed activity against tetracycline-nonsusceptible isolates identified in patients in the phase III OPTIC, OASIS-1 and OASIS-2 trials, including *S. aureus* exhibiting a doxycycline nonsusceptible phenotype (MIC 0.25–0.5 µg/mL, 8 isolates) and *S. pneumoniae* with tetracycline and doxycycline and/or MLS_B nonsusceptible phenotypes (MIC 0.03–0.06 µg/mL, 16 isolates). The drug also had activity against Gram-negative isolates carrying tetracycline efflux-pump genes, including *E. coli* (MIC 0.5–2 µg/mL, 8 isolates), *E. cloacae* (MIC 2 µg/mL, 2 isolates) and *K. pneumoniae* (MIC 2–16 µg/mL, 6 isolates) [15].

The area under the plasma concentration-time curve (AUC) divided by the MIC is considered the best pharmacodynamic/pharmacokinetic (PD/PK) predictor of tetracycline activity [16]. In vivo studies in murine models of thigh infection and pneumonia have confirmed that the AUC/MIC ratio is the best predictor of omadacycline efficacy (correlation coefficient 0.74 in the pneumonia model) [16, 17]. In an *S. aureus* thigh infection model (10 strains including MRSA), the mean 24 h free-drug AUC (*f*AUC)/MIC values for stasis and 1-log kill (from start of therapy) were 23.7 and 78.1 [17]. In a *S. pneumoniae* pneumonia model of strains with phenotypic resistance to other antibacterials, including tetracyclines, the mean 24 h plasma *f*AUC/MIC values for stasis and 1-log kill were 16–20 and 6.1–180, while the mean 24 h epithelial lining fluid (ELF) *f*AUC/MIC values for stasis and 1-log kill were 14–18 and 6.0–200. The mean 24 h plasma and ELF *f*AUC/MIC values for 2-log kill were 19–56 and 17–47 [16]. In PD/PK target attainment analyses of various omadacycline treatment regimens for patients with CABP, the probabilities of target attainment were ≥ 90% at an MIC of 0.5 µg/mL for *S. pneumoniae* (i.e. one dilution higher than MIC_{100}) and 82.7–99.5% at an MIC of 1 µg/mL for *H. influenzae* (i.e. MIC_{90}) [18].

In vitro, omadacycline inhibits binding of H-scopolamine to the M2 subtype of the muscarinic acetylcholine receptor. However, in phase III ABSSSI and CABP studies, omadacycline had no clinically meaningful effect on blood pressure, heart rate, ECG parameters and cardiac safety, and in a thorough QT study, there was no clinically meaningful prolongation of the QTc interval [5, 19].

2.2 Pharmacokinetics

Omadacycline demonstrated dose-proportional pharmacokinetics (over a 300–450 mg dose range) after administration of a single oral dose of in healthy adult volunteers [5]. The bioavailability of omadacycline is 34.5% after a single oral 300 mg dose. Exposure to omadacycline is similar between a 100 mg IV dose and a 300 mg oral dose administered in healthy, fasted volunteers. Steady-state peak plasma concentrations (C_{maxss}) were achieved 0.5 h after administration of intravenous (IV) omadacycline 100 mg once daily and 2.5 h after administration of oral omadacycline 300 mg once daily. Mean C_{maxss} values for the respective dosages were 2120 and 952 ng/mL and mean AUC values at steady state were 12,140 and 11,156 ng · h/mL [5].

The rate and extent of oral omadacycline absorption was reduced (C_{max} by ≈ 40%; AUC by ≈ 60%) when a high-fat meal was ingested 2 h prior to drug administration. However, oral administration of the drug 4 h after a high-fat meal did not affect omadacycline pharmacokinetics. Likewise, ingesting food 2 h after administration of an oral dose of the drug had no significant effect on omadacycline pharmacokinetics. Omadacycline must be taken with water, and the patient must fast for at least 4 h prior to administration and must not have food or drink, apart from water, for 2 h and no dairy products, antacids or multivitamins for 4 h after administration [5].

Features and properties of omadacycline	
Alternative names	NUZYRA™, amadacycline, BAY 73-6944, BAY 73-7388, MK-2764, neopentyl aminomethylminocycline, PTK-0796, ZL 2401
Class	Antibacterials, small molecules, tetracyclines
Mechanism of action	Bacterial protein synthesis inhibitor
Route of administration	IV, oral
Pharmacodynamics	binds to the 30S ribosomal subunit and blocks protein synthesis; active against tetracycline-resistant bacterial pathogens expressing ribosomal protection or efflux resistance genes
Pharmacokinetics	AUC 12,140 ng · h/mL, C_{max} 2120. ng/mL, t_{max} 0.5 h and $t_{½}$ 16.0 h at steady state with a 100 mg IV once daily dosage AUC 11,156 ng · h/mL, C_{max} 952 ng/mL, t_{max} 2.5 h and $t_{½}$ 15.5 h at steady state with a 300 mg oral once daily dosage
Adverse events	
Most frequent	Nausea, vomiting
Occasional	Headache, diarrhoea
Rare	
ATC codes	
WHO ATC code	J01A (tetracyclines); J01A-A (tetracyclines)
EphMRA ATC code	J1A (tetracyclines and combinations)
Chemical name	(4*S*,4a*S*,5a*R*,12a*S*)-4,7-Bis(dimethylamino)-9-(2,2-dimethylpropylaminomethyl)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

The accumulation ratio of omadacycline is 1.5. Plasma protein binding is low (20%) and is concentration independent. The volume of distribution at steady state is 190 L after IV administration of omadacycline 100 mg, and the apparent volume of distribution after a single oral 300 mg dose is 794 L [5].

Omadacycline is not metabolized in the liver and is primarily excreted as the unchanged drug in urine (27% of a 100 mg IV dose and 14.4% of a radiolabelled 300 mg oral dose) and faeces (81.1% after oral administration). Systemic clearance at steady state is 8.8 L/h after IV administration of omadacycline 100 mg and apparent systemic clearance after a single oral 300 mg dose is 34.6 h. Renal clearance of omadacycline is 2.4–3.3 L/h and the terminal elimination half-life is 15.5–16 h [5].

Omadacycline has good lung penetration. At steady state, after IV administration of multiple doses of omadacycline in healthy volunteers, AUC_{24} in alveolar cells was 25.8-fold higher than plasma AUC_{24}, and that in lung epithelial lining fluid was 1.5-fold higher [5, 20].

Age and gender had no clinically relevant effect on the pharmacokinetic profile of omadacycline in studies in volunteers [21]. The pharmacokinetic profile of omadacycline was similar in patients with end-stage renal disease on haemodialysis and volunteers, indicating dosage adjustment is not required in the presence of any degree of renal impairment [22]. The pharmacokinetics of omadacycline are not affected by hepatic impairment and dosage adjustments are not required [5].

2.3 Therapeutic Trials

2.3.1 Community-Acquired Bacterial Pneumonia

Omadacycline was non-inferior to moxifloxacin for the treatment of CABP in the phase III OPTIC study (NCT02531438). Patients with CABP were randomized to 7–14 days' treatment with IV omadacycline 100 mg once every 12 h for two doses then once daily ($n = 386$) or IV moxifloxacin 400 mg once daily ($n = 388$). Patients had the option to transition to oral treatment (omadacycline 300 mg once daily, moxifloxacin 400 mg once daily) after ≥ 3 days of IV treatment. In the intent-to-treat (ITT) population, 81.1% of omadacycline and 82.7% of moxifloxacin recipients achieved early clinical response [assessed 72–120 h after the first dose and defined as survival, no rescue antibacterial therapy and improvement in at least two of four subject symptoms (cough, sputum production, pleuritic chest pain, dyspnoea) without deterioration in any of these four symptoms], and 87.6 and 85.1% achieved clinical success at post-therapy evaluation (assessed at 5–10 days after the last dose and defined as survival with resolution of signs and symptoms of the infection to the extent that further antibacterial therapy was not necessary). Clinical success at post therapy evaluation in patients with ≥ 1 causative bacterial pathogen identified (from respiratory or blood cultures or a culture-independent method) was 85.2 and 87.5% in omadacycline and moxifloxacin recipients with causative Gram-positive bacteria identified, 84.8 and 81.2% in patients with causative Gram-negative bacteria identified and 92.4 and 91.5% in patients with atypical pathogens identified. In the clinically evaluable population ($n = 340$ in the omadacycline

Key clinical trials of omadacycline (Paratek Pharmaceuticals)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Omadacycline, linezolid	ABSSSI	III	Completed	Multinational	NCT02378480; EudraCT#2013-003644-23 (OASIS-1)
Omadacycline, moxifloxacin	Community-acquired bacterial pneumonia	III	Completed	Multinational	NCT02531438; EudraCT #2013-004071-13 (OPTIC)
Omadacycline, linezolid	ABSSSI	III	Completed	USA	NCT02877927 (OASIS-2)
Omadacycline, nitrofurantoin	Cystitis	II	Recruiting	USA	NCT03425396

group and 345 in the moxifloxacin group), clinical success at post-therapy evaluation was achieved in 92.9 and 90.4% of patients [23].

2.3.2 Skin and Skin Structure Infections

2.3.2.1 Phase III Monotherapy with once-daily IV/oral omadacycline was non-inferior to twice-daily IV/oral linezolid as treatment for ABSSSI in the double-blind phase III OASIS-1 study (NCT02378480). Patients with ABSSSI known or suspected to be caused by a Gram-positive pathogen were randomized to treatment with IV omadacycline 100 mg once every 12 h for two doses then once daily, or IV linezolid 600 mg once every 12 h. After ≥ 3 days on IV therapy, patients on omadacycline could be switched to a 300 mg once daily oral dose and patients on linezolid could be switched to a 600 mg twice daily oral dose. In the modified ITT population (patients without a sole Gram-negative pathogen at baseline) early clinical response (defined as a reduction in lesion size of ≥ 20%) was observed in 84.8% of omadacycline ($n = 316$) and 85.5% of linezolid ($n = 311$) recipients. Clinical success at post therapy evaluation was achieved in 86.1 and 83.6% of omadacycline and linezolid recipients. In the clinically evaluable population ($n = 269$ in the omadacycline group and 260 in the linezolid group) clinical success at post-therapy evaluation was achieved in 96.3 and 93.5% of patients [24].

Monotherapy with once-daily oral omadacycline was non-inferior to twice-daily oral linezolid as treatment for ABSSSI in the double-blind phase III OASIS-2 study (NCT02877927). Patients were randomized to omadacycline 450 mg once daily for two doses then 300 mg once daily ($n = 360$) or linezolid 600 mg ($n = 360$) twice daily for a total treatment duration of 7–14 days (median duration was 8.2 and 8.0 days). In the modified ITT population (as per OASIS-1) early clinical response was observed in 87.5 and 82.5% of omadacycline and linezolid recipients, with 84.2 and 80.8% achieving clinical success at post-therapy evaluation. In the clinically evaluable population ($n = 284$ in the omadacycline group and 292 in the linezolid group) clinical success at post-therapy evaluation was achieved in 97.9 and 95.5% of patients [25].

2.3.2.2 Phase II IV/oral omadacycline was noninferior to IV/oral linezolid as treatment for complicated skin and skin structure infections in the efficacy analyses of an investigator-blind, phase II safety and tolerability trial. In the ITT population, successful clinical response was achieved by 88.3 and 75.9% of omadacycline and linezolid recipients. In the clinically evaluable population, 98.0 and 93.2% of patients in the respective treatment groups had a successful clinical response. The clinical success rate was 97.2% (70 of 72 patients) and 92.7% (51 of 55 patients), respectively, in microbiologically evaluable patients with *S. aureus* infections. In this study, patients were randomized to omadacycline 100 mg IV once daily (with an option to transition to 200 mg orally once daily) or linezolid 600 mg IV twice daily (with an option to transition to 600 mg orally twice daily). Patients with suspected or documented Gram-negative infections received aztreonam (2 g IV once every 12 h) or matched placebo in the linezolid and omadacycline groups, respectively. A comparison of the efficacy of omadacycline and linezolid was a key secondary outcome [26].

2.4 Adverse Events

Adverse reactions occurring in ≥ 2% of patients with CABP treated with omadacycline in the OPTIC trial ($n = 382$) included increased alanine aminotransferase levels [3.7% (vs. 4.6% with moxifloxacin)], hypertension (3.4 vs. 2.8%), increased gamma-glutamyl transferase levels (2.6 vs. 2.1%), insomnia (2.6 vs. 2.1%), vomiting (2.6 vs. 1.5%), constipation (2.4 vs. 1.5%), nausea (2.4 vs. 5.4%), increased aspartate aminotransferase levels (2.1 vs. 3.6%) and headache (2.1 vs. 1.3%) [5]. Diarrhoea was reported in 1% of omadacycline recipients compared with 8% of moxifloxacin recipients. No omadacycline recipients and eight moxifloxacin recipients developed *Clostridium difficile* infection [23]. Discontinuation of treatment due to adverse events occurred in 5.5% of omadacycline recipients and 7.0% of moxifloxacin

recipients. Eight omadacycline recipients (2%) and four moxifloxacin recipients (1%) died during the OPTIC trial; all were aged > 65 years and most had multiple comorbidities [5].

Adverse reactions occurring in ≥ 2% of patients with ABSSSI treated with omadacycline in the OASIS-1 and OASIS-2 trials ($n = 691$) included nausea [21.9% (vs. 8.7% with linezolid)], vomiting (11.4 vs. 3.9%), infusion site reactions (5.2 vs. 3.6%), increased alanine aminotransferase levels (4.1 vs. 3.6%), increased aspartate aminotransferase levels (3.6 vs. 3.5%), headache (3.3 vs. 3.0%) and diarrhoea (3.2 vs. 2.9%). Across both trials, treatment discontinuation due to adverse events occurred in 12 (1.7%) omadacycline and 10 (1.5%) linezolid recipients. Only one omadacycline recipient in each trial discontinued treatment because of nausea and vomiting [5].

Adverse events occurring in < 2% of patients treated with omadacycline in OPTIC, OASIS-1 and OASIS-2 included tachycardia, atrial fibrillation, anaemia, thrombocytosis, vertigo, abdominal pain, dyspepsia, fatigue, hypersensitivity, oral candidiasis, vulvovaginal mycotic infection, increased creatinine phosphokinase levels, increased bilirubin levels, increased alkaline phosphatase levels, dysgeusia, lethargy, oropharyngeal pain, pruritus, erythema and urticaria [5].

2.5 Ongoing Clinical Trials

A study comparing the safety and efficacy of oral omadacycline to that of oral nitrofurantoin as treatment for cystitis (NCT03425396) is currently recruiting patients.

3 Current Status

Omadacycline received its first global approval on 2nd October 2018 in the USA for the treatment of CABP and ABSSSI in adults caused by designated susceptible bacteria [1] and is under evaluation in the EU for the same indications [2].

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflicts of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. A. Markham, a contracted employee of Adis/Springer, and Susan Keam, an employee of Adis/Springer, are responsible for the article content and declare no relevant conflicts of interest.

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