This supplement was sponsored by Paratek Pharmaceuticals, Inc. It was edited and peer reviewed by *The Journal of Family Practice*.

SUPPLEMENT TO
THE JOURNAL OF FAMILY PRACTICE®

VOL 71, NO 5 | JUNE 2022 | MDEDGE.COM/FAMILYMEDICINE

Omadacycline: An Oral Antibiotic for the Treatment of Bacterial Skin Infections and Pneumonia in an Era of Unmet Clinical Need

Current Challenges in the Management of Skin and Soft Tissue Infections and Community-Acquired Pneumonia

Melanie Lauterio, PhD; Daniel H. Deck, PharmD, BCIDP

doi: 10.12788/jfp.0423

ABSTRACT

Skin and soft tissue infections (SSTI) and community-acquired pneumonia (CAP) are major public health problems that are commonly encountered in the primary care setting. Establishing the severity of disease is an important step in the diagnosis of SSTI and CAP, because this can affect decisions about optimal management, including level of care. Due to antibiotic resistance, allergies, and adverse effect profiles of current therapies, there is a need for new treatment options for both SSTI and CAP. Improved utilization of oral outpatient antibiotic treatments can also minimize the risk of serious adverse effects or nosocomial infections, leading to better patient outcomes. As these infections are mostly treated in outpatient settings, primary care clinicians are best suited to implement changes such as use of oral antibiotics, where appropriate, to reduce hospitalization, with its associated costs and risks to the patient.

INTRODUCTION

Skin and soft tissue infections (SSTI), including acute bacterial skin and skin structure infections (ABSSSI),[1*] and community-acquired pneumonia (CAP) are major public health problems. They are associated with significant morbidity and mortality and place a substantial burden on the healthcare system.[2-7]

Despite many advances in the management of SSTI and CAP, significant challenges persist. Commonly prescribed antibiotic treatment regimens may be ineffective due to antibiotic resistance. There are also safety concerns with certain antibiotics used to treat SSTI or CAP, including drug allergies and other adverse events such as QT prolongation and *Clostridioides difficile* infection (CDI).[8-14] Here we consider the management of these common community-acquired infections from a primary care viewpoint, including epidemiology and bacterial pathogens, diagnosis and risk stratification, treatment, challenges, and unmet needs.

OVERVIEW OF EPIDEMIOLOGY AND BACTERIAL ETIOLOGY

SSTI

The incidence of SSTI is estimated at 48.5 per 1000 person-years, with >14 million physician office visits and 750,000 hospitalizations each year in the United States.[5,15,16] Patients with SSTI frequently seek medical care at an emergency department (ED), and 15% of these patients are admitted to the hospital.[17,18] Patients with underlying comorbidities or certain risk factors—including diabetes, vascular disease, obesity, and intravenous drug use—are at increased risk for developing SSTI.[6,7,15,19] Cellulitis and erysipelas are the most common non-purulent SSTI and are caused in most cases by streptococci. In contrast, purulent infections, including abscesses and wounds, are commonly caused by *Staphylococcus aureus*, often methicillin resistant (MRSA).[6,20] Wound infections can

Melanie Lauterio, PhD and Daniel H. Deck, PharmD, BCIDP
Paratek Pharmaceuticals, Inc., King of Prussia, PA

DISCLOSURES
Both authors are employees and shareholders of Paratek Pharmaceuticals, Inc.

ACKNOWLEDGMENTS
Medical writing and editorial assistance were provided by Felicity Leigh, PhD, and Agnella Matic, PhD, of Innovative Strategic Communications (Milford, PA), funded by Paratek Pharmaceuticals, Inc.

FUNDING
This work was supported by Paratek Pharmaceuticals, Inc. (King of Prussia, PA).

*ABSSSI include a subset of SSTI defined by the US Food and Drug Administration (FDA) for the purpose of registration trials as bacterial infections of the skin with a lesion size area of ≥75 cm^2. ABSSSI include major cutaneous abscesses, wound infections, or cellulitis/erysipelas.

also be caused by Gram-negative or anaerobic bacteria.[6,20] Community-acquired MRSA has been identified in 59% of patients presenting to the ED with SSTI.[21]

CAP

CAP affects approximately 4.9 million patients annually in the United States,[2] and together with influenza, pneumonia was the ninth leading cause of death in 2020.[3] In the United States, there are ~4.5 million ambulatory visits per year for CAP,[22] and ~60% of patients who present to an ED with CAP are treated as outpatients.[23] The percentage of patients with CAP who are admitted to hospital varies by country; in the United States, the annual incidence of CAP requiring hospitalization is estimated to be 24.8 cases per 10,000 adults.[24] However, the rate is higher in older adults and patients with comorbidities, such as chronic obstructive pulmonary disease (COPD), congestive heart failure, and diabetes.[4]

The most common bacterial pathogen associated with CAP is *Streptococcus pneumoniae*.[24,25] Other bacterial pathogens in adults with CAP include *S aureus*, *Haemophilus influenzae*, and atypical pathogens (eg, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*).[24]

MANAGEMENT OF SSTI AND CAP IN THE OUTPATIENT SETTING

Diagnosis and risk stratification

An important step in the optimal management of patients with SSTI or CAP is establishing the severity of disease. An accurate assessment of disease severity can guide the clinician's choice of antibiotics, including route of delivery and preferred site of care. Risk stratification tools may also help clinicians avoid unnecessary hospital admissions, thereby reducing treatment costs and the risk of hospital-associated complications.[26-28]

SSTI

Robust outcomes data that would inform hospital admission decisions have not been reported for patients with SSTI; however, it is known that the mortality rate of patients hospitalized with SSTI is low (~0.5%).[5,28] In the absence of validated risk assessment tools, clinicians make decisions about the optimal site of care based on markers of disease severity and an assessment of social factors that may compromise outpatient treatment.[27] Infectious Diseases Society of America (IDSA) SSTI guidelines from 2014 recommend outpatient therapy for patients without systemic signs and symptoms of infection (ie, systemic inflammatory response syndrome [SIRS], altered mental status, or hemodynamic instability).[27] Hospitalization is recommended when there is concern about a deeper or necrotizing infection, or for patients who have failed outpatient therapy, have poor adherence, or are severely immunocompromised.[27]

CAP

The IDSA/American Thoracic Society (ATS) CAP guidelines recommend that clinicians use a validated clinical prediction rule for prognosis, in addition to clinical judgment, to determine the need for hospitalization.[26] The most frequently used scoring systems for predicting prognosis and the potential need for hospital treatment are the Pneumonia Severity Index (PSI) and CURB-65 (see **BOX**),[29,30] with PSI being preferred over CURB-65 in current CAP guidelines.[26] However, in the primary care setting, CURB-65 is considered more practical given the need for only 5 clinical data elements commonly collected for patients presenting with signs and symptoms of CAP.[26,29,30]

Treatment

SSTI

Empiric antibiotic treatment is recommended in all patients with cellulitis or wound infection.[27] Uncomplicated abscesses are primarily managed with incision

BOX. Commonly used scoring systems for pneumonia

Pneumonia Severity Index (PSI)

- PSI is composed of 20 items, including age, coexisting illnesses (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, and renal disease), physical examination findings, and laboratory and radiographic findings.[29] It classifies patients into 5 categories of severity that are associated with the risk of mortality.[29]
- PSI risk classes I, II, and III represent 69% of CAP patients, who are at sufficiently low risk for death and other adverse medical outcomes that physicians can consider outpatient treatment or an abbreviated course of inpatient care.[29]

CURB-65

- CURB-65 scoring system uses 5 items (Confusion, Urea level >20 mg/dL, Respiratory rate ≥30 breaths/minute, Blood pressure systolic <90 mm Hg or diastolic ≤60 mm Hg, and age ≥65 years) but does not account for comorbidities.[30]
- Patients with CURB-65 scores of 0 to 1 have a low mortality risk and may be considered for management as outpatients.[30]

and drainage and topical antisepsis measures. The 2014 IDSA SSTI guidelines recommend that patients who present with a cutaneous abscess and systemic signs of infection should also receive antibiotics.[27] More recent studies in patients with uncomplicated cutaneous abscess suggest that antibiotic treatment is associated with modest reductions in the rates of treatment failure and 30-day recurrence.[31] The choice of antibiotic is influenced by infection type and likely pathogens, local resistance patterns, and patient characteristics.[27] Guideline-concordant oral antibiotics for the empirical treatment of non-purulent SSTI (eg, cellulitis, erysipelas) include penicillin V potassium, cephalosporins, dicloxacillin, and clindamycin.[27] For the empirical treatment of purulent infections (eg, cutaneous abscesses), guidelines recommend oral agents with MRSA activity including sulfamethoxazole/trimethoprim, a tetracycline (doxycycline or minocycline), clindamycin, and linezolid.[27]

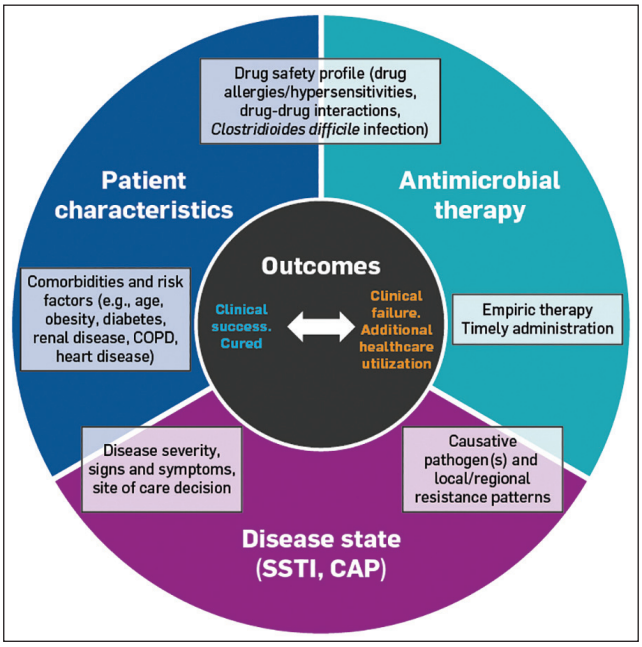
CAP

Empiric antibiotic treatment is recommended for all patients with bacterial CAP, including outpatients.[26] Antibiotic selection should take into consideration up-to-date local guidelines for microorganism prevalence and susceptibility patterns when available. The IDSA/ATS CAP guidelines recommend that outpatients without comorbidities be treated with amoxicillin, doxycycline, or a macrolide (only in areas where pneumococcal resistance to macrolides is <25%).[26] For outpatients with CAP who have comorbidities, the guidelines recommend broader-spectrum coverage, not only because patients with comorbidities are at higher risk for antibiotic resistance through increased contact with the healthcare system, but also because they are more vulnerable to poor outcomes if the initial empiric antibiotic regimen is inadequate. In addition to targeting *S pneumoniae* and atypical bacteria, treatment regimens for patients with comorbidities should also provide coverage for *H influenzae*, *S aureus*, and Gram-negative bacilli; thus, recommendations are to use a combination of amoxicillin/clavulanate or an oral cephalosporin plus a macrolide or doxycycline, or monotherapy with a respiratory fluoroquinolone.[26]

CHALLENGES AND UNMET NEEDS IN THE MANAGEMENT OF SSTI AND CAP

SSTI and CAP in the primary care setting can be challenging diseases to manage (patient, disease, and treatment factors that can influence treatment outcomes are illustrated in the **FIGURE**).

FIGURE. Infectious diseases and factors influencing their outcomes



CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; SSTI, skin and soft tissue infection.

For SSTI, treatment challenges include the emergence of antibiotic-resistant pathogens such as community-acquired MRSA and beta-hemolytic *Streptococcus*. Clinicians are forced to rely on older, repurposed oral antibiotics to treat MRSA SSTI in the community. These agents have only been rigorously studied in uncomplicated SSTI; their efficacy in more complicated SSTI, including infections in patients with complicating comorbidities,[32] has not been established. This is important, as patients with SSTI often have comorbidities such as diabetes and obesity that are known to adversely affect treatment outcomes.[33-35]

In CAP, a definitive microbiological etiology is rarely established, and clinicians may not have access to local antibiotic susceptibility data that would help inform their choice of empiric antibiotics.[25,26,36] Uncertainty around the etiology of CAP, coupled with current rates of resistance to commonly prescribed antibiotics in key pathogens such as *S pneumoniae*, puts patients at risk for receiving inadequate treatment, contributing to poor outcomes. Patients with underlying comorbidities are at greater risk for infections caused by antibiotic-resistant pathogens and poor treatment outcomes. In this setting, clinicians may opt to prescribe a respiratory fluoroquinolone that has more reliable activity but a less favorable safety profile.[25,26,36]

Antibiotic resistance: an increasing problem worldwide

As a result of antibiotic resistance, antibiotics may become less effective (or ineffective), allowing infections to persist and thereby increasing morbidity, mortality, and the risk of spreading infection to others.[37-39] A recent estimate has suggested that over 186,000 people die annually in North America due to antibiotic-resistant infections.[40] The majority of United States antibiotic prescriptions originate in outpatient settings, and a number of studies provide strong evidence of an association at the individual patient level between antibiotic prescribing rates in primary care and antimicrobial resistance in bacteria at different anatomic sites, including the skin and respiratory tract.[41,42] This may present an opportunity to ensure that the right drug, dose, and duration are selected to help combat the problem of antibiotic resistance.[41]

S aureus and *S pneumoniae* —leading causes of SSTI and pneumonia, respectively—have developed resistance to many clinically relevant antibiotics.[38] *S aureus*, including MRSA, has been classified by the Centers for Disease Control and Prevention (CDC) as an urgent threat and has developed resistance to many first-line oral antibiotics such as beta-lactams and clindamycin.[38] In a United States-based study of 471,550 episodes of SSTI, *S aureus* was isolated in 81% of pathogen-positive specimens, of which 46% were MRSA.[43] Clindamycin resistance has been reported in 17% to 20% of isolates of *S aureus* from outpatient and inpatient settings at a hospital in the United States.[44] In a global antimicrobial surveillance program (SENTRY) from 1997 to 2016, rates of clindamycin resistance were consistently higher in MRSA than in methicillin-susceptible *S aureus* (MSSA).[45]

Drug-resistant *S pneumoniae* has been classified by the CDC as a serious threat based on current rates of resistance to commonly used antibiotics,[38] including azithromycin, doxycycline, and oral penicillin. In 2018 to 2019, macrolide resistance was found in ~40% of *S pneumoniae* isolates from adult ambulatory and inpatient settings in >300 United States hospitals. *S pneumoniae* macrolide resistance exceeded the CAP guideline threshold of >25% in most United States regions.[46] Therefore, considering macrolide alternatives is now a necessity nationwide. However, current alternatives, such as doxycycline, are also significantly affected by resistance, with ~20% of *S pneumoniae* strains in the United States being doxycycline resistant.[47-49] *S pyogenes* and other β-hemolytic streptococci are sensitive to penicillin, but nonsusceptibility to alternative oral antibiotics such as macrolides, clindamycin, and tetracycline has been described in 23%, 8%, and 23% of isolates, respectively.[50]

Few novel oral antibiotics have been developed in the last 2 decades to address the issue of resistant pathogens in the community, which may contribute to treatment failure.[51,52] Antibiotic resistance has shifted prescribing patterns toward higher risk antibiotics, with increasing reports of community-onset CDI. A surveillance study performed in 8 United States found that >80% of patients with community-associated CDI had recent outpatient healthcare exposure, and 64% had received outpatient antibiotics within 12 weeks of infection.[53] SSTI and respiratory tract infections were among the most commonly reported reasons for these patients receiving antibiotics.[53]

Antibiotic safety concerns

Despite the availability of multiple antibiotic therapies, current guideline-recommended antibiotics used to treat SSTI and CAP are limited by potentially severe adverse events, including allergies, boxed warnings, and increased risk of CDI. Moreover, many patients with SSTI and CAP have comorbidities and are older, which affects drug pharmacokinetics, potentially necessitating dose adjustments for end-organ dysfunction and increasing the risk for potential drug–drug interactions.[4,6,54]

Patients with proven and serious allergies to beta-lactam, sulfonamide, or macrolide antibiotics have limited alternative options, which may also be less efficacious.[8-12] Certain antibiotic classes are associated with serious safety concerns for adults that are noted in the FDA prescribing information, including:

- **Warnings and precautions**—eg, QT prolongation with macrolides, such as azithromycin[11,12]; photosensitivity with tetracyclines[55]; myelosuppression, peripheral neuropathy, and serotonin syndrome with the oxazolidinones, such as linezolid[56]
- **Boxed warnings**—eg, tendon rupture and central nervous system effects with fluoroquinolones, such as levofloxacin and moxifloxacin[57,58]

Two CDC-sponsored studies have found that adverse events associated with antibiotics are a common cause of ED visits by adults.[59,60] Penicillins (eg, amoxicillin), sulfonamides (eg, trimethoprim–sulfamethoxazole), cephalosporins, and quinolones were the antibiotic classes with the highest risk of adverse events leading to ED visits,[59,60] and quinolones were associated with the highest rate of visits resulting in hospitalization.[60]

Antibiotic use is the most important risk factor for CDI, specifically the number of antibiotics used, the duration of antibiotic use, and the use of high-risk antibiotics.[13,61,62] Although nearly all antibiotic classes have been associated with CDI, antibiotics considered to harbor the

TABLE. Clinical considerations for oral antibiotics commonly used in the outpatient treatment of SSTI or CAP

Oral antibiotic	Pathogen coverage	Considerations
Amoxicillin[70]	• Good activity against *S pneumoniae* • Approximately 1/3 of *H influenzae* are resistant[25] • No coverage of atypical pathogens	• Caution in patients with penicillin or beta-lactam allergy
Macrolides Azithromycin[12]	• Good activity against *H influenzae* and atypical pathogens • *S pneumoniae* resistance rates >25% in most United States regions[46]	• Macrolide allergy • Risk of QT prolongation
Tetracyclines Doxycycline[71,72]	• Broad spectrum of activity against *S pneumoniae*, *S aureus* (MSSA), *H influenzae*, and atypical pathogens • Resistance in *S pneumoniae* approaches 20% • *S pyogenes* resistance approaches 20%	• Not recommended during second and third trimester of pregnancy and in children up to the age of 8 years
Cephalosporins Cefpodoxime[73] Amoxicillin/Clavulanate[74]	• Broad spectrum of activity including *S pneumoniae*, *S aureus* (MSSA), and *H influenzae* • No coverage of atypical pathogens	• Increased risk of *C difficile*–associated infection compared with other antibiotics[13] • Caution in patients with penicillin or beta-lactam allergy
Fluoroquinolones Levofloxacin[58]	• Broad spectrum of activity including *S pneumoniae*, *S aureus* (MSSA), *H influenzae*, and atypical pathogens	• Increased risk of *C difficile*–associated infection compared with other antibiotics[13] • Risk of QT prolongation and aortic aneurysm; boxed warnings (tendon rupture, peripheral neuropathy, CNS reactions)
Clindamycin[72,75,76]	• Activity against *S aureus* and *S pyogenes* • Resistance to MRSA >25%	• Increased risk of *C difficile*–associated infections compared with other agents[13]
Sulfamethoxazole/ Trimethoprim[76,77]	• Activity against *Staphylococcus* and MRSA • May not provide reliable coverage against *S pyogenes*	• Not recommended in pregnant women in the third trimester, or in infants aged <2 months • Patients at risk for hyperkalemia (elderly, renal insufficiency, concurrent inhibitors of the renin-angiotensin system)
Oxazolidinone Linezolid[56,76]	• Activity against *S aureus* including MRSA, *S pyogenes*, and *S agalactiae* • No Gram-negative activity	• Has been associated with myelosuppression, neuropathy, and lactic acidosis during prolonged therapy • Patients at risk for serotonin syndrome

FDA, Food and Drug Administration; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus*; SSTI, skin and soft tissue infection.

greatest risk are clindamycin, third-generation cephalosporins (eg, cefixime and cefuroxime), and fluoroquinolones (eg, moxifloxacin and levofloxacin).[14] Tetracycline-class antibiotics have been associated with a low risk of CDI.[14,63]

Key clinical considerations for oral antibiotics that are commonly used in the outpatient treatment of SSTI and CAP are summarized in the **TABLE**.

Treatment failure

Multiple factors play into treatment failure in patients with SSTI and CAP, including antimicrobial resistance, inappropriate antibiotic therapy, severity of disease, patient age, and comorbidities.

SSTI

For SSTI, treatment failure ranges from 10% to 24%, and their management is often complicated by underlying comorbidities, especially in elderly patients, some of whom have impairment in multiple organs, or diabetes.[33-35] Predictors of treatment failure in outpatients with SSTI include obesity, diabetes, heart failure, and larger lesion size (>75 cm^2).[34,35,64] Among patients who require hospitalization for skin infections, an apparent failure of outpatient treatment is common (up to 34%).[65] However, in patients with skin abscesses, an apparent lack of clinical response could be due to inadequate drainage of the abscess (the mainstay of treatment) rather than true failure of antibiotic therapy.[65] Further research is needed to

investigate the underlying reasons for the apparent lack of clinical response to outpatient treatment.[65]

CAP

Literature describing outcomes of CAP in the outpatient setting is sparse, but treatment failure is known to be common and to contribute to the economic and humanistic burdens of CAP by increasing morbidity, mortality, and healthcare costs.[66-69] A large retrospective claims analysis concluded that 1 in 5 adults with CAP who were treated in the outpatient setting with a guideline-concordant antibiotic (fluoroquinolone, macrolides, beta-lactam, or tetracycline) experienced treatment failure.[68] Patients who experienced treatment failure had 4 times greater 30-day mortality (18.1%); these outcomes were more pronounced in patients aged ≥65 years.[68]

SUMMARY OF UNMET NEEDS

For both SSTI and CAP, there is an opportunity for improved antibiotic prescribing to overcome increasing antibiotic resistance. Improved utilization of oral outpatient antibiotic treatments may result in better patient outcomes and minimize the risk of serious adverse events.[13,26,61] As most of these infections are treated in outpatient settings, primary care clinicians are best equipped to implement changes, such as optimizing use of oral antibiotics to reduce the need for hospitalization, with its associated costs and risks to the patient.[26,27,61] New antibiotic therapies, with activity against common pathogens including drug-resistant strains, could help address some of the unmet needs in SSTI and CAP.

REFERENCES

1. Food and Drug Administration (FDA). Guidance for industry. Acute bacterial skin and skin structure infections: Developing drugs for treatment. Accessed February 26, 2022. https://www.fda.gov/media/71052/download
2. Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008-2014. *BMC Health Serv Res*. 2018;18(1):715. doi:10.1186/s12913-018-3529-4
3. Murphy SL, Kochanek KD, Xu J, Arias E. Mortality in the United States, 2020. *NCHS Data Brief*. Dec 2021;(427):1-8.
4. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis*. 2017;65(11):1806-1812. doi:10.1093/cid/cix647
5. Kaye KS, Petty LA, Shorr AF, Zilberberg MD. Current epidemiology, etiology, and burden of acute skin infections in the United States. *Clin Infect Dis*. 2019; 68(Suppl3):S193-S199. doi:10.1093/cid/ciz002
6. Ramakrishnan K, Salinas RC, Agudelo Higuita NI. Skin and soft tissue infections. *Am Fam Physician*. 2015;92(6):474-483.
7. Daum RS. Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. *N Engl J Med*. 2007;357(4):380-390. doi:10.1056/NEJMcp070747
8. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet*. 2019;393(10167):183-198. doi:10.1016/S0140-6736(18)32218-9
9. Sakoulas G, Geriak M, Nizet V. Is a reported penicillin allergy sufficient grounds to forgo the multidimensional antimicrobial benefits of beta-lactam antibiotics? *Clin Infect Dis*. 2019;68(1):157-164. doi:10.1093/cid/ciy557
10. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA*. 2001;285(19):2498–2505. doi:10.1001/jama.285.19.2498
11. Pfizer. ZITHROMAX IV (azithromycin) Prescribing Information. July 2000. Accessed March 17, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/50733s5lbl.pdf
12. Pfizer. ZITHROMAX Oral (azithromycin) Prescribing Information. January 2013. Accessed March 17, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050710s039,050711s036,050784s023lbl.pdf
13. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1-e48. doi:10.1093/cid/cix1085
14. Brown KA, Langford B, Schwartz KL, Diong C, Garber G, Daneman N. Antibiotic prescribing choices and their comparative C. difficile infection risks: a longitudinal case-cohort study. *Clin Infect Dis*. 2021;72(5):836-844. doi:10.1093/cid/ciaa124
15. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med*. 2008;168(14):1585-1591. doi:10.1001/archinte.168.14.1585
16. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. *PLoS One*. 2015;10(11):e0143276. doi:10.1371/journal.pone.0143276
17. Mistry RD, Shapiro DJ, Goyal MK, et al. Clinical management of skin and soft tissue infections in the U.S. emergency departments. *West J Emerg Med*. 2014;15(4):491-498. doi:10.5811/westjem.2014.4.20583
18. Talan DA, Salhi BA, Moran GJ, et al. Factors associated with decision to hospitalize emergency department patients with skin and soft tissue infection. *West J Emerg Med*. 2015;16(1):89-97. doi:10.5811/westjem.2014.11.24133
19. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA, Jr. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant Staphylococcus aureus. *Ann Emerg Med*. 2008;51(3):291-298. doi:10.1016/j.annemergmed.2007.12.004
20. Esposito S, Noviello S, Leone S. Epidemiology and microbiology of skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29(2):109-115. doi:10.1097/QCO.0000000000000239
21. Talan DA, Krishnadasan A, Gorwitz RJ, et al. Comparison of Staphylococcus aureus from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. *Clin Infect Dis*. 2011;53(2):144-149. doi:10.1093/cid/cir308
22. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. *Vital Health Stat 13*. 2011;(169):1-38.
23. Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. *N Engl J Med*. 2014;370(6):543-551. doi:10.1056/NEJMcp1214869
24. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415-427. doi:10.1056/NEJMoa1500245
25. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med*. 2014;371(17):1619-1628. doi:10.1056/NEJMra1312885
26. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67. doi:10.1164/rccm.201908-1581ST
27. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):147-159. doi:10.1093/cid/ciu296
28. Claeys KC, Zasowski EJ, Lagnf AM, et al. Development of a risk-scoring tool to determine appropriate level of care in acute bacterial skin and skin structure infections in an acute healthcare setting. *Infect Dis Ther*. 2018;7(4):495-507. doi:10.1007/s40121-018-0212-3
29. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk pa-

tients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250. doi:10.1056/NEJM199701233360402

30. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009;64(Suppl3):iii1-55. doi:10.1136/thx.2009.121434
31. Wang W, Chen W, Liu Y, et al. Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis. *BMJ Open*. 2018;8(2):e020991. doi:10.1136/bmjopen-2017-020991
32. Dryden MS. Complicated skin and soft tissue infection. *J Antimicrob Chemother*. 2010;65(Suppl3):iii35-44. doi:10.1093/jac/dkq302
33. Pulido-Cejudo A, Guzman-Gutierrez M, Jalife-Montano A, et al. Management of acute bacterial skin and skin structure infections with a focus on patients at high risk of treatment failure. *Ther Adv Infect Dis*. 2017;4(5):143-161. doi:10.1177/2049936117723228
34. Cieri B, Conway EL, Sellick JA, Mergenhagen KA. Identification of risk factors for failure in patients with skin and soft tissue infections. *Am J Emerg Med*. 2019;37(1):48-52. doi:10.1016/j.ajem.2018.04.046
35. Conway EL, Sellick JA, Kurtzhalts K, Mergenhagen KA. Obesity and heart failure as predictors of failure in outpatient skin and soft tissue infections. *Antimicrob Agents Chemother*. 2017;61(3):e02389-16. doi:10.1128/AAC.02389-16
36. Musher DM, Abers MS, Bartlett JG. Evolving understanding of the causes of pneumonia in adults, with special attention to the role of Pneumococcus. *Clin Infect Dis*. 2017;65(10):1736-1744. doi:10.1093/cid/cix549
37. O'Neill J. The Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. May 2016. Accessed November 9, 2021. https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf
38. Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States. 2019. Accessed November 9, 2021. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
39. World Health Organisation (WHO). Antimicrobial resistance: Global report on surveillance. 2014. Accessed November 9, 2021. https://apps.who.int/iris/handle/10665/112642
40. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0
41. Centers for Disease Control and Prevention (CDC). Measuring outpatient antibiotic prescribing (webpage updated 12 October 2021). Accessed March 24, 2022. https://www.cdc.gov/antibiotic-use/data/outpatient-prescribing/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fantibiotic-use%2Fcommunity%2Fprograms-measurement%2Fmeasuring-antibiotic-prescribing.html
42. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010;340:c2096. doi:10.1136/bmj.c2096
43. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. *BMC Infect Dis*. 2013;13:252. doi:10.1186/1471-2334-13-252
44. Vicetti Miguel CP, Mejias A, Leber A, Sanchez PJ. A decade of antimicrobial resistance in Staphylococcus aureus: a single center experience. *PLoS One*. 2019;14(2):e0212029. doi:10.1371/journal.pone.0212029
45. Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. Twenty-Year Trends in Antimicrobial Susceptibilities Among Staphylococcus aureus From the SENTRY Antimicrobial Surveillance Program. *Open Forum Infect Dis*. 2019;6(Suppl 1):S47-S53. doi:10.1093/ofid/ofy270
46. Gupta V, Yu KC, Schranz J, Gelone SP. A multicenter evaluation of the US prevalence and regional variation in macrolide-resistant S. pneumoniae in ambulatory and hospitalized adult patients in the United States. *Open Forum Infect Dis*. 2021;8(7):ofab063. doi:10.1093/ofid/ofab063
47. Jones RN, Jacobs MR, Sader HS. Evolving trends in Streptococcus pneumoniae resistance: implications for therapy of community-acquired bacterial pneumonia. *Int J Antimicrob Agents*. 2010;36(3):197-204. doi:10.1016/j.ijantimicag.2010.04.013
48. Sader HS, Mendes RE, Le J, Denys G, Flamm RK, Jones RN. Antimicrobial susceptibility of Streptococcus pneumoniae from North America, Europe, Latin America, and the Asia-Pacific Region: results from 20 years of the SENTRY antimicrobial surveillance program (1997-2016). *Open Forum Infect Dis*. 2019;6(Suppl 1):S14-S23. doi:10.1093/ofid/ofy263
49. Flamm RK, Steenbergen JN, Huband MD, Rhomberg PR, Sader HS. Activity of omadacycline when tested against respiratory pathogens Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus isolated during 2016 from medical centers in the USA. presented at: American Thoracic Society International Conference; May 19-24, 2017; Washington, DC.
50. Huband MD, Pfaller MA, Streit JM, Sader HS, Castanheira M. Activity of omadacycline against 7,000 bacterial isolates from the United States in the SENTRY Antimicrobial Surveillance Program (2020). Presented at: World Microbe Forum; 2021.
51. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2016;22(5):416-422. doi:10.1016/j.cmi.2015.12.002
52. Giacomini E, Perrone V, Alessandrini D, Paoli D, Nappi C, Degli Esposti L. Evidence of antibiotic resistance from population-based studies: a narrative review. *Infect Drug Resist*. 2021;14:849-858. doi:10.2147/idr.S289741
53. Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. *JAMA Intern Med*. 2013;173(14):1359-1367. doi:10.1001/jamainternmed.2013.7056
54. Giarratano A, Green SE, Nicolau DP. Review of antimicrobial use and considerations in the elderly population. *Clin Interv Aging*. 2018;13:657-667. doi:10.2147/CIA.S133640
55. Shutter MC, Akhondi H. Tetracycline. StatPearls Publishing; 2022.
56. Pfizer. ZYVOX (linezolid) Prescribing Information. October 2021. Accessed March 17, 2022. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021130
57. Bayer. AVELOX (moxifloxacin) Prescribing Information. July 2016. Accessed March 17, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021085s063lbl.pdf
58. Janssen. LEVAQUIN (levofloxacin) Prescribing Information. October 2004. Accessed March 17, 2022. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021721
59. Geller AI, Lovegrove MC, Shehab N, Hicks LA, Sapiano MRP, Budnitz DS. National estimates of emergency department visits for antibiotic adverse events among adults-United States, 2011-2015. *J Gen Intern Med*. 2018;33(7):1060-1068. doi:10.1007/s11606-018-4430-x
60. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*. 2016;316(20):2115-2125. doi:10.1001/jama.2016.16201
61. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):e51-e77. doi:10.1093/cid/ciw118
62. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med*. 2015;372(16):1539-1548. doi:10.1056/NEJMra1403772
63. Tariq R, Cho J, Kapoor S, et al. Low risk of primary Clostridium difficile infection with tetracyclines: a systematic review and metaanalysis. *Clin Infect Dis*. 2018;66(4):514-522. doi:10.1093/cid/cix833
64. Labreche MJ, Lee GC, Attridge RT, et al. Treatment failure and costs in patients with methicillin-resistant Staphylococcus aureus (MRSA) skin and soft tissue infections: a South Texas Ambulatory Research Network (STARNet) study. *J Am Board Fam Med*. 2013;26(5):508-517. doi:10.3122/jabfm.2013.05.120247
65. Jenkins TC, Knepper BC, McCollister BD, et al. Failure of outpatient antibiotics among patients hospitalized for acute bacterial skin infections: what is the clinical relevance? *Am J Emerg Med*. 2016;34(6):957-962. doi:10.1016/j.ajem.2016.02.013
66. Welte T. Managing CAP patients at risk of clinical failure. *Respir Med*. 2015;109(2):157-169. doi:10.1016/j.rmed.2014.10.018
67. Micek ST, Lang A, Fuller BM, Hampton NB, Kollef MH. Clinical implications for patients treated inappropriately for community-acquired pneumonia in the emergency department. *BMC Infect Dis*. 2014;14:61. doi:10.1186/1471-2334-14-61
68. Tillotson G, Lodise T, Classi P, Mildvan D, McKinnell JA. Antibiotic treatment failure and associated outcomes among adult patients with community-acquired pneumonia in the outpatient setting: a real-world US insurance claims

database study. *Open Forum Infect Dis*. 2020;7(3):ofaa065. doi:10.1093/ofid/ofaa065

69. Hess G, Hill JW, Raut MK, et al. Comparative antibiotic failure rates in the treatment of community-acquired pneumonia: results from a claims analysis. *Adv Ther*. 2010;27(10):743-755. doi:10.1007/s12325-010-0062-1
70. GlaxoSmithKline. Amoxil (amoxicillin) Prescribing Information. November 2006. Accessed March 17, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050760s11,050761s11,050754s12,050542s25lbl.pdf
71. Chilcott W. Doryx tablets (doxycycline hyclate) Prescribing Information. June 2008. Accessed March 17, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050795s005lbl.pdf
72. Paratek. Keystone JMI SENTRY Surveillance Database. https://paratek-keystone.com/
73. Pfizer. Vantin tablets and oral suspension (cefpodoxime) Prescribing Information. September 2018. Accessed Sept 1, 2021. http://labeling.pfizer.com/ShowLabeling.aspx?id=1034
74. GlaxoSmithKline. AUGMENTIN (amoxicillin/clavulanate potassium) Prescribing Information. Accessed September 1, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050575s037550597s044050725s025050726s019lbl.pdf
75. Pharmacia and Upjohn Company. Cleocin HCl (clindamycin hydrochloride capsules) Prescribing Information. Accessed February 11, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050162s085lbl.pdf
76. Centers for Disease Control and Prevention (CDC). Outpatient management of SSTIs. Factsheet. Accessed March 17, 2022. https://www.cdc.gov/mrsa/pdf/flowchart_pstr.pdf
77. AR Scientific, Inc. Bactrim (sulfamethoxazole and trimethoprim) tablets and double-strength tablets. Prescribing Information. Accessed March 17, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017377s068s073lbl.pdf

Omadacycline in Skin Infections and Pneumonia: A Review of the Evidence

Steve Vacalis, DO; Stephen Brunton, MD, FAAFP; Jeff Gindi, MD

doi: 10.12788/jfp.0424

ABSTRACT

Given the growing prevalence of antibiotic resistance globally, there is an urgent need for new therapy options that are effective and well tolerated for treatment of common infections such as bacterial skin infections and pneumonia. Here, we summarize the findings of 3 phase 3 clinical trials of omadacycline, a novel tetracycline-derived aminomethylcycline, in patients with acute bacterial skin and skin structure infections (ABSSSI; OASIS-1 [NCT02378480] and OASIS-2 [NCT02877927]) or community-acquired bacterial pneumonia (CABP; OPTIC [NCT02531438]). The primary endpoint in all studies was early clinical response (early response) at 2 to 3 days (skin studies) or 3 to 5 days (pneumonia study) after the first dose. Other endpoints included post-treatment evaluation (late response) and safety evaluations. Early and late responses were similar for omadacycline (85% to 88%) and linezolid (83% to 86%) in the skin infection studies. Similarly in the pneumonia study, early and late responses were similar for omadacycline and moxifloxacin: 81% and 88% vs 83% and 85%, respectively. No differences were observed in subgroup analyses, and high rates of clinical response were seen for all treatments against common pathogens. The most frequent adverse event reported was nausea, which was mostly associated with the loading dose in the oral-only regimen in OASIS-2. Overall, omadacycline was well tolerated and showed high rates of clinical response in patients with skin infections and pneumonia, including in those with comorbidities.

Steve Vacalis, DO[1]; Stephen Brunton, MD FAAFP[2], Jeff Gindi, MD[3]

[1]CaroMont Regional Medical Center, Gastonia, NC
[2]Primary Care Education Consortium, Winnsboro, SC
[3]Hackensack Meridian, Southern Ocean Medical Center, Manahawkin, NJ

ACKNOWLEDGMENTS

Medical writing and editorial assistance were provided by Jenny Engelmoer, PhD, of Innovative Strategic Communications (Milford, PA), funded by Paratek Pharmaceuticals, Inc.

FUNDING

This work was supported by Paratek Pharmaceuticals, Inc. (King of Prussia, PA).

CONFLICTS OF INTEREST

Stephen Brunton and Steve Vacalis declare no conflicts of interest. Jeff Gindi has served on an advisory board for AstraZeneca, Paratek Pharmaceuticals Inc., and Seres Therapeutics.

INTRODUCTION

Bacterial skin infections and pneumonia both cause a substantial burden to patients and healthcare systems.[1-3] With the increasing incidence of antibiotic resistance worldwide, there is an urgent unmet need for new treatment options for patients that maximize clinical response while being used effectively and safely within antibiotic stewardship programs.

Omadacycline, a first-in-class, tetracycline-derived aminomethylcycline, has been approved in the United States in intravenous (IV) and oral formulations for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) or community-acquired bacterial pneumonia (CABP).[4] Omadacycline has the potential to address some of the current unmet treatment needs in ABSSSI and CABP, such as increasing antimicrobial resistance, management of patients with comorbidities, and safety concerns for select antibiotics, particularly for patients in the outpatient setting (see earlier article in this supplement, "Current Challenges in the Management of Skin and Soft Tissue Infections and Community-Acquired Pneumonia").

Omadacycline has a proven efficacy profile in both diseases,[5-7] and potent in vitro activity against the most common pathogens, including those resistant to other

antibiotic classes and earlier-generation tetracyclines.[8] The safety profile of omadacycline is consistent with other tetracycline-class drugs but materially different from other antibiotic classes, as omadacycline does not require dose adjustments for end-organ dysfunction, has no clinically relevant QTc prolongation, minimal drug–drug interactions (DDIs), and a low potential for precipitating *Clostridioides difficile* infection (CDI).[9-14] Initially prescribing appropriate and safe antibiotics provides an opportunity to improve clinical outcomes, reduce unintended consequences, and even reduce costs by avoiding and/or reducing the duration of a hospital stay.

To date, omadacycline has been evaluated in preclinical and phase 1 to 3 clinical studies.[15-19] This article provides an overview of the clinical evidence for the use of omadacycline in skin infections (ABSSSI) and pneumonia (CABP) from the phase 3 clinical trial program.

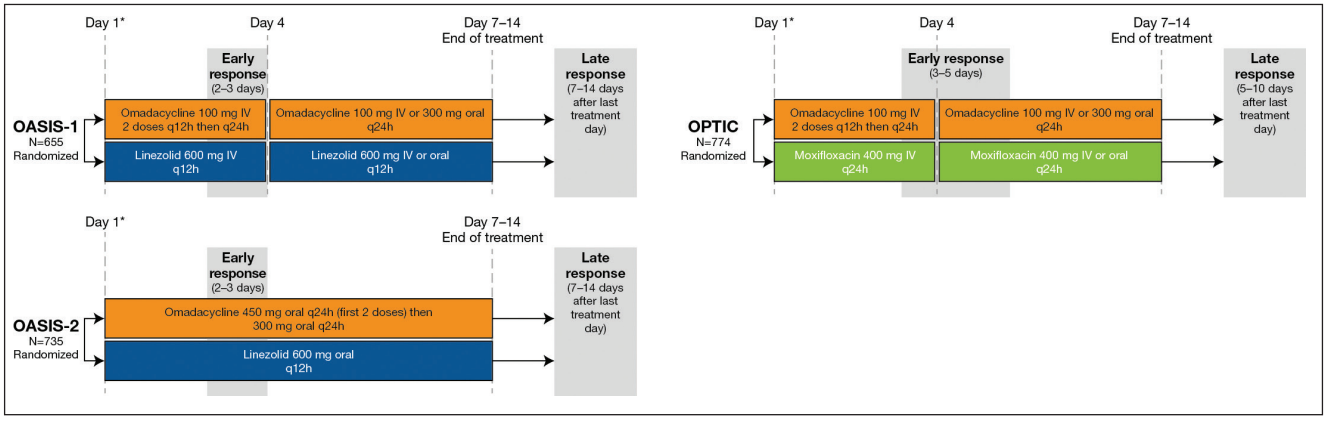
METHODS

Study designs and participants

Two phase 3 studies in patients with ABSSSI (OASIS-1 [NCT02378480] and OASIS-2 [NCT02877927]) and one phase 3 study in patients with CABP (OPTIC [NCT02531438]) are included in this summary. Study designs for all 3 studies, including full inclusion and exclusion criteria, have been published previously.[5-7] All 3 studies were conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from all participants prior to enrollment, and the protocols, amendments, and informed consent forms were approved by the institutional review board or ethics committee at each participating site prior to study start. In brief, patients were eligible for enrollment in the skin infection studies if they were aged ≥18 years and had a wound infection, cellulitis, erysipelas, or major abscess (capped at ≤30% of patients) with a contiguous surface area of ≥75 cm^2 (approximately the size of the palm of a hand) and showed clear evidence of erythema, edema, or induration; and evidence of inflammatory response.[5-7] Patients were eligible for enrollment in the pneumonia study if they were aged ≥18 years with ≥3 symptoms of: cough, purulent sputum production, dyspnea, and pleuritic chest pain; ≥2 abnormal vital signs; ≥1 clinical sign or laboratory finding associated with CABP; radiologically confirmed pneumonia, and disease severity characterized as Pneumonia Severity Index (PSI) risk class II (capped at ≤15% of patients), III, or IV.[6] These risk classes correspond to patients suitable for outpatient treatment (risk class II); brief inpatient observation could be considered (risk class III); and patients requiring hospitalization (risk class IV) (see earlier article in this supplement).

In the bacterial skin infection studies, patients were randomly assigned 1:1 to receive omadacycline or linezolid regimens (**FIGURE 1**). Randomization in the pneumonia study was also 1:1 to receive IV omadacycline

FIGURE 1. Study design



IV, intravenous; q12h, every 12 hours; q24h, every 24 hours.

*Blood was collected at baseline and at PTE for assessment of bacterial pathogens.

Definitions of clinical success: Skin infection studies (OASIS-1 and -2)—Early response (ECR) was defined as survival with a reduction in lesion size of ≥20% at 48 to 72 hours after the first dose without rescue antibacterial therapy; late response (PTE) was defined as survival with resolution or improvement in signs and symptoms of infection to the extent that further antibacterial therapy was unnecessary.

Pneumonia study (OPTIC)—Early response (ECR) was defined as survival with improvement of ≥1 level (eg, from moderate to mild) relative to baseline in ≥2 symptoms of community-acquired bacterial pneumonia (cough, sputum production, pleuritic chest pain, and dyspnea) and no worsening of ≥1 levels in other symptoms of community-acquired bacterial pneumonia, without receipt of rescue antibacterial therapy; late response (PTE) was defined as survival with resolution or improvement in signs and symptoms of infection to the extent that further antibacterial therapy was unnecessary.

or moxifloxacin. In OASIS-1 and OPTIC, patients had the option to transition to an oral formulation of the drug after ≥3 days of IV treatment (on Day 4), whereas all recipients in OASIS-2 received oral formulations throughout the study. The total study treatment was 7 to 14 days for all 3 studies.

Primary and secondary endpoints

In the skin infection studies, the primary endpoint was early clinical response (ECR; early response), at 48 to 72 hours after first dose, defined as survival with a reduction in lesion area ≥20% from baseline, without rescue antibiotic therapy. A co-primary endpoint in OASIS-2 and secondary endpoint in OASIS-1 was investigator-assessed clinical response at the post-treatment evaluation (PTE; late response), 7 to 14 days after the last dose, with clinical response defined as survival with resolution or improvement such that no further antibiotic therapy was needed.

In the pneumonia study, the primary endpoint was early response at 72 to 120 hours after the first dose, defined as survival with improvement in ≥2 symptoms (cough, sputum production, dyspnea, and pleuritic chest pain) and no worsening of other symptoms, without the need of rescue antibiotic therapy. Late response (survival with resolution or improvement such that no further antibiotic therapy was needed) 5 to 10 days after the last dose was a secondary study endpoint.

All 3 studies evaluated safety of the drugs in terms of serious adverse events, treatment-emergent adverse events (TEAEs), and TEAEs leading to treatment discontinuation.

Statistical analysis

All 3 studies assessed the non-inferiority of omadacycline compared with the comparator antibiotic (linezolid for skin infections, moxifloxacin for pneumonia) for the primary endpoint. Non-inferiority was concluded if the lower bound of the 95% confidence interval for the difference in clinical response between treatments was greater than –10%. In the skin infection studies, analysis was performed in the modified intent-to-treat population (mITT), which included all randomized patients who did not have a sole Gram-negative causative pathogen at baseline. For the pneumonia study, the intent-to-treat (ITT) population was used, which included all randomized patients. Early and late responses were also assessed across studies for subgroups (skin infections: people who inject drugs [PWID], body mass index [BMI], diabetes history, renal function, and formulation; pneumonia: age group, biological sex, disease severity [PSI risk class], BMI, diabetes history, renal function, and categorically for patients with ≥1 comorbidity).

RESULTS

Skin infection studies (ABSSSI)

Baseline characteristics

Baseline characteristics were broadly similar in the 2 skin infection studies (**TABLE 1**). Across the studies, the median lesion area was 294 to 322 cm^2, approximately the size of a tablet device. Differences in infection type were seen across the 2 studies, with more patients in OASIS-2 with wound infection (58% to 59%) compared with OASIS-1 (32% to 33%), and fewer with major abscess (17% to 18% vs 29%) or cellulitis/erysipelas (23% to 24% vs 38% to 39%). Additionally, there were higher rates of skin infections due to injection drug use in OASIS-2 (70% to 73% across treatments vs 52% to 54% in OASIS-1).

Efficacy

Early and late responses were similar for omadacycline (85% to 88%) and linezolid (81% to 86%), and as the lower bound of the 95% confidence interval of the difference between treatments was greater than –10%, omadacycline was considered non-inferior to linezolid (**FIGURE 2**). Additional analyses for infection and patient types were conducted, which were consistent with the primary analysis demonstrating similar and high rates for early response that was then maintained through the late response assessment. For this review, only the late response is illustrated, to demonstrate the durability of the response.

For the individual infection types, late response rates were similar between treatments: 82% to 90% for omadacycline and 78% to 88% for linezolid (**FIGURE 3**). No efficacy differences were observed by baseline lesion size for either treatment, although sample sizes were small for the larger lesions.

Similar findings were seen when late responses were assessed for common skin pathogens (**TABLE 2**). High rates of clinical response were observed in both groups against methicillin-resistant and -susceptible *Staphylococcus aureus* (81% to 85% across treatments) and vancomycin-susceptible *Enterococcus faecalis* (94% in omadacycline group, 84% in linezolid group), with responses against *Streptococcus* spp. varying from 70% to 81% and subject to smaller sample sizes.

Late response was also assessed for each treatment for patient types, with no differences in response evident between the treatments in any of the subgroups (injection drug use, BMI category, diabetes history, or renal function) (**FIGURE 4**).[20-22] Additionally, assessment of late response by use of an IV- vs oral-omadacycline initiation

TABLE 1. Baseline characteristics in the bacterial skin infection studies (safety and mITT populations)[4,5,7]

	OASIS-1 (IV to oral)		OASIS-2 (oral only)	
Characteristic	**Omadacycline (n=323)**	**Linezolid (n=322)**	**Omadacycline (n=368)**	**Linezolid (n=367)**
Age, median (range), y	48 (19–88)	46 (18–90)	41 (32–53)	46 (33–53)
Sex				
Female	37 (120)	34 (109)	34 (126)	40 (147)
Male	63 (203)	66 (213)	66 (242)	60 (220)
Race				
White	91 (294)	93 (300)	89 (327)	93 (341)
Black/African American	5 (16)	2 (8)	6 (22)	4 (13)
American Indian/Alaska Native	2 (7)	2 (5)	2 (7)	1 (3)
Other	2 (6)	3 (9)	3 (12)	3 (10)
Body mass index, mean (range), kg/m^2	28 (17–54)	28 (16–55)	28 (16–71)	28 (17–54)
mITT population[a]	n=316	n=311	n=360	n=360
Past medical history				
Injection drug use	54 (174)	52 (169)	73 (268)	70 (258)
Hepatitis C	29 (94)	28 (90)	32 (116)	35 (129)
Hypertension	20 (66)	25 (81)	16 (58)	16 (59)
Anxiety	20 (63)	21 (69)	21 (76)	21 (78)
Depression	15 (50)	15 (49)	19 (69)	17 (62)
Median lesion area (range), cm^2	299.5 (77–4100)	315.0 (88–6739)	322 (198–495)	294 (190–462)
Infection type				
Wound infection	32 (102)	33 (104)	58 (210)	59 (214)
Cellulitis or erysipelas	39 (123)	38 (118)	24 (86)	23 (84)
Major abscess	29 (91)	29 (89)	18 (64)	17 (62)
Primary infection site				
Leg	40.5 (128)	39.9 (124)	36.4 (131)	32.8 (118)
Arm	26.3 (83)	28.0 (87)	33.1 (119)	34.7 (125)
Buttock	7.3 (23)	7.1 (22)	9.2 (33)	10.3 (37)
Other[b]	33.9 (107)	30.2 (94)	21.7 (78)	22.5 (81)
Patients with inflammatory response within 24 hours of randomization				
Lymphadenopathy proximal to primary lesion	75 (236)	74 (231)	87 (314)	81 (293)
Lymphangitis proximal to primary lesion	22 (70)	20 (61)	19 (67)	19 (69)
Leukocytosis or leukopenia,[c] % (n/N)	45 (141/313)	44 (136/310)	32 (113/360)	38 (133/360)
Fever[d]	19 (59)	22 (67)	4 (16)	3 (10)

IV, intravenous; mITT, modified intent-to-treat population. Data are shown as % (n) unless otherwise indicated.

[a] Modified intent-to-treat population, ie, all randomized patients without a sole Gram-negative causative pathogen at baseline.
[b] Includes hand, shoulder, abdomen, axillary, foot, chest, back, neck, elbow, face, knee, groin, and scalp; >1 site of infection was recorded if infection covered multiple sites.
[c] Defined as white blood cell count ≥10,000 or ≤4000 cells/μL.
[d] Body temperature ≥38°C.

FIGURE 2. Clinical early (ECR) and late responses (PTE) in the skin infection and pneumonia studies for the overall study population (mITT/ITT population)[5-7]

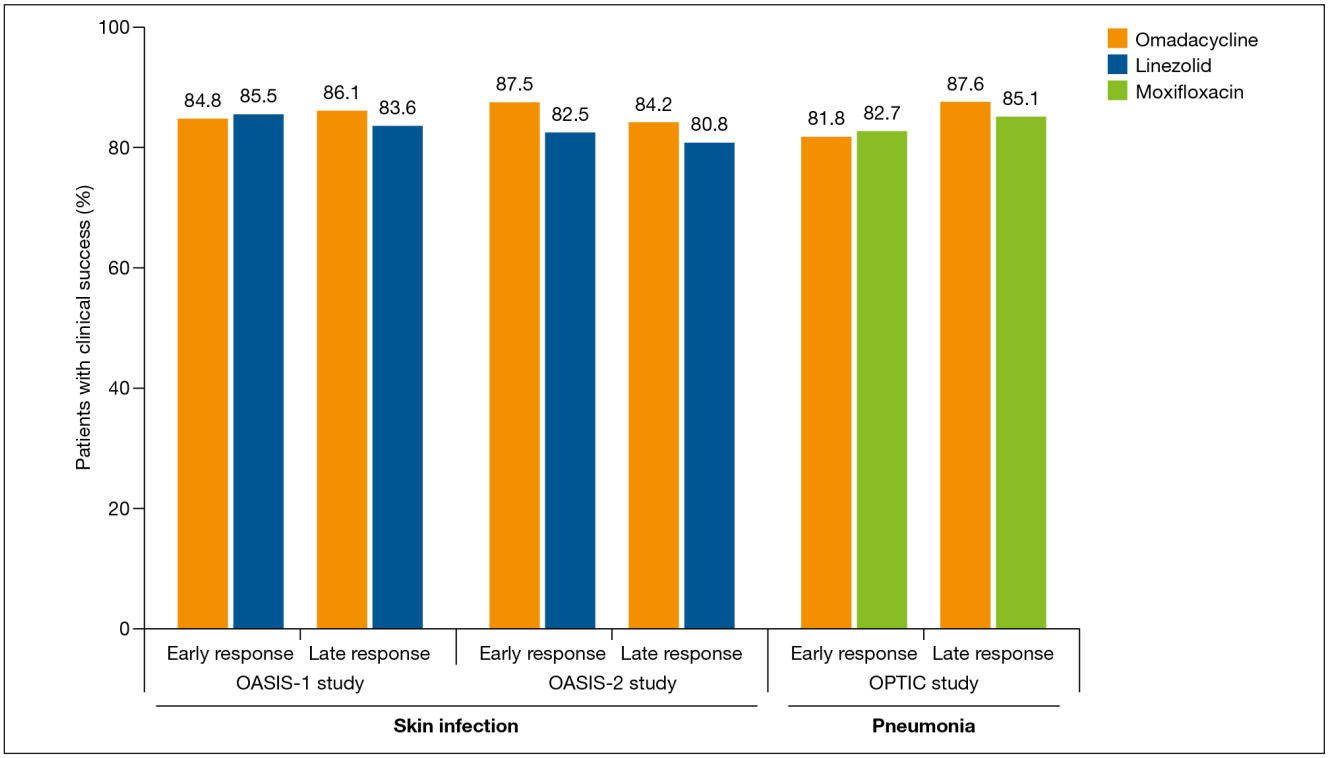
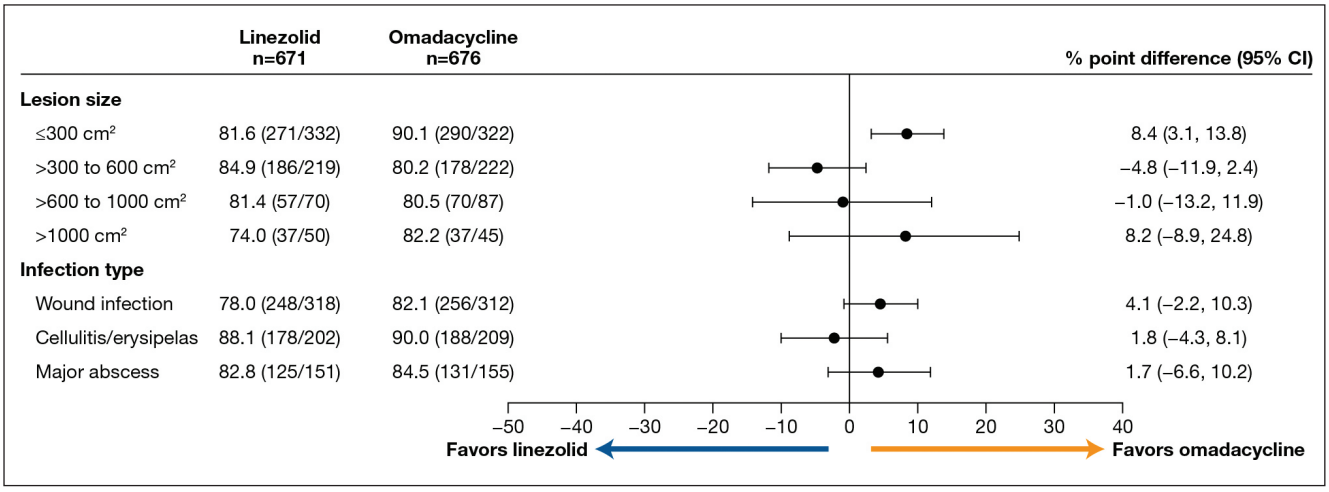


FIGURE 3. Late responses (PTE) by lesion size and infection type pooled across the bacterial skin infection studies (mITT population)[15]



CI, confidence interval; mITT, modified intent-to-treat; PTE, post-treatment evaluation.
Data are presented as % (n/N).

showed similar outcomes, including for patients with risk factors for failure—specifically those with inflammatory response, lesion sizes >300 cm², obesity (BMI >30 kg/m²), or skin infection due to injection drug use (**FIGURE 5**).

Pneumonia study (CABP)

Baseline characteristics

Overall, baseline characteristics were similar across the 2 treatment groups: most patients were white (92%), with a

median age of 61 to 63 years across groups (**TABLE 3**). The majority of patients (54% in both groups) had CURB score 1 (low mortality risk) at baseline; none had CURB score ≥4 (high mortality risk). Symptomatic asthma with wheezing was reported by 5% of patients in each group, and 13% to 15% had mild-to-moderate chronic obstructive pulmonary disease (COPD).

TABLE 2. Late response (PTE) by pathogen in bacterial skin infection studies (micro-mITT populations)[15]

	Omadacycline (n=504)	Linezolid (n=514)
Gram positive, % (n/N)		
Staphylococcus aureus	83.0 (312/376)	81.3 (312/384)
MSSA	82.2 (171/208)	80.6 (187/232)
MRSA	84.4 (146/173)	81.5 (128/157)
Staphylococcus lugdunensis	90.9 (10/11)	66.7 (2/3)
Streptococcus anginosus group[a]	80.8 (84/104)	72.0 (59/82)
Streptococcus pyogenes	70.0 (28/40)	73.5 (25/34)
Enterococcus faecalis	94.4 (17/18)	84.0 (21/25)
Gram negative, % (n/N)		
Enterobacter cloacae	87.5 (7/8)	100.0 (7/7)
Klebsiella pneumoniae	72.7 (8/11)	54.5 (6/11)

micro-mITT, microbiological modified intent-to-treat; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus*; PTE, post-treatment evaluation.

Microbiological modified intent-to-treat population included all patients in the modified intent-to-treat population (randomized patients without solely Gram-negative ABSSSI pathogens at baseline) who had a causative pathogen or pathogens identified at baseline from culture of a respiratory specimen or blood or with the use of a culture-independent method.

[a] *S anginosus* group includes *S anginosus*, *S intermedius*, and *S constellatus*.

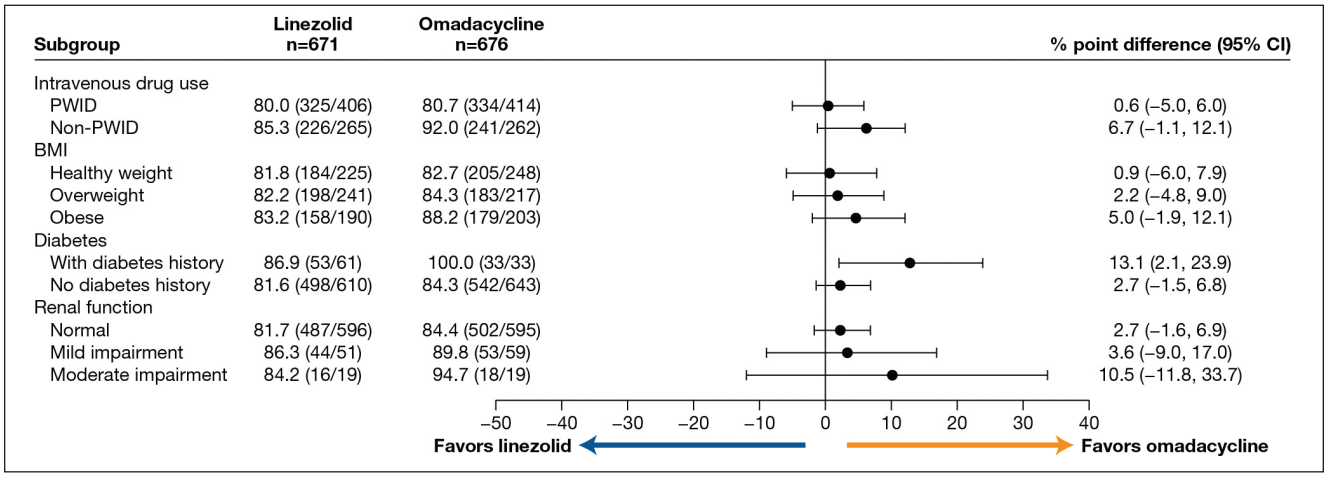
Efficacy

Omadacycline showed a non-inferior early and late response compared with those treated with moxifloxacin. Early response was seen in 82% to 83% of the overall patient population, and 85% to 88% had clinical success at the late response (**FIGURE 2**). Similar to the skin infection studies, additional analyses for disease severity and infection and patient types were conducted, which were consistent with the primary analysis demonstrating similar and high rates for early response that was then maintained through the late response assessment. For this review, only the late response is illustrated, to demonstrate the durability of the response.

Subgroup analysis showed similar outcomes for the 2 treatments across age group, biological sex, disease severity (PSI risk classes), diabetes history, BMI, and renal function (**FIGURE 6**). In addition, for patients with ≥1 comorbidity and eligible for treatment as an outpatient (based on PSI score), similar outcomes were also observed (**FIGURE 7**).

When evaluated by pathogen, both treatments showed high rates of late response against common pneumonia pathogens and atypical pathogens, including resistant strains (**TABLE 4**). Late response against resistant

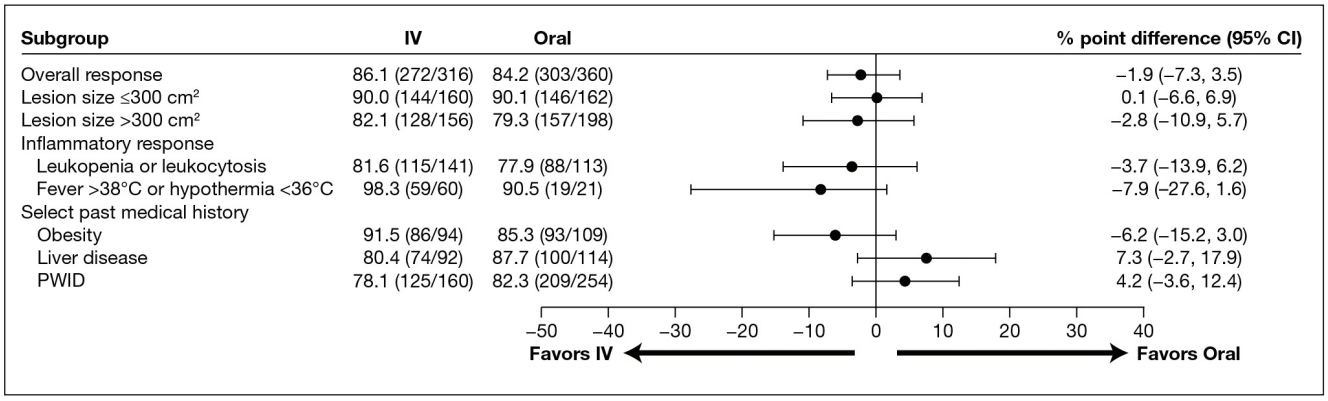
FIGURE 4. Late response (PTE) by subgroups pooled across the bacterial skin infection studies (mITT populations)[20-22]



BMI, body mass index.

BMI categories were defined as healthy weight: BMI 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2, obese: ≥30 kg/m^2. Renal function categories were defined as normal: >89 mL/min, mild impairment: >60–89 mL/min, moderate impairment: >30–60 mL/min. Data are presented as % (n/N).

FIGURE 5. Late response (PTE) for IV-to-oral and oral-only formulations of omadacycline by subgroups in bacterial skin infection studies (mITT population)[31]



CI, confidence interval; IV, intravenous; mITT, modified intent-to-treat; PTE, post-treatment evaluation; PWID, person who injects drugs.

Obesity was defined as body mass index ≥30 kg/m². Leukopenia/leukocytosis was defined as white blood cell count ≤4000 or ≥10,000 cells/μL. Liver disease was defined as a medical history of any hepatitis B, any hepatitis C, hepatic steatosis, alcoholic liver disease, hepatic cirrhosis, non-alcoholic steatohepatitis, or hepatic failure. Data are presented as % (n/N).

S pneumoniae strains ranged from 86% to 100% for omadacycline, and from 77% to 100% for moxifloxacin. Overall, 92% of omadacycline and moxifloxacin recipients achieved late response against atypical bacteria, including *Mycoplasma pneumoniae, Legionella pneumophila*, and *Chlamydophila pneumoniae*.

Safety

The most frequently reported adverse event across the 2 indications was nausea, occurring in 2% to 22% of omadacycline recipients vs 5% to 9% of comparator (linezolid/moxifloxacin) recipients (**TABLE 5**). Higher rates of vomiting were also seen in the omadacycline group (3% to 11%) than the comparator group (2% to 4%). The nausea and vomiting in the omadacycline group were predominantly associated with the 450 mg loading in the first 2 days of the oral-only OASIS-2 study, with similar nausea and vomiting rates to comparators seen in the OASIS-1 and OPTIC studies (IV start). Very few patients discontinued due to gastrointestinal adverse events (≤2 patients per treatment group in any of the studies). Overall study discontinuation rates were 1.7% and 1.5% for omadacycline and linezolid, respectively, in the skin infection studies, and 5.5% and 7.0% for omadacycline and moxifloxacin, respectively, in the pneumonia study. Death occurred in 1 (0.1%) omadacycline-treated patient and 3 (0.4%) linezolid-treated patients in the pooled skin trials, and 8 (2%) omadacycline-treated patients and 4 (1%) moxifloxacin-treated patients in the pneumonia study. No cases of CDI were reported in the omadacycline or linezolid groups in any of the studies, whereas 8 (2%) cases were reported in the moxifloxacin group in the pneumonia study.

DISCUSSION

All 3 phase 3 studies demonstrated non-inferiority of omadacycline compared with linezolid and moxifloxacin in patients with skin infections and pneumonia, respectively. High rates of early and late response were seen across a range of comorbidities, sex, age groups, disease severity, and renal function levels, indicating consistency of outcomes across all patient types examined. At the pathogen level, omadacycline demonstrated efficacy against common causative pathogens of skin infections and pneumonia, as well as resistant strains and atypical pathogens.

An important finding of these studies was the high rates of early response, including in patients with comorbidities. This early response shows high concordance with late response findings for omadacycline,[19] providing a key time point at 2 to 3 days after therapy start by which clinicians can expect to see signs of a positive clinical outcome in most patients. The oral-only formulation of omadacycline provides the option of outpatient treatment where appropriate. Many patients with comorbidities, particularly older patients, have limited treatment options for bacterial infections and require dose adjustments for other antibiotics, which may alter treatment effectiveness.[23,24] Furthermore, these patients often take multiple medications, increasing the potential for DDIs. Omadacycline has few DDIs, and this, coupled with the fact that no omadacycline dose reductions are needed in patients

TABLE 3. Baseline characteristics in the pneumonia study (ITT population)[6]

Characteristic	Omadacycline (n=386)	Moxifloxacin (n=388)
Age, median (range), y	61 (19–97)	63 (19–94)
>65 years	39.4 (152)	44.3 (172)
>75 years	19.4 (75)	21.4 (83)
Body mass index, mean (range), kg/m^2	27 (16–51)	27 (13–55)
Sex		
Female	46.1 (178)	43.6 (169)
Male	53.9 (208)	56.4 (219)
Race		
White	92.2 (356)	91.5 (355)
Black	2.8 (11)	1.8 (7)
Asian	4.4 (17)	4.6 (18)
Other	0.5 (2)	2.1 (8)
PSI risk class[a]		
II	14.2 (55)	13.9 (54)
III	58.8 (227)	55.7 (216)
IV	26.4 (102)	29.6 (115)
CURB score		
0	32.6 (126)	31.2 (121)
1	53.6 (207)	54.1 (210)
2	13.5 (52)	13.7 (53)
3	0.3 (1)	1.0 (4)
Past medical history		
Mild-to-moderate COPD	14.8 (57)	13.1 (51)
Symptomatic asthma with wheezing	4.7 (18)	5.2 (20)
Mild renal impairment (>50 to 80 mL/min)	33.2 (128)	30.7 (119)
Moderate renal impairment (>30 to 50 mL/min)[b]	18.4 (71)	16.0 (62)
Diabetes mellitus	16.3 (63)	18.3 (71)
Hypertension	49.5 (191)	50.3 (195)
Atrial fibrillation	10.1 (39)	9.0 (35)
Coronary artery disease	9.1 (35)	8.5 (33)
Smoking history		
Current smoker	27.2 (105)	21.1 (82)
Past smoker	19.7 (76)	20.4 (79)
Multilobar infiltrates	24.1 (93)	29.1 (113)
Pleural effusion	15.5 (60)	16.8 (65)
Bacteremia	3.9 (15)	4.6 (18)

[a] Patients with PSI risk class I and V were excluded from the study. PSI risk classes are calculated based on a multi-point assessment of physical findings, laboratory findings, comorbidities, and age factors. In brief, PSI II indicates patient suitable for outpatient treatment; III indicates brief inpatient observation should be considered; and IV indicates the patient requires hospitalization.

[b] Includes 1 patient in the omadacycline group who had severe renal impairment (<30 mL/min). Per study protocols, patients with severe impairment were excluded from participation.

Data presented as % (n) unless otherwise indicated.

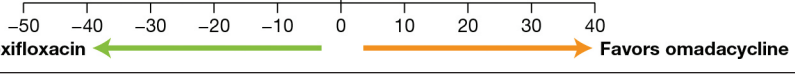
with comorbidities and obesity,[9,17,21,25] indicates that omadacycline could be particularly suitable for older adults and those with multiple comorbidities, who may presently have limited treatment options available for skin infection or pneumonia. Additionally, the once-daily dosing regimen (**TABLE 6**) can aid with treatment adherence, particularly in patient groups who often have poor therapy adherence or who have to manage multiple medication dosing schedules.[26] Finally, the clinical efficacy against a broad range of pathogens indicates the suitability of omadacycline as a monotherapy, thus contributing to antibiotic stewardship by reducing the use of multiple antibiotics and potential for development of drug resistance.[27]

Omadacycline was well tolerated in clinical studies, with gastrointestinal side effects generally associated with the oral loading dose and mostly tolerable: only one patient in each trial stopped treatment because of nausea and vomiting side effects. Given that gastrointestinal adverse effects were lower with the IV vs oral loading dose, preferential use of an IV loading dose might mitigate nausea or vomiting. An additional potential benefit of omadacycline is the low risk of CDI observed in the studies compared with other drug classes commonly used to treat skin infections or pneumonia, particularly for patients at higher risk for CDI, such as patients >65 years or those with renal impairment.[28,29] Multiple studies have indicated that tetracycline-class drugs in general are associated with a low risk of developing CDI, and therefore should be considered as an option for patients at higher risk for developing CDI.[11-14,30]

The main strengths of these studies were the extensive testing for pathogens and consistent results across subgroups of patients, including patients with large lesion sizes (skin infection studies), increased disease severity (pneumonia study), and comorbidities including renal impairment, diabetes, and obesity. In addition, although OPTIC enrolled inpatients with pneumonia, IDSA/ATS guidelines note that the evidence from inpatients with pneumonia covers

FIGURE 6. Late response (PTE) in the overall population and by subgroups in the bacterial pneumonia study (ITT population)[6,20,22,25,32]

Subgroup	Moxifloxacin n=388	Omadacycline n=386	% point difference (95% CI)
Overall	85.1 (330/388)	87.6 (338/386)	2.5 (–2.4, 7.4)
Age			
<65 years	85.9 (176/205)	88.3 (197/223)	2.5 (–3.9, 9.0)
≥65 years	84.2 (154/183)	86.5 (141/163)	2.4 (–5.3, 9.9)
≥75 years	81.8 (72/88)	89.4 (76/85)	7.6 (–3.1, 18.4)
Sex			
Female	89.9 (152/169)	84.3 (150/178)	–5.7 (–12.9, 1.5)
Male	81.3 (178/219)	90.4 (188/208)	9.1 (2.5, 15.8)
Past medical history			
Asthma/COPD	84.8 (56)	81.1 (60)	–3.8 (–16.4, 9.2)
Diabetes	87.3 (62/71)	88.5 (53/62)	–1.8 (–14.4, 10.1)
Heart disease	93.0 (80/86)	91.4 (85/93)	–1.6 (–10.1, 6.9)
BMI			
Healthy weight	88.6 (124/140)	83.6 (117/140)	–5.0 (–13.3, 3.2)
Overweight	80.7 (109/135)	90.2 (120/133)	9.5 (1.1, 18.1)
Obese	86.1 (93/108)	88.5 (92/104)	2.4 (–6.9, 11.6)
Renal function			
Normal	85.0 (176/207)	90.2 (185/205)	5.2 (–1.2, 11.7)
Mild impairment	83.3 (85/102)	89.2 (83/93)	5.9 (–4.0, 15.8)
Moderate impairment	87.3 (69/79)	80.5 (70/87)	–6.9 (–18.2, 4.6)
Severity			
CURB-65 score			
<2	85.6 (220/257)	90.2 (248/275)	4.6 (–1.0, 10.3)
≥2	84.0 (110/131)	81.1 (90/111)	–2.9 (–12.8, 6.7)
PSI risk class			
II	83.9 (47/56)	82.5 (47/57)	–1.5 (–15.7, 12.8)
III	88.0 (190/216)	90.7 (206/227)	2.8 (–3.0, 8.7)
IV	80.2 (93/116)	83.3 (85/102)	3.2 (–7.4, 13.4)

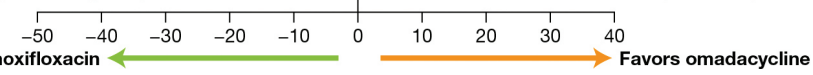


PSI, Pneumonia Severity Index.

Heart disease was defined as a medical history of coronary artery disease, cardiomyopathy, hypertensive heart disease, left ventricular failure, left ventricular hypertrophy, or myocardial fibrosis. BMI categories were defined as healthy weight: BMI 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2, obese: ≥30 kg/m^2. Renal function categories were defined as normal: >89 mL/min, mild impairment: >60–89 mL/min, moderate impairment: >30–60 mL/min. Includes 1 patient in the omadacycline group who had severe renal impairment (<30 mL/min). Per study protocols, patients with severe impairment were excluded from participation. Data are presented as % (n/N).

FIGURE 7. Late response (PTE) in patients with Pneumonia Severity Index risk class II or III, and ≥1 comorbidity (ITT population)[33]

Subgroup	Moxifloxacin n=222	Omadacycline n=237	% point difference (95% CI)
Patients with PSI II/III and ≥1 comorbidity	87.4 (194/222)	89.1 (213/237)	1.7 (–4.2, 7.8)
≥2 comorbidities	90.4 (66/73)	93.2 (69/74)	2.8 (–6.7, 12.7)
Select past medical history			
Chronic heart disease	94.9 (56/59)	93.0 (53/57)	–1.9 (–12.4, 8.0)
Diabetes	92.5 (37/40)	87.8 (36/41)	–4.7 (–19.4, 9.6)
Asthma/COPD	88.6 (39/44)	88.3 (53/60)	–0.3 (–12.9, 13.9)
Renal Impairment			
Overall	89.0 (89/100)	84.9 (90/106)	–4.1 (–13.6, 5.4)
Mild	87.7 (57/65)	86.8 (59/68)	–0.9 (–12.8, 11.1)
Moderate	91.4 (32/35)	81.6 (31/38)	–9.8 (–26.5, 6.8)



COPD, chronic obstructive pulmonary disease; ITT, intent-to-treat; PTE, post-treatment evaluation.

Comorbidities included in the analysis were liver disease (any hepatitis B, any hepatitis C, hepatic steatosis, alcoholic liver disease, hepatic cirrhosis, non-alcoholic steatohepatitis, or hepatic failure); heart disease (coronary artery disease, cardiomyopathy, hypertensive heart disease, left ventricular failure, left ventricular hypertrophy, or myocardial fibrosis); renal impairment, creatinine clearance <89 mL/min (mild impairment: >60–89 mL/min, moderate impairment: >30–60 mL/min); asthma (bronchospasm and obstruction, or emphysema); and any history of diabetes mellitus (type 1 or 2). Liver disease was not included on the graph due to small sample size (clinical success: 5/5 omadacycline, 4/6 moxifloxacin). Data are presented as % (n/N).

TABLE 4. Late response (PTE) by pathogen in the pneumonia study (micro-mITT population)[6]

Baseline pathogen, % (n/N)	Omadacycline (n=204)	Moxifloxacin (n=182)
Gram-positive bacteria (aerobes)	85.2 (52/61)	87.5 (49/56)
Streptococcus pneumoniae	86.0 (37/43)	91.2 (31/34)
Penicillin-susceptible[a]	88.5 (23/26)	95.5 (21/22)
Macrolide-resistant[a]	100 (10/10)	100 (5/5)
Tetracycline-resistant[a]	87.5 (14/16)	76.5 (13/17)
Staphylococcus aureus[b]	72.7 (8/11)	81.8 (9/11)
Gram-negative bacteria (aerobes)	84.8 (67/79)	81.2 (56/69)
Haemophilus influenzae	81.3 (26/32)	100.0 (16/16)
Haemophilus parainfluenzae	83.3 (15/18)	76.5 (13/17)
Klebsiella pneumoniae	76.9 (10/13)	84.6 (11/13)
Atypical bacteria[c]	92.4 (109/118)	91.5 (97/106)
Mycoplasma pneumoniae	94.3 (66/70)	87.7 (50/57)
Legionella pneumophila	94.6 (35/37)	97.3 (36/37)
Chlamydophila pneumoniae	89.3 (25/28)	89.3 (25/28)

micro-mITT, microbiological modified intent-to-treat.

Percentages were based on the number of patients with the specified baseline pathogen.

Patients with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Patients were counted only once in the overall tabulations for Gram-positive bacteria (aerobes), Gram-negative bacteria (aerobes), and atypical bacteria if they had >1 respective pathogen at baseline.

[a] Resistance was defined in accordance with Clinical Laboratory Standards Institute document M100-S25.
[b] Methicillin resistance was observed in only 1 *S aureus* isolate in the moxifloxacin group.
[c] For identification by serology, considers an indeterminate or positive convalescent serology result as positive. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were identified by serology only. *Legionella pneumophila* may have been identified by culture, serology, or urinary antigen.

TABLE 5. Safety summary from phase 3 studies adverse events occurring in ≥2% of patients treated with omadacycline (safety populations)[4]

	Pooled OASIS studies in skin infection		OPTIC study in pneumonia	
Patients with adverse event, % (n)	Omadacycline (n=691)	Linezolid (n=689)	Omadacycline (n=382)	Moxifloxacin (n=388)
Nausea[a]	21.9 (151)	8.7 (60)	2.4 (9)	5.4 (21)
Vomiting	11.4 (79)	3.9 (27)	2.6 (10)	1.5 (6)
Infusion-site reactions[b]	5.2 (36)	3.6 (25)	1.0 (4)	0.8 (3)
ALT increased	4.1 (28)	3.6 (25)	3.7 (14)	4.6 (18)
AST increased	3.6 (25)	3.5 (24)	2.1 (8)	3.6 (14)
Headache	3.3 (23)	3.0 (21)	2.1 (8)	1.3 (5)
Diarrhea[c]	3.2 (22)	2.9 (20)	1.0 (4)	8.0 (31)
Constipation	1.0 (7)	0.7 (5)	2.4 (9)	1.5 (6)
Hypertension	0.9 (6)	0.7 (5)	3.4 (13)	2.8 (11)
GGT increased	0.7 (5)	1.2 (8)	2.6 (10)	2.1 (8)
Insomnia	0.6 (4)	0.9 (6)	2.6 (10)	2.1 (8)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

[a] Nausea and vomiting were more common with OASIS-2 (omadacycline: 30% [111], linezolid: 17% [62]), compared with OASIS-1 (omadacycline: 12% [40], linezolid: 5% [17]). Nausea was mild to moderate and lasted a median of 2 days, aligning with receipt of the oral loading dose in OASIS-2. One patient in each trial discontinued treatment with omadacycline due to nausea and vomiting.

[b] Infusion-site extravasation, pain, erythema, swelling, inflammation, irritation, peripheral swelling, and skin induration.

[c] *Clostridioides difficile* (reported as *C difficile* infection, *C difficile* colitis, or pseudomembranous colitis) was reported in no omadacycline or linezolid patients and 2.1% (8) moxifloxacin patients.

more severe disease and a broader range of pathogens and therefore can be reasonably applied to outpatient treatment as well. Limitations of the skin infection studies were the exclusion of certain groups of patients (eg, those with chronic skin infections, based on regulatory guidance), and the studies were not powered to assess non-inferiority in subgroups. Limitations of the pneumonia study were exclusion of those with the most severe pneumonia often necessitating care in the intensive care unit (PSI risk class V), outpatient-treated patients, and immunocompromised patients. The disproportionate enrollment of white compared to non-white patients was another limitation across all studies.

Overall, across the phase 3 clinical development program, omadacycline demonstrated high rates of clinical response and was well tolerated in patients with skin infections or pneumonia, with a substantial proportion of patients achieving early responses, within 2 to 3 days of the first dose, that were durable through the late response time point. Efficacy and safety were similar across subgroups of patients, including those with comorbidities, as well as by biological sex, age group, BMI class, renal function, and disease severity.

TABLE 6. Omadacycline dosing for adults with ABSSSI and CABP[4]

Infection	Loading doses	Maintenance dose
ABSSSI[a]	Oral: Day 1 and Day 2: 450 mg once daily IV: 200 mg over 60 minutes OR 100 mg over 30 minutes twice	Oral: 300 mg once daily IV: 100 mg over 30 minutes once daily
CABP[b]	Oral: Day 1: 300 mg twice[c] IV: Day 1: 200 mg over 60 minutes OR 100 mg over 30 minutes twice	Oral: 300 mg once daily IV: 100 mg over 30 minutes once daily

[a] Indicated for adults with acute bacterial skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus anginosus* grp. (includes *S anginosus*, *S intermedius*, and *S constellatus*), *Enterococcus faecalis, Enterobacter cloacae*, and *Klebsiella pneumoniae*.

[b] Indicated for adults with community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae*, *S aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *H parainfluenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*.

[c] Oral-only CABP regimen was approved outside of the Phase 3 pivotal trials.

REFERENCES

1. Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008-2014. *BMC Health Serv Res*. 2018;18(1):715. doi: 10.1186/s12913-018-3529-4
2. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. *PLoS One*. 2015;10(11):e0143276. doi: 10.1371/journal.pone.0143276
3. Kaye KS, Petty LA, Shorr AF, Zilberberg MD. Current epidemiology, etiology, and burden of acute skin infections in the United States. *Clin Infect Dis*. 2019;68(Suppl 3):S193-S199. doi: 10.1093/cid/ciz002
4. Paratek Pharmaceuticals. NUYZRA (omadacycline) Prescribing Information. May 2021. Accessed March 17, 2021. https:www.nuzyra.com/nuzyra-pi.pdf
5. O'Riordan W, Green S, Overcash JS, et al. Omadacycline for acute bacterial skin and skin-structure infections. *N Engl J Med*. 2019;380(6):528-538. doi: 10.1056/NEJMoa1800170
6. Stets R, Popescu M, Gonong JR, et al. Omadacycline for community-acquired bacterial pneumonia. *N Engl J Med*. 2019;380(6):517-527. doi: 10.1056/NEJMoa1800201
7. O'Riordan W, Cardenas C, Shin E, et al. Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial. *Lancet Infect Dis*. 2019;19(10):1080-1090. doi: 10.1016/s1473-3099(19)30275-0
8. Macone AB, Caruso BK, Leahy RG, et al. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. *Antimicrob Agents Chemother*. 2014;58(2):1127-1135. doi: 10.1128/aac.01242-13
9. Berg JK, Tzanis E, Garrity-Ryan L, et al. Pharmacokinetics and safety of omadacycline in subjects with impaired renal function. *Antimicrob Agents Chemother*. 2018;62(2) :e02057-17. doi: 10.1128/aac.02057-17
10. Flarakos J, Du Y, Gu H, et al. Clinical disposition, metabolism and in vitro drug-drug interaction properties of omadacycline. *Xenobiotica*. 2017;47(8):682-696. doi: 10.1080/00498254.2016.1213465
11. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *Antimicrob Agents Chemother*. 2013;57(5):2326-2332. doi: 10.1128/aac.02176-12
12. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother*. 2013;68(9):1951-1961. doi: 10.1093/jac/dkt129
13. Tariq R, Cho J, Kapoor S, et al. Low risk of primary *Clostridium difficile* infection with tetracyclines: a systematic review and metaanalysis. *Clin Infect Dis*. 2018;66(4):514-522. doi: 10.1093/cid/cix833
14. Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(4):881-891. doi: 10.1093/jac/dkt477
15. Abrahamian FM, Sakoulas G, Tzanis E, et al. Omadacycline for acute bacterial skin and skin structure infections. *Clin Infect Dis*. 2019;69(Suppl 1):S23-S32. doi: 10.1093/cid/ciz396
16. Karlowsky JA, Steenbergen J, Zhanel GG. Microbiology and preclinical review of omadacycline. *Clin Infect Dis*. 2019;69(Suppl 1):S6-S15. doi: 10.1093/cid/ciz395
17. Rodvold KA, Pai MP. Pharmacokinetics and pharmacodynamics of oral and intravenous omadacycline. *Clin Infect Dis*. 2019;69(Suppl 1):S16-S22. doi: 10.1093/cid/ciz309
18. Opal S, File TM, van der Poll T, Tzanis E, Chitra S, McGovern PC. An integrated safety summary of omadacycline, a novel aminomethylcycline antibiotic. *Clin Infect Dis*. 2019;69(Suppl 1):S40-S47. doi: 10.1093/cid/ciz398
19. Ramirez JA, Tzanis E, Curran M, et al. Early clinical response in community-acquired bacterial pneumonia: from clinical endpoint to clinical practice. *Clin Infect Dis*. 2019;69(Suppl 1):S33-S39. doi: 10.1093/cid/ciz397
20. Sakoulas G, Eckburg PB, Amodio-Groton M, et al. Clinical efficacy of patients with secondary bacteremia treated with omadacycline: results from phase 3 acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia studies. *Open Forum Infect Dis*. 2021;8(6):ofab136. doi: 10.1093/ofid/ofab136
21. Pai MP, Wilcox MH, Chitra S, McGovern PC. Safety and efficacy of omadacycline by BMI categories and diabetes history in two phase III randomized studies of patients with acute bacterial skin and skin structure infections. *J Antimicrob Chemother*. 2021;76(5):1315-1322. doi: 10.1093/jac/dkaa558
22. Cornely OA, File TM, Garrity-Ryan L, Chitra S, Noble R, McGovern PC. Safety and efficacy of omadacycline for treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections in patients with mild-to-moderate renal impairment. *Int J Antimicrob Agents*. 2021;57(2):106263. doi: https://doi.org/10.1016/j.ijantimicag.2020.106263
23. Pulido-Cejudo A, Guzman-Gutierrez M, Jalife-Montano A, et al. Management of acute bacterial skin and skin structure infections with a focus on patients at high risk of treatment failure. *Ther Adv Infect Dis*. Sep 2017;4(5):143-161. doi:10.1177/2049936117723228
24. Giarratano A, Green SE, Nicolau DP. Review of antimicrobial use and considerations in the elderly population. *Clin Interv Aging*. 2018;13:657-667. doi:10.2147/CIA.S133640
25. Pai MP, Wilcox M, Chitra S, McGovern P. Safety and efficacy of omadacycline by body mass index in patients with community-acquired bacterial pneumonia: subanalysis from a randomized controlled trial. *Respir Med*. 2021;184:106442. doi: 10.1016/j.rmed.2021.106442
26. Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. Im-

pact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. *Patient Prefer Adherence*. 2013;7:419-434. doi: 10.2147/ppa.S44646

27. Centers for Disease Control and Prevention (CDC). The core elements of hospital antibiotic stewardship programs. 2019. Accessed May 2, 2022. https://www.cdc.gov/antibiotic-use/core-elements/hospital.html
28. Furuya-Kanamori L, Stone JC, Clark J, et al. Comorbidities, exposure to medications, and the risk of community-acquired *Clostridium difficile* infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2015;36(2):132-141. doi: 10.1017/ice.2014.39
29. Garey KW, Dao-Tran TK, Jiang ZD, Price MP, Gentry LO, Dupont HL. A clinical risk index for *Clostridium difficile* infection in hospitalised patients receiving broad-spectrum antibiotics. *J Hosp Infect.* 2008;70(2):142-147. doi: 10.1016/j.jhin.2008.06.026
30. Garey KW, Rose W, Gunter K, Serio AW, Wilcox MH. Omadacycline and *Clostridioides difficile*: a systematic review of preclinical and clinical evidence. *Ann Pharmacol*. In press.
31. Warren N, Yashayev R, Rodriguez G. Clinical response to intravenous versus oral treatment in patients with acute bacterial skin and skin structure infections (ABSSSI). Presented at: 24th Annual MAD-ID Meeting; 2022; Orlando, FL.
32. Torres A, Garrity-Ryan L, Kirsch C, et al. Omadacycline vs moxifloxacin in adults with community-acquired bacterial pneumonia. *Int J Infect Dis*. 2021;104:501-509. doi: 10.1016/j.ijid.2021.01.032
33. Warren N, Yashayev R, Chitra S, Amodio-Groton M, Wright K, Rodriguez G. Omadacycline in the treatment of community-acquired bacterial pneumonia (CABP) in patients with comorbidities. Presented at: 24th Annual MAD-ID Meeting; 2022; Orlando, FL.

Plain Language Summary

Omadacycline: An oral antibiotic for the treatment of bacterial skin infections and pneumonia in an era of unmet clinical need

This plain language summary reviews **O**madacycline in **A**cute Bacterial **S**kin and Skin Structure **I**nfections **S**tudy (OASIS)-1 and is intended for healthcare professionals working in a family practice setting. It is based on a supplement to *The Journal of Family Practice* and the linked article, below. Clinicians may wish to share and discuss this information with patients, as appropriate.

Linked article: O'Riordan W, Green S, Overcash JS, et al. Omadacycline for acute bacterial skin and skin-structure infections (OASIS-1). *N Engl J Med*. 2019;380:528–538. doi: 10.1056/NEJMoa1800170

The once-daily intravenous (IV) and oral tetracycline antibiotic omadacycline is similar in efficacy to linezolid, an approved treatment twice daily, for treating acute bacterial skin infections in adults.

Acute bacterial skin and skin structure infections (ABSSSI) include abcesses, cellulitis, erysipelas, and infected wounds. These infections place a huge burden on patients and are estimated to cause over 800,000 hospitalizations each year in the United States.[1]

Use of effective oral antibiotics could help more patients to be treated at home by reducing the need for hospitalization for administration of IV antibiotics.[2,3]

Why was this study done?

OASIS-1 looked at whether IV-to-oral omadacycline was similar in efficacy and safety to linezolid for treating acute bacterial skin infections in adults. This is a standard way to establish safety and efficacy of a drug. OASIS-1 was not designed to show which antibiotic was the best. In this study patients could switch from IV to oral omadacycline or oral linezolid after 3 days, and the total duration of treatment was 7–14 days.

Study sites	Study duration	Patients
55	June 2015 to May 2016	655 adults with acute bacterial skin infections

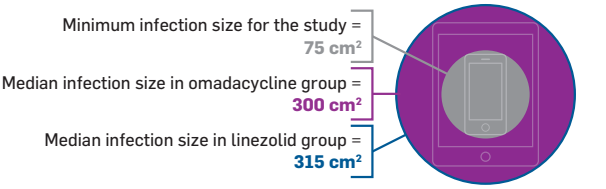
What care did patients get?

Patients received either omadacycline or linezolid (all treatment doses looked identical to doctors and patients).

Omadacycline is a treatment for acute bacterial skin infections in adults, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[4] Omadacycline is now FDA approved for use either orally or by IV infusion.[4] At the time of the study, it was only being used in clinical trials.	Linezolid is being used to treat acute bacterial skin infections (including those caused by MRSA). Linezolid was FDA approved at the time of the study. This made it a good comparator to omadacycline.
All patients received study treatment for 7–14 days.	
Patients on omadacycline received 100 mg IV every 12 hours for two doses, then 100 mg IV every day; at 3+ days, patients could be switched to oral omadacycline 300 mg once daily.[a]	Patients on linezolid received 600 mg IV every 12 hours; at 3+ days, patients could be switched to oral linezolid 600 mg twice daily. (600 mg [IV or oral] twice daily is the standard adult dosage for linezolid)
All patients had regular follow-up. In particular, doctors looked at **early clinical response** (**early response**) and **post-treatment evaluation** (**late response**).	

[a]When taking omadacycline tablets, patients should not eat or drink (except water) for at least 4 hours and then take the tablets with water. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours.

Key results of OASIS-1, a study comparing omadacycline and linezolid treatment in adults with acute bacterial skin infections



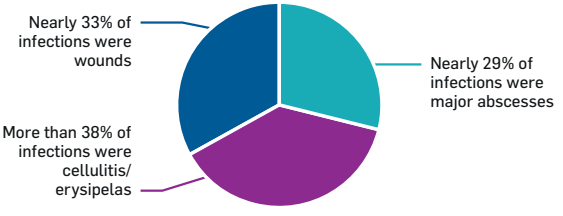
Who took part?

Omadacycline group		Linezolid group
323	Adults with wound infection, cellulitis, erysipelas, or abscess	322
48	Median age, years	46
63%	Male	66%
80	Median weight, kg	79
316	Patients with data for early response and late response	311

What were patients' signs and symptoms of infection?

Omadacycline group		Linezolid group
68%	*Staphylococcus aureus* was the most common bacteria found...	66%
30%	...including some MRSA infections	22%
19%	Fever	22%
45%	White blood cell counts ↑ or ↓	44%

There were roughly equal proportions of wounds, cellulitis/erysipelas, and abscesses



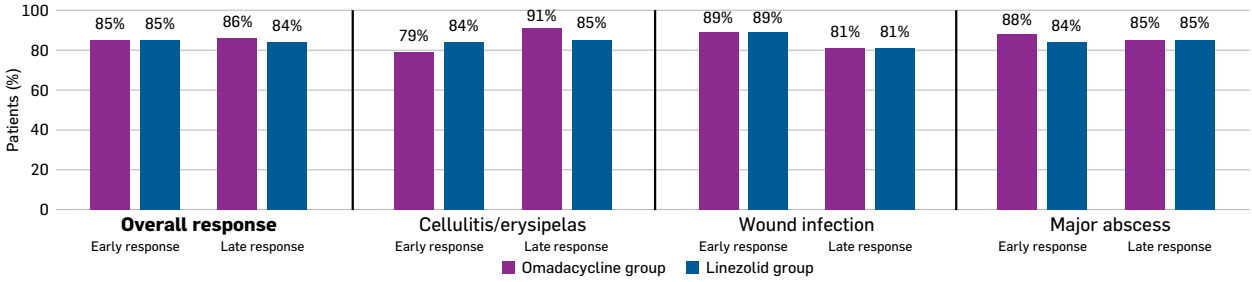
Omadacycline can work on certain bacteria that are resistant to other tetracycline antibiotics.[5] Antibiotic resistance can limit the use of older antibiotics for treating acute bacterial skin infections.[6]

Other studies have shown that omadacycline is a good antibiotic option for adults with community-acquired bacterial pneumonia and acute bacterial skin infections.[7,8] Of these, OASIS-2 demonstrated efficacy of oral-only omadacycline for acute bacterial skin infectons.[8]

What did the study show?

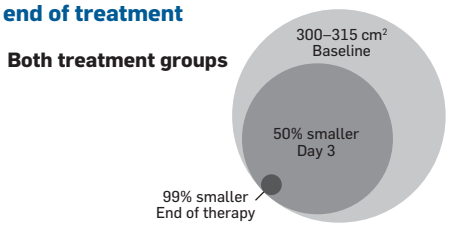
Patients with acute bacterial skin infections treated with omadacycline had similar efficacy to patients treated with linezolid

Overall clinical success and success by infection type

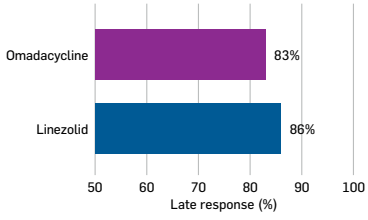


Early response was measured 2–3 days after first dose of study drug and late response 7–14 days after last dose of study drug.

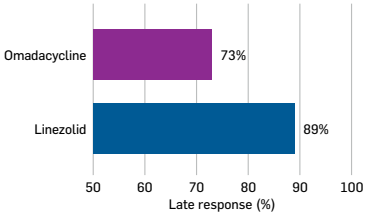
In both treatment groups, the size of the skin infections was reduced by approximately 50% on Day 3 and by approximately 99% at the end of treatment



Omadacycline eliminated 83% of MRSA infections



Omadacycline eliminated 73% of *S pyogenes* infections



Safety

Nausea and infusion-site extravasation were the most frequent adverse events after treatment in both groups.

- There was no *Clostridioides difficile* infection in either treatment group
- Nausea occurred in 12% of patients on omadacycline and 10% of patients on linezolid
- Serious adverse events occurred in 12 (3.7%) patients treated with omadacycline and 8 (2.5%) patients treated with linezolid
- There was 1 death (0.3%) reported in omadacycline-treated patients and 2 deaths (0.6%) reported in linezolid-treated patients

Adverse events in ≥4% of patients in either treatment group

	Omadacycline group (n=323)	Linezolid group (n=322)
Nausea	12% (40)	10% (32)
Infusion-site extravasation[a]	9% (28)	6% (19)
Subcutaneous abscess	5% (17)	6% (19)
Vomiting	5% (17)	5% (16)
Cellulitis	5% (15)	5% (15)
Headache	3% (10)	4% (13)
Alanine aminotransferase increased	3% (9)	4% (14)
Aspartate aminotransferase increased	3% (8)	4% (12)

[a]Events were reported as IV site infiltration and were typically caused by difficulty in finding reliable venous access sites in patients who injected drugs.

Take-away findings from OASIS-1

Omadacycline is a safe and effective option for the treatment of adult patients with acute bacterial skin infections caused by susceptible pathogens.

Potential benefits of omadacycline treatment include:

- Similar efficacy compared to linezolid
- Rapid improvement in skin infection
- Safety profile consistent with the tetracycline class of antibiotics:
  - A low risk of *Clostridioides difficile* infection
  - The most frequent adverse event was nausea
- Omadacycline may be given orally (tablets) or by IV infusion, and no dose adjustments are needed in any patients, including patients ≥65 years of age, or in patients with impaired hepatic or renal function[4]

Please see Full Prescribing Information for NUZYRA® (omadacycline).

References

1 Edelsberg J, Taneja C, Zervos M, et al. *Emerg Infect Dis*. 2009;15:1516-1518.
2. Falcone M, Concia E, Giusti M, et al. *Intern Emerg Med*. 2016;11:637-648.
3. Lane S, Johnston K, Sulham KA, et al. *Clin Ther*. 2016;38:531-544.
4. NUZYRA. Prescribing Information. Paratek Pharmaceuticals, Inc; 2021.
5. Villano S, Steenbergen J, Loh E, et al. *Future Microbiol*. 2016;11:1421-1434.
6. Chahine EB, Sucher AJ. Skin and soft tissue infections. In: Murphy JE, Lee MW, eds. *PSAP 2015 Book 1, Infectious Diseases*. American College of Clinical Pharmacy; 2015:1-27.
7. Stets R, Popescu M, Gonong JR, et al. *N Engl J Med*. 2019;380: 517-527.
8. O'Riordan W, Cardenas C, Shin E, et al. *Lancet Infect Dis*. 2019;19:1080-1090.

This plain language summary was prepared by Innovative Strategic Communications (Milford, PA). Medical writing and editorial assistance was funded by Paratek Pharmaceuticals, Inc. (King of Prussia, PA).

PARATEK

Plain Language Summary

Omadacycline: An oral antibiotic for the treatment of bacterial skin infections and pneumonia in an era of unmet clinical need

This plain language summary reviews **O**madacycline in **A**cute Bacterial **S**kin and Skin Structure **I**nfections **S**tudy (OASIS)-2 and is intended for healthcare professionals working in a family practice setting. It is based on a supplement to *The Journal of Family Practice* and the linked article, below. Clinicians may wish to share and discuss this information with patients, as appropriate.

Linked article: O'Riordan W, Cardenas C, Shin E, et al. Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial. *Lancet Infect Dis*. 2019;19:1080–1090. doi:10.1016/S1473-3099(19)30275-0

The once-daily oral tetracycline antibiotic omadacycline is similar in efficacy to linezolid, an approved treatment twice daily, for treating acute bacterial skin infections in adults.

Increasing numbers of patients are seeking care for acute bacterial skin and skin-structure infections (which include abscesses, cellulitis, erysipelas, and infected wounds) in outpatient settings, and hospital admissions for treatment of these infections are also increasing.[1]

Use of effective oral antibiotics could help more patients to be treated at home by reducing the need for hospitalization for administration of intravenous (IV) antibiotics.

Why was this study done?

OASIS-2 looked at whether once-daily oral omadacycline was similar in efficacy and safety to twice-daily oral linezolid for treating acute bacterial skin infections. This is a standard way to establish safety and efficacy of a drug. OASIS-2 was not designed to show which antibiotic was the best.

Study sites	Study duration	Patients
33	August 11, 2016 to June 6, 2017	735 adults with acute bacterial skin infections

What care did patients get?

Patients received either omadacycline or linezolid. All tablets and doses looked identical to doctors and patients.

Omadacycline is a treatment for acute bacterial skin infections in adults, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Omadacycline is now FDA-approved for use either orally or by intravenous infusion.[2] At the time of the study, it was only being used in clinical trials.	Linezolid is being used to treat acute bacterial skin infections, including those caused by MRSA. Linezolid was FDA approved at the time of the study. This made it a good comparator to omadacycline.

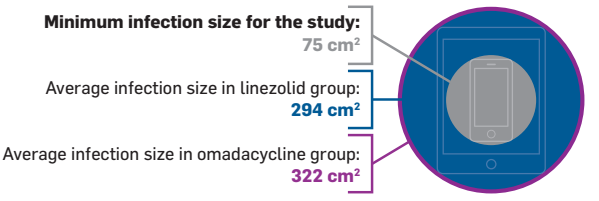
All patients in this trial were treated for 7 to 14 days.

On Days 1 and 2, patients on omadacycline took 450 mg; the remaining doses were 300 mg daily.[a] Patients on omadacycline took 2 doses each day, but 1 dose was a placebo.	Patients on linezolid took 600-mg doses, twice daily. This is standard treatment.

All patients had regular follow-up. In particular, doctors looked at **early clinical response (early response, 2–3 days after the first dose was taken)**, and **post-treatment evaluation (late response, 7–14 days after the last dose was taken)**.

[a]When taking omadacycline tablets, patients should not eat or drink (except water) for at least 4 hours and then take the tablets with water. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours.

Key results of OASIS-2, a study comparing oral omadacycline and linezolid treatment in adults with acute bacterial skin infections



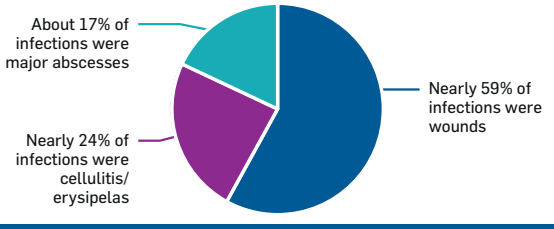
Who took part?

Omadacycline group		Linezolid group
368	Adults with wound infection, cellulitis, erysipelas, or abscess	367
41	Mean age, years	46
66%	Male	60%
79	Median weight, kg	76
360	Patients with data for early response and late response	360

What were patients' signs and symptoms of infection?

Omadacycline group		Linezolid group
80%	*Staphylococcus aureus* was the most common bacteria found...	81%
38%	...including some MRSA infections	37%
4%	Fever	3%
32%	White blood cell counts ↑ or ↓	38%

Over half the infections were wounds; nearly one-quarter were cellulitis/erysipelas



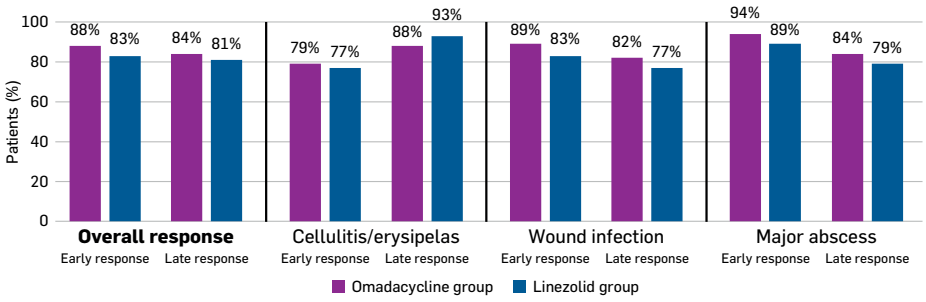
Omadacycline can work on certain bacteria that are resistant to other tetracycline antibiotics.[3] Antibiotic resistance can limit the use of older antibiotics for treating acute bacterial skin infections.[4]

Some other studies showed that omadacycline is a good antibiotic option for adults with acute bacterial skin infections treated in hospitals.[5] OASIS-2 was the first study of oral-only omadacycline.

What did the study show?

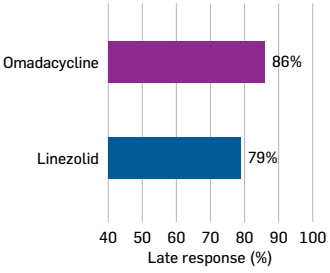
Omadacycline showed similar efficacy to linezolid at treating acute bacterial skin infections

Overall clinical success and success by infection type



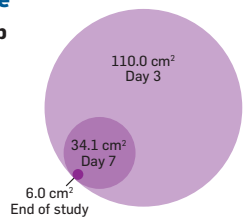
Early response was measured 2–3 days after first dose of study drug; late response was measured 7–14 days after last dose of study drug.

Omadacycline eliminated 86% of MRSA infections



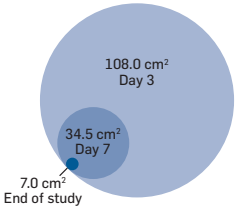
Infections were 66% smaller by Day 3, and 98% smaller at the end of the study with omadacycline

Omadacycline group



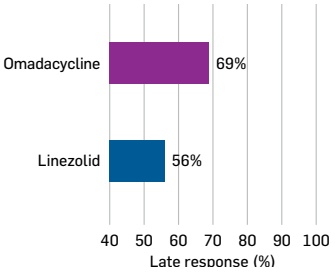
Average infection size at baseline: 322 cm²
66% smaller by Day 3 (110.0 cm²)
89% smaller by Day 7 (34.1 cm²)
98% smaller by end of study (6.0 cm²)

Linezolid group



Average infection size at baseline: 294 cm²
63% smaller by Day 3 (108.0 cm²)
88% smaller by Day 7 (34.5 cm²)
98% smaller by end of study (7.0 cm²)

Omadacycline eliminated 69% of *S pyogenes* infections



Safety

Nausea, vomiting, wound infection, and increased liver enzymes were the most frequent adverse events after treatment in both groups.

- Nausea occurred in 30% of patients on omadacycline and 8% of patients on linezolid
- Nausea usually happened on the first 2 days, when patients were taking higher doses of omadacycline, and rarely caused patients to stop taking omadacycline (1 person)
- Serious adverse events occurred in 5 (1%) patients treated with omadacycline and 5 (1%) patients treated with linezolid
- There were no deaths reported in omadacycline-treated patients and 1 death (<1%) reported in linezolid-treated patients

Adverse events in ≥4% of patients in either treatment group

	Omadacycline group (n=368)	Linezolid group (n=367)
Nausea[a]	30% (111)	8% (28)
Vomiting	17% (62)	3% (11)
Wound infection	6% (22)	5% (17)
Alanine aminotransferase increased	5% (19)	3% (11)
Aspartate aminotransferase increased	5% (17)	3% (12)
Diarrhea[b]	4% (15)	3% (10)
Headache	4% (13)	2% (8)

[a]Omadacycline, 75% mild, 25% moderate; linezolid, 86% mild, 14% moderate.
[b]No reports of *Clostridioides difficile* infection in either treatment group.

Take-away findings from OASIS-2

Omadacycline expands oral treatment options for acute bacterial skin infections caused by susceptible pathogens. Potential benefits include:

- Similar efficacy compared to linezolid
- Once-daily oral dosing, with no dose adjustments[2]
- Rapid improvement in skin infection
- Safety profile consistent with the tetracycline class of antibiotics:
  - A low risk of *Clostridioides difficile* infection
  - The most frequent adverse event was nausea
- Omadacycline may be given orally (tablets) or by IV infusion, and no dose adjustments are needed in any patients, including patients ≥65 years of age, or in patients with impaired hepatic or renal function[2]

Please see Full Prescribing Information for NUZYRA® (omadacycline).

References

1. Kaye KS, Patel DA, Stephens JM, et al. *PLoS One*. 2015;10:e0143276.
2. NUZYRA. Prescribing Information. Paratek Pharmaceuticals, Inc; 2021.
3. Villano S, Steenbergen J, Loh E. *Future Microbiol*. 2016;11:1421-1434.
4. Chahine EB, Sucher AJ. Skin and soft tissue infections. In: Murphy JE, Lee MW, eds. *PSAP 2015 Book 1, Infectious Diseases*. American College of Clinical Pharmacy; 2015:1-27.
5. O'Riordan W, Green S, Overcash JS, et al. *N Engl J Med*. 2019;380:528-538.

This plain language summary was prepared by Innovative Strategic Communications (Milford, PA). Medical writing and editorial assistance was funded by Paratek Pharmaceuticals, Inc (King of Prussia, PA).

PARATEK

Plain Language Summary

Omadacycline: An oral antibiotic for the treatment of bacterial skin infections and pneumonia in an era of unmet clinical need

This plain language summary reviews **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity (OPTIC) and is intended for healthcare professionals working in a family practice setting. It is based on a supplement to *The Journal of Family Practice* and the linked article, below. Clinicians may wish to share and discuss this information with patients, as appropriate.

Linked article: Stets R, Popescu M, Gonong JR, et al. Omadacycline for community-acquired bacterial pneumonia (OPTIC). *N Engl J Med*. 2019;380:517–527. doi: 10.1056/NEJMoa1800201.

The once-daily tetracycline antibiotic omadacycline is similar in efficacy to moxifloxacin, an approved once-daily treatment, for treating community-acquired bacterial pneumonia in adults.

Community-acquired pneumonia carries a heavy burden in the United States, with more than 1.5 million adults hospitalized each year,[1] and more than 10 million physician visits attributed to community-acquired pneumonia.[2] CABP refers to an acute bacterial infection of the lung (pulmonary parenchyma) and is acquired outside of the hospital.

Using effective oral antibiotics could help more patients be treated at home by reducing the need for hospitalization for administration of intravenous (IV) antibiotics.

Why was this study done?

OPTIC looked at whether IV-to-oral omadacycline was similar in efficacy and safety to moxifloxacin for treating CABP in adults. This is a standard way to establish safety and efficacy of a drug. OPTIC was not designed to show which antibiotic was the best. In this study, patients could switch from IV to oral treatment with omadacycline or moxifloxacin after 3 days, and the total duration of treatment was 7–14 days.

Study sites	Study duration	Patients
86	November 2015 to February 2017	774 adults with community-acquired bacterial pneumonia

What care did patients get?

Patients received either omadacycline or moxifloxacin (all treatment doses looked identical to doctors and patients).

Omadacycline	Moxifloxacin
Omadacycline is a treatment for adult patients with community-acquired bacterial pneumonia caused by bacteria including *Streptococcus pneumoniae*.[3] Omadacycline is now FDA approved for use either orally or by IV infusion.[3] At the time of the study, it was only being used in clinical trials.	Moxifloxacin is used to treat community-acquired pneumonia (including cases caused by multi-drug resistant *S pneumoniae*). Moxifloxacin was FDA approved at the time of the study. This made it a good comparator to omadacycline.
All patients received study treatment for 7–14 days.	
Patients on omadacycline received 100 mg IV every 12 hours for 2 doses, then 100 mg IV every day; after 3+ days, patients could be switched to oral omadacycline 300 mg once daily.[a]	Patients on moxifloxacin received 400 mg IV every day; after 3+ days, patients could be switched to oral moxifloxacin 400 mg once daily. (400 mg once daily [orally or IV] is the standard adult dose of moxifloxacin)
All patients had regular follow-up. In particular, doctors looked at **early clinical response (early response, 3–5 days after the first dose was taken)** and **post-treatment evaluation (late response, 5–10 days after the last dose was taken)**.	

[a]When taking omadacycline tablets patients should not eat or drink (except water) for at least 4 hours and then take the tablets with water. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours.

Key results of OPTIC, a study comparing omadacycline and moxifloxacin treatment in adults with community-acquired bacterial pneumonia

Who took part?

Omadacycline group		Moxifloxacin group
386	Adults with community-acquired bacterial pneumonia	388
61	Median age, years	63
54%	Male	56%
76	Median weight, kg	78

What clinical characteristics were seen in these patients?

Omadacycline group (n=386)		Moxifloxacin group (n=388)
27% / 20%	Current / past smoker	21% / 20%
12%	Previous lung infection	10%
15%	Mild-to-moderate COPD	13%
12%	Severe pneumonia, according to modified ATS criteria	14%

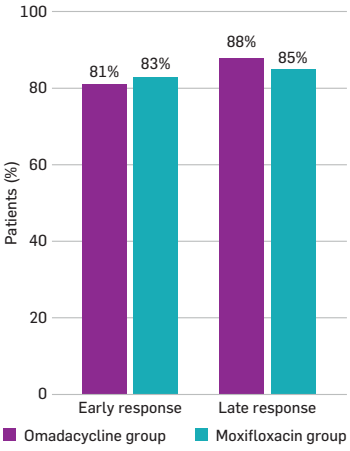
ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease.

Omadacycline can work on certain bacteria that are resistant to other tetracycline antibiotics.[3] Resistance to commonly used antibiotics has complicated the treatment of many bacterial infections, including pneumonia.[4,5]

Other studies have shown that omadacycline is a good antibiotic option for adults with acute bacterial skin infections treated in the community and in hospitals.[6,7] Of these, OASIS-2 was the first study of oral-only omadacycline.[7]

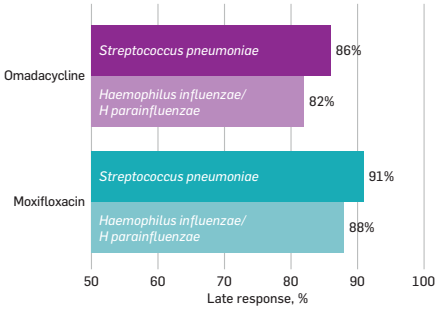
What did the study show?

Omadacycline had similar efficacy to moxifloxacin



A rapid and sustained response was seen in >80% of patients on omadacycline

The response seen with omadacycline was consistent across subgroups of patients categorized as being at lower/higher risk of death (Pneumonia Severity Index risk class II, III, or IV) and with pneumonia caused by different types of microorganisms (Gram-positive, Gram-negative, and atypical bacteria).



Early response was measured 3–5 days after first dose of study drug; late response was measured 5–10 days after last dose of study drug. Success at early response meant patients were living and had improvement in at least 2 symptoms and no worsening of symptoms, without rescue antibiotics. Success at late response meant patients infection was resolved or improved enough that further antibiotics weren't needed.

Patients with normalized vital signs at early response

Omadacycline group		Moxifloxacin group
82%	Heart rate	78%
97%	Temperature	96%
54%	Respiratory rate	57%
92%	Oxygen saturation	94%

Data represent the subset of patients who had abnormal vital signs at baseline.

Safety

The most frequent adverse events observed in omadacycline patients included increased liver enzymes, hypertension, insomnia, nausea and vomiting, constipation, and headache.

- Diarrhea was reported more frequently with moxifloxacin than with omadacycline. *Clostridioides difficile* infection was reported in no patients on omadacycline and in 8 patients (2%) on moxifloxacin
- Serious adverse events occurred in 23 (6%) patients treated with omadacycline and 26 (7%) patients treated with moxifloxacin
- There were 8 deaths (2%) that occurred in omadacycline-treated patients and 4 deaths (1%) in moxifloxacin-treated patients

Adverse events in ≥2% of patients in either treatment group

	Omadacycline group (n=382)	Moxifloxacin group (n=388)
Alanine aminotransferase increased	4% (14)	5% (18)
Hypertension	3% (13)	3% (11)
γ-glutamyltransferase increased	3% (10)	2% (8)
Insomnia	3% (10)	2% (8)
Vomiting	3% (10)	2% (6)
Constipation	2% (9)	2% (6)
Nausea	2% (9)	5% (21)
Aspartate aminotransferase increased	2% (8)	4% (14)
Headache	2% (8)	1% (5)
Diarrhea	1% (4)	8% (31)

Take-away findings from OPTIC

Omadacycline is a safe and effective option for the treatment of adult patients with community-acquired bacterial pneumonia caused by susceptible pathogens.

Potential benefits of omadacycline treatment include:

- Similar efficacy compared to moxifloxacin
- Rapid improvement in symptoms of pneumonia
- Safety profile consistent with the tetracycline class of antibiotics:
  - A low risk of *Clostridioides difficile* infection
  - The most frequent adverse event was alanine aminotransferase increased
- Omadacycline may be given orally (tablets) or by IV infusion, and no dose adjustments are needed in any patients, including those ≥65 years of age, or in patients with impaired hepatic or renal function[3]

Please see Full Prescribing Information for NUZYRA® (omadacycline).

References

1. Ramirez JA, Wiemken TL, Peyrani P, et al. *Clin Infect Dis*. 2017;65:1806-1812.
2. Park H, Adeyemi AO, Rascati KL. *Clin Ther*. 2015:37:1466-1476.
3. NUZYRA. Prescribing Information. Paratek Pharmaceuticals, Inc; 2021.
4. Gupta V, Yu KC, Schranz J, et al. *Open Forum Infect Dis*. 2021;8:ofab063.
5. Metlay JP, Waterer GW, Long AC, et al. *Am J Respir Crit Care Med*. 2019;200:e45-e67.
6. O'Riordan W, Green S, Overcash JS, et al. *N Engl J Med*. 2019;380:528-538.
7. O'Riordan W, Cardenas C, Shin E, et al. *Lancet Infect Dis*. 2019;19:1080-1090.

This plain language summary was prepared by Innovative Strategic Communications (Milford, PA). Medical writing and editorial assistance was funded by Paratek Pharmaceuticals, Inc. (King of Prussia, PA).

PARATEK

SUPPLEMENT TO
THE JOURNAL OF
FAMILY
PRACTICE®