SUPPLEMENT ARTICLE

Omadacycline: A Modernized Tetracycline

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When tetracyclines were introduced in the 1940s, these antibiotics offered a broad spectrum of activity against multiple types of pathogens. However, their utility waned after the selection of tetracycline resistance in the pathogens against which they were effective. Omadacycline is a semisynthetic aminomethylcycline antibacterial derived from the tetracycline class of antibiotics that is unaffected by these resistance mechanisms. It has an appropriate spectrum of activity for community-acquired infections, including those caused by many resistant organisms. Omadacycline offers a well-tolerated treatment for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Omadacycline has minimal known drug–drug interactions, and should be administered in a fasting state, avoiding dairy and cation-containing products for at least 4 hours after dosing. It does not require dose adjustments for sex, age, or hepatic or renal impairment, and has a safety profile similar to that of other oral tetracyclines. Because omadacycline can be administered effectively orally, it can help reduce hospitalization costs associated with intravenous antibiotic administration. This special supplement to *Clinical Infectious Diseases* offers an in-depth examination of omadacycline development, including discussions of pharmacokinetic and pharmacodynamic trials, spectrum of activity and preclinical data, early clinical trials, phase III clinical trials, and an integrated safety summary.

Keywords. acute bacterial skin and skin structure infections; community-acquired bacterial pneumonia; antibiotic; novel tetracycline; aminomethylcycline.

Tetracyclines are familiar drugs, first available in the late 1940s. When introduced, they featured a broad spectrum of activity against common pathogens that was recognized as one of their most important assets [1, 2]. However, over time, the continuous evolution of bacterial resistance greatly reduced their utility for many of the more clinically relevant pathogens that they once treated. New categories of tetracyclines have been developed to circumvent tetracycline-resistant pathogens, although these efforts have not produced new orally available agents since minocycline in the 1970s [1].

Efforts to develop new tetracyclines were eventually renewed, leading to the development and approval of tigecycline in 2006. Tigecycline was engineered to retain activity against organisms expressing tetracycline-specific mechanisms of resistance, restoring much of the spectrum of the class. However, low bioavailability limits tigecycline use to intravenous (IV) therapy, and a US Food and Drug Administration (FDA) black box warning of increased mortality in patients treated with tigecycline has discouraged widespread use. Furthermore, adverse events (AEs)

related to nausea and vomiting with tigecycline have been shown to be dose limiting [3].

The search for a well-tolerated, oral agent that is active against bacteria expressing tetracycline resistance led to the development of omadacycline. Omadacycline, a novel aminomethylcycline, was designed with modifications on the tetracycline D-ring that protect it from both active efflux and ribosomal modifications that lead to resistance to most other tetracyclines [4]. Omadacycline has been approved in the United States to treat community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults. IV and oral formulations of omadacycline are available. IV treatment can be initiated with a loading dose of 200 mg IV once or 100 mg IV twice on day 1, followed by 100 mg IV or 300 mg oral daily. For ABSSSI only, oral treatment can be initiated with 450 mg oral on days 1 and 2, followed by 300 mg oral daily.

Omadacycline has a spectrum of activity that expands upon that of its oral precursors. It is active against several types of resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA); penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*; and vancomycin-resistant *Enterococcus* (VRE) spp. It is also active against pathogens that are important in community-acquired respiratory tract infections, including *Haemophilus influenzae*, *Moraxella catarrhalis*, and species of *Legionella*, *Chlamydia*, and *Mycoplasma*. However, no activity has been demonstrated against *Proteus*, *Providencia*, *Pseudomonas*, or *Morganella*

species [5]. Importantly, omadacycline demonstrates activity against tetracycline-resistant strains of *S. pneumoniae*, MRSA, and VRE by circumventing ribosomal protection and active tetracycline efflux in these pathogens [6].

UNMET MEDICAL NEED FOR NEW ANTIBIOTICS FOR CABP AND ABSSSI

While there is no shortage of antibiotics for CABP, none of them is without shortcomings. Increasing resistance rates, increasing comorbid conditions (eg, diabetes mellitus, IV drug use, and immunosuppressed populations), increasing rates of *Clostridioides difficile* infections, limitations via black box warnings, drug–drug interactions, allergies, and lack of oral options all contribute to the unmet needs for new antibiotics [5, 7–9]. For example, fluoroquinolones have been commonly used for many infections including CABP, but the FDA has recently issued safety warnings to limit their use for some indications [10]. The β-lactams are well tolerated, but resistance is a concern in some organisms and they lack activity against atypical pathogens. Resistance to macrolides is widespread [5]. Many medical needs of patients with ABSSSI and CABP remain unmet, especially regarding oral antibiotic therapies; patients often require IV antibiotic administration in the hospital setting [11, 12]. Additionally, although other available antibiotics can be used successfully in ABSSSI, there remain a number of unmet clinical needs in ABSSSI treatment, in addition to increasing resistance; these include concerns over AEs, drug–drug interactions, optimal dosing, and monotherapy options to cover multiresistant pathogens [13, 14].

IMPACT OF ORAL THERAPY ON HOSPITALIZATION COSTS

Many patients with ABSSSI are admitted to the hospital solely for IV antibiotic administration [15], with an average length of hospital stay of 4–7 days [16]. The majority of antibiotics developed in the last decade for both CABP and skin infections can only be administered IV, with the exception of oxazolidinones and 1 recently approved fluoroquinolone [9, 17]. Intravenous administration of antibiotics often requires patient hospitalization [11], and oral treatments are sorely needed in an era where a goal is to decrease hospital stays, as increased hospital stays have been associated with not only higher costs, but also increased morbidity and mortality [12].

The development of novel oral antibiotics could also have a substantial impact on treatment-associated costs. Studies have shown that IV therapy in CABP and ABSSSI can result in substantial increases in cost, including extended durations of hospital stays [18–20]. Omadacycline could have a positive effect on hospitalization-associated expenses for both CABP and ABSSSI by providing another oral agent active against resistant gram-positive pathogens. Treatments such as omadacycline could enable hospitals to discharge patients who cannot take other oral options, reduce the length of a hospital stay, or allow for treatment on an outpatient basis, which could further decrease hospitalization costs and risks [11, 20–22].

A BRIEF DESCRIPTION OF OMADACYCLINE DEVELOPMENT HIGHLIGHTS

The Preclinical Picture of Omadacycline

Like other tetracyclines, omadacycline inhibits bacterial protein synthesis by binding to the primary tetracycline binding site on the bacterial ribosome 30S subunit [4]. The chemical structure of omadacycline has modifications at the C-7 and C-9 positions of the tetracycline D-ring. The C-7 modification circumvents the tetracycline efflux pump resistance mechanism, and the C-9 modification circumvents the ribosomal protection resistance mechanism.

In vitro and in vivo studies show that omadacycline is active against gram-positive bacteria, some gram-negative bacteria (eg, *H. influenzae*, *M. catarrhalis*, *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Serratia marcescens*, *Salmonella* spp., *Shigella* spp., *and Stenotrophomonas maltophilia*), as well as a number of anaerobes (eg, *Bacteroides fragilis*, *C. difficile*, *and Clostridium perfringens*) and atypical pathogens (eg, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia* species), and shows in vitro activity against biofilm-producing organisms [5, 23]. However, in vitro studies have shown that omadacycline lacked notable activity against *Proteus*, *Providencia*, *Pseudomonas*, and *Morganella* species [5]. In vivo studies with a murine pneumonia model showed that area under the plasma concentration–time curve (AUC)/minimum inhibitory concentration was predictive of omadacycline antibacterial activity in plasma and epithelial lining fluid measurements [24]. The results of preclinical trials with omadacycline are further described elsewhere in this supplement [25].

Pharmacokinetics and Pharmacodynamics in Healthy Adults and Special Populations

Studies of omadacycline have demonstrated an absolute bioavailability of 34.5% [26]. The results of a phase I study showed that omadacycline should be administered in a fasting state, as bioavailability was decreased if taken 2–4 hours after a meal [27]. The pharmacokinetics (PK) of the agent are linear, and the oral administration of 300 mg omadacycline produces a similar exposure (AUC) to the administration of a 100 mg IV dose. The half-life is approximately 17 hours and the drug is eliminated through fecal (81.1%) and urinary (14.4%) routes [7]. Omadacycline accumulated by approximately 50% from day 1 of dosing to steady state, and appears to be a substrate for the P-glycoprotein (P-gp) transporter, but does not inhibit or induce P-gp [7]. A study comparing the PK characteristics of omadacycline and tigecycline showed that omadacycline treatment resulted in higher sustained concentrations in the

epithelial lining fluid, alveolar cells, and plasma of healthy adult patients, compared with tigecycline [28].

Though there is evidence indicating that omadacycline exposure may be approximately 30% higher in female patients, results from 2 phase I studies have shown that no dose adjustments are required for age and sex [5, 29, 30]. PK and pharmacodynamics (PD) studies performed in subjects with varying degrees of hepatic impairment, ranging from mild to severe, and in healthy subjects found no relationship between omadacycline exposure parameters and the degree of hepatic impairment. Therefore, no omadacycline dose adjustment is necessary when administered to patients with varying degrees of hepatic impairment [31]. Furthermore, trials examining PK and safety in patients with renal impairments, including end-stage renal disease, showed that omadacycline dose adjustments were not necessary for patients with renal impairment or who were undergoing hemodialysis [32]. The results of PK/PD trials with omadacycline in adults and subpopulations are further described elsewhere in this supplement [33].

IV and Oral Omadacycline for CABP and ABSSSI

Two phase III Omadacycline in Acute Skin and Skin Structure Infections Studies (OASIS) examined the safety and efficacy of omadacycline in the treatment of adults with ABSSSI [34, 35]. Both OASIS-1 and OASIS-2 were randomized, double-blind, double-dummy, noninferiority studies. The primary FDA endpoint for both studies was early clinical response (ECR) at 48–72 hours after treatment initiation, and the primary European Medicines Agency (EMA) endpoint was the investigator assessment of clinical response (IACR) at the posttreatment evaluation (PTE), occurring 7–14 days after the last dose. Both studies also assessed microbiological response at the end of treatment and at the follow-up visit. OASIS-1, which enrolled a global population, initiated participants on IV omadacycline or IV linezolid and had an option to transition to oral formulations after ≥3 days. OASIS-2, conducted in the United States, investigated only oral omadacycline or oral linezolid.

The results of the OASIS-1 and OASIS-2 studies show that omadacycline was noninferior to linezolid for both the FDA- and EMA-recommended endpoints. In a pooled analysis, omadacycline was noninferior to linezolid for the primary FDA endpoint of ECR (86.2% vs 83.9%; difference, 2.3 [95% confidence interval {CI} −1.5 to 6.2]). Similarly, omadacycline was noninferior to linezolid for the primary EMA endpoint of IACR at PTE (in the modified intent-to-treat population consisting of intent-to-treat patients without a sole gram-negative pathogen, used because of a lack of gram-negative coverage with linezolid: 85.1% vs 82.1%; difference: 2.9 [95% CI −1.0 to 6.9]). Both IV and oral formulations were effective across study populations, regardless of ABSSSI type and baseline pathogen.

The phase III Omadacycline for Pneumonia Treatment In the Community (OPTIC) study demonstrated the noninferiority of omadacycline to moxifloxacin for the treatment of adults with CABP, and was the basis for the FDA approval of omadacycline for the treatment of CABP in October 2018 [32, 36]. The FDA, with the help of the Biomarkers Consortium of the Foundation for the National Institutes of Health, developed the ECR endpoint based on a review of historical and modern symptom response data that suggest antibiotic treatment effects are most apparent during the first few days of therapy [37, 38]. Omadacycline is the first antibiotic for CABP to be approved using the ECR endpoint. This study examined ECR and PTE outcomes with omadacycline, as ECR was defined as the primary endpoint for CABP trials by the FDA in 2014. The ECR primary endpoint for the OPTIC study was survival with improvement in ≥2 of 4 patient symptoms (eg, cough, sputum production, pleuritic chest pain, and dyspnea), and no worsening of any symptom 72–120 hours after first dose of study drug without receipt of another antibiotic.

Omadacycline was noninferior to moxifloxacin for the treatment of CABP and met the primary FDA endpoint. Omadacycline showed statistical noninferiority compared to moxifloxacin. ECR rates and IACR at PTE were high, and comparable between groups. Omadacycline was noninferior (10% noninferiority margin) to moxifloxacin for the primary ECR endpoint (81.1% vs 82.7%; difference, −1.6 [95% CI −7.1 to 3.8]). Omadacycline was also noninferior to moxifloxacin for the secondary endpoint of IACR at PTE (in the intent-to-treat population): 87.6% vs 85.1%; difference, 2.5 [95% CI −2.4 to 7.4]). Omadacycline was generally safe and well tolerated following IV and oral administration, and had an overall safety profile similar to that of moxifloxacin. Four subjects receiving omadacycline experienced treatment-emergent AEs (TEAEs) of diarrhea, but there was no reported incidence of *C. difficile*–associated diarrhea with omadacycline. During the ECR period, similar rates of clinical stability were observed for omadacycline and moxifloxacin; consistent results were also obtained when analyzing the data by Pneumonia Outcomes Research Team (PORT) risk class. The results of the OPTIC trial suggest that ECR and attainment of clinical stability may both be predictors of clinical success at PTE but are poor predictors of clinical failure at PTE. The results of the phase III trials with omadacycline are further described elsewhere in this supplement [39, 40].

Safety of Omadacycline

The integrated safety summary of omadacycline incorporates data from the phase III studies and focuses on frequent AEs and the overall safety profile of omadacycline. AEs and TEAEs are reported and show that, similar to other tetracyclines, the most frequently observed AEs were related to the gastrointestinal system. Events of nausea (14.9%, 8.7%, and 5.4% of patients receiving omadacycline, linezolid, and moxifloxacin, respectively) and vomiting (8.3%, 3.9%, and 1.5% of patients receiving

omadacycline, linezolid, and moxifloxacin, respectively) were the most frequent TEAEs among all treatment groups but did not result in treatment discontinuation. The highest frequencies of nausea and vomiting in the omadacycline group (32.6% and 8.2% of patients, respectively), were observed during the first 2 days of the oral-only OASIS-2 study when patients received a loading dose of 450 mg; this effect was not treatment limiting [35], and most AEs resolved during the testing period. Omadacycline's affinity for muscarinic M_2 receptors resulted in moderate and transient heart rate increases during the treatment period; there was no effect of treatment on QTcF values [41]. Minor to moderate increases in hepatic enzyme levels were also noted during the treatment period, similar to effects seen with tetracycline treatment. The integrated analysis of the 3 ABSSSI and CABP studies demonstrates that omadacycline is safe and well tolerated. In the CABP study, a nonsignificant difference in mortality was seen between omadacycline (2% [8/386]) and moxifloxacin (1% [3/388]). The cause is not known. All deaths in both groups were seen in patients >65 years of age. No imbalance was seen in the ABSSSI studies (omadacycline <1% [1/691]; linezolid <1% [2/689]), and a follow-up CABP study is being performed. Information on the safety of omadacycline in phase III clinical trials is further described elsewhere in this supplement [42]. Omadacycline shares tetracycline-class effects of tooth discoloration, inhibition of bone growth, and a potential effect on anticoagulants.

THE POTENTIAL IMPACT OF A MODERN ORAL TETRACYCLINE

Oral antibiotics such as omadacycline offer safe treatment options for patients with CABP and ABSSSI, possibly eliminating the need for hospitalization, and can provide substantial cost savings for patients and the healthcare system. Furthermore, the revitalization of the activity of the tetracyclines, while still retaining the known safety profile of the class (eg, a low risk of *C. difficile* infection), could increase possibilities for the successful treatment of pathogens resistant to other tetracyclines, clindamycin, β-lactams, oxazolidinones, and other antimicrobial agents. A novel antibiotic such as omadacycline also offers a possible solution for patients who cannot take other oral antibiotics such as fluoroquinolones or β-lactams. Additionally, omadacycline provides coverage across many gram-positive organisms, as well as some gram-negative and atypical pathogens; requires no dose adjustments by age, sex, weight, or renal/hepatic insufficiency; and could address an unmet need in CABP and ABSSSI patients for whom other drugs are not suitable due to drug–drug interactions.

Notes

References

1. Nelson ML, Levy SB. The history of the tetracyclines. Ann N Y Acad Sci **2011**; 1241:17–32.
2. Honeyman L, Ismail M, Nelson ML, et al. Structure-activity relationship of the aminomethylcyclines and the discovery of omadacycline. Antimicrob Agents Chemother **2015**; 59:7044–53.
3. Stein GE, Craig WA. Tigecycline: a critical analysis. Clin Infect Dis **2006**; 43:518–24.
4. Draper MP, Weir S, Macone A, et al. Mechanism of action of the novel aminomethylcycline antibiotic omadacycline. Antimicrob Agents Chemother **2014**; 58:1279–83.
5. Villano S, Steenbergen J, Loh E. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. Future Microbiol **2016**; 11:1421–34.
6. Macone AB, Caruso BK, Leahy RG, et al. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. Antimicrob Agents Chemother **2014**; 58:1127–35.
7. Flarakos J, Du Y, Gu H, et al. Clinical disposition, metabolism and in vitro drug-drug interaction properties of omadacycline. Xenobiotica **2017**; 47:682–96.
8. Jenkins TC, Sabel AL, Sarcone EE, Price CS, Mehler PS, Burman WJ. Skin and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. Clin Infect Dis **2010**; 51:895–903.
9. Paulson SK, Wood-Horrall RN, Hoover R, Quintas M, Lawrence LE, Cammarata SK. The pharmacokinetics of the CYP3A substrate midazolam after steady-state dosing of delafloxacin. Clin Ther **2017**; 39:1182–90.
10. US Food and Drug Administration. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm511530.htm. Accessed 19 February 2019.
11. Montravers P, Dinh AT, Tanaka S. The role of omadacycline in skin and soft tissue infections. Curr Opin Infect Dis **2018**; 31:148–54.
12. Watkins RR, Lemonovich TL. Diagnosis and management of community-acquired pneumonia in adults. Am Fam Physician **2011**; 83:1299–306.
13. Quinn DK, Stern TA. Linezolid and serotonin syndrome. Prim Care Companion J Clin Psychiatry **2009**; 11:353–6.
14. Ramakrishnan K, Salinas RC, Agudelo Higuita NI. Skin and soft tissue infections. Am Fam Physician **2015**; 92:474–83.
15. Verastegui JE, Hamada Y, Nicolau DP. Transitions of care in the management of acute bacterial skin and skin structure infections: a paradigm shift. Expert Rev Clin Pharmacol **2016**; 9:1039–45.
16. Suaya JA, Mera RM, Cassidy A, et al. Incidence and cost of hospitalizations associated with *Staphylococcus aureus* skin and soft tissue infections in the United States from 2001 through 2009. BMC Infect Dis **2014**; 14:296.
17. Eckmann C, Nathwani D, Lawson W, et al. Comparison of vancomycin and linezolid in patients with peripheral vascular disease and/or diabetes in an observational European study of complicated skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus*. Clin Microbiol Infect **2015**; 21(Suppl 2):S33–9.
18. Chandy SJ, Naik GS, Balaji V, Jeyaseelan V, Thomas K, Lundborg CS. High cost burden and health consequences of antibiotic resistance: the price to pay. J Infect Dev Ctries **2014**; 8:1096–102.

19. Asche C, McAdam-Marx C, Seal B, Crookston B, Mullins CD. Treatment costs associated with community-acquired pneumonia by community level of antimicrobial resistance. J Antimicrob Chemother 2008; 61:1162–8.

20. Russo A, Concia E, Cristini F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. Clin Microbiol Infect 2016; 22(Suppl 2):S27–36.

21. Ektare V, Khachatryan A, Xue M, Dunne M, Johnson K, Stephens J. Assessing the economic value of avoiding hospital admissions by shifting the management of gram+ acute bacterial skin and skin-structure infections to an outpatient care setting. J Med Econ 2015; 18:1092–101.

22. Revankar N, Ward AJ, Pelligra CG, Kongnakorn T, Fan W, LaPensee KT. Modeling economic implications of alternative treatment strategies for acute bacterial skin and skin structure infections. J Med Econ 2014; 17:730–40.

23. Waites KB, Crabb DM, Liu Y, Duffy LB. In vitro activities of omadacycline (PTK 0796) and other antimicrobial agents against human mycoplasmas and ureaplasmas. Antimicrob Agents Chemother 2016; 60:7502–4.

24. Lepak AJ, Zhao M, Marchillo K, VanHecker J, Andes DR. In vivo pharmacodynamic evaluation of omadacycline (PTK 0796) against *Streptococcus pneumoniae* in the murine pneumonia model. Antimicrob Agents Chemother 2017; 61. doi:10.1128/AAC.02368-16.

25. Karlowsky JA, Steenbergen J, Zhanel GG. Microbiology and non-clinical review of omadacycline. Clin Infect Dis 2019; 69(Suppl 1):S6–15.

26. Sun H, Ting L, Machineni S, et al. Randomized, open-label study of the pharmacokinetics and safety of oral and intravenous administration of omadacycline to healthy subjects. Antimicrob Agents Chemother 2016; 60:7431–5.

27. Tzanis E, Manley A, Villano S, Tanaka SK, Bai S, Loh E. Effect of food on the bioavailability of omadacycline in healthy participants. J Clin Pharmacol 2017; 57:321–7.

28. Gotfried MH, Horn K, Garrity-Ryan L, et al. Comparison of omadacycline and tigecycline pharmacokinetics in the plasma, epithelial lining fluid, and alveolar cells of healthy adult subjects. Antimicrob Agents Chemother 2017; 61. doi:10.1128/AAC.01135-17.

29. Tanaka SK, Tzanis E, Villano S. Effect of age and gender on the pharmacokinetics of oral and IV omadacycline, a new class of aminomethylcyclines. In: 26th European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, the Netherlands, 2016:1318.

30. van Wart SA, Manley A, Bhavnani SM, et al. Population pharmacokinetics of omadacycline following intravenous or oral administration to phase 1 subjects. In: 26th European Congress of Clinical Microbiology and Infectious Diseases. Amsterdam, the Netherlands, 2016:P1320.

31. Ting L, Kovacs SJ, Praestgaard J, et al. Pharmacokinetics of omadacycline (PTK0796) in subjects with hepatic impairment. In: 52nd Annual Interscience Conference of Antimicrobial Agents and Chemotherapy, San Francisco, CA, 2012:1282.

32. 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. doi:10.1128/AAC.02057-17.

33. Rodvold KA, Pai MP. Pharmacokinetics and pharmacodynamics of oral and intravenous omadacycline. Clin Infect Dis 2019; 69(Suppl 1):S16–22.

34. O'Riordan W, Green S, Overcash JS, et al. Omadacycline for acute bacterial skin and skin-structure infections. N Engl J Med 2019; 380:528–38.

35. O'Riordan W, Cardenas C, Sirbu A, et al. A phase 3 randomized, double-blind, multi-centre study to compare the safety and efficacy of oral omadacycline to oral linezolid for treating adult subjects with ABSSSI (OASIS-2 study). In: 28th European Congress of Clinical Microbiology and Infectious Diseases, Madrid, Spain, 21–24 April 2018.

36. Stets R, Popescu M, Gonong JR, et al. Omadacycline for community-acquired bacterial pneumonia. N Engl J Med 2019; 380:517–27.

37. US Food and Drug Administration. Guidance for industry community-acquired bacterial pneumonia: developing drugs for treatment. Silver Spring, MD: FDA, 2014.

38. Talbot GH, Powers JH, Hoffmann SC; Biomarkers Consortium of the Foundation for the National Institutes of Health CABP-ABSSSI and HABP-VABP Project Teams. Developing outcomes assessments as endpoints for registrational clinical trials of antibacterial drugs: 2015 update from the biomarkers consortium of the Foundation for the National Institutes of Health. Clin Infect Dis 2016; 62:603–7.

39. Abrahamian FM, Sakoulas G, Tzanis E, et al. Omadacycline for acute bacterial skin and skin structure infection. Clin Infect Dis 2019; 69(Suppl 1): S23–32.

40. 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):S33–39.

41. Villano S, Tanaka SK. Omadacycline, an aminomethylcycline antibiotic, has no effect on QT/QTc intervals in healthy subjects. In: 26th European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, Netherlands, 9–12 April 2016.

42. Opal S, File Jr. T, van der Poll T, McGovern PC, Tzanis E, Chitra S. An integrated safety summary of the novel aminomethylcycline antibiotic omadacycline. Clin Infect Dis 2019; 69(Suppl 1):S40–7.