Omadacycline *p*-Toluenesulfonate Tablets and Injection

For the Treatment of

Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP)

Briefing Document for:

Antimicrobial Drugs Advisory Committee (AMDAC)

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ABG	arterial blood gas
ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BID	twice daily
BMI	body mass index
BP	blood pressure
CABP	community-acquired bacterial pneumonia
CAP	community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CDI	*C. difficile* infection
CE	clinically evaluable
CFU	colony forming unit
CI	confidence interval
C_{max}	peak plasma concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
cSSSI	complicated skin and skin structure infection
CT	computed tomography
ECG	Electrocardiogram
ECR	early clinical response
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	end of treatment
ER	emergency room
FDA	Food and Drug Administration
GI	Gastrointestinal

Hb	Hemoglobin
HCO_3	Bicarbonate
hERG	human ether-a-go-go-related gene
HR	heart rate
IACR	investigator's assessment of clinical response
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
ITT	intent-to-treat
iv	Intravenous
LDH	lactate dehydrogenase
LPF	low power field
MDRSP	multidrug resistant *S. pneumoniae*
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration for at least 50% of the isolates tested for a given species or genus
mITT	modified intent-to-treat
micro-mITT	microbiological modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *S. aureus*
$PaCO_2$	partial pressure of carbon di-oxide
PaO_2	partial pressure of arterial oxygen
P-gp	P-glycoprotein transporter
PK	Pharmacokinetic
PK-PD	pharmacokinetic-pharmacodynamic
PMN	polymorphonuclear neutrophil
po	Oral
PORT	Pneumonia Outcomes Research Team
PRSP	penicillin-resistant *S. pneumoniae*
PT	preferred term
PTE	post-therapy evaluation
q12h	every 12 hours
q24h	every 24 hours
QD	once daily
QTc	corrected QT interval

QTcF	QT interval corrected for heart rate using Fridericia's formula
RCTs	randomized clinical trials
RCS	randomized controlled study
RML	Right middle lobe
RLL	right lower lobe
RUL	right upper limit
SEC	squamous epithelial cells
SIRS	systemic inflammatory response syndrome
SOC	system organ class
SPA	Special Protocol Assessment
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WBC	white blood cell (count)

1 INTRODUCTION

This briefing document has been prepared by Paratek Pharmaceuticals with the purpose of providing background information on omadacycline to the Food and Drug Administration (FDA) Antimicrobial Drugs Advisory Committee (AMDAC). Contained in this document is an overview of the efficacy, safety, and tolerability data supporting the review of the oral (po) and intravenous (iv) omadacycline New Drug Applications (NDAs) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).

Omadacycline (PTK-0796) is a next generation tetracycline that that was specifically designed to retain activity against bacteria that carry common tetracycline resistance mechanisms, efflux and ribosomal protection. The tetracycline-specific mechanism of action and the lack of cross-resistance to other antibiotics classes allows omadacycline to treat infections caused by bacteria with other clinically important mechanisms of bacterial resistance.

The data and accompanying analyses provided in this briefing book support the conclusions that:

- Omadacycline demonstrated substantial evidence of efficacy for the treatment of ABSSSI in 2 Phase 3 studies.
- Omadacycline demonstrated substantial evidence of efficacy for the treatment of CABP in a large Phase 3 study
- Omadacycline was safe and well- tolerated, with similar rates of treatment-emergent AEs (TEAEs), vital sign changes, laboratory changes, and mortality rates across the 3 pivotal Phase 3 studies.

Omadacycline has been developed as a once-daily, antibiotic to treat patients with ABSSSI and CABP. Omadacycline has been formulated for both po and iv administration providing physicians and patients flexibility (Table 1).

Table 1. Omadacycline Dosing Regimens

Loading Doses	Maintenance Dose	Treatment Duration
100-mg infused over 30 minutes, twice on the first day	100 mg intravenous or 300 mg orally once daily	7 to 14 days
450-mg orally once daily on the first and second day	300 mg orally once daily	7 to 14 days

1.1 Unmet Need

The emergence and spread of antibiotic-resistant organisms continues to outpace the development of antibiotics to treat these pathogens.[1] Infections caused by antibiotic-resistant organisms increase morbidity and mortality in patients and increase the resource consumption for healthcare systems globally. The Centers for Disease Control and Prevention (CDC) has estimated that 2 million patients per year have infections due to drug-resistant bacteria, resulting in 23,000 deaths annually in the United States (US).[2] Methicillin-resistant *Staphylococcus aureus*

(MRSA) and *Streptococcus pneumoniae* (*S. pneumoniae*, or pneumococcus), known to be leading causes of bacterial skin and community-acquired pneumonia infections, have been classified as serious threats by the CDC.[2] Bacterial resistance, including multi-drug resistance, have presented a therapeutic challenge to clinicians with respect to the selection of appropriate empiric antibiotic therapies,[3] especially as bacterial resistance to the current guideline-recommended antibiotics has increased. The World Health Organization (WHO) priority pathogen list for research and development of new antibiotics includes penicillin-resistant *S. pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, vancomycin-resistant *Enterococcus faecium* and MRSA.[4] In the presence of these resistance phenotypes and mechanisms, omadacycline retains activity and provides an alternative treatment option. The issue of resistance among bacterial pathogens and the lack of available therapeutic options clearly emphasizes the need for new antibacterial agents to treat these serious infections.

1.1.1 Acute Bacterial Skin and Skin Structure Infections

Acute bacterial skin and skin structure infections is a serious condition requiring antibiotic therapy, surgical management, and/or hospitalization. The increasing incidence of ABSSSI requiring hospitalization or clinic visits is imposing a substantial burden on the US healthcare system.[5,6,7] In the early 2000s, with the emergence of a community-acquired MRSA epidemic, an annual excess of 850,000 hospitalizations, 6 million primary care visits, and 3 million emergency department encounters for skin infections were observed. Although recent data suggest that the number of infections has stabilized, an estimated 17% increase in hospitalizations for ABSSSI was reported between 2005 and 2011.[8,9,10,11] There has been a significant increase in the prevalence of severe ABSSSI requiring hospital intervention caused by antibiotic-resistant pathogens, in particular MRSA.[12] Beginning in the mid-1990s, the most prevalent type of MRSA shifted from healthcare-associated MRSA to community-associated MRSA strains. Since ABSSSI are often treated empirically, and with the emergence of community-associated MRSA, patients may be admitted for iv antibiotic therapy to treat drug-resistant pathogens.[13]

When ABSSSI is caused by an antibiotic-resistant pathogen or a highly-virulent pathogen, such as MRSA, the choice of appropriate therapy is more challenging, and poor clinical outcomes may result from inappropriate initial antimicrobial therapy.[14,15] Methicillin-resistant *S. aureus* accounts for nearly half of all *S. aureus* skin and soft tissue infections in the US, and can complicate the effective antibiotic therapy choice for this serious infection.[16] Additonally, underlying comorbidities in this patient population, including diabetes, obesity, vascular disease, and malignancies can also complicate management and antibiotic selection.[17] Failure of initial antibiotic therapy may result in treatment failure or infection re-occurrence, leading to increased hospitalizations and patient morbidity.[16,18,19] Elderly patients with skin infections are more likely to be hospitalized and to fail initial antibiotic treatment compared to their younger counterparts.[5]

Infectious Diseases Society of America (IDSA) stewardship guidelines recommend conversion from parenteral to oral therapy, when the patient condition allows.[20] Since 2013, lipoglycopeptides and glycopeptides (dalbavancin, oritavancin, telavancin and daptomycin); and cephalosporins (ceftaroline), were approved; all available only as an iv formulation. The only recent oral antibiotic approvals with MRSA coverage include oxazolidinones (tedizolid) and fluoroquinolones (delafloxacin), both classes of agents associated with safety concerns. Additionally, fluoroquinolones and cephalosporins are associated with an increased risk of

Clostridium difficile infection (CDI).[21,22,23] Therefore, additional oral antibiotics that provide treatment options are needed.

Though there are approved therapies for the treatment of ABSSSI, resistance to available antibiotics continues to increase, and antibiotic allergies, adverse effects, and drug-drug interactions can further complicate treatment choices. Therefore, new antibacterial drugs will always be needed to address evolving resistance concerns and safety limitations of older agents. Few oral treatment options exist for patients with infections due to MRSA and other drug-resistant pathogens. Omadacycline has demonstrated high clinical efficacy for the treatment of ABSSSI caused by common pathogens including drug-resistant strains and MRSA. Omadacycline provides a treatment option for patients with ABSSSI with the flexibility of iv or oral dosing.

1.1.2 Community-Acquired Bacterial Pneumonia

Community-acquired pneumonia (CAP) is the most common infectious disease leading to hospitalization and mortality among all age groups.[24,25,26,27,28] Together with influenza, CAP is currently the eighth leading cause of death in the US.[29] In a recent prospective US population-based surveillance study, the annual incidence of CAP was 24.8 cases per 10,000 adults, with the highest rates among adults 65 to 79 years of age (63.0 cases per 10,000 adults) and those 80 years of age or older (164.3 cases per 10,000 adults).[30] The CDC estimated that in the US, antibiotic resistant *S. pneumoniae* are responsible for 19,000 excess hospitalizations and 7,000 deaths per year. Community-acquired pneumonia often occurs in patients with comorbidities, such as heart failure, chronic obstructive pulmonary disease (COPD), coronary artery disease, and diabetes where the risk of complications and mortality is higher.[31] Failure of therapy due to resistance will continue to contribute to the morbidity and mortality of CABP, and treatment failures will result in increased hospitalizations and contribute to increased healthcare costs.[18,19]

The rising incidence of antibiotic resistance in *S. pneumoniae* and other common pathogens has led to challenges in the treatment choice for antibiotics and contributes to the unmet need for new antibiotics in CABP.[32] For respiratory pathogens such as *S. pneumoniae* and *H. influenzae*, increased rates of antimicrobial resistance to β-lactams, macrolides, and older generation tetracyclines in many geographic regions highlight the need for new treatment alternatives for CABP.[24,32] Penicillin-nonsusceptible *S.*[24,32] Penicillin-nonsusceptible *S. pneumoniae*, including multi-drug resistant *S. pneumoniae* (MDRSP) and ampicillin-resistant *H. influenzae*[33] in the community pose treatment challenges and are included in the World Health Organization priority pathogen list for research and development of new antibiotics.[4] In a recent study, 12.7%, 21.5%, 45.6%, and 15.1% of *S. pneumoniae* isolates from pneumonia specimens were non-susceptible to penicillin, and resistant to tetracycline, erythromycin, and trimethoprim-sulfamethoxazole, respectively.[34] United States surveillance data has documented a > 30% resistance rate to ampicillin in *H. influenzae* isolates.[35,36] *Staphylococcus aureus*, including MRSA, remains an infrequent cause of CABP but has been associated with severe cases and requires consideration when choosing empiric therapy.[20]

Treatment for CABP is largely empiric as a microbiologic diagnosis may be achieved in only 10% of patients.[37] Current US guidelines recommend the use of an antimicrobial regimen with

coverage against both typical and atypical pathogens.[38] A third-generation cephalosporin plus a macrolide or a fluoroquinolone are therefore recommended by the American Thoracic Society (ATS) guidelines as first line empiric therapy in non-intensive care unit hospitalized CABP patients.

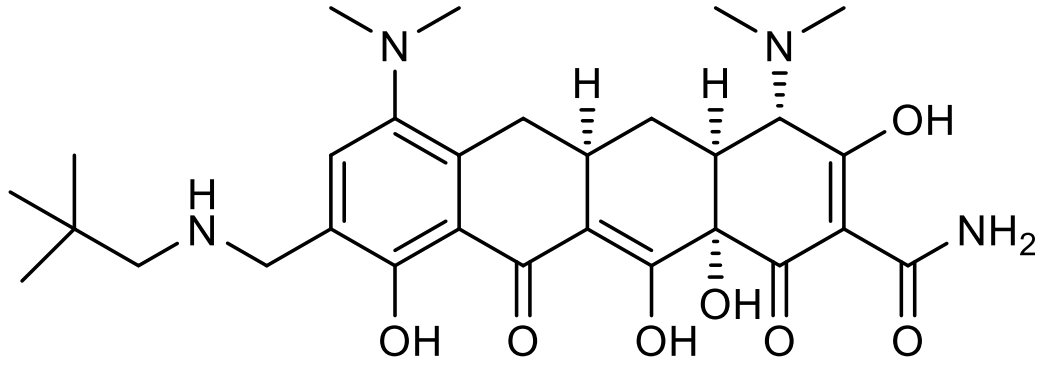
There are known safety and antibiotic resistance concerns with current antibiotics used for CABP which exemplify the need for additional antibiotics to choose from in the treatment of CABP. For instance, β-lactam allergy limits the use of first-line ceftriaxone treatment for some patients.[39] Additionally, high rates of macrolide resistance and doxycycline resistance in *S. pneumoniae* compromises the potential clinical effectiveness of the macrolides and older tetracyclines. Known safety concerns with macrolides (QT prolongation) and fluoroquinolones (QT prolongation, tendon rupture, peripheral neuropathy and central nervous system [CNS] reactions), in addition to the risk of CDI with fluoroquinolones and cephalosporins, pose risks for a subset of patients. The incidence of CABP is greatest in patients aged 65 years or older where the risk of comorbidity, drug-drug interaction, and CDI is higher.

Appropriate, timely, and effective antibiotic therapy are among the most important factors in ensuring successful treatment of CABP.[40] It is beneficial to have different antibacterial options that can provide timely, appropriate therapy against drug-resistant strains. Because of the diversity of the patient populations, antibiotic allergies, patient comorbidities, and drug-drug interactions, it is imperative to have antibacterial drugs with different safety profiles to provide physicians with options for patient care. The antibacterial activity of omadacycline against common CABP pathogens, including drug-resistant *S. pneumoniae,* as well as high clinical success rates support its use as an iv and oral option for patients for the treatment of CABP.

1.2 Pharmacokinetics

Omadacycline is a unique next-generation tetracycline antibiotic, known as an aminomethylcycline. The tetracycline class of antibiotics have been in clinical use for approximately 70 years and have a well-described safety and tolerability profile; however, over the years, have lost activity against many pathogens. Omadacycline was identified through classical structure–activity relationship determinations.[41] The chemical structure of omadacycline (Figure 1) is characterized by an aminomethyl group at the C-9 position on the tetracycline structure and modifications at the C-7 position that results in stability to ribosomal protection proteins and efflux pump mechanisms of tetracycline resistance, respectively.

Figure 1. Omadacycline Chemical Structure



The pharmacokinetics (PK) of omadacycline have been well-characterized in 22 single- and multiple-dose Phase 1 clinical studies. In these studies, single iv doses of 25 to 600 mg and single po doses of 50 to 600 mg were investigated. Multiple iv doses of 100 mg and 200 mg once daily for up to 14 and 7 consecutive days, respectively, and multiple po doses of 300 to 600 mg once daily for up to 5 consecutive days were also investigated. The exposure to omadacycline after iv administration is linear over a wide dose range (25 to 600 mg) and is consistent and predictable for both genders. The prolonged terminal-phase elimination half-life ($t_{½,z}$) supports once daily dosing. The large volume of distribution is consistent with the extensive distribution noted with the tetracycline class. However, unlike other tetracyclines, the protein binding of omadacycline is low, approximately 21%.[42] This protein binding is consistent and is unaffected by concentration. This low protein binding translates into higher free (pharmacologically active) drug concentrations and facilitates tissue penetration. A summary of the mean PK parameters of omadacycline after single- and multiple-dose administration for the 100 mg iv and 300 mg po doses is provided in Table 2.

Table 2. Pharmacokinetic Parameters of Omadacycline After Single and Multiple Doses

Dosage (mg)	Intravenous		Oral	
	100 mg iv Single Dose	**100 mg iv Steady State**	**300 mg Oral Single Dose**	**300 mg Oral Steady State**
N	63	41	103	43
C_{max} (mg/L)	1.51 (38.6)	2.12 (32.0)	0.55 (26.7)	0.95 (44.2)
CL_{total} (L/h)[a]	11.2 (23.8)	8.8 (25.2)	34.6 (30.9)	NR
T ½ (h)	16.2 (14.7)	16.0 (21.7)	15.0 (16.5)	15.5 (10.7)
T_{max} (h)	0.55 (0.25, 0.68)	0.50 (0, 1.0)	2.50 (1.0, 4.1)	2.50 (0, 8.0)
AUC (h-mg/L)[b]	9.36 (22.1)	12.14 (26.6)	9.4 (27.2)	11.16 (44.9)
Vd (L)	256 (25.6)	190 (27.7)	794 (23.6)	NR

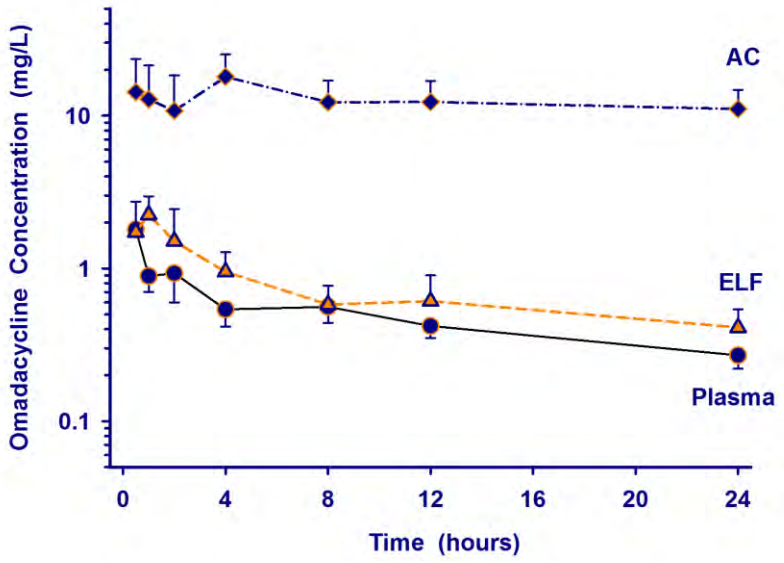
Data presented as mean (CV%)
a. CL/F for oral
b. $AUC_{0\text{-}inf}$ for single dose or $AUC_{0\text{-}24}$ for steady state
AUC = area under the concentration-time curve, C_{max} = peak plasma concentration, CL_{total} = total clearance, CV% = percentage coefficient of variance, iv = intravenous, NR = not reported, V_d = volume of distribution, $T_{½}$ = half-life, T_{max} = time to maximum concentration.

1.2.1 Distribution, Metabolism, Excretion

Unlike many other tetracyclines, omadacycline is not metabolized, and no metabolites of omadacycline have been detected in any human biological matrices studied. Omadacycline is eliminated as the parent drug primarily through biliary excretion (81%). Renal elimination accounts for approximately 14% of total omadacycline elimination.[43]

Consistent with the observed large volume of distribution, omadacycline exhibits excellent penetration into the lung including epithelial lining fluid (ELF) and alveolar macrophages. In a study examining lung tissue concentrations following iv administration of omadacycline in healthy subjects at the proposed label doses, demonstrated at steady-state, the concentration of omadacycline was 25.79-fold higher in alveolar cells (area under the concentration-time curve [AUC] 302.46 h·µg/mL) than in plasma, and 1.47-fold higher in ELF (AUC 17.23 h·µg/mL) than in plasma. The mean (±SD) concentration-time profile data are graphically depicted in Figure 2.[44]

Figure 2. Omadacycline Concentration-time Profile (Mean [SD])



1.2.2 Effect of Hepatic and Renal Dysfunction on Pharmacokinetics

To assess the impact of hepatic dysfunction on omadacycline PK, subjects with mild, moderate, or severe hepatic impairment (Child Pugh classes A, B, or C) were studied. Omadacycline exposures were similar in all subjects with hepatic impairment, regardless of severity, compared to healthy subjects.

In a study of iv omadacycline in subjects with end-stage renal disease on a stable hemodialysis regimen and age – and weight-matched healthy subjects, omadacycline exposure and systemic clearance were comparable between the renally-impaired subjects and the matching healthy subjects. During dialysis, 7.9% of the omadacycline dose was recovered in the dialysate.

Based on these data, dosage modification is not required in patients with either hepatic or renal impairment, including dialysis.

1.2.3 Effect of Age and Gender on Pharmacokinetics

Two studies were conducted to evaluate the influence of age and gender on the PK of iv and po omadacycline. There was no significant difference in omadacycline exposure between healthy young and elderly subjects or between men and women. No dose adjustment is necessary based on age or gender.

1.2.4 Effect of Food on Oral Absorption

Following oral administration, omadacycline is rapidly absorbed, reaching peak concentrations approximately 2.5 hours after oral administration. The effect of food content and timing on the PK of omadacycline was evaluated in 4 studies. The oral bioavailability of 300 mg omadacycline is approximately 34.5% in healthy, fasted subjects but declines significantly with food intake less than 6 h before, or less than 2 h after, dosing. In a study evaluating the relative bioavailability of a single 300-mg po dose of omadacycline under fasted and fed conditions in healthy subjects, omadacycline exposure (peak plasma concentration [C_{max}] and AUC) was reduced by 15% to 17% for a nondairy meal 4 h before dosing, 40% to 42% for a nondairy meal 2 h before dosing, and 59% to 63% for a dairy meal 2 h before dosing compared to dosing in the fasted state.

Therefore, omadacycline tablets should be taken with water in a fasting state (6 h). After oral dosing, no food or drink (except water) should be consumed for 2 h, and no dairy products, antacids, or multivitamins should be taken for 4 h. This is consistent with the known tetracycline class binding to calcium and other multivalent cations (eg, magnesium, aluminum, iron, bismuth, or zinc), which reduces absorption after oral administration. Therefore, co-administration of oral omadacycline with products containing calcium or other multivalent cations (eg, dairy products, antacids, or multivitamins) should be avoided.

1.2.5 Drug-Drug and Other Interactions

In vitro metabolism studies have shown that omadacycline is not a substrate, inhibitor, or inducer of human metabolizing enzymes (CYP 450). Thus, omadacycline is unlikely to be affected by concomitant medications via metabolism or transporter mechanisms. Furthermore, it is not expected that omadacycline will be influenced by co-administration of other medications that inhibit or induce these enzymes.

In vitro studies have shown that omadacycline is a substrate of the P-glycoprotein (P-gp) transporter. In a study that investigated the effects of a single, 240-mg po dose of verapamil extended release, a P-gp inhibitor, on the absorption of 300-mg po dose of omadacycline, verapamil dosing increased the omadacycline geometric mean of the AUC by approximately 18% to 24% and the C_{max} by 13%. The small increase in omadacycline exposure suggests that no dose adjustment is necessary when omadacycline is given with a known P-gp inhibitor.

Additional studies have also demonstrated that omadacycline is neither a substrate nor an inhibitor of human organic ion transporters OAT1, OAT2, OAT3, multi-drug resistance associate protein-2, or Breast Cancer Resistance Protein.

1.3 Microbiology

The mechanism of action of omadacycline is the inhibition of the initial codon recognition step of transfer RNA accommodation to the A-Site of the 30S ribosomal subunit, resulting in inhibition of protein synthesis.

Omadacycline was designed specifically to overcome the common tetracycline-specific resistance mechanisms: efflux pumps (eg, Tet(A)) and ribosomal protection proteins (eg, Tet(M)) (Table 3), which have rendered older generation tetracyclines limited in their clinical utility. Accordingly, omadacycline restores the broad-spectrum in vitro activity against bacteria that carry classical tetracycline resistance mechanisms.

Table 3. In Vitro Activity of Omadacycline and Tetracycline Against Selected Organisms With Characterized Tetracycline Resistance Genes

Organism	Tetracycline Resistance Gene(s)	Number of Isolates	Omadacycline MIC Range (µg/mL)	Tetracycline MIC Range (µg/mL)
Staphylococcus aureus	*tet*(M)	19	0.125 - 1.0	32 - > 64
	tet(K)	5	0.125 - 0.25	16 – 32
Streptococcus pneumoniae	*tet*(M)	22	≤ 0.06	4 – 64
Haemophilus influenzae	*tet*(B)	20	0.5- 2	8 – 64
	tet(B) and *tet*(M)	2	1 – 2	16
Escherichia coli	*tet*(A)	4	2	64 - > 64

MIC = minimum inhibitory concentration.

Single- and multi-step resistance studies demonstrate that target-based resistance to omadacycline is unlikely to arise quickly. In time-kill analyses, omadacycline was bactericidal against *Escherichi coli*, *S. pneumoniae*, and *H. influenzae*. In vitro analyses demonstrated that omadacycline activity was not adversely affected in the presence of other classes of antibiotics.

The in vitro activity of omadacycline has been assessed in large global surveillance studies of clinical isolates.[45] The spectrum of activity for omadacycline includes common ABSSSI and CABP pathogens (see Appendix Table 42, Table 43, and Table 44, page 93. Omadacycline has in vitro antibacterial activity against Gram-positive, many Gram-negative, aerobic, anaerobic, and atypical bacteria. Omadacycline has in vitro antibacterial activity against multiple Gram-positive drug-resistant pathogens including tetracycline-resistant pathogens, macrolide-resistant pathogens, MRSA, penicillin-resistant *S. pneumoniae* (PRSP) and MDRSP, and vancomycin-resistant enterococci. The following species are intrinsically resistant to omadacycline: *Proteus* spp., *Providencia* spp., *Morganella* spp., and *Pseudomonas aeruginosa*.

The in vitro activity of omadacycline was not affected by serum or lung surfactant, important characteristics that are consistent with potential utility in systemic infections and those involving the lower respiratory tract, including CABP. The in vivo efficacy of omadacycline was demonstrated against Gram-positive, Gram-negative, and anaerobic pathogens using several different murine models of infection. The efficacy of omadacycline was studied in the following infection models: sepsis, pneumonia, urinary tract infection (UTI), burn wound, intra-abdominal,

and thigh infection. Omadacycline activity was comparable to or better than comparator antibiotics evaluated against all pathogens studied, including tetracycline-resistant *S. aureus.*

1.4 Pharmacokinetics/Pharmacodynamics

1.4.1 Population Pharmacokinetics

The population PK model describing the disposition of iv and po omadacycline was developed using pooled data from 13 Phase 1 studies in healthy subjects, a Phase 1b study in patients with uncomplicated UTI (Study PTK0796-UUTI-15103), 2 Phase 3 studies in patients with skin infections (Studies PTK0796-CSSI-0804 and OASIS-1), and the Phase 3 OPTIC study in patients with CABP.[44,46] The results of this analysis demonstrated that the plasma PK of omadacycline in both healthy volunteers and patients were best described by a linear 3-compartment model with zero-order iv input or first-order absorption using transit compartments to account for a delay in oral absorption following administration of various tablet or capsule formulations. The final model could also characterize omadacycline ELF concentration-time profiles.

Results of the covariate analysis demonstrated that sex was a significant covariate on multiple PK parameters. However, despite the large number of relationships between PK parameters and sex included in the final model, the net effect on the omadacycline concentration-time profile was found to be minimal, as indicated by a less than 20% difference in omadacycline concentrations in typical males versus typical females at any given time. The final model estimated omadacycline total-drug ELF:free-drug plasma penetration ratio to be 2.06 when a protein binding estimate of 21% was utilized.[42] Goodness-of-fit diagnostics indicated an unbiased fit to the data, and the prediction-corrected visual predictive checks indicated that the final model was robust in its ability to predict both plasma and ELF exposures following omadacycline administration. Additionally, results of a subsequent assessment to qualify the population PK model using PK data from an external dataset, developed using data from OASIS-2, demonstrated that the predictive performance of the model was robust. These data further increase the confidence in individual predicted AUC values for the PK-pharmacodynamic (PD) analysis for efficacy described below. This population PK model, together with Monte Carlo simulation, were used to provide support for the dose justification for omadacycline in the CABP and ABSSSI indications.

1.4.2 Pharmacokinetics-Pharmacodynamics and Dose Justification

For the tetracyclines class, the PK-PD index associated with efficacy has been shown to be the AUC/MIC ratio.[47]

Data from a neutropenic-thigh infection model for omadacycline against Gram-positive and Gram-negative pathogens demonstrated that AUC/MIC ratio was the PK-PD index most closely associated with efficacy.[48] Omadacycline AUC/MIC ratio targets for *S. pneumoniae*, *H. influenzae*, and *S. aureus* efficacy were determined using data from a one-compartment in vitro and neutropenic murine-thigh and –lung infection models. The magnitude of the AUC/MIC ratio associated with net bacterial stasis as well as 1 and 2-$\log_{10}$ colony forming unit (CFU) reductions from baseline for each pathogen are summarized in Table 4.

Table 4. AUC/MIC Ratio Associated With Net Bacterial Stasis and 1 and 2 Log_{10} CFU Reductions From Baseline[a]

Organism	Infection Model (Exposure Matrix)	Magnitude of AUC/MIC Ratio by Endpoint		
		Net Bacterial Stasis	1-log_{10} CFU Reduction	2-log_{10} CFU Reduction
S. pneumoniae	Lung (ELF)	16.00 (14.2, 17.8)	13.3 (6.00, 17.6)[b]	23.20 (17.3, 47.3)
S. pneumoniae	Thigh (plasma)	31.2 (17.5, 53.4)	65.8 (30.4, 83.0)[b]	Not available
H. influenzae	in vitro (ELF)	6.91 (4.38, 8.76)	8.91 (5.44,11.60)	11.1 (6.72, 15.5)
S. aureus	Thigh (plasma)	21.9 (13.8, 51.1)	57.7 (32.2, 302.5)	Not available

a. Data presented as median (min, max).[49]

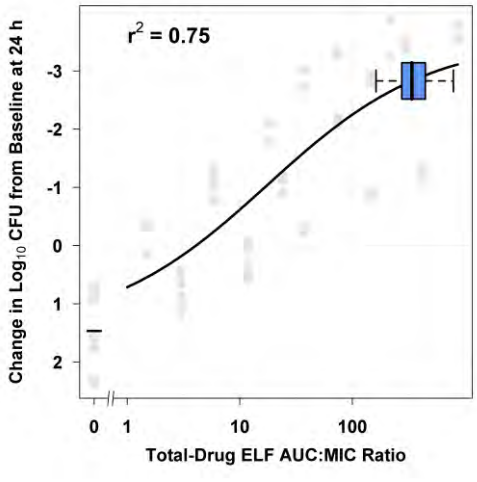
b. Determined excluding data for one *S. pneumoniae* isolate considered to be an outlier. The magnitude of the median (min, max) total-drug ELF AUC/MIC ratio target based on the inclusion of the outlier was 15.5 (6.00, 200.6).

AUC = area under the concentration-time curve, CFU = colony forming unit, ELF = epithelial lining fluid, MIC = minimum inhibitory concentration

Fitted functions showing the relationship between change in log_{10} CFU from baseline at 24 h and omadacycline AUC/MIC ratio, based on Hill-type models fit to data from in vitro and in vivo infection models, are shown in Figure 3. Distributions of expected AUC/MIC ratios based on average 24-h AUC values on Days 1-2 for simulated patients after iv doses (100 mg iv every 12 hours [q12h] on Day 1 followed by 100 mg iv every 24 h [q24h] on Day 2) and MIC values from 2016 in vitro surveillance data collected from North America are overlaid on the fitted functions. Given the importance of considering effect site exposures, distributions of AUC/MIC ratios overlaid on the Hill functions for *S. pneumoniae* and *H. influenzae* were based on total-drug ELF exposures. These data demonstrate that all patients would be expected to achieve AUC/MIC ratio targets associated with the endpoints of greatest interest for each indication (a 1-log_{10} CFU reduction from baseline for CABP and net bacterial stasis for ABSSSI).[50,51,52] Similar data were evident for simulated patients after a 300 mg po switch or who received the po dosing regimen (450 mg po q24h on Days 1 and 2 followed by 300 mg po q24h on Day 3). These data provide support for omadacycline iv-to-po and po dosing regimens studied in the Phase 3 clinical program.

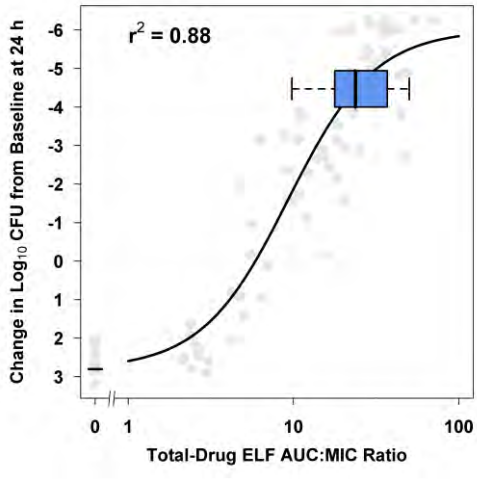
Figure 3. Nonclinical PK/PD Relationships for Efficacy, Overlaid with Box-And-Whisker Plots of AUC/MIC Ratios for Simulated Patients After Administration of the Omadacycline iv to po Dosing Regimen

S. pneumoniae



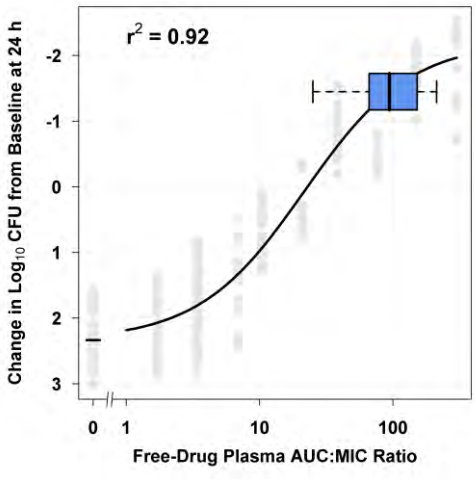
A

H. influenzae



B

S. aureus



C

The above-described average 24-h AUC values on Days 1-2 for simulated patients after iv doses were also used to assess percent probabilities of PK-PD target attainment by MIC. These data, overlaid on MIC distributions from in vitro surveillance data, are shown in Figure 4. Percent probabilities of PK-PD target attainment on Days 1-2 and the days of po switch, based on the total-drug ELF AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, of ≥ 90% at MIC values up to and including 0.5 µg/mL were achieved for the iv to po dosing regimen. Percent probabilities of PK-PD target attainment on Days 1-2 and the days of po switch based on the total-drug ELF AUC/MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* and *H. influenzae* of ≥ 90% at MIC values up to and including 0.5 and 1 µg/mL, respectively, were achieved for the iv to po dosing regimen. Percent

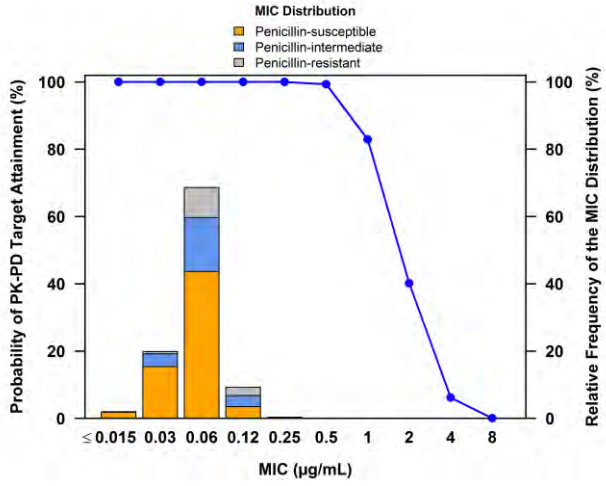
probabilities of PK-PD target attainment over the same periods of assessment based on the free-drug plasma AUC/MIC ratio target associated with net bacterial stasis for *S. aureus* of ≥ 90% at MIC values up to and including 0.12 µg/mL were achieved.

These data, which demonstrated high percent probabilities of PK-PD target attainment at the upper margins of the MIC distribution, also provide support for the omadacycline iv-to-po dosing regimen. For the po dosing regimen, percent probabilities on Days 1-2 of ≥ 90% were achieved at MIC values one dilution lower for each of the above-described 3 pathogens.

Figure 4. Percent Probabilities of PK/PD Target Attainment by MIC on Days 1-2 for *S. pneumoniae, H. influenzae,* and *S. aureus* Among Simulated Patients after the Omadacycline iv-to-po Dosing Regimen

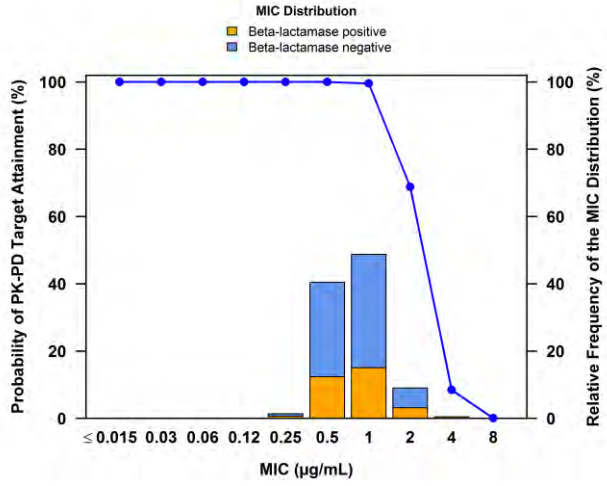
***S. pneumoniae* (ELF exposures and 1-log10 CFU reduction endpoint)**

A



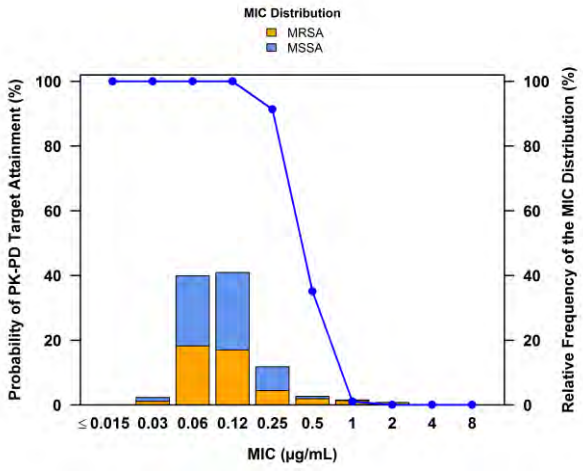
***H. influenzae* (ELF exposures and 1-log10 reduction endpoint)**

B



***S. aureus* (plasma exposures and stasis endpoint)**

C



In addition to the PK-PD target attainment analyses described above, PK-PD analyses for efficacy were conducted to assess the relationships between AUC/MIC ratio and efficacy endpoints using data from omadacycline-treated patients with ABSSSI or CABP. Note, PK-PD analyses for efficacy could not be carried out based on data for omadacycline-treated patients with CABP in OPTIC due to the limited PK data available (n = 11). Successful response was, however, observed for all patients at the end of treatment (EOT) and post-therapy evaluation (PTE) visits and for all but one patient at the Early Clinical Response (ECR) visits. The simulated total-drug ELF AUC/MIC ratios approached or exceeded nonclinical PK-PD targets for efficacy for patients with *S. pneumoniae* and *H. influenzae* or *Haemophilus parainfluenzae*.

Results of the PK-PD analyses for efficacy based on data from omadacycline-treated patients with ABSSSI and *S. aureus* at baseline in OASIS-1 and OASIS-2 revealed relationships between ECR and free-drug plasma AUC/MIC ratio evaluated in multiple forms. As free-drug plasma AUC/MIC ratio evaluated as a continuous variable increased, so too did the probability of clinical success at ECR ($p = 0.07$). For free-drug plasma AUC/MIC ratio evaluated as a 2-group variable, the percentage of patients with successful ECR was 80% (20/25) and 96.0% (96/100) for free-drug AUC/MIC ratio less than and greater than or equal to 12.5, respectively ($p = 0.016$). This free-drug plasma AUC/MIC ratio threshold was closely similar to that associated with net bacterial stasis described in Table 4. Model-predicted percent probabilities of a successful ECR in patients with *S. aureus* with a MIC value of 0.5 µg/mL ranged from 87.2 to 95.6% across univariable models with different forms of free-drug AUC/MIC ratio for the iv to po dosing and po dosing.

The above-described assessments based on nonclinical and clinical PK-PD data provide support for the proposed omadacycline iv to po and po dosing regimens with a loading dose for the common pathogens associated with both ABSSSI and CABP.

1.5 Nonclinical Studies

A robust nonclinical program of pharmacology, PK/absorption, distribution, metabolism, excretion, and toxicology studies has been completed to support the use of omadacycline in patients with serious ABSSSI and CABP infections. Omadacycline was well-tolerated in single and repeat-dose (up to 13 weeks for both iv and po dose administration) nonclinical toxicity studies conducted in rats and monkeys. Nonclinical findings were consistent with effects seen for the tetracycline class.

1.6 Clinical Development Program

The comprehensive clinical development program of omadacycline consisted of 22 Phase 1 studies and 5 Phase 2/3 clinical studies that enrolled more than 3,300 subjects. In total, 1,947 subjects were exposed to omadacycline, and 1,073 patients were exposed to omadacycline in the large pivotal Phase 3 studies at the proposed doses (Appendix Table 45, page 96).

The clinical development program for omadacycline initiated in 2005. During the clinical development for omadacycline, Paratek maintained an open and constructive dialogue with the US FDA. The omadacycline Phase 3 clinical program was paused as a result of the evolving regulatory science for antibiotic development. Following the passing of the Generating

Antibiotic Incentives Now (GAIN) Act by Congress to promote the development of new antibiotics to combat resistance, as well as clarity from the FDA on clinical study requirements, Paratek and the FDA agreed on the design of the Phase 3 program.

Paratek conducted 2 Phase 3 iv-to-oral studies (OPTIC in CABP and OASIS-1 in ABSSSI) for which the protocol designs were approved through the FDA's Special Protocol Assessment (SPA) process. As part of the approved SPAs, as well as alignment with the current guidance, FDA agreed that a single positive ABSSSI study and a single positive CABP study could support approval of omadacycline for both indications. Omadacycline was then granted Qualified Infectious Disease Product (QIDP) status and subsequently Fast Track designation for both the ABSSSI and CABP indications. Paratek conducted an additional Phase 3 Study (OASIS-2) in patients with ABSSSI to further demonstrate efficacy with oral-only treatment. These 3 pivotal Phase 3 studies were completed in accordance with both FDA[53] and European Medicines Agency (EMA)[54,55] guidances and comprise the Phase 3 pivotal studies supporting the NDA. All 3 studies are non-inferiority studies versus standard-of-care comparators. It was agreed with FDA that the comparators used (linezolid in ABSSSI and moxifloxacin in CABP) were the optimal and most appropriate choices based upon efficacy and in vitro spectrum.

Results of these 3 pivotal Phase 3 studies provide the required substantial evidence of efficacy and establish the safety and tolerability profile of omadacycline for the treatment of patients with ABSSSI and patients with CABP. For the primary efficacy outcome of ECR, omadacycline was non-inferior to linezolid in the ABSSSI studies and non-inferior to moxifloxacin in the CABP study. In these studies, omadacycline was safe and well tolerated, with similar percentages of patients with at least 1 TEAE in the pivotal Phase 3 studies among the omadacycline and comparator groups.

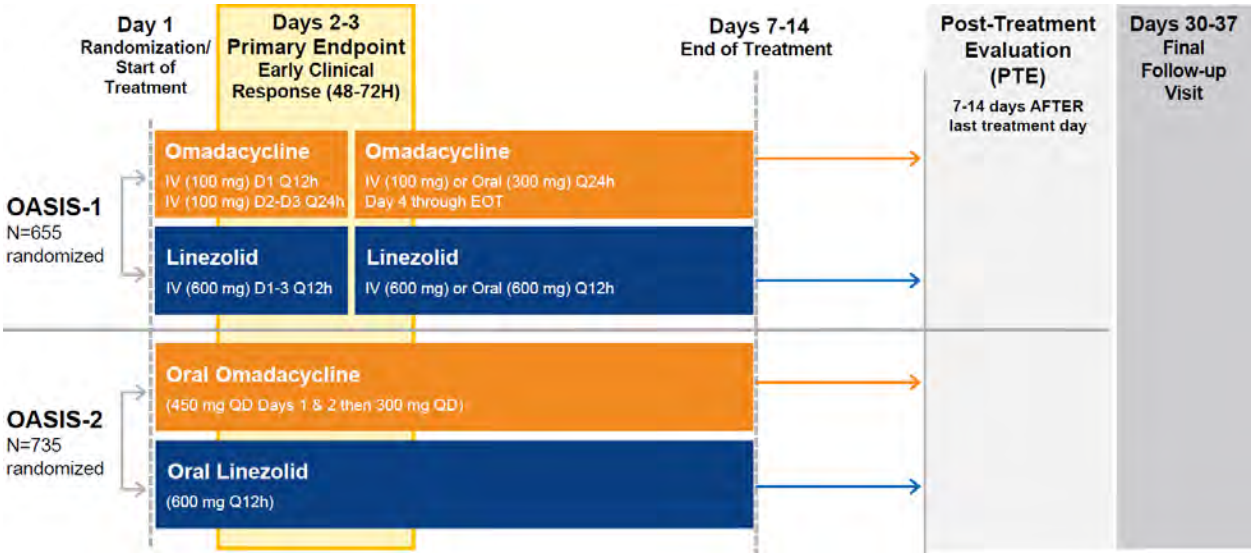
2 EFFICACY IN ABSSSI

2.1 Study Designs

The OASIS-1 and OASIS-2 studies were randomized (1:1), double-blind, double-dummy, active comparator-controlled, Phase 3 non-inferiority studies comparing omadacycline and linezolid for the treatment of adults with ABSSSI that was known or suspected to be due to a Gram-positive pathogen(s). The designs and dosing are summarized in Figure 5.

The number of patients with major abscess was limited to no more than 30% of randomized patients, and receipt of a prior antibiotic was not permitted in OASIS-1 whereas a single dose of a short-acting prior antibiotic was permitted in up to 25% of patients in OASIS-2. Patient randomization was stratified by type of infection (wound infection, cellulitis/erysipelas, and major abscess) and geographic region (OASIS-1 only; Western Europe/North America, Eastern Europe, and Rest of World). In OASIS-1, all patients were expected to present with ABSSSI severe enough that it required a minimum of at least 3 days of iv treatment.

Figure 5. Design of Omadacycline Pivotal, Double-blind Phase 3 Studies OASIS-1 and OASIS-2



The primary efficacy assessment occurred on Days 2 to 3 and the secondary efficacy assessment occurred at the PTE, which was 7 to 14 days after the last treatment day. For safety, patients were followed from time of consent to the final follow-up visit which occurred between Days 30 and 37.

Due to the lack of Gram-negative coverage for linezolid, a modified intent-to-treat (mITT) population was needed to exclude subjects with sole Gram-negative infections. The primary efficacy outcome was the percentage of patients with an ECR of clinical success at 48 to 72 h following the first dose of test article in the mITT population. The mITT population included all patients in the intent-to-treat (ITT) population who did not have an infection caused by a sole, potentially causative Gram-negative pathogen. Consistent with the FDA ABSSSI guidance, a margin of 10% was used for the assessment of non-inferiority. This margin was based on the historical data regarding the treatment effect of antibiotics in ABSSSI.[53]

In OASIS-1 for the primary efficacy endpoint of ECR, assuming a clinical success rate of 82% for both treatment groups, a non-inferiority margin of 10%, 90% power and a one-sided alpha of 0.025, using the sample size determination method of Farrington and Manning, a total of 632 patients were required.

In OASIS-2, for the ECR primary efficacy endpoint, assuming a clinical success rate of 79% for both treatment groups, a non-inferiority margin of 10%, 90% power and a one-sided alpha of 0.025, using the sample size determination method of Farrington and Manning, a total of 704 patients were required.

As patients with a sole Gram-negative potentially causative pathogen(s) were to be excluded from the primary analysis set, additional patients (approximately 3%) were added to provide an mITT population of sufficient size to demonstrate non-inferiority.

2.1.1 Selection of Patients

2.1.1.1 OASIS-1 (iv Followed by Oral)

Patients who were 18 years of age or older, had a qualifying skin and skin structure infection, and had evidence of a systemic response to infection were eligible for enrollment.

All qualifying lesions were ≥ 75 cm^2 in total surface area of contiguous involved tissue. Involved tissue was defined as tissue exhibiting clear evidence of one or more of the following: erythema, edema, or induration. The classification of qualifying skin and skin structure infections was as follows:

- **Wound infection:** an infection characterized by purulent drainage from a wound with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound.
- **Cellulitis/erysipelas:** a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration.
- **Major abscess:** an infection characterized by a collection of pus within the dermis or deeper with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the abscess.

Evidence of a systemic response to infection within the 24 h prior to randomization was indicated by one or more of the following:

- **Elevated white blood cell (WBC) count (≥ 10,000 cells/mm^3) or leukopenia (≤ 4,000 cells/mm^3);**
- **Elevated immature neutrophils** (≥ 15% band forms) regardless of total peripheral WBC count;
- **Lymphatic involvement**: lymphangitis or lymphadenopathy that was proximal to and in a location that suggested drainage from the qualifying infection; or
- **Fever or hypothermia** documented by the investigator (temperature > 38.0°C [100.4°F] or less than 36.0°C [95.5°F]).

The principal criteria for exclusion from the study were:

- Patients who received one or more doses of a potentially effective systemic antibacterial agent within 72 h prior to first dose of study drug;
- Patients who, for any reason, had used a topical antibacterial agent(s) with specific antibacterial activity continuously within 72 h prior to first dose of test article, if the agent(s) had been applied to the skin for ≥ 72 h;
- Infections:
  - Where the outcome was strongly influenced by factors other than protocol-defined treatment and procedures,
  - That required antibacterial treatment for greater than 14 days,

- Were associated with chronic skin lesions that could have obscured determination of response even after successful bacterial eradication had been achieved, or
- Were suspected or known to be caused by a pathogen resistant to either test article.

To exclude patients from participating in the study due to known side effects and contraindications for linezolid, patients who received a monoamine oxidase inhibitor within 14 days prior to Screening could not participate in the study.

2.1.1.2 OASIS-2 (Oral Only)

The selection criteria for patients in oral-only OASIS-2 were identical to the criteria above except for the following exclusion criteria:

- The patient's infection did not require the need of IV therapy
- Patients may have been eligible despite prior antibacterial therapy if they had been treated with a single dose of a short-acting antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day) in the 72 h prior to randomization.
- The limit for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values prior to randomization was increased from ≥ 2 times the upper limit of normal (ULN) to ≥ 3 times the ULN.
- The inability to tolerate po medication (eg, nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of po medication).

2.2 Efficacy Analysis

The primary efficacy outcome was the percentage of patients with an ECR of clinical success at 48 to 72 h after the first infusion of test article in the mITT population. To be considered as an early clinical success, the patient had to be alive, have at least a 20% reduction in lesion area from Screening, and not have received rescue antibiotics or other antibacterial therapy that may be effective for the ABSSSI. A 2-sided 95% confidence interval (CI) for the observed difference (omadacycline minus linezolid) in early clinical success rates was calculated using the method of Miettinen and Nurminen without adjustment for the randomization stratification factors. If the lower bound of the CI was greater than -10%, non-inferiority was to be declared.

The key secondary efficacy outcome was the percentage of patients with an investigator's assessment of clinical success (patient alive with infection sufficiently resolved such that further antibacterial therapy was not needed) at the PTE in the mITT population and clinically evaluable (CE) population (all patients in the ITT population who had a qualifying skin and skin structure infection, received the correct test article for at least 5 calendar days, had the necessary clinical evaluations performed, and did not receive potentially confounding nonstudy antibiotics). A 2-sided unadjusted 95% CI was constructed for the observed difference in the clinical success rates (omadacycline minus linezolid) using the method of Miettinen and Nurminen. The 2-sided 95% CI was for descriptive purposes only and no conclusions of non-inferiority were made.

2.3 Study Populations in the Pivotal Phase 3 Studies in ABSSSI

The pivotal Phase 3 studies in ABSSSI included patients with a range of infection types and severity, with median lesion sizes exceeding entry criteria by approximately 4-fold in each study. The demographic and disease characteristics of the ABSSSI study populations are generally consistent with the current demographics of patients presenting with ABSSSI worldwide and in the US. The worldwide increase in the rates of injection drug abuse, including in the US, have resulted in larger numbers of younger patients presenting with new or recurrent ABSSSI, including infections caused by MRSA.[56,57]

In both studies, the demographic characteristics were well matched between the 2 treatment groups (Appendix Table 46, page 97).

The majority of patients in both treatment groups were male (64.5% in OASIS-1 and 62.9% in OASIS-2). Approximately 90% of patients in OASIS-1 and 96% in OASIS-2 were aged between 18 and 64 years (overall mean age: 46.8 years and 43.7 years, respectively). In OASIS-1, a significant proportion of patients (37.5%) were inpatients at the time of initiation of test article. No patients were hospitalized for their skin infections at the start of treatment in the oral-only OASIS-2.

The most frequently reported conditions that preceded ABSSSI were recent trauma, infection from injection drug use, and a prior history of ABSSSI at rates of 61.9%, 52.0%, and 48.6%, respectively, in OASIS-1 and 73.6%, 68.6%, and 55.3%, respectively, in OASIS-2.

The incidences and distribution of pathogens observed in the studies were consistent with those observed in other recent ABSSSI studies.[58] *Staphylococcus aureus* was the most prevalent ABSSSI pathogen isolated at Baseline in both studies (OASIS-1: 68.4% omadacycline, 66.5% linezolid; OASIS-2: 79.7% omadacycline, 81.2% linezolid), followed by *Streptococcus anginosus* group (OASIS-1: 20.6% omadacycline, 16.3% linezolid; OASIS-2: 20.7% omadacycline, 15.7% linezolid), and *Streptococcus pyogenes* (OASIS-1: 4.8% omadacycline, 7.9% linezolid; OASIS-2: 10.5% omadacycline, 5.6% linezolid). The rates of MRSA were high in both studies (OASIS-1: 30.3% omadacycline, 22.0% linezolid; OASIS-2: 37.7% omadacycline, 37.3% linezolid).

2.4 Efficacy Results in the Pivotal Phase 3 ABSSSI Studies

2.4.1 Primary Efficacy Analysis

In both studies, omadacycline demonstrated non-inferiority to linezolid for ECR in the mITT population (Table 5).

OASIS-1

Clinical success rates at ECR were high (84.8% omadacycline, 85.5% linezolid) and similar between treatment groups (difference [95% CI]: 0.7 [-6.3, 4.9], Table 5). Given that the lower limit of the 95% CI for the treatment difference (omadacycline – linezolid) was greater than -10, omadacycline was considered non-inferior to linezolid.

The percentages of patients assessed as either clinical failure or indeterminate were similar between treatment groups. Reasons for clinical failure included lack of reduction in lesion size by at least 20% (5.1% omadacycline, 4.5% linezolid), adverse event (AE) requiring discontinuation of test article (1.6% omadacycline, 0.6% linezolid), discontinuation of test article with need for rescue antibacterial therapy (1.3% in both groups), and receipt of potentially effective systemic antibacterial therapy for a different infection than the ABSSSI during the study (0.6% omadacycline, 0% linezolid).

Of the patients who had an indeterminate outcome, most had an assessment outside of the 48 to 72 h window (5.1% omadacycline, 5.8% linezolid) or were lost to follow-up or withdrew consent (2.8% omadacycline, 2.6% linezolid).

OASIS-2

Clinical success rates at ECR were high (87.5% omadacycline and 82.5% linezolid) and similar between treatment groups (difference [95% CI]: 5.0 [-0.2, 10.3], Table 5). Given that the lower limit of the 95% CI for the treatment difference (omadacycline – linezolid) was greater than -10, omadacycline was considered non-inferior to linezolid.

The percentages of patients assessed as clinical failure were similar between treatment groups. The most common reason for clinical failure was less than a 20% reduction in lesion size from Baseline (5.8% omadacycline, 7.2% linezolid). Discontinuation of test article with need for rescue antibacterial therapy was uncommon at this early assessment time point (1.4% omadacycline, 1.7% linezolid).

A total of 5.3% and 8.6% of omadacycline and linezolid patients had an indeterminate response. Of the patients who had an indeterminate outcome, most had an assessment outside of the 48 to 72 h window (3.1% omadacycline, 5.6% linezolid), were lost to follow-up, or withdrew consent (2.2% omadacycline, 3.1% linezolid).

Table 5. ECR 48 to 72 h After the First Infusion of the Test Article in OASIS-1 and OASIS-2 (mITT Population)

Primary Efficacy Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
OASIS-1	**N = 316**	**N = 311**	
Clinical success	268 (84.8)	266 (85.5)	-0.7 (-6.3, 4.9)
Clinical failure or indeterminate	48 (15.2)	45 (14.5)	
Clinical failure	23 (7.3)	19 (6.1)	
Indeterminate	25 (7.9)	26 (8.4)	
OASIS-2	**N = 360**	**N = 360**	
Clinical success	315 (87.5)	297 (82.5)	5.0 (-0.2, 10.3)
Clinical failure or indeterminate	45 (12.5)	63 (17.5)	
Clinical failure	26 (7.2)	32 (8.9)	
Indeterminate	19 (5.3)	31 (8.6)	

Difference = observed difference in early clinical success rate between the omadacycline and linezolid groups.
95% CI was constructed based on the Miettinen and Nurminen method without stratification.
Percentages were based on the number of patients in each treatment group.
CI = confidence interval, ECR = Early Clinical Response, mITT = modified intent-to-treat.

2.4.2 Secondary and Additional Analyses

2.4.2.1 Investigator Assessment of Clinical Response

Analyses of secondary outcomes of investigator's assessment of clinical response (IACR) at end of treatment (EOT) and PTE in the mITT and CE populations in OASIS-1 and OASIS-2 supported the results seen for the primary efficacy outcome in the mITT population.

As summarized in Table 6, in both studies, the clinical success rates were high and similar between the treatment groups at PTE. In OASIS-1, in the mITT population, clinical success was 86.1% for omadacycline and 83.6% for linezolid at PTE. In OASIS-2, in the mITT population, clinical success at PTE was 84.2% for omadacycline and 80.8% for linezolid.

Clinical success rates were also high and similar between treatment groups in the CE population (OASIS-1: 96.3% omadacycline, 93.5% linezolid and OASIS-2: 97.9% omadacycline, 95.5% linezolid; Appendix Table 47, page 99).

Table 6. Comparison of Clinical Response at EOT and PTE in OASIS-1 and OASIS-2 (mITT Population)

	IACR at the EOT Visit		IACR at the PTE Visit	
Efficacy Outcome	**Omadacycline n (%)**	**Linezolid n (%)**	**Omadacycline n (%)**	**Linezolid n (%)**
OASIS-1	**N = 316**	**N = 311**	**N = 316**	**N = 311**
Clinical success	281 (88.9)	272 (87.5)	272 (86.1)	260 (83.6)
Clinical failure or indeterminate	35 (11.1)	39 (12.5)	44 (13.9)	51 (16.4)
Clinical failure	15 (4.7)	19 (6.1)	20 (6.3)	27 (8.7)
Indeterminate	20 (6.3)	20 (6.4)	24 (7.6)	24 (7.7)
OASIS-2	**N = 360**	**N = 360**	**N = 360**	**N = 360**
Clinical success	322 (89.4)	306 (85.0)	303 (84.2)	291 (80.8)
Clinical failure or indeterminate	38 (10.6)	54 (15.0)	57 (15.8)	69 (19.2)
Clinical failure	11 (3.1)	19 (5.3)	12 (3.3)	21 (5.8)
Indeterminate	27 (7.5)	35 (9.7)	45 (12.5)	48 (13.3)

Percentages were based on the number of patients in each treatment group.
EOT = end of treatment, IACR = Investigator's assessment of clinical response, mITT = modified intent-to-treat, PTE = post therapy evaluation, US = United States.

2.4.2.2 Clinical Response in Microbiologic Populations

Overall clinical response at the PTE visit was similar between the 2 treatment groups for the ME-PTE population in both studies (Table 7).

Table 7. Overall Clinical Response at the PTE Visit Based on Investigator Assessments in OASIS-1 and OASIS-2 (ME-PTE Populations)

Efficacy Outcome	Omadacycline n (%)	Linezolid n (%)	Difference	95% CI Without Stratification[a]	95% CI With Stratification[b]
OASIS-1					
ME-PTE	**(N = 188)**	**(N = 192)**			
Clinical success	183 (97.3)	180 (93.8)	3.6	(-0.6, 8.3)	(-0.6, 8.3)
Clinical failure	5 (2.7)	12 (6.3)	-	-	-
OASIS-2					
ME-PTE	**N = 220**	**N = 225**			
Clinical success	215 (97.7)	214 (95.1)	2.6	(-0.9, 6.6)	(-0.8, 6.7)
Clinical failure	5 (2.3)	11 (4.9)			

Difference was observed difference in overall clinical success rate at PTE between the omadacycline and linezolid groups.
Overall clinical response at PTE was based on the investigator assessment at the EOT and PTE visits.
Percentages were based on the number of subjects in each treatment group.
CI = confidence interval; EOT = end of treatment, ME = microbiologically evaluable; PTE = post therapy evaluation.

[a] 95% CI was constructed based on the Miettinen and Nurminen method without stratification.

[b] 95% CI was adjusted for type of infection and geographic region based on the Miettinen and Nurminen method with stratification, using Cochran-Mantel-Haenszel weights as stratum weights. The 4 geographic regions were combined into 1 group. Infection type was not combined.

2.4.2.3 Clinical Response by Pathogen

High rates of clinical success by Baseline pathogen (from the ABSSSI site or blood culture) were observed in both treatment groups and both studies at the ECR assessment and the investigator's assessments at PTE in the microbiological modified intent-to-treat (micro-mITT population) (Appendix Table 48, page 100 and Table 49, page 102, respectively).

In the pooled analysis of the ABSSSI Phase 3 studies, high investigator assessed clinical success rates at PTE were observed for common ABSSSI pathogens (Table 8). Specifically, clinical success rates at PTE were high for *S. aureus* (83.0% omadacycline and 81.3% linezolid), including MRSA, (84.4% omadacycline, 81.5% linezolid), and the *S. anginosus* group (80.8% omadacycline, 72.0% linezolid).

At the ECR assessments, early clinical success rates were high for MRSA (91.9% omadacycline, 88.5% linezolid) and methicillin-susceptible *S. aureus* (MSSA) (85.6% omadacycline, 81.9% linezolid). In patients with Group A or *S. pyogenes* (n = 40 omadacycline, n = 34 linezolid), clinical success rates were high and similar between treatment groups at the ECR (80.0% omadacycline, 88.2% linezolid) and PTE (70.0% omadacycline, 73.5% linezolid) assessments.

Table 8. Overall Clinical Success at PTE Visit Based on Investigator's Assessment by Baseline Pathogen From the ABSSSI Site or Blood Culture in Greater Than or Equal to 6 Patients in OASIS-1 and OASIS-2 (micro-mITT Population)

	Pooled OASIS-1 and OASIS-2	
Baseline Pathogen	**Omadacycline (N = 504) n/N1 (%)**	**Linezolid (N = 514) n/N1 (%)**
Gram-positive organisms (aerobes)		
Staphylococcus aureus	312/376 (83.0)	312/384 (81.3)
MRSA	146/173 (84.4)	128/157 (81.5)
MSSA	171/208 (82.2)	187/232 (80.6)
Staphylococcus lugdunensis	10/11 (90.9)	2/3 (66.7)
Streptococcus anginosus group	84/104 (80.8)	59/82 (72.0)
Streptococcus anginosus	31/35 (88.6)	21/27 (77.8)
Streptococcus intermedius	28/35 (80.0)	30/42 (71.4)
Streptococcus constellatus	24/34 (70.6)	14/21 (66.7)
Enterococcus faecalis	17/18 (94.4)	21/25 (84.0)
VSE	16/17 (94.1)	19/23 (82.6)
Beta hemolytic streptococcus	35/49 (71.4)	30/41 (73.2)
Group A or *Streptococcus pyogenes*	28/40 (70.0)	25/34 (73.5)
Streptococcus mitis	7/7 (100.0)	4/4 (100.0)
Streptococcus sanguinis	3/3 (100.0)	6/6 (100.0)
Gram-positive organisms (anaerobes)		
Peptostreptococcus species	12/13 (92.3)	8/9 (88.9)
Finegoldia magna	7/7 (100.0)	5/6 (83.3)
Clostridium species	15/16 (93.8)	17/22 (77.3)
Clostridium perfringens	5/6 (83.3)	11/14 (78.6)
Gram-negative organisms (aerobes)		
Enterobacteriaceae	30/38 (78.9)	30/40 (75.0)
Enterobacter cloacae	11/14 (78.6)	9/11 (81.8)
Escherichia coli	6/6 (100.0)	4/4 (100.0)
Klebsiella pneumoniae	8/11 (72.7)	6/11 (54.5)
Proteus mirabilis	3/4 (75.0)	7/8 (87.5)
Gram-negative organisms (anaerobes)		
Prevotella species	17/23 (73.9)	11/15 (73.3)
Prevotella melaninogenica	6/9 (66.7)	7/9 (77.8)

N1 = number of patients in the micro-mITT population in the treatment group with the Baseline pathogen. Percentages were based on N1, the number of patients with the indicated pathogen.
Patients with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Patients with the same pathogen identified from both the blood and primary ABSSSI cultures were counted only once.
ABSSSI = acute bacterial skin and skin structure infection, ECR = Early Clinical Response, micro-mITT = microbiological modified intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*, PTE = post therapy evaluation, VSE = vancomycin-susceptible enterococci.

2.4.2.3.1 Bacteremic Patients

Of the small number of patients who had bacteremia, most patients with bacteremia demonstrated clinical success at ECR and PTE in both ABSSSI studies (Table 9).

Table 9. Clinical Success at ECR and PTE in Subjects with Bacteremia in OASIS-1 and OASIS-2

	OASIS-1		OASIS-2	
	Omadacycline n (%)	**Linezolid n (%)**	**Omadacycline n (%)**	**Linezolid n (%)**
ECR (ME Population)				
Patients with bacteremia	9	9	2	6
Clinical Success	7 (77.8)	8 (88.9)	1 (50.0)	6 (100.0)
Clinical Failure	2 (22.2)	1 (11.1)	1 (50.0)	0
PTE (ME* Population)				
Patients with bacteremia	10	9	2	7
Clinical Success	9 (90.0)	9 (100.0)	1 (50.0)	5 (71.4)
Clinical Failure	1 (10.0)	0	1 (50.0)	2 (28.6)

*ME and CE population are the same when n (%) are based on patients in each treatment group with bacteremia.
CE = clinically evaluable, ECR = Early Clinical Response, ME = microbiological evaluable, PTE = post therapy evaluation.

2.4.2.4 Microbiological Outcomes

High eradication and presumed eradication per-patient microbiologic response rates at the PTE and EOT visits were observed in both treatment groups in both studies (Table 10). Very few patients had an unfavorable response at all time points.

There was no evidence of decreasing susceptibility to omadacycline during therapy in either study. Superinfections and new infections were rare in the micro-mITT population.

Table 10. Per-patient Favorable Microbiological Response at EOT and PTE Visits in OASIS-1 and OASIS-2 (micro-mITT Population)

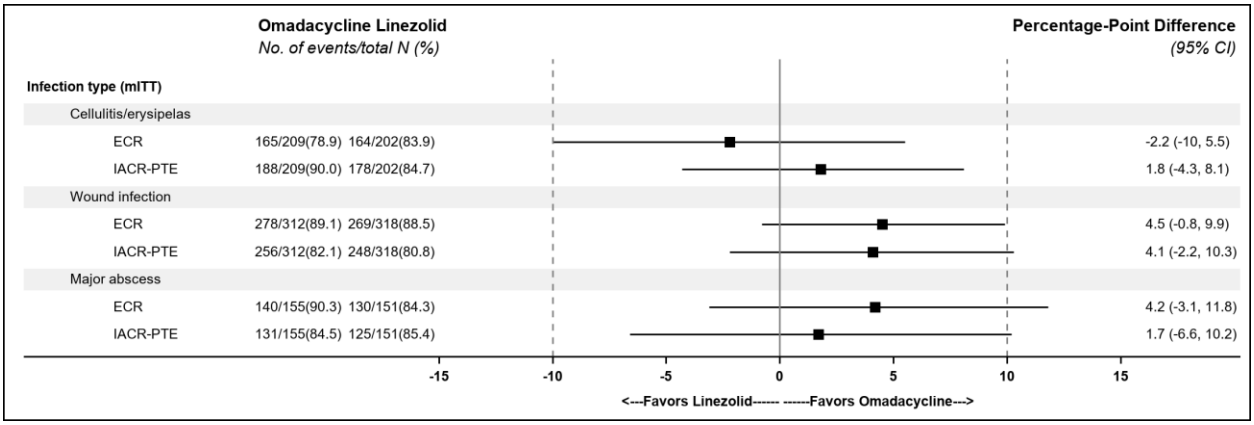
Visit/Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
OASIS-1	**N = 228**	**N = 227**	
Microbiological response at EOT visit	202 (88.6)	199 (87.7)	0.9 (-5.1, 7.0)
Overall microbiological response at PTE visit	194 (85.1)	189 (83.3)	1.8 (-4.9, 8.6)
OASIS-2	**N = 276**	**N = 287**	
Microbiological response at EOT visit	246 (89.1)	238 (82.9)	6.2 (0.5, 12.0)
Overall microbiological response at PTE visit	229 (83.0)	224 (78.0)	4.9 (-1.7, 11.5)

Difference = observed difference in favorable microbiological response rate between the omadacycline and linezolid groups.
95% CI was constructed based on the Miettinen and Nurminen method without stratification.
Percentages were based on the total number of patients at each visit in each treatment group.
CI = confidence interval, EOT = end of treatment, micro-mITT- = microbiological modified intent-to-treat, PTE = post therapy evaluation.

2.5 Subpopulation Analyses

Subpopulation analyses were performed to determine if there was an impact of infection type and lesion size on clinical outcome. A subpopulation evaluation of the pooled Phase 3 ABSSSI studies demonstrated that regardless of the infection type, omadacycline and linezolid had high clinical response rates that were similar to the overall results at ECR and PTE and were comparable between treatment arms (Figure 6).

Figure 6. Outcome by Infection Type at ECR and PTE in OASIS-1 and OASIS-2



ECR = Early Clinical Response, IACR = investigator's assessment of clinical response, PTE = post therapy evaluation.

Evaluation of the combined ABSSSI studies demonstrated similar clinical success at ECR regardless of lesion size group for both omadacycline and comparator (Table 11).

Table 11. Early Clinical Response 48 to 72 h After the First Dose of the Test Article by Size of Lesion at Baseline in OASIS-1 and OASIS-2 (mITT population)

	Omadacycline (N = 676)	Linezolid (N = 671)	Difference
Lesion area: ≤ 300 cm²	**322**	**332**	
Clinical Success	286 (88.8)	276 (83.1)	5.7 (0.4, 11.1)
Clinical Failure or Indeterminate	36 (11.2)	56 (16.9)	
Clinical Failure	16 (5.0)	27 (8.1)	
Indeterminate	20 (6.2)	29 (8.7)	
Lesion area: > 300 - 600 cm²	**222**	**219**	
Clinical Success	192 (86.5)	188 (85.8)	0.6 (-5.9, 7.2)
Clinical Failure or Indeterminate	30 (13.5)	31 (14.2)	
Clinical Failure	13 (5.9)	10 (4.6)	
Indeterminate	17 (7.7)	21 (9.6)	
Lesion area: > 600 - 1000 cm²	**87**	**70**	
Clinical Success	72 (82.8)	59 (84.3)	-1.5 (-13.2, 10.8)
Clinical Failure or Indeterminate	15 (17.2)	11 (15.7)	
Clinical Failure	9 (10.3)	6 (8.6)	
Indeterminate	6 (6.9)	5 (7.1)	
Lesion area: > 1000 cm²	**45**	**50**	
Clinical Success	33 (73.3)	40 (80.0)	-6.7 (-24.0, 10.5)
Clinical Failure or Indeterminate	12 (26.7)	10 (20.0)	
Clinical Failure	11 (24.4)	8 (16.0)	
Indeterminate	1 (2.2)	2 (4.0)	

mITT = modified intent-to-treat.

2.6 Efficacy Conclusions in ABSSSI

In OASIS-1 and OASIS-2, the following conclusions are based on the results of efficacy analyses:

- OASIS-1 and OASIS-2 provide the substantial evidence of efficacy required via FDA guidance and agreements to support the approval of ABSSSI.
- Omadacycline was non-inferior to linezolid for ECR in the mITT population. Clinical success rates were high in OASIS-1 (84.8% omadacycline, 85.5% linezolid; difference [95% CI]: 0.7 [-6.3, 4.9]) and OASIS-2 (87.5% omadacycline and 82.5% linezolid; difference [95% CI]: 5.0 [-0.2, 10.3])
- Analyses of secondary outcomes support the results seen for the primary efficacy outcome. Investigator assessed clinical success rates were high and similar between treatment groups at both the PTE and EOT visits.
- Among patients with ABSSSI caused by Gram-positive aerobes, including MRSA, EOT and PTE clinical success rates were high and similar between treatment groups for all of the major pathogens.

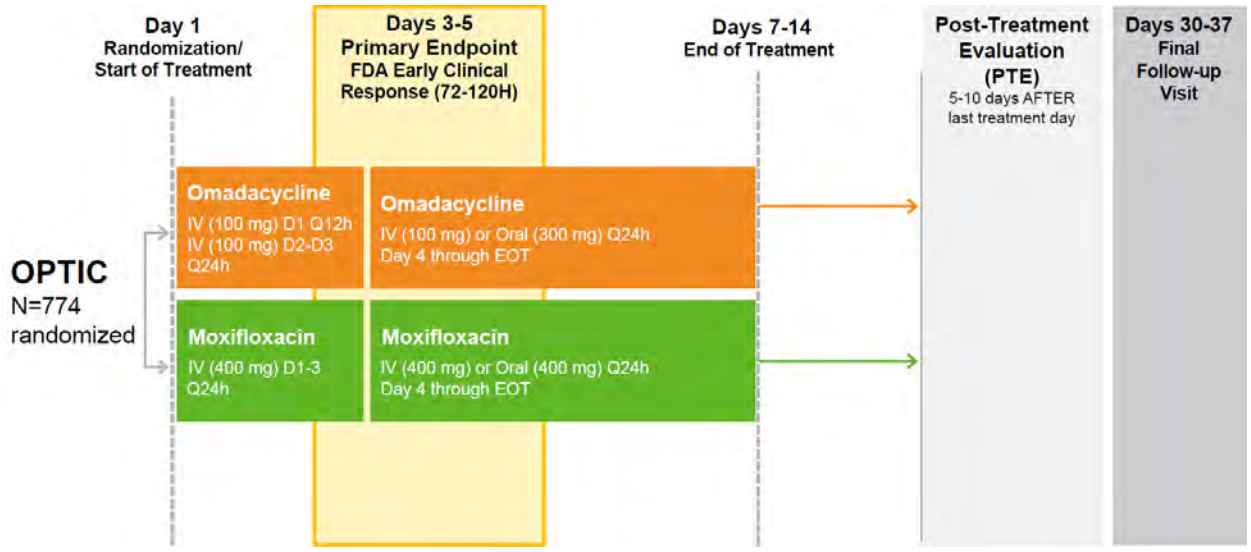
- Clinical success at ECR and PTE in bacteremia patients were similar.
- By-patient favorable microbiological response rates were high and similar between treatment groups at the EOT and PTE visits.
- Clinical response rates were high and similar between treatment groups at the ECR and PTE visits, including for MRSA.
- There was no evidence of decreasing susceptibility to omadacycline during therapy, and superinfections/new infections were rare.
- By infection type and lesion size, omadacycline demonstrated high clinical success rates that were similar to linezolid.

3 EFFICACY IN CABP

3.1 Study Design

OPTIC was a randomized (1:1), double-blind, double-dummy, active comparator-controlled, Phase 3 non-inferiority study comparing omadacycline and moxifloxacin for the treatment of adults with CABP. Patient randomization was stratified by 3 parameters: 1) Pneumonia Outcomes Research Team (PORT) Risk Class (II or III/IV), 2) receipt of an allowed antibacterial therapy in the 72 h prior to study treatment (yes or no), and 3) geographic region (Western Europe/North America, Eastern Europe, or Rest of World). Randomization of patients who had received an allowed antibacterial therapy in the 72 h prior to study treatment was capped at 25% of the patients randomized. The number of patients in Port Risk Class II was limited to no more than 15% of randomized patients. All patients were expected to present with CABP severe enough to require a minimum of at least 3 days of iv treatment. The study design and dosing regimens are summarized in Figure 7.

Figure 7. Design of Omadacycline Pivotal, Double-blind Phase 3 Study OPTIC



At the Screening visit, collection of an adequate quality respiratory specimen (quality expectorated or induced sputum or other respiratory specimen reflecting fluid from the lower respiratory tract such as, respiratory fluid obtained by bronchoalveolar lavage (BAL) or bronchoscopy, pleural fluid obtained by thoracentesis) was attempted from all patients and submitted to the local microbiology laboratory for Gram stain and culture, with isolates sent to the central laboratory for confirmation of identification of bacteria to genus and species. Additionally, blood samples were collected for serology testing for *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* by the central laboratory. Urine was collected at the Screening visit to test for the presence of *L. pneumophila* and *S. pneumoniae* antigens.

Consistent with the FDA guidelines,[38] the study was designed to show non-inferiority in the primary efficacy outcome of the percentage of patients with an ECR of clinical success at 72 to 120 hours following the first dose of test article in the ITT population. A non-inferiority margin of 10% was used for the analysis in the ITT population. The non-inferiority margin was based on the historical data regarding the treatment effect of antibiotics in pneumonia.

For ECR, assuming, a clinical success rate of 79% for both treatment groups, non-inferiority margin of 10%, a 1-sided alpha level of 0.025, there was 92% power to show non-inferiority with 750 patients in the ITT population.

3.1.1 Selection of Patients

3.1.1.1 Key Inclusion Criteria

Patients who were 18 years of age or older must have met all of the inclusion criteria, including the following, to be enrolled in the study.

1. Had at least 3 of the following symptoms:
    - Cough
    - Production of purulent sputum
    - Dyspnea (shortness of breath)
    - Pleuritic chest pain
2. Had at least 2 of the following abnormal vital signs:
    - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
    - Hypotension with systolic blood pressure (BP) less than 90 mm Hg
    - Heart rate (HR) greater than 90 bpm)
    - Respiratory rate (RR) greater than 20 breaths/min

3. Had at least 1 clinical sign or laboratory finding associated with CABP:
    - Hypoxemia (partial pressure of arterial oxygen [PaO_2] < 60 mm Hg by arterial blood gas [ABG] or oxygen saturation < 90% by pulse oximetry)
    - Physical examination findings of pulmonary consolidation (eg, dullness on percussion, bronchial breath sounds, or egophony)
    - An elevated total WBC count (> 12,000 cells/mm^3) or leukopenia (WBC < 4,000 cells/mm^3) or elevated immature neutrophils (> 15% band forms regardless of total peripheral WBC count)
4. Radiographically-confirmed pneumonia, ie, new or progressive pulmonary infiltrate(s) on chest X-ray or chest computed tomography (CT) scan consistent with acute bacterial pneumonia within 24 h prior to the first dose of test article.
5. Had disease categorized as being PORT Risk Class II, III, or IV at Screening.
6. Was expected to require a minimum of at least 3 days of iv therapy for the initial treatment of CABP.

3.1.1.2 Key Exclusion Criteria

Patients, who met any of the exclusion criteria, including the following, were not to be enrolled in the study:

1. Had received 1 or more dose(s) of a potentially effective systemic antibacterial treatment within the 72 h prior to the first dose of test article (a patient was considered to have received a potentially effective systemic antibacterial treatment if the pathogen identified as causing the infection was shown to be susceptible to the antibacterial given or, in the circumstance where a pathogen was not identified, if the antibacterial agent was approved for the treatment of pneumonia or was known to have activity against any of the leading causes of CABP [eg, *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus, L. pneumophila*]). Patients may have been eligible despite prior antibacterial therapy if they had been treated with a single dose of a short-acting antibacterial (ie, an antibacterial whose standard dosing regimen was more frequent than once per day).
2. Was known or suspected to have CABP caused by a pathogen that may have been resistant to either test article (eg, *K. pneumoniae*, *P. aeruginosa*, *P. jiroveci*, obligate anaerobes, mycobacteria, fungal pathogens).
3. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any fluoroquinolone antibiotic.
4. Had suspected or confirmed empyema (a parapneumonic pleural effusion was not an exclusion criteria) or lung abscess.
5. Patients with known or suspected hospital-acquired pneumonia or healthcare-associated pneumonia. Hospital-acquired pneumonia was defined as pneumonia with an onset of clinical signs and symptoms greater than or equal to 48 h after hospitalization in an acute in-patient healthcare facility. Healthcare-associated pneumonia was defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility (eg, nursing home) or in a patient

admitted with pneumonia following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for ≥ 48 h).

6. Required acute pharmacologic intervention to stabilize BP and/or adequate tissue perfusion, or had evidence of septic shock, defined by all of the following:
   - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
   - HR greater than 90 bpm
   - Respiratory rate greater than 20 breaths/min
   - WBC greater than 12,000 cells/mm^3 or less than 4,000 cells/mm^3 or greater than 10% immature (band) forms regardless of the total peripheral WBC count
   - Hypotension with systolic BP less than 90 mm Hg despite an iv fluid challenge of 20 to 30 cc/kg over a 30minute period
   - Perfusion abnormalities that include but were not limited to lactic acidosis (blood lactate concentration ≥ 4 mmol/L), oliguria, or acute alteration in mental status.
7. Known or suspected primary or metastatic neoplastic lung disease, aspiration pneumonia, cystic fibrosis, active tuberculosis, bronchiectasis, bronchial obstruction (eg, post-obstructive pneumonia), chronic neurological disorder preventing clearance of pulmonary secretions, or severe COPD.

Patients who had contraindications for moxifloxacin were excluded from participating in the study, including patients with a QT interval corrected for HR using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females) and who were known to have long QT syndrome, use drugs of potential proarrhythmic or QT prolonging effect and/or present with tachyarrhythmia could not participate in the study.

3.2 Efficacy Analysis

The efficacy analysis was designed to be consistent with the FDA guidelines for the development of drugs for the treatment of CABP.[38] The primary efficacy outcome was percentage of patients in the ITT population with an early clinical success at 72 to 120 h after administration of the first dose of test article using the investigator's assessment of the subject's symptoms associated with CABP entered into the electronic case report form. The severity of the subject's CABP symptoms of cough, sputum production, pleuritic chest pain and dyspnea will be evaluated on a 4-point scale (absent, mild, moderate, or severe) based upon the CABP Subject Symptom Severity Guidance Framework for Investigator Assessment (Table 12).

Table 12. CABP Subject Symptom Severity Guidance Framework for Investigator Assessment in OPTIC

	Severity			
Symptom	**Absent**	**Mild**	**Moderate**	**Severe**
Cough?	No cough or resolution (to pre-CABP Baseline)	Cough present but it does not interfere with subject's usual daily activities	Cough present, frequent and it does interfere with some of the subject's usual daily activities	Cough is present throughout the day and night; it limits most of the subjects' usual daily activities and sleep patterns
Pleuritic chest pain?	No chest pain or resolution of chest pain related to CABP	Chest pain present occasionally with deep breathing but it does not interfere with subject's usual daily activities	Chest pain is present with normal breaths and it does interfere with the subject's usual daily activities	Chest pain is present at rest and/or with shallow breathing; it limits most of the subject's usual daily activities
Shortness of breath?	No shortness of breath or resolution (to pre-CABP Baseline)	Shortness of breath with strenuous activities only but it does not interfere with subject's usual daily activities	Shortness of breath with usual activities and it does interfere with the subject's usual daily activities	Shortness of breath with minimal exertion or at rest; it limits most of the subject's usual daily activities
Phlegm/sputum production?	No coughing up of phlegm/sputum or resolution (to pre-CABP Baseline)	Subject coughs up a small amount of phlegm/sputum	Subject coughs up a moderate amount of phlegm/sputum	Subject coughs up a large amount of phlegm/sputum

CABP = community-acquired bacterial pneumonia, CSR = clinical study report.

The categories of ECR were defined as follows:

Clinical Success at the ECR assessment was defined as meeting the following:

- Survival with improvement of at least 1 level (ie, severe to moderate, moderate to mild, mild to absent) compared to Baseline (Screening) in at least 2 CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) with no worsening by at least 1 level in the other inclusion CABP symptoms.
- The patient did not meet any criteria for clinical failure or indeterminate ECR (see below for definitions).

Clinical Failure was defined as meeting any of the following criteria:

- There was no improvement by at least 1 level (ie, severe to moderate, moderate to mild, mild to absent) compared to Baseline (Screening) in 2 CABP symptoms,
- Any of the 4 CABP symptoms were worse (by at least 1 level) compared to Baseline (Screening),
- The patient required alternative (rescue) antibacterial treatment for CABP prior to the ECR assessment related to either (a) progression or development of new symptoms attributable to

CABP or (b) development of infectious complications of CABP (eg, empyema, lung abscess),

- The patient was receiving antibacterial therapy that may have been effective for the infection under study for a different infection from the one under study,
- Discontinued study therapy due to an AE prior to the ECR assessment,
- Death prior to the ECR assessment.

Indeterminate was defined as the clinical response to test article could not be adequately inferred because the patient was not seen for the evaluation because they withdrew consent, was lost to follow-up, or other specified reason.

The non-inferiority hypothesis test was performed at the 1-sided 2.5% level of significance. This was based on the lower limit of the 2-sided 95% CI (calculated using the method of Miettinen and Nurminen without stratification) for the observed difference in ECR rates (omadacycline group minus moxifloxacin group).

The key secondary efficacy outcome was investigator assessment at the PTE visit (derived from the assessments at the EOT and PTE visit). Clinical success was defined as survival without receiving any systemic antibacterial therapy other than test article, resolution of signs and symptoms of the infection present at Screening with no new symptoms or complications attributable to CABP and no need for further antibacterial therapy.

The per-patient microbiological response at the EOT and PTE visits in the microbiological intent-to-treat (microITT), microbiologically evaluable (ME)-EOT (EOT visit only) and ME-PTE (PTE visit only) populations were determined to support the clinical findings.

3.3 Study Population

The patients enrolled in OPTIC were representative of patients with moderate to severe CABP symptoms requiring initial non-intensive care unit hospitalization and iv therapy based on age, PORT Risk Class, comorbidity, bacterial pathogen, and symptom severity.[30,59]

The treatment groups were well matched with respect to demographic and other disease characteristics at Baseline (Table 13). Most of the patients were white males, and the overall population mean age was 61.5 years; 42% of patients were 65 years of age or older and 20% of patients were 75 years of age or older.

Overall, 64% of patients were enrolled in Eastern Europe, 24% in Western Europe/North America, and 12% in the Rest of World.

Table 13. Demographic and Baseline Characteristics in OPTIC (ITT Population)

Characteristics	Omadacycline N = 386	Moxifloxacin N = 388
Gender, n (%)		
Female	178 (46.1)	169 (43.6)
Male	208 (53.9)	219 (56.4)
Race, n (%)		
White	356 (92.2)	355 (91.5)
Black	11 (2.8)	7 (1.8)
Asian	17 (4.4)	18 (4.6)
American Indian or Alaska Native	0	2 (0.5)
Other	2 (0.5)	6 (1.5)
Ethnicity, n (%)		
Hispanic or Latino	10 (2.6)	14 (3.6)
Not Hispanic or Latino	372 (96.4)	370 (95.4)
Not reported/unknown	4 (1.0)	4 (1.0)
CrCL (local lab), n (%)		
Normal renal function (> 80 mL/min)	187 (48.4)	207 (53.4)
Mild renal impairment (> 50-80 mL/min)	128 (33.2)	119 (30.7)
Moderate renal impairment (30-50 mL/min)	70 (18.1)	62 (16.0)
Severe renal impairment (< 30 mL/min)	1 (0.3)	0

For each categorical parameter, the denominator for the percentage was the number of patients who had that parameter assessed.
BMI = body mass index, CABP = community-acquired bacterial pneumonia, CrCL = creatinine clearance, ITT = intent-to-treat.
[a] P-values for differences between treatment groups were from Fisher's exact test (for categorical variables) or Wilcoxon Rank Sum test (for continuous variables).
[b] Age was calculated from the date of birth to the informed consent date.

Hypertension, diabetes mellitus, and COPD were the most common comorbidities, each present in greater than 10% of the patients in both treatment groups at Baseline (Table 14). Approximately 44% of patients were current (24%) or former (20%) smokers.

Table 14. Summary of Medical and Procedural History (≥ 5% of Patients) in OPTIC (ITT Population)

Characteristics	Omadacycline N = 386 n (%)	Moxifloxacin N = 388 n (%)
Subjects with at least 1 medical history and/or procedural history event	321 (83.2)	313 (80.7)
Hypertension	191 (49.5)	195 (50.3)
Diabetes mellitus	63 (16.3)	71 (18.3)
COPD	57 (14.8)	50 (12.9)
Atrial fibrillation	39 (10.1)	35 (9.0)
Coronary artery disease	35 (9.1)	33 (8.5)
Cardiac failure	28 (7.3)	26 (6.7)
Menopause	28 (7.3)	30 (7.7)
Asthma	26 (6.7)	26 (6.7)
Myocardial ischemia	24 (6.2)	27 (7.0)
Chronic cardiac failure	22 (5.7)	20 (5.2)
Pneumonia	21 (5.4)	13 (3.4)
Obesity	13 (3.4)	21 (5.4)
Appendectomy	10 (2.6)	21 (5.4)

Percentages were based on the ITT population.
Coding of PTs was based on MedDRA Version 17.1.
COPD = chronic obstructive pulmonary disease; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

Clinical symptoms of CABP present at Baseline including cough and dyspnea were considered moderate to severe for ≥ 70% of patients. In addition, approximately half of all patients had moderate to severe pleuritic chest pain and phlegm/sputum production at Baseline.

Based on radiologic evaluation of pneumonia at Baseline, all patients had pulmonary infiltrates as required for study enrollment. Furthermore, 24.1% of omadacycline patients and 29.1% of moxifloxacin patients had multilobar infiltrates. Pleural effusion was present in 15.5% omadacycline patients and 16.8% of moxifloxacin patients.

To be eligible for the study, patients needed to have 2 abnormal vital signs and 1 clinical sign or laboratory finding associated with CABP. The presentation of abnormal vital signs, clinical signs, and laboratory findings was balanced between the groups. In both groups, most patients had a respiratory rate of greater than 20 breaths/min (87.4% omadacycline, 88.4% moxifloxacin). Fever (> 38.0°C) was present in 47.2% and 45.6% of the omadacycline and moxifloxacin groups, respectively. Hypoxemia (defined as PaO_2 < 60 mm Hg by ABG or oxygen saturation < 90% by pulse oximetry) was present in 46.6% and 46.8% of the omadacycline and moxifloxacin groups, respectively. In addition, an elevated WBC count (defined as > 12,000 cells/mm^3), leukopenia (defined as a WBC count of < 4,000 cells/mm^3), or elevated immature neutrophils (defined as > 15% bands) was present in 37.9% and 37.1% of the omadacycline and moxifloxacin groups, respectively. Tachycardia (> 90 bpm) was observed in a

higher percentage of patients in the omadacycline group versus the moxifloxacin group (42.2% versus 34.0%, respectively) (Appendix Table 50, page 104).

Patients enrolled in OPTIC had moderate-to-severe CABP requiring hospitalization (Table 15). In both groups, over 85% of patients had a PORT Risk Class of III or IV, with 58.8% of omadacycline and 55.7% moxifloxacin of patients having a PORT Risk Class of III and 26.4% omadacycline patients and 29.6% moxifloxacin having PORT Risk Class IV, as summarized in Table 15.

Most patients had evidence of systemic inflammatory response syndrome (SIRS) at Baseline (74.6% omadacycline, 73.7% moxifloxacin). Few patients in either treatment group had bacteremia at Baseline (3.9% omadacycline, 4.6% moxifloxacin). More moxifloxacin patients (22.4%) than omadacycline patients (16.6%) received corticosteroids.

Table 15. Baseline Factors in OPTIC (ITT Population)

Characteristics	Omadacycline N = 386	Moxifloxacin N = 388	All Patients N = 774
PORT Risk Class (actual), n (%)[a]			
I (0 ≤ Port Score ≤ 50)	2 (0.5)	2 (0.5)	4 (0.5)
II (51 ≤ Port Score ≤ 70)	55 (14.2)	54 (13.9)	109 (14.1)
III (71 ≤ Port Score ≤ 90)	227 (58.8)	216 (55.7)	443 (57.2)
IV (91 ≤ Port Score ≤ 130)	102 (26.4)	115 (29.6)	217 (28.0)
III-IV (71 ≤ Port Score ≤ 130)	329 (85.2)	331 (85.3)	660 (85.3)
V (Port Score ≥ 131)[a]	0	1 (0.3)	1 (0.1)
Patients who met the modified ATS criteria for severe CABP, n (%)[b]			
n	368	370	738
Yes	44 (12.0)	53 (14.3)	97 (13.1)
No	324 (88.0)	317 (85.7)	641 (86.9)
Patients with SIRS, n (%)[c]			
Yes	288 (74.6)	286 (73.7)	574 (74.2)
No	98 (25.4)	102 (26.3)	200 (25.8)
Patients with bacteremia, n (%)[d]			
Yes	15 (3.9)	18 (4.6)	33 (4.3)
No	371 (96.1)	370 (95.4)	741 (95.7)
Received corticosteroids 72 hours pre or post first infusion, n (%)			
Yes	64 (16.6)	87 (22.4)	151 (19.5)
No	322 (83.4)	301 (77.6)	623 (80.5)

For each categorical parameter, percentages are based on the number of patients who had that parameter assessed.
ATS = American Thoracic Society, bpm = beats per min, HR = heart rate, ITT = intent-to-treat, max = maximum, min = minimum, PaO_2 = partial pressure of arterial oxygen, PORT = Pneumonia Outcomes Research Team, RR = respiratory rate, SD = standard deviation, SBP = systolic blood pressure, SIRS = systemic inflammatory response syndrome, WBC = white blood cell.

[a] Patients with PORT Risk categories I and V were thought to have a qualified PORT Risk Class of II, III, or IV at enrollment (based on the inclusion criteria), but were later determined to be PORT Risk I or V.

[b] Defined as the presence of ≥ 3 of the following 9 criteria at Baseline: RR ≥ 30 breaths/min, O_2 saturation < 90% or PaO_2 < 60 mm Hg, urea ≥ 20 mg/dL, WBC < 4,000 cells/mm^3, confusion, multilobar

Table 15. Baseline Factors in OPTIC (ITT Population)

Characteristics	Omadacycline N = 386	Moxifloxacin N = 388	All Patients N = 774

infiltrates, platelets < 100,000 cells/mm^3, temperature < 36°C, and SBP < 90 mm Hg.

[c] Defined as having 2 or more of the following 4 symptoms at Baseline: temperature < 36°C or > 38°C (oral or oral equivalent), HR > 90 bpm, RR > 20 breaths/min, WBC < 4,000 cells/mm^3 or WBC > 12,000 cells/mm^3, or bands > 10%.

[d] Patients with a positive blood culture (bacteremia).

3.4 Microbiology

The microITT population consisted of all patients in the ITT population who had at least 1 causative bacterial pathogen identified at Baseline and included a total of 52.8% of omadacycline patients and 46.9% of moxifloxacin patients.

The distribution of pathogenic organisms from the blood specimens, respiratory specimens, urinary antigen test, and/or serology at Baseline was similar between treatment groups. *S. pneumoniae* was the most common pathogen identified from respiratory specimens (21.1% omadacycline, 18.7% moxifloxacin) and also the most common pathogen causing bacteremia: 10 patients in the omadacycline group and 16 patients in the moxifloxacin group. The majority of *S. pneumoniae* were penicillin-susceptible (26 of 43 omadacycline patients and 22 of 34 moxifloxacin patients) and multi-drug resistant (MDR) *S. pneumoniae* was present in 7 omadacycline patients and 6 moxifloxacin patients; no patients in either treatment group were infected with penicillin-nonsusceptible *S. pneumoniae*. Macrolide-resistant *S. pneumoniae* was present in 10 omadacycline patients and 5 moxifloxacin patients. Seventeen omadacycline patients and 16 moxifloxacin patients had tetracycline-resistant pathogens. Nearly 40% of patients with pathogens identified were infected with aerobic Gram-negative pathogens.

3.5 Efficacy Results in the Pivotal Phase 3 Study in CABP

3.5.1 Primary Efficacy Analysis

In this large study, in the ITT population (Table 16), ECR clinical success rates were high (81.1% omadacycline, 82.7% moxifloxacin) and similar between treatment groups (difference [95% CI]: -1.6 [-7.1, 3.8]). Given that the lower limit of the 95% CI for the treatment difference (omadacycline – moxifloxacin) was greater than -10, omadacycline was considered non-inferior to moxifloxacin.

The percentages of patients assessed as either clinical failure or indeterminate were similar between treatment groups. Reasons for clinical failure at 72 to 120 h included (more than 1 reason could have applied to a given patient):

- Any of the 4 CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) were worse by at least 1 level (7.3% omadacycline, 5.4% moxifloxacin).

- No improvement by at least 1 level was observed in 2 of the CABP symptoms (5.7% omadacycline, 5.9% moxifloxacin).
- AE requiring discontinuation of test article (2.1% omadacycline, 1.8% moxifloxacin)
- Patient required an alternative (rescue) antibacterial treatment (1.3% omadacycline, 2.3% moxifloxacin).
- Patient received antibacterial therapy that may have been effective for the infection under the study (0.5% omadacycline patients, no moxifloxacin patients).

Of the patients who had an indeterminate outcome, 4.7% omadacycline and 3.9% moxifloxacin patients either withdrew consent, were lost to follow-up, or missed the visit; 1.6% omadacycline and 1.3% moxifloxacin patients had an assessment completed outside of the 72 to 120 h window.

Table 16. ECR 72 to 120 h After the First Infusion of the Test Article in OPTIC (ITT Population)

Efficacy Outcome	Omadacycline N = 386 n (%)	Moxifloxacin N = 388 n (%)	Difference (95% CI)
Clinical success	313 (81.1)	321 (82.7)	-1.6 (-7.1, 3.8)
Clinical failure or indeterminate	73 (18.9)	67 (17.3)	
Clinical failure	49 (12.7)	47 (12.1)	
Indeterminate	24 (6.2)	20 (5.2)	

Difference = observed difference in early clinical success rate between the omadacycline and moxifloxacin groups.
95% CI was constructed based on the Miettinen and Nurminen method without stratification.
Percentages were based on the number of patients in each treatment group.
CABP = community-acquired bacterial pneumonia; CI = confidence interval, ECR = Early Clinical Response, ITT = intent-to-treat.

3.5.2 Secondary and Additional Analyses

3.5.2.1 Investigator Assessment of Clinical Response

Analyses of outcomes of Investigators assessment at EOT and PTE in the ITT and CE populations supported the results seen for the primary efficacy outcome in the ITT population (Table 17).

The rates of clinical success were high in both treatment groups for IACR in the ITT and CE populations at the EOT and PTE visits. In the omadacycline group, the clinical success rates at all timepoints ranged from 81.1% to 90.4% in the ITT population, and 87.0% to 92.9% in the CE populations. Similar results were observed in the moxifloxacin group.

Table 17. Clinical Response at EOT and PTE Visits in OPTIC (ITT and CE Populations)

Analysis Population Efficacy Outcome	IACR at the EOT Visit Omadacycline n (%)	IACR at the EOT Visit Moxifloxacin n (%)	IACR at the PTE Visit Omadacycline n (%)	IACR at the PTE Visit Moxifloxacin n (%)
ITT	**N = 386**	**N = 388**	**N = 386**	**N = 388**
Clinical success	349 (90.4)	341 (87.9)	338 (87.6)	330 (85.1)
Clinical failure or indeterminate	37 (9.6)	47 (12.1)	48 (12.4)	58 (14.9)
Clinical failure	27 (7.0)	36 (9.3)	32 (8.3)	42 (10.8)
Indeterminate	10 (2.6)	11 (2.8)	16 (4.1)	16 (4.1)
CE-EOT / CE-PTE	**N = 357**	**N = 357**	**N = 340**	**N = 345**
Clinical success	336 (87.0)	329 (84.8)	316 (92.9)	312 (90.4)
Clinical failure	21 (5.4)	28 (7.2)	24 (7.1)	33 (9.6)

Percentages were based on the number of patients in each treatment group.
CE = clinically evaluable; CI = confidence interval; EOT = end of treatment; IACR = investigator assessment of clinical response; ITT = intent-to-treat, PTE = post therapy evaluation.

Table 18 shows the clinical failures by treatment and the reason for failure at EOT and PTE.

Table 18. Reasons for Investigator Assessment of Clinical Failure at EOT and for Overall Assessment at PTE in OPTIC (ITT Population)

Reason for Clinical Failure	Omadacycline (N=386) n(%)	Moxifloxacin (N=388) n(%)
EOT (Number of Clinical Failures)	27	36
Subject required alternative antibacterial treatment for CABP related to progression or development of new symptoms to CABP	0	0
Development of infectious complications of CABP	2 (0.5)	5 (1.3)
Development of an AE that required discontinuation of study therapy	7 (1.8)	10 (2.6)
Subject received antibacterial therapy for an infection unrelated to CABP	1 (0.3)	2 (0.5)
Subject died before evaluation	4 (1.0)	1 (0.3)
Overall Assessment at PTE (Number of Clinical failures)	32	42
Clinical failure at the EOT visit	26 (6.7)	36 (9.3)
Subject required alternative antibacterial treatment for CABP related to progression or development of new symptoms to CABP	0	0
Development of infectious complications of CABP	2 (0.5)	2 (0.5)
Subject received antibacterial therapy for an infection unrelated to CABP	3 (0.8)	4 (1.0)
Subject died before evaluation	4 (1.0)	3 (0.8)

Percentages are based on the number of subjects in each treatment group.
Reasons for failure are not mutually exclusive.
EOT = end of treatment; ITT = intent-to-treat, PTE = post therapy evaluation.

In additional to the aforementioned results, in a prespecified analysis for the European Medicines Agency (EMA), the co-primary efficacy endpoint was the overall assessment of clinical response at PTE (derived from the investigator's assessments at the EOT and PTE visits) in the ITT and

CE-PTE populations. All analyses of the IACR at the EOT and PTE visits were limited to subjects with a PORT Risk Class of III/IV. However, in this analysis, a more stringent non-inferiority margin was used. If the lower limit of the 97.5% CI for the difference in both the ITT and CE-PTE populations exceeded -10%, then the null hypothesis was rejected and the non-inferiority of omadacycline to moxifloxacin was declared. In this analysis Omadacycline was non-inferior to moxifloxacin for the overall clinical response at PTE. The number and percentage of subjects classified as clinical success, clinical failure, and indeterminate by the investigator's assessment at PTE calculated for each treatment group in subjects with a PORT Risk Class of III/IV (ITT and CE populations) is summarized in Table 19.

Table 19. Overall Clinical Response at the PTE Visit Based on Investigator's Assessments (ITT and CE-PTE Populations – Subjects With a PORT Risk Class of III/IV)

Efficacy Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (97.5% CI)
ITT	N = 329	N = 331	
Clinical success	291 (88.4)	282 (85.2)	3.3 (-2.7, 9.3)
Clinical failure or indeterminate	38 (11.6)	49 (14.8)	
Clinical failure	27 (8.2)	35 (10.6)	
Indeterminate	11 (3.3)	14 (4.2)	
CE-PTE	N = 295	N = 296	
Clinical success	273 (92.5)	268 (90.5)	2.0 (-3.2, 7.4)
Clinical failure	22 (7.5)	28 (9.5)	

Difference was observed difference in overall clinical success rate at PTE between the omadacycline and moxifloxacin groups.
Overall clinical response at the PTE was based on the investigator's assessment at the EOT and PTE visits.
Percentages were based on the number of subjects in each treatment group.
97.5% CI was constructed based on the Miettinen and Nurminen method with stratification.
CE = clinically evaluable, CI = confidence interval, EOT = end of treatment, ITT = intent-to-treat, PORT = Pneumonia Outcomes Research Team, PTE = post therapy evaluation.

3.5.2.2 Clinical Response by Pathogen

Clinical success based on the ECR assessment and the overall clinical success at PTE (based on the investigator's assessment) for the most frequently identified pathogens is shown in (Table 20) for the microITT population and for the ME-PTE population (Table 21). Clinical success by baseline pathogen was high and similar in the microITT and ME-PTE populations. In general, clinical success increased between ECR and PTE increased. This increase in clinical success rates was most notable for omadacycline-treated patients. Therefore, the difference in clinical success rates noted based on the ECR assessment was smaller or not present at the PTE visit. The lower success rates for pathogens were not associated with higher MIC values, and the rate of clinical success at ECR and PTE for Gram-positive and Gram-negative bacteria were similar between omadacycline and moxifloxacin.

The clinical success rates by pathogen were similar to a previous, contemporary CABP study and demonstrate the consistency of pathogen isolation and efficacy.[60] Although follow-up cultures

were uncommon, there were no isolates identified with decreased susceptibility to either test article.

Table 20. Clinical Success by Baseline Pathogen From Blood Specimens, Respiratory Specimens, UATs, and/or Serology in Greater Than or Equal to 6 Patients in Either Treatment Group in OPTIC (microITT Population)

	Clinical Success			
	ECR		PTE	
Baseline Pathogen	Omadacycline N = 204 n/N1 (%)	Moxifloxacin N = 182 n/N1 (%)	Omadacycline N = 204 n/N1 (%)	Moxifloxacin N = 182 n/N1 (%)
Gram-positive bacteria (aerobes)	**51/61 (83.6)**	**49/56 (87.5)**	**52/61 (85.2)**	**49/56 (87.5)**
Streptococcus pneumoniae[a]	34/43 (79.1)	30/34 (88.2)	37/43 (86.0)	31/34 (91.2)
MDRSP	7/7 (100.0)	6/6 (100.0)	7/7 (100.0)	6/6 (100.0)
PSSP	20/26 (76.9)	21/22 (95.5)	23/26 (88.5)	21/22 (95.5)
Macrolide-resistant	10/10 (100.0)	5/5 (100.0)	10/10 (100.0)	5/5 (100.0)
Staphylococcus aureus	10/11 (90.9)	9/11 (81.8)	8/11 (72.7)	9/11 (81.8)
MSSA	10/11 (90.9)	8/10 (80.0)	8/11 (72.7)	8/10 (80.0)
Gram-negative bacteria (aerobes)	**62/79 (78.5)**	**58/69 (84.1)**	**67/79 (84.8)**	**56/69 (81.2)**
Escherichia coli	4/6 (66.7)	6/7 (85.7)	4/6 (66.7)	4/7 (57.1)
Haemophilus influenzae	22/32 (68.8)	14/16 (87.5)	26/32 (81.3)	16/16 (100.0)
Haemophilus parainfluenzae	15/18 (83.3)	14/17 (82.4)	15/18 (83.3)	13/17 (76.5)
Klebsiella pneumoniae	11/13 (84.6)	11/13 (84.6)	10/13 (76.9)	11/13 (84.6)
Atypical pathogens[b]	**92/118 (78.0)**	**91/106 (85.8)**	**109/118 (92.4)**	**97/106 (91.5)**
Mycoplasma pneumoniae[c]	54/70 (77.1)	49/57 (86.0)	66/70 (94.3)	50/57 (87.7)
Legionella pneumophila[d]	31/37 (83.8)	32/37 (86.5)	35/37 (94.6)	36/37 (97.3)
Chlamydophila pneumoniae[c]	18/28 (64.3)	22/28 (78.6)	25/28 (89.3)	25/28 (89.3)

Table 20. Clinical Success by Baseline Pathogen From Blood Specimens, Respiratory Specimens, UATs, and/or Serology in Greater Than or Equal to 6 Patients in Either Treatment Group in OPTIC (microITT Population)

	Clinical Success			
	ECR		PTE	
Baseline Pathogen	Omadacycline N = 204 n/N1 (%)	Moxifloxacin N = 182 n/N1 (%)	Omadacycline N = 204 n/N1 (%)	Moxifloxacin N = 182 n/N1 (%)
Atypical pathogens[e]	**55/73 (75.3)**	**54/64 (84.4)**	**66/73 (90.4)**	**58/64 (90.6)**
Mycoplasma pneumoniae[c]	25/35 (71.4)	24/29 (82.8)	31/35 (88.6)	25/29 (86.2)
Legionella pneumophila[d]	25/29 (86.2)	24/28 (85.7)	27/29 (93.1)	27/28 (96.4)
Chlamydophila pneumoniae[c]	9/15 (60)	12/14 (85.7)	14/15 (93.3)	13/14 (92.9)

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 with the same pathogen from a blood specimen, respiratory specimen, UAT, and/or serology were counted only once for that pathogen.
Patients were counted only once in the overall tabulations if they had more than 1 respective pathogen at Baseline.
Includes pathogens identified in ≥ 6 patients in either treatment group.
AE = adverse event; CABP = community-acquired bacterial pneumonia; ECR = early clinical response, MDRSP = multidrug-resistant Streptococcus pneumoniae, microITT = microbiological intent-to-treat, MSSA = methicillin susceptible- Staphylococcus aureus, N1 = Number of patients with the specified Baseline pathogen, PSSP = penicillin susceptible- Streptococcus pneumoniae, PTE = post-therapy evaluation, UAT = urinary antigen test.

[a] Overall tabulation of *S. pneumoniae* included identification from a urinary antigen only which did not have susceptibility data.

[b] Defined in the Statistical Analysis Plan which considers an indeterminate convalescent serology result as positive.

[c] Identified only from serology.

[d] *L. pneumophila* may have been detected from culture, serology, and/or a UAT.

[e] For identification by serology, considers only a positive convalescent serology result as positive. Per the Statistical Analysis Plan (SAP), a positive serology result consisted of: a positive baseline or PTE IgM serology result, OR a negative baseline and indeterminate PTE IgG serology result, OR a negative baseline and positive PTE IgG serology result. Tables were also generated that considered only a positive convalescent serology result as positive, which is the more stringent criterion described in the package inserts

Table 21. Clinical Success by Baseline Pathogen From Blood Specimens, Respiratory Specimens, UATs, and/or Serology in Greater Than or Equal to 6 Patients in Either Treatment Group in OPTIC (ME-PTE Population)

	Clinical Success			
	ECR		PTE	
Baseline Pathogen	Omadacycline N = 188 n/N1 (%)	Moxifloxacin N = 169 n/N1 (%)	Omadacycline N = 188 n/N1 (%)	Moxifloxacin N = 169 n/N1 (%)
Gram-positive bacteria (aerobes)	**48/55 (87.3)**	**44/51 (88.0)**	**50/55 (90.9)**	**47/50 (94.0)**
Streptococcus pneumoniae[a]	32/38 (84.2)	28/31 (90.3)	35/38 (92.1)	30/31 (96.8)
MDRSP	7/7 (100.0)	6/6 (100.0)	7/7 (100.0)	6/6 (100.0)
PSSP	19/23 (82.6)	19/20 (95.0)	22/23 (95.7)	20/20 (100.0)
Macrolide-resistant	10/10 (100.0)	5/5 (100.0)	10/10 (100.0)	5/5 (100.0)
Staphylococcus aureus	9/10 (90.0)	6/8 (75.0)	8/10 (80.0)	8/8 (100.0)
MSSA	9/10 (90.0)	5/7 (71.4)	8/10 (80.0)	7/7 (100.0)
Gram-negative bacteria (aerobes)	**56/70 (80.0)**	**56/65 (86.2)**	**62/70 (88.6)**	**56/65 (86.2)**
Escherichia coli	3/4 (75.0)	6/7 (85.7)	3/4 (75.0)	4/7 (57.1)
Haemophilus influenzae	21/29 (72.4)	14/16 (87.5)	25/29 (86.2)	16/16 (100.0)
Haemophilus parainfluenzae	12/15 (80.0)	13/14 (92.9)	13/15 (86.7)	13/14 (92.9)
Klebsiella pneumoniae	10/11 (90.9)	11/13 (84.6)	9/11 (81.8)	11/13 (84.6)
Atypical pathogens[b]	**86/112 (76.8)**	**86/101 (85.1)**	**104/112 (92.9)**	**94/101 (93.1)**
Mycoplasma pneumoniae[c]	51/67 (76.1)	46/54 (85.2)	66/70 (94.3)	50/57 (87.7)
Legionella pneumophila[d]	29/35(82.9)	31/36 (86.1)	35/37 (94.6)	36/37 (97.3)
Chlamydophila pneumoniae[c]	17/27 (63.0)	21/27 (77.8)	25/27 (92.6)	25/27 (88.9)

Table 21. Clinical Success by Baseline Pathogen From Blood Specimens, Respiratory Specimens, UATs, and/or Serology in Greater Than or Equal to 6 Patients in Either Treatment Group in OPTIC (ME-PTE Population)

	Clinical Success			
	ECR		PTE	
Baseline Pathogen	Omadacycline N = 188 n/N1 (%)	Moxifloxacin N = 169 n/N1 (%)	Omadacycline N = 188 n/N1 (%)	Moxifloxacin N = 169 n/N1 (%)
Atypical pathogens[e]	**51/69 (73.9)**	**50/60 (83.3)**	**66/73 (90.4)**	**58/64 (90.6)**
Legionella pneumophila[d]	23/33 (69.7)	21/26 (80.8)	27/29 (93.1)	27/28 (96.4)
Chlamydophila pneumoniae[c]	23/27 (85.2)	24/28 (85.7)	14/15 (93.3)	13/14 (92.9)
Mycoplasma pneumoniae[c]	9/15 (60.0)	11/13 (84.6)	31/35 (88.6)	25/29 (86.2)

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 with the same pathogen from a blood specimen, respiratory specimen, UAT, and/or serology were counted only once for that pathogen.
Patients were counted only once in the overall tabulations if they had more than 1 respective pathogen at Baseline.
Includes pathogens identified in ≥ 6 patients in either treatment group.
ECR = early clinical response; IgG = immunoglobulin G; IgM = immunoglobulin M; MDRSP = multidrug-resistant Streptococcus pneumoniae; ME = microbiological evaluable; MSSA = methicillin susceptible- Staphylococcus aureus; N1 = Number of patients with the specified Baseline pathogen; PSSP = penicillin susceptible- Streptococcus pneumoniae; PTE = post-therapy evaluation; UAT = urinary antigen test.

[a] Overall tabulation of *S. pneumoniae* included identification from a urinary antigen only which did not have susceptibility data.

[b] Defined in the Statistical Analysis Plan which considers an indeterminate convalescent serology result as positive.

[c] Identified only from serology.

[d] *L. pneumophila* may have been detected from culture, serology, and/or a UAT.

[e] For identification by serology, considers only a positive convalescent serology result as positive. Per the Statistical Analysis Plan (SAP), a positive serology result consisted of: a positive baseline or PTE IgM serology result, OR a negative baseline and indeterminate PTE IgG serology result, OR a negative baseline and positive PTE IgG serology result. Tables were also generated that considered only a positive convalescent serology result as positive, which is the more stringent criterion described in the package inserts.

3.5.2.3 Microbiological Outcomes

High per-patient favorable microbiologic response rates were observed at the EOT and PTE visits in both treatment groups.

There was no evidence of decreasing susceptibility to omadacycline during therapy. Superinfections/new infections were rare. Only 1 (0.5%) subject in the omadacycline group and no subjects in the moxifloxacin group had a superinfection (defined as a non-baseline pathogen isolated from blood or respiratory cultures while the subject was assessed as a clinical failure at the EOT visit and while the subject was on test article). A total of 3 (1.5%) omadacycline subjects and 3 (1.6%) moxifloxacin subjects had a new infection (defined as a non-baseline pathogen isolated from a post-treatment culture of a blood or respiratory specimen and while the subject was assessed as a clinical failure at the PTE visit).

Table 22. Per-patient Microbiological Response at EOT and PTE Visits in OPTIC (microITT Population)

Visit/Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (95% CI)
microITT	**N = 204**	**N = 182**	
Microbiological response at EOT visit			
Favorable	186 (91.2)	166 (91.2)	0.0 (-5.8, 5.9)
Eradication	4 (2.0)	8 (4.4)	
Presumed eradication	182 (89.2)	158 (86.8)	
Unfavorable	16 (7.8)	13 (7.1)	
Persistence	1 (0.5)	2 (1.1)	
Presumed persistence	15 (7.4)	11 (6.0)	
Indeterminate	2 (1.0)	3 (1.6)	
Overall microbiological response at PTE visit			
Favorable	184 (90.2)	158 (86.8)	3.4 (-3.0, 10.1)
Eradication	2 (1.0)	3 (1.6)	
Presumed eradication	182 (89.2)	155 (85.2)	
Unfavorable	18 (8.8)	19 (10.4)	
Persistence	1 (0.5)	2 (1.1)	
Presumed persistence	17 (8.3)	17 (9.3)	
Indeterminate	2 (1.0)	5 (2.7)	

Difference = observed difference in favorable microbiological response rate between the omadacycline and moxifloxacin groups.
95% CI was constructed based on the Miettinen and Nurminen method without stratification.
Percentages were based on the total number of patients at each visit in each treatment group.
CABP = community-acquired bacterial pneumonia, CI = confidence interval, EOT = end of treatment, microITT = microbiological intent-to-treat, PTE = posttherapy evaluation.

3.5.2.4 Clinical Response in Microbiologic Populations

Early Clinical Response at 72 to 120 hours after the first dose of test article in the microITT population and the overall clinical response at the PTE visit (based on the investigator's assessment) in the microITT and ME-PTE population is shown in Table 23. Based on the ECR assessment, clinical success rates were 79.9% omadacycline, 85.7% moxifloxacin. Overall clinical response at the PTE visit was comparable between the 2 treatment groups for both the microITT and ME-PTE populations.

Table 23. ECR 72 to 120 h After the First Infusion of the Test Article (microITT and Expanded microITT Populations) and Overall Clinical Response at the PTE Visit Based on Investigator Assessments in OPTIC (microITT and ME-PTE Populations)

Efficacy Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (95% CI)
ECR			
microITT	**N = 204**	**N = 182**	
Clinical success	163 (79.9)	156 (85.7)	-5.8 (-13.3, 1.8)
Clinical failure or indeterminate	41 (20.1)	26 (14.3)	
Clinical failure	31 (15.2)	21 (11.5)	
Indeterminate	10 (4.9)	5 (2.7)	
Overall PTE[a]			
microITT	**N = 204**	**N = 182**	
Clinical success	182 (89.2)	159 (87.4)	1.9 (-4.6, 8.5)
Clinical failure or indeterminate	22 (10.8)	23 (12.6)	
Clinical failure	19 (9.3)	18 (9.9)	
Indeterminate	3 (1.5)	5 (2.7)	
ME-PTE	**N = 188**	**N = 169**	
Clinical success	172 (91.5)	154 (91.1)	0.4 (-5.6, 6.6)
Clinical failure	16 (8.5)	15 (8.9)	

Difference was observed difference in early clinical success rate between the omadacycline and moxifloxacin groups.
95% CI was constructed based on the Miettinen and Nurminen method without stratification.
Percentages were based on the number of subjects in each treatment group.
CI = confidence interval; ECR = Early Clinical Response; ME = microbiologically evaluable; microITT = microbiological intent-to-treat; PTE = post therapy evaluation.

[a] Overall clinical response at the PTE was based on the investigator assessment at the End of Treatment and PTE visits.

3.5.2.4.1 Bacteremic Patients

Of the small number of patients who had bacteremia, most patients with bacteremia demonstrated clinical success at ECR, EOT, and PTE in OPTIC (Table 24). Overall, a numerically greater number of omadacycline patients had an indeterminate response compared to moxifloxacin patients at ECR (2 [15.4%] omadacycline patients versus no moxifloxacin patients).

The clinical response rates at ECR, EOT, and PTE for subjects with bacteremia is provided by PORT risk class in Appendix Table 52 (page 107).

Table 24. Clinical Response at ECR, EOT, and PTE in Subjects with Bacteremia in OPTIC (ME-EOT and ME-PTE Populations)

	ECR		EOT		PTE	
	OMC (N = 193)	MOX (N = 172)	OMC (N = 193)	MOX (N = 172)	OMC (N = 188)	MOX (N = 169)
Patients with bacteremia	11	18	13	18	12	17
Clinical Success	10 (90.9)	16 (88.9)	12 (92.3)	15 (83.3)	11 (91.7)	14 (82.4)
Clinical Failure	1 (9.1)	2 (11.1)	1 (7.7)	3 (16.7)	1 (8.3)	3 (17.6)

ECR = early clinical response; EOT = end of treatment; MOX = moxifloxacin; OMC = omadacycline; PTE = post-therapy evaluation.

3.5.2.5 CABP Signs and Symptoms

To determine clinical stability early in treatment, the percentage of patients with a HR less than 90 bpm, systolic BP greater than 90 mm Hg, a PaO_2 of greater than or equal to 60 mm Hg by ABG or an oxygen saturation of greater than or equal to 90% by pulse oximetry, and those who did not have a fever or hypothermia were assessed at 72 to 120 h after the first dose of test article. (Table 25). Overall, these assessments demonstrated a > 90% achievement of clinical stability across all parameters and were consistent with the high ECR response rates observed in both treatment arms.

Table 25. Normalization of Vital Signs Associated with CABP at 72 to 120 h After First Dose in OPTIC (ITT population)

	Number (%) of Patients	
	Omadacycline N = 386	Moxifloxacin N = 388
Stabilization of vital signs findings associated with CABP	363/386 (94.0)	365/388 (94.1)
Heart rate < 90 bpm	334/363 (92.0)	341/365 (93.4)
Temperature (no fever or hypothermia)	357/363 (98.3)	358/365 (98.1)
Systolic blood pressure > 90 mm Hg	360/363 (99.2)	364/365 (99.7)
Respiratory rate ≤ 24 breaths/min	346/362 (95.6)	350/365 (95.9)
PaO2 (≥ 60 mm Hg by ABG) or oxygen saturation (≥ 90% by pulse oximetry)	321/325 (98.8)	329/337 (97.6)

ABG = arterial blood gas; bpm = beats per minute; CABP = community-acquired bacterial pneumonia; ITT = intent-to-treat; PaO_2 = partial pressure of arterial oxygen.

Table 26 demonstrates that when analyzed in Port Risk Class subgroups, a similar and high percentage of patients across all PORT Risk Class categories achieved clinical stability at or prior to the ECR time point between treatment groups.

Table 26. Normalization of Vital Signs Associated with CABP at 72 to 120 h After First Dose by PORT Risk Class in OPTIC (ITT Population)

	PORT Risk Class II		PORT Risk Class III		PORT Risk Class IV		PORT Risk Class III/IV	
Vital Sign	**OMC (N=55)**	**MOX (N=54)**	**OMC (N=227)**	**MOX (N=216)**	**OMC (N=102)**	**MOX (N=115)**	**OMC (N=329)**	**MOX (N=331)**
Stabilization of vital signs findings associated with CABP	48/55 (87.3)	47/54 (87.0)	218/227 (96.0)	210/216 (97.2)	95/102 (93.1)	105/115 (91.3)	313/329 (95.1)	315/331 (95.2)
Heart rate < 90 bpm	42/48 (87.5)	44/47 (93.6)	203/218 (93.1)	197/210 (93.8)	87/95 (91.6)	97/105 (92.4)	290/313 (92.7)	294/315 (93.3)
Temperature (no fever or hypothermia)	48/48 (100.0)	47/47 (100.0)	213/218 (97.7)	206/210 (98.1)	94/95 (98.9)	102/105 (97.1)	307/313 (98.1)	308/315 (97.8)
Systolic blood pressure > 90 mm Hg	47/48 (97.9)	47/47 (100.0)	216/218 (99.1)	209/210 (99.5)	95/95 (100.0)	105/105 (100.0)	311/313 (99.4)	314/315 (99.7)
Respiratory rate ≤ 24 breaths/min	47/47 (100.0)	47/47 (100.0)	208/218 (95.4)	198/210 (94.3)	89/95 (93.7)	102/105 (97.1)	297/313 (94.9)	300/315 (95.2)
PaO2 (≥ 60 mm Hg by ABG) or oxygen saturation (≥ 90% by pulse oximetry)	38/39 (97.4)	40/40 (100.0)	195/197 (99.0)	192/196 (98.0)	87/88 (98.9)	95/99 (96.0)	282/285 (98.9)	287/295 (97.3)

Note: Subjects with PORT Risk categories I and V, who were thought to have a qualified PORT Risk classification of II, III, or IV at enrollment (based on the inclusion criteria), but were later determined to be PORT Risk I or V, were excluded from the table based on Actual PORT Risk class.

ABG = arterial blood gas, bpm = beats per minute, CABP = community-acquired bacterial pneumonia, ITT = intent-to-treat, MOX = moxifloxacin, OMC = omadacycline, PaO_2 = partial pressure of arterial oxygen, PORT = Pneumonia Outcomes Research Team

The number and percentage of patients with resolution of all clinical symptoms that were present at Baseline was evaluated for each visit throughout the study. At the PTE visit, a majority of patients had complete resolution with rates that were similar between treatment groups (74.5% omadacycline, 75.4% moxifloxacin). Of the patients who did not have complete resolution of symptoms at the PTE visit, a majority (76.1% omadacycline, 73.3% moxifloxacin) was determined to be clinical successes by the investigators at PTE with residual or minimal clinical symptoms of CABP at PTE that did not require further systemic antimicrobial therapy.

3.5.2.6 Subgroup Analyses

Subgroup analyses of ECR and IACR at the PTE visit were conducted for descriptive purposes by PORT Risk Class, and CURB-65 score (Table 27). Post hoc subgroup analyses of ECR and IACR at the PTE visit were also conducted for descriptive purposes for age, asthma/COPD and smoking status, and modified ATS severity criteria.

PORT Risk Class was a stratification factor for OPTIC and a validated classification schema for estimating risk of mortality. Clinically, it guides site of care decisions. CURB-65 is a similar classification schema with mostly bedside criteria validated and used for similar purposes as the PORT Risk Class. The modified minor ATS criteria (based upon physiological criteria) is a validated screening tool for identifying patients with a higher severity of illness and potential need for increased level of care. These classification schemes were used to categorize patients to analyze efficacy at the ECR and PTE endpoints in patients with a higher risk of mortality or higher severity at baseline.

ECR and IACR at the PTE assessment were similar by PORT Risk Class. Since age is a major component of the PORT Risk Class and a driver of the overall score, efficacy was examined partitioned by age. Among the oldest patients (age $\geq$ 65 or age $\geq$ 75 years), similar rates of clinical success were observed between treatment groups at ECR and for IACR at the PTE assessment.

Similar results were observed between different CURB-65 scores, with the exception of patients who had a CURB-65 score of 2, for which a higher percentage of patients in the moxifloxacin group had clinical success compared to omadacycline patients. However, by PTE, omadacycline and moxifloxacin patients had similar efficacy.

For the modified ATS minor criteria classification and the SMART-COP which are principally used to assess for severity of CAP, patients with $\geq$ 3 ATS minor criteria or > 3 SMART-COP criteria represent the severe patients. For patients meeting these criteria, clinical success at ECR and PTE are similar between omadacycline and moxifloxacin. SIRS and qSOFA are used to define patients with sepsis criteria. Similar efficacy at ECR and PTE for both treatment groups were observed.

Table 27. Clinical Response at ECR and PTE by Subgroups in OPTIC (ITT Population)

Parameter		Omadacycline	Moxifloxacin	Difference	LCL(95%)	UCL(95%)
Actual PORT Risk Class[a]						
ECR	II	43/57(75.4)	41/56(73.2)	2.2	-14	18.4
	III	191/227(84.1)	187/216(86.6)	-2.4	-9.1	4.2
	IV	79/102(77.5)	93/116(80.2)	-2.7	-13.8	8.1
PTE	II	47/57(82.5)	47/56(83.9)	-1.5	-15.7	12.8
	III	206/227(90.7)	190/216(88.0)	2.8	-3	8.7
	IV	85/102(83.3)	93/116(80.2)	3.2	-7.4	13.4
Age category						
ECR	<65	190/223(85.2)	177/205(86.3)	-1.1	-7.8	5.6
	≥ 65	123/163(75.5)	144/183(78.7)	-3.2	-12.2	5.6
	≥ 75	65/85(76.5)	68/88(77.3)	-0.8	-13.5	11.8
PTE	<65	197/223(88.3)	176/205(85.9)	2.5	-3.9	9
	≥ 65	141/163(86.5)	154/183(84.2)	2.4	-5.3	9.9
	≥ 75	76/85(89.4)	72/88(81.8)	7.6	-3.1	18.4
No. of Curb-65 Score Criteria						
ECR	<2	276/333(82.9)	270/331(81.6)	1.3	-4.5	7.2
	≥ 2	37/53(69.8)	51/57(89.5)	-19.7	-34.7	-4.8
PTE	<2	293/333(88.0)	281/331(84.9)	3.1	-2.1	8.4
	≥	45/53(84.9)	49/57(86.0)	-1.1	-15.1	12.6
No. of SIRS Criteria Met						
ECR	<2	82/98(83.7)	85/102(83.3)	0.3	-10.2	10.8
	=2	127/150(84.7)	138/163(84.7)	0	-8.2	8.1
	=3	74/96(77.1)	78/97(80.4)	-3.3	-15	8.3
	=4	30/42(71.4)	20/26(76.9)	-5.5	-25.6	17.2
PTE	<2	88/98(89.8)	91/102(89.2)	0.6	-8.4	9.5
	=2	137/150(91.3)	136/163(83.4)	7.9	0.5	15.4
	=3	78/96(81.3)	81/97(83.5)	-2.3	-13.2	8.7
	=4	35/42(83.3)	22/26(84.6)	-1.3	-18.7	19.2
No. of qSOFA Criteria						
ECR	<2	68/86(79.1)	70/87(80.5)	-1.4	-13.5	10.7
	≥	245/296(82.8)	251/301(83.4)	-0.6	-6.7	5.4
PTE	<2	74/86(86.0)	78/87(89.7)	-3.6	-13.9	6.4
	≥ 2	264/296(89.2)	252/301(83.7)	5.5	0	11
No. of Modified ATS Criteria						
ECR	<3	265/317(83.6)	257/307(83.7)	-0.1	-6	5.7
	>=3	35/49(71.4)	47/62(75.8)	-4.4	-21.2	12
PTE	<3	284/317(89.6)	263/307(85.7)	3.9	-1.3	9.2
	≥ 3	39/49(79.6)	50/62(80.6)	-1.1	-16.8	13.8

Table 27. Clinical Response at ECR and PTE by Subgroups in OPTIC (ITT Population)

Parameter	Omadacycline	Moxifloxacin	Difference	LCL(95%)	UCL(95%)
No. of SMART-COP Risk Criteria					
ECR <3	167/200(83.5)	167/201(83.1)	0.4	-7	7.8
≥ 3	138/173(79.8)	150/182(82.4)	-2.6	-10.9	5.5
PTE <3	178/200(89.0)	174/201(86.6)	2.4	-4.1	9
≥ 3	152/173(87.9)	153/182(84.1)	3.8	-3.5	11.1

ATS = American Thoracic Society, ECR = early clinical response, ITT = intent-to-treat, LCL = lower confidence limit, PORT = Pneumonia Outcomes Research Team, PTE = post therapy evaluation, qSOFA = quick sequential organ failure assessment, SIRS = systemic inflammatory response syndrome, UCL = upper confidence limit.

[a] Patients with PORT Risk categories I and V were thought to have a qualified PORT Risk Class of II, III, or IV at enrollment (based on the inclusion criteria), but were later determined to be PORT Risk I or V.

Asthma and/or COPD are common co-morbidities in hospitalized patients with CABP. In addition, asthma/COPD are clinically important co-morbidity demographics associated with a potentially more severe presentation and associated with potentially worse outcomes in CABP patients.[31] Table 28 demonstrates that the presence or absence of Asthma or COPD did not impact overall clinical success rates in these patient populations across all efficacy assessments.

Smoking impairs the mucocilliary apparatus, decreases mucous clearance and pre-disposes patients to pneumonia. Evaluation of smoking status and efficacy is shown in Table 29. Past or present smoking did not impact overall efficacy with clinical success rates that were similar for both omadacycline and moxifloxacin treated patients. High and similar efficacy rates were observed between patients with a smoking history and those who were reported as a non-smoker.

Table 28. Clinical Response at ECR and PTE by Subgroups of Baseline COPD or Asthma in OPTIC (ITT Population)

	No COPD or Asthma (N = 634)		Mild to Moderate COPD or Asthma (N = 140)	
	Omadacycline (N =312)	Moxifloxacin (N = 322)	Omadacycline (N =74)	Moxifloxacin (N = 66)
ECR				
Clinical Success	257 (82.4)	266 (82.6)	56 (75.7)	55 (83.3)
Clinical Failure or Indeterminate	55 (17.6)	56 (17.4)	18 (24.3)	11 (16.7)
Clinical Failure	38 (12.2)	38 (11.8)	11 (14.9)	9 (13.6)
Indeterminate	17 (5.4)	18 (5.6)	7 (9.5)	2 (3.0)
PTE				
Clinical Success	278 (89.1)	274 (85.1)	60 (81.1)	56 (84.8)
Clinical Failure or Indeterminate	34 (10.9)	48 (14.9)	14 (18.9)	10 (15.2)
Clinical Failure	20 (6.4)	35 (10.9)	12 (16.2)	7 (10.6)
Indeterminate	14 (4.5)	13 (4.0)	2 (2.7)	3 (4.5)

COPD = chronic obstructive pulmonary disease, ECR = early clinical response, ITT = intent-to-treat, PTE = post-therapy evaluation

Table 29. Clinical Response at ECR and PTE by Subgroups of Baseline History of Smoking in OPTIC (ITT Population)

	Never Smoker (N = 432)		Current Smoker (N = 187)		Past Smoker (N = 155)		Past/Current Smoker (N = 342)	
	OMC (N=205)	MOX (N =227)	OMC (N=105	MOX (N = 82)	OMC (N = 76)	MOX (N = 79)	OMC (N=181)	MOX (N=161)
ECR								
Clinical Success	165 (80.5)	190 (83.7)	83 (79.0)	70 (85.4)	65 (85.5)	61 (77.2)	148 (81.8)	131 (81.4)
Clinical Failure or Indeterminate	40 (19.5)	37 (16.3)	22 (21.0)	12 (14.6)	11 (14.5)	18 (22.8)	33 (18.2)	30 (18.6)
Clinical Failure	32 (15.6)	26 (11.5)	12 (11.4)	7 (8.5)	5 (6.6)	14 (17.7)	17 (9.4)	21 (13.0)
Indeterminate	8 (3.9)	11 (4.8)	10 (9.5)	5 (6.1)	6 (7.9)	4 (5.1)	16 (8.8)	9 (5.6)
PTE								
Clinical Success	183 (89.3)	197 (86.8)	88 (83.8)	70 (85.4)	67 (88.2)	63 (79.7)	155 (85.6)	133 (82.6)
Clinical Failure or Indeterminate	22 (10.7)	30 (13.2)	17 (16.2)	12 (14.6)	9 (11.8)	16 (20.3)	26 (14.4)	28 (17.4)
Clinical Failure	17 (8.3)	20 (8.8)	8 (7.6)	8 (9.8)	7 (9.2)	14 (17.7)	15 (8.3)	22 (13.7)
Indeterminate	5 (2.4)	10 (4.4)	9 (8.6)	4 (4.9)	2 (2.6)	2 (2.5)	11 (6.1)	6 (3.7)

ECR = early clinical response, ITT = intent-to-treat, MOX = moxifloxacin, OMC = omadacycline, PTE = post therapy evaluation.

Overall, within the above subgroup analyses (PORT, CURB-65, ATS, age, SMART-COP, SIRS, qSOFA Asthma/COPD, smoking) there were high and similar clinical success rates between

omadacycline and moxifloxacin at all efficacy timepoint assessments, including ECR, EOT and IACR PTE.

3.6 Efficacy Conclusions in the Pivotal Phase 3 Study in CABP

In OPTIC, the following conclusions are based on the results of efficacy analyses:

- The OPTIC study provides the substantial evidence of efficacy required via FDA guidance and agreements to support the approval of CABP
- Omadacycline was found to be non-inferior to moxifloxacin for the primary efficacy outcome of ECR. Clinical success rates were high in both treatment groups (81.1% omadacycline, 82.7% moxifloxacin [95% CI]: -1.6 [-7.1, 3.8]).
- Rates of Investigator assessment of clinical success at PTE were high and similar between the treatment groups for both the ITT (87.6% omadacycline, 85.1% moxifloxacin [95% CI]: 2.5 [-2.4, 7.4]) and CE-PTE (92.9% omadacycline, 90.4% moxifloxacin [95% CI]: 2.5 [1.7, 6.8]) populations.
- By-pathogen, the IACR at PTE clinical success rates were high and similar between treatment groups for the common pneumonia pathogens including *S. pneumoniae* and *H. influenzae*.
- Clinical success rates were also high for drug-resistant *S. pneumoniae* including multi-drug resistant, macrolide-resistant, and tetracycline-resistant *S. pneumoniae* strains.
- There was no evidence of decreasing susceptibility to omadacycline during therapy, and superinfections/new infections were infrequent.
- By subgroup, clinical success rates between omadacycline and moxifloxacin were high and similar at all efficacy timepoint assessments.

4 SAFETY IN THE PIVOTAL PHASE 3 STUDIES

4.1 Extent of Exposure

The safety database for omadacycline includes 2,509 patients treated in 5 studies: Phase 2 (n = 1) and Phase 3 (n = 1) studies in complicated skin and skin structure infections (cSSSI), Phase 3 studies in ABSSSI (n = 2), and CABP (n = 1).

The focus of this overview of safety is on the safety findings from 2,150 total patients treated in the 3 pivotal Phase 3 studies in ABSSSI (n = 2) and CABP (n = 1), of which 1,073 patients were exposed to omadacycline (Table 30). These pivotal Phase 3 studies include a total of 705 patients who received the combined iv and po omadacycline regimen for treatment of ABSSSI or CABP (n = 323 patients in OASIS-1; n = 382 in OPTIC), as well as 368 patients who received the oral-only omadacycline regimen for the treatment of ABSSSI in OASIS-2. Overall, 705 patients were exposed to iv omadacycline and > 900 patients were exposed to po omadacycline in the 3 Phase 3 studies of ABSSSI and CABP.

In the pooled pivotal Phase 3 studies, the mean total duration of exposure (regardless of whether the patient received the iv/po treatment or the po-only treatment) was similar between all

treatment groups (8.5 to 9.6 days across treatment groups). In the individual studies, most patients received 7 to 10 days of treatment.

Table 30. Omadacycline Exposure in OASIS-1, OASIS-2, and OPTIC (Pooled Safety Population)

Analysis Pool Phase 3 Pivotal Study	Omadacycline All Doses (iv + po)	Linezolid 600 mg (iv + po)	Moxifloxacin 400 mg (iv + po)	Total
Phase 3 ABSSSI and CABP studies				
OASIS-1	323	322	-	645
OASIS-2	368	367	-	735
OPTIC	382	-	388	770
Total	**1073**	**689**	**388**	**2150**

ABSSSI = acute bacterial skin and skin structure infection, CABP = community-acquired bacterial pneumonia, iv = intravenous, po = per oral, SCS = Summary of Clinical Safety.

As summarized in Table 31 for OASIS-1 and OASIS-2, the percentage of patients who discontinued study treatment prematurely was low, with ≥ 87.5% of patients in each treatment group completing study treatment as planned. The most frequent reason for discontinuation from treatment was lost to follow up (3.3% of omadacycline and 4.9% of linezolid patients). Few patients discontinued study treatment due to AEs. Similar results were observed for the percentage of patients who discontinued from the study.

The majority of patients also completed study treatment in OPTIC (Table 32). Adverse events were the most frequent reason for premature discontinuation from study treatment (4.4% of omadacycline and 7.2% of moxifloxacin patients). Similar results were observed for overall completion from the study.

Table 31. Patient Disposition in OASIS-1 and OASIS-2 (Pooled Safety Population)

Category/ Reason	Omadacycline (N = 691) n (%)	Linezolid (N = 689) n (%)
Completed study treatment	624 (90.3)	603 (87.5)
Prematurely discontinued from study treatment	67 (9.7)	86 (12.5)
Reason for premature discontinuation from study treatment		
AE	12 (1.7)	11 (1.6)
Lost to follow-up	23 (3.3)	34 (4.9)
Withdrawal by subject	14 (2.0)	14 (2.0)
Physician decision	10 (1.4)	16 (2.3)
Death[a]	0	1 (0.1)
Other	8 (1.2)	10 (1.5)
Completed study[b]	615 (89.0)	604 (87.7)
Prematurely discontinued from study	76 (11.0)	85 (12.3)
Reason for premature discontinuation from study		
AE	1 (0.1)	1 (0.1)
Lost to follow-up	48 (6.9)	56 (8.1)
Withdrawal by subject	20 (2.9)	16 (2.3)
Physician decision	1 (0.1)	2 (0.3)
Death[a]	0	2 (0.3)
Other	6 (0.9)	8 (1.2)

AE = adverse event

[a] Does not represent the total number of deaths in the studies.

[b] Summary of patients who completed the study (ie, received at least 1 dose of test article and completed EOT, PTE, and Follow-up).

Table 32. Patient Disposition in OPTIC (Randomized Patients [ITT Population])

Parameter/ Category	Omadacycline N = 386 n (%)	Moxifloxacin N = 388 n (%)
Randomized	386 (100.0)	388 (100.0)
Completed study treatment	352 (91.2)	346 (89.2)
Prematurely discontinued from study treatment	34 (8.8)	42 (10.8)
Reason for premature discontinuation from study treatment		
AE	17 (4.4)	28 (7.2)
Lost to follow-up	0	1 (0.3)
Withdrawal by subject	4 (1.0)	3 (0.8)
Physician decision	3 (0.8)	9 (2.3)
Death[a]	4 (1.0)	1 (0.3)
Other	6 (1.6)	0
Completed study[b]	356 (92.2)	362 (93.3)
Prematurely discontinued from study	30 (7.8)	26 (6.7)
Reason for premature discontinuation from study		
AE	7 (1.8)	9 (2.3)
Lost to follow-up	0	3 (0.8)
Withdrawal by subject	7 (1.8)	8 (2.1)
Physician decision	0	1 (0.3)
Death[a]	6 (1.6)	3 (0.8)
Other	10 (2.6)	2 (0.5)

Percentages were based on the ITT population.
AE = adverse event; EOT = end of treatment, ITT = intent-to-treat; PTE = post-therapy evaluation.
[a] Does not represent the total number of deaths in the study.
[b] Summary of patients who completed the study (ie, received at least 1 dose of test article and completed EOT, PTE, and Follow-up).

4.2 Adverse Events

All Phase 3 clinical studies conducted with omadacycline included a thorough evaluation of safety, with special assessments conducted based on the known safety profile of the tetracycline class and information obtained in early phase studies. Standard safety evaluations were conducted in all studies and included physical examinations, vital signs, ECGs, and clinical laboratory evaluations, as well as monitoring for AEs.

4.2.1 Overall Summary of TEAEs

Overviews of the incidences of TEAEs are provided for the pooled Phase 3 studies in ABSSSI in Table 33, and for OPTIC in Table 34.

Pivotal Phase 3 Studies in ABSSSI

In the Phase 3 ABSSSI studies, the incidences of TEAEs reported for any patient was 51.1% in the omadacycline group and 41.2% in the linezolid group. Drug-related TEAEs occurred in 28.5% of omadacycline patients versus 16.1% of linezolid patients. The higher rate of omadacycline drug-related TEAEs was primarily due to the higher number of nausea and vomiting TEAEs assessed by the investigator as drug-related in OASIS-2.

The incidences of TEAEs that led to discontinuation of test article were similar between omadacycline (1.7%) and linezolid (1.5%). Infection and infestation events were the most frequent type of TEAEs that led to test article discontinuation (1.2% omadacycline and 0.3% linezolid patients).

Serious TEAEs were uncommon, occurring in 2.3% of omadacycline patients and 1.9% of linezolid patients (Section 4.3).

TEAEs that led to death were reported in 0.1% of omadacycline and 0.4% of linezolid patients. Mortality is discussed in more detail in Section 4.6.

Table 33. Overview of Pooled TEAEs in OASIS-1 and OASIS-2 (Safety Population)

Number of Patients (%) with:	Omadacycline (N=691)	Linezolid (N=689)
Any TEAE	353 (51.1)	284 (41.2)
Drug-related TEAE	197 (28.5)	111 (16.1)
Serious TEAE	16 (2.3)	13 (1.9)
Drug-related serious TEAE	0	1 (0.1)
TEAE leading to premature discontinuation of test article	12 (1.7)	10 (1.5)
TEAE leading to dose interruption of test article	2 (0.3)	0
Serious TEAEs leading to premature discontinuation of test article	6 (0.9)	5 (0.7)
Patients who died	1 (0.1)	3 (0.4)

Percentages were based on the Safety population.
A TEAE was defined as an AE occurring after first dose of active test article.
AE = adverse event; TEAE = treatment-emergent adverse event.

Pivotal Phase 3 Study in CABP

In OPTIC, the incidences of TEAEs reported for any patient were 41.1% in the omadacycline group and 48.5% in the moxifloxacin group. Drug-related TEAEs occurred in 10.2% of omadacycline patients and 17.8% of moxifloxacin patients. The higher rate of moxifloxacin drug-related TEAEs was primarily due to the higher number of QT prolonged and diarrhea TEAEs assessed by the investigator as drug-related in OPTIC.

TEAEs that led to discontinuation of test article were reported in 5.5% of omadacycline and 7.0% of moxifloxacin patients. Infection and infestation events were the most frequent type of TEAEs that led to test article discontinuation, primarily represented by progression or worsening

of the index CABP and need for rescue antibiotic therapy (1.3% omadacycline and 3.6% moxifloxacin patients).

The percentage of patients with serious TEAEs was low, occurring in 6.0% of omadacycline patients and 6.7% of moxifloxacin patients.

TEAEs that led to death were reported in 2.1% of omadacycline and 1.0% of moxifloxacin patients. Mortality is discussed in more detail in Section 4.6.

Table 34. Overview of TEAEs in OPTIC (Safety Population)

Number of Patients (%) with:	Omadacycline N = 382	Moxifloxacin N = 388
Any TEAE	157 (41.1)	188 (48.5)
Drug-related TEAE	39 (10.2)	69 (17.8)
Serious TEAE	23 (6.0)	26 (6.7)
Drug-related serious TEAE	2 (0.5)	2 (0.5)
TEAE leading to premature discontinuation of test article	21 (5.5)	27 (7.0)
TEAE leading to dose interruption of test article	0	0
Serious TEAEs leading to premature discontinuation of test article	10 (2.6)	11 (2.8)
Patients who died	8 (2.1)	4 (1.0)

Percentages were based on the Safety population.
A TEAE was defined as an AE occurring after first dose of active test article.
AE = adverse event; TEAE = treatment-emergent adverse event.

4.2.2 Frequent TEAEs

The most frequently reported TEAEs (≥ 2% for the omadacycline treatment group) are summarized by system organ class (SOC) and preferred term (PT) in Table 35 for the Phase 3 ABSSSI studies and in Table 36 for the Phase 3 CABP study.

In the 3 Phase 3 studies, gastrointestinal events were the most frequent type of TEAEs, consistent with the known gastrointestinal adverse effect profiles of the tetracycline, oxazolidinone, and fluoroquinolone antibiotic classes. AEs associated with the tetracyclines as a class (ie, blood urea nitrogen increased and azotemia; CNS side effects including light-headedness, vertigo or dizziness; hypersensitivity; photosensitivity; pseudotumor cerebri; acute pancreatitis; fungal infections (eg, vulvovaginal fungal infections); and pill esophagitis) were either not observed or were observed at low frequencies and were similar in the omadacycline and comparator groups in the Phase 3 studies (Appendix Table 53, page 108).

Pivotal Phase 3 Studies in ABSSSI

The most frequently reported TEAEs by PT that occurred at a greater frequency in the omadacycline group compared to the linezolid group were nausea (21.9% omadacycline, 8.7% linezolid) and vomiting (11.1% omadacycline, 3.9% linezolid) (Table 35). While these events occurred in both ABSSSI studies, higher rates of nausea and vomiting events occurred in

the oral-only study (OASIS-2) associated with the loading dose period on Days 1 and 2. Onset on Day 1 and 2 was 25.3% for nausea and 12.5% for vomiting in the omadacycline treatment group in OASIS-2. From Day 3 through the EOT, onset of nausea and vomiting were each 4.1%.

Most of the nausea and vomiting TEAEs were of mild or moderate intensity. Only 2 (0.3%) omadacycline-treated patients in the Phase 3 ABSSSI studies discontinued treatment for nausea or vomiting.

Infusion site extravasation occurred in a similar percentage of patients in the omadacycline (4.1%) and linezolid (2.8%) groups. The majority of these patients had a history of iv drug abuse.

The overall frequencies of TEAEs were generally similar between the iv and po treatment periods, except for nausea and vomiting as noted above in the OASIS-2 study (Table 35).

Table 35. Percent of Patients With the Most Frequent TEAEs (≥ 2% for Omadacycline Total Group) Overall and by PT in OASIS-1 and OASIS-2 (Pooled Safety Population)

	Omadacycline (%)			Linezolid (%)
PT	OASIS-1 N = 323	OASIS-2 N = 368	Total N = 691	Total N = 689
Patients with at least 1 TEAE	48.9	53.5	51.1	41.2
Nausea	12.4	30.2	21.9	8.7
Vomiting	5.3	16.8	11.4	3.9
Wound infection	2.5	6.0	4.3	3.2
Alanine aminotransferase increased	2.8	5.2	4.1	3.6
Infusion site extravasation	8.7		4.1	2.8
Cellulitis	4.6	3.3	3.9	3.5
Aspartate aminotransferase increased	2.5	4.6	3.6	3.5
Headache	3.1	3.5	3.3	3.0
Subcutaneous abscess	5.3	1.6	3.3	3.9
Diarrhoea	2.2	4.1	3.2	2.9

Coding of PTs were based on MedDRA Version 17.1.
A TEAE was defined as an AE with a start date/time on or after the date/time of the first dose of active test article.
If a patient had more than 1 TEAE with the same PT, the patient was counted only once for that PT.
Percentages were based on the number of patients in each treatment group. Patients may have been counted in more than 1 row.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event.

Pivotal Phase 3 Study in CABP

The overall frequencies of TEAEs were generally similar between omadacycline and moxifloxacin treatment groups with the exception of diarrhea (omadacycline 1.0% versus moxifloxacin 8.0%). No patients who received omadacycline in OPTIC had CDIs compared to 8 (2.1%) patients in the moxifloxacin group. In the Phase 1, Phase 2 and 3 studies, no patients

who received omadacycline had CDI. No TEAE associated with a CABP disease state (worsening, recurrence, or complications) occurred at a rate exceeding 1.0% in omadacycline treated patients.

Table 36. Percent of Patients With the Most Frequent TEAEs (≥ 2% for Omadacycline Group) Overall and by PT in OPTIC (Safety Population)

PT	Omadacycline N = 382 (%)	Moxifloxacin N = 388 (%)
Patients with at least 1 TEAE	41.1	48.5
Alanine aminotransferase increased	3.7	4.6
Hypertension	3.4	2.8
Gamma-glutamyl transferase increased	2.6	2.1
Insomnia	2.6	2.1
Vomiting	2.6	1.5
Constipation	2.4	1.5
Nausea	2.4	5.4
Aspartate aminotransferase increased	2.1	3.6
Headache	2.1	1.3

Coding of PTs were based on MedDRA Version 17.1.
A TEAE was defined as an AE with a start date/time on or after the date/time of the first dose of active test article.
If a patient had more than 1 TEAE with the same PT, the patient was counted only once for that PT.
Percentages were based on the number of patients in each treatment group. Patients may have been counted in more than 1 row.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event.

4.3 Serious Adverse Events

Pivotal Phase 3 studies in ABSSSI

Serious TEAEs were low, occurring in 2.3% of omadacycline patients and 1.9% of linezolid patients. Infection and infestation events were the most frequent type of serious TEAEs (1.7% of omadacycline patients, 0.7% of linezolid patients) (Appendix Table 55, page 112). Serious TEAEs representative of progression or worsening of an ABSSSI (wound infection, cellulitis, and subcutaneous abscess) were the most frequent events in this SOC. Serious TEAEs of cardiac disorders were infrequent, being reported in no omadacycline patients and 2 linezolid patients.

Pivotal Phase 3 study in CABP

The incidence of serious TEAEs was similar in the omadacycline (6.0%) and moxifloxacin (6.7%) groups, as summarized in Appendix Table 56 (page 113). Overall, infection and infestation events were the most frequent type of serious TEAEs, most of which represented progression CABP or complications of CABP, and occurred at a similar frequency in the

moxifloxacin group compared to the omadacycline (2.1% omadacycline, 4.1% moxifloxacin) group. No serious TEAE associated with a CABP disease state (worsening, recurrence, or complications) occurred at a rate exceeding 0.5% in omadacycline treated patients. Serious TEAEs of cardiac disorders were reported in 5 omadacycline patients and 2 moxifloxacin patients.

4.4 Cardiac Safety

The results of nonclinical studies demonstrated that omadacycline inhibits the binding of carbamylcholine to the M_2 subtype of the muscarinic acetylcholine receptor (vagolytic effect), resulting in a transient, generally asymptomatic increase in HR, primarily observed in healthy volunteer subjects exposed to omadacycline. Omadacycline has no relevant effects on other muscarinic receptor subtypes (M_1, M_3, M_4, M_5), nicotinic receptors, adrenergic receptors or hERG channels.

In Phase 1 studies in healthy subjects, transient, dose-dependent increases in HR were observed that peaked approximately 60 minutes after the start of the infusion, which appeared to be related to maximum plasma concentrations of omadacycline. The highest median peak increases in HR were 7 to 12 beats per minute (bpm) for omadacycline iv doses from 25 to 100 mg, and 18 to 24 bpm for omadacycline iv doses from 200 to 600 mg. The changes were transient (resolving approximately 6 h after dosing), generally asymptomatic, and were not associated with clinically significant changes in blood pressure or electrocardiogram (ECG) findings.

As a result of these findings, in addition to routine monitoring of vital signs throughout the Phase 3 pivotal studies, an extensive monitoring program utilizing ECGs to measure HR changes pre- and post- the Day 1 (ie, dose 1) and Day 2 (ie, dose 3) iv dosing timepoints in the OASIS-1 and OPTIC studies was implemented. This ECG sampling approach (30 minutes pre- and 30-90 minutes post-omadacycline infusion) was chosen to best represent timepoints that would most closely represent C_{max} exposure to omadacycline. Further, in order to determine if any of these indirect (vagolytically mediated) increases in HR were associated with cardiac AEs, the sponsor focused on codifying cardiac-related AE preferred terms in the pivotal Phase 3 clinical program to include a thorough analysis of the incidence rates of myocardial ischemia, myocardial infarction, cardiac failure, cardiac failure congestive, and tachyarrhymias including atrial fibrillation.

Treatment-emergent Adverse Events of Cardiac Disorders

Table 37 summarizes cardiac TEAEs of interest by PT in the 3 Phase 3 studies. The incidences of all cardiac TEAEs of interest were similar between the omadacycline group and the linezolid and moxifloxacin treatment groups. In the omadacycline group, the majority of these events were mild or moderate in severity and most events resolved with no sequelae. Serious cardiac TEAEs were reported in 5 omadacycline patients, 2 moxifloxacin patients, and 2 linezolid subjects. Most of the cardiac TEAEs of interest occurred in OPTIC with an older, more co-morbid patient population. Appendix Table 57 (page 115) summarizes HR and cardiac TEAEs of interest by PT in OPTIC.

Table 37. Summary of Heart Rhythm and Cardiac TEAEs of Interest by PT in OASIS-1, OASIS-2, and OPTIC (Pooled Safety Population)

PT	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
Acute myocardial infarction	2 (0.2)	0	0
Acute pulmonary edema	1 (0.1)	0	0
Angina pectoris	0	0	2 (0.5)
Atrial fibrillation	5 (0.5)	0	1 (0.3)
Atrial flutter	1 (0.1)	0	0
Cardiac arrest	1 (0.1)	1 (0.1)	0
Cardio-respiratory arrest	1 (0.1)	0	0
Cardiac failure	3 (0.3)	1 (0.1)	3 (0.8)
Cardiac failure congestive	0	1 (0.1)	1 (0.3)
Cardiogenic shock	2 (0.2)	0	1 (0.3)
Myocardial ischemia	1 (0.1)	1 (0.1)	2 (0.5)
Right ventricular failure	0	0	1 (0.3)
Sinus tachycardia	1 (0.1)	0	0

Coding of PT based on MedDRA Version 17.1.
A TEAE was defined as an AE with a start date/time on or after the date/time of the first dose of active test article. If a subject had more than 1 TEAE with the same category or PT, the subject was counted only once for that category or PT.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event.

Electrocardiograms

Heart Rate

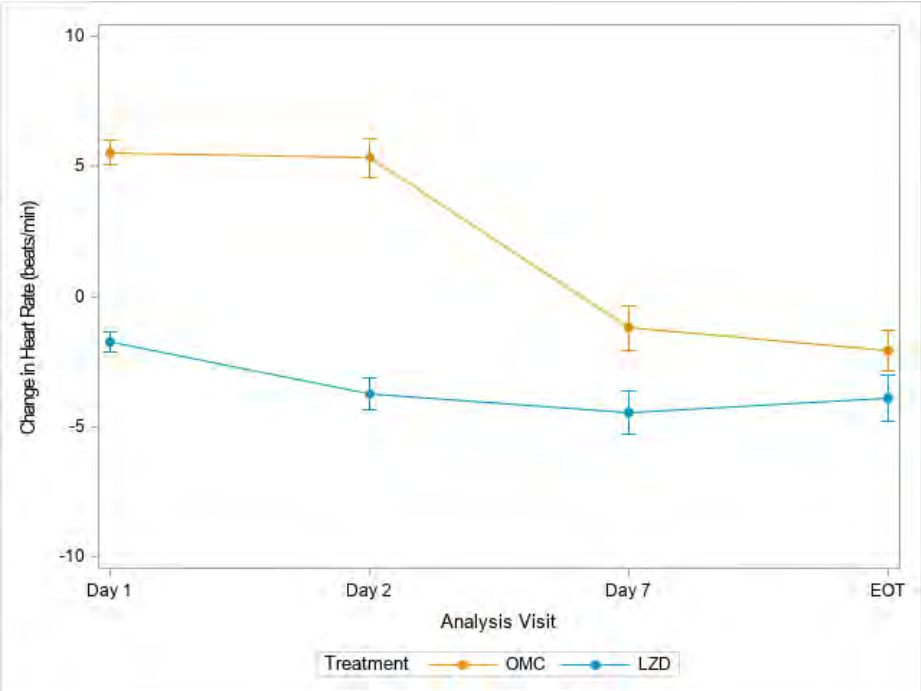
Electrocardiogram parameters (HR, RR interval, PR interval, QRS interval, QT interval, and QTc) were summarized using descriptive statistics (actual values and change from Baseline) for all time points at which ECGs were performed. Overall, the mean and median values for HR, RR interval, PR interval, QRS interval, QT interval, and QTc interval were within the normal range at Baseline and at the EOT visit for all treatment groups, and no clinically important changes were observed for any treatment group. Appendix Table 58 (page 116) summarizes the change from Baseline to the EOT visit for HR and QTcF interval in the pivotal Phase 3 studies in ABSSSI and CABP.

As noted in the introductory paragraph to Section 4.4, an extensive monitoring program utilizing ECGs to measure HR changes pre- and post- the Day 1 (ie, Dose 1) and Day 2 (ie, Dose 3) iv dosing timepoints in the OASIS-1 and OPTIC studies was implemented. Accordingly, this ECG sampling approach (30 minutes pre- and 30-90 minutes post-omadacycline infusion) was chosen to best represent timepoints that would most closely represent C_{max} exposure to omadacycline. These mean HR changes (± SEM) from baseline on Day 1 and Day 2 are shown for OASIS-1 and OPTIC in Figure 8 and Figure 9, respectively. Day 7 and EOT timepoint HR changes are

also included but did not have the protocol-mandated timing proximity to iv infusion/oral administration of omadacycline that was implemented for the Day 1 and Day 2 HR assessments.

In OASIS-1, the difference in mean post-dose changes in HR were small in magnitude for the omadacycline treatment group (5.4 bpm) and the linezolid treatment group (-1.8 bpm) on Day 1. Similarly, the difference in mean post-dose changes in HR were small in magnitude for the omadacycline treatment group (5.6 bpm) and the linezolid treatment group (-3.7 bpm) on Day 2. Over the treatment duration through Day 7, the magnitude of change in HR remained small with a trend towards a reduction in the mean change in HR concordant with the clinical improvement observed in both treatment groups (Figure 8).

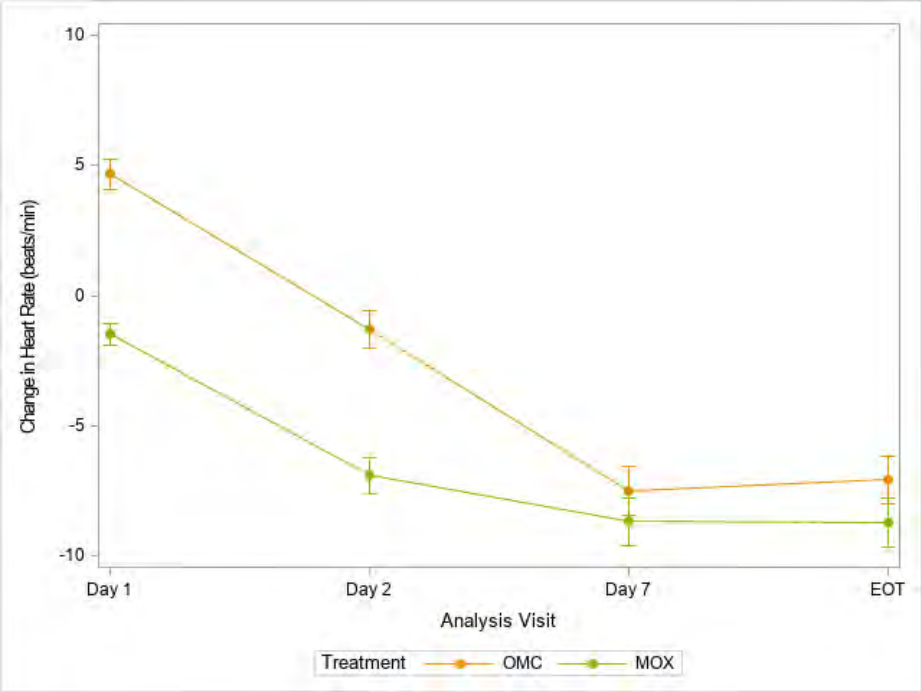
Figure 8. Change from Baseline in Heart Rate over Time as Measured by ECG in OASIS-1



ECG = electrocardiogram, EOT = end of treatment, OMC = omadacycline, LZD = Linezolid.

In OPTIC, the difference in mean post-dose changes in HR were small in magnitude for the omadacycline treatment group (4.3 bpm) and the moxifloxacin treatment group (-1.5 bpm) on Day 1. Similarly, the difference in mean post-dose changes in HR were small in magnitude for the omadacycline treatment group (-1.1 bpm) and the moxifloxacin treatment group (-6.8 bpm) on Day 2. Over the treatment duration through Day 7, the magnitude of change in HR remained small with a trend towards a reduction in the absolute mean baseline HR concordant with the clinical improvement observed in both treatment groups (Figure 9).

Figure 9. Change from Baseline in Heart Rate over Time as Measured by ECG in OPTIC



ECG = electrocardiogram, EOT = end of treatment, OMC = omadacycline, MOX = Moxifloxacin.

QT Interval

Omadacycline has no clinically relevant effect on QTc interval based on non-clinical and clinical data. Non-clinical data showed no effect on the human ether-a-go-go-related gene (hERG) channel binding studies.

A thorough corrected QT (QTc) study was conducted per the International Council on Harmonisation E14 Guideline to assess the potential effect of omadacycline on QTc prolongation. Single omadacycline infusions of 100 mg (over 30 minutes) and 300 mg (over 60 minutes) were compared to the effects of placebo, and a single oral dose of 400-mg moxifloxacin in a double-blind, randomized, crossover study in 64 healthy patients. Per guidance, positive assay sensitivity was met as moxifloxacin produced a maximum placebo-subtracted change in QT interval corrected with Fridericia's method mean value of 9.25 msec, with a lower bound of the 95% CI exceeding 5 msec (7.26 msec). Neither dose of omadacycline produced evidence of QTc prolongation.

The QTcF changes in the combined pivotal Phase 3 studies in ABSSSI and CABP are summarized in Appendix Table 58 (page 116). For OPTIC, mean values and change from Baseline predose and postdose at Day 1 (ie, dose 1) and Day 2 (ie, dose 3) for QTcF are summarized in Appendix Table 59 (page 116). Similar “assay sensitivity” parameters were observed with an increase in median QTcF values was seen in the moxifloxacin group (5.8 msec (dose 1) and 11.1 msec (dose 3)). No change in QTcF were observed in the omadacycline group

(-1.0 msec (dose 1) and 2.0 msec (dose 3)), a consistent observation with what was documented in the preclinical hERG binding data and thorough corrected QTc study – thus, supporting the conclusion that there is no effect of omadacycline on cardiac repolarization.

Vital Signs

Table 38 summarizes the protocol-specified clinically notable values for increased HR and increases in systolic BP at any post-Baseline time point in the 3 Phase 3 studies. These values appear similar across all of the analysis categories without differences between treatment groups.

Appendix Table 60 (page 117) summarizes the protocol-specified clinically notable values for HR, measured during vital signs assessments, and systolic BP at any post-Baseline time point in OPTIC. These values appear similar across all of the analysis categories without differences between treatment groups.

Table 38. Clinically Notable Values for Heart Rate and Systolic BP at Any Post-Baseline Time Point in OASIS-1, OASIS-2, and OPTIC (Pooled Safety Population)

Clinically Notable Criteria	Omadacycline (N = 1073) n (%)	Linezolid (N = 689) n (%)	Moxifloxacin (N = 388) n (%)
Subjects with HR value at any post-Baseline visit	1073	689	388
HR ≥ 120 bpm	33 (3.1)	17 (2.5)	22 (5.7)
Subjects with HR value at Baseline and any post-Baseline visit	1073	689	388
HR ≥ 120 bpm and increase of ≥ 15 bpm	16 (1.5)	15 (2.2)	8 (2.1)
Subjects with systolic BP value at any post-Baseline visit	1073	689	388
Systolic BP ≥ 180 mmHg	22 (2.1)	15 (2.2)	8 (2.1)
Subjects with systolic BP value at Baseline and any post-Baseline visit	1073	689	388
Systolic BP ≥ 180 mmHg and increase of ≥ 20 mmHg	18 (1.7)	13 (1.9)	6 (1.5)

Baseline was defined as the value closest to but prior to the initiation of test article administration.
Percentages were based on the number of subjects with the specific parameter assessed.
BP = blood pressure, bpm = beats per minute, HR = heart rate.

Cardiac Safety Summary

The effect of omadacycline on HR was most pronounced in healthy volunteers in Phase 1 studies (younger age and lower resting HR) consistent with a specific, but indirect vagolytically-mediated increase in HR via omadacycline interaction with the M_2 subtype of the muscarinic receptor. These effects were less pronounced in hospitalized patients with ABSSSI and OPTIC, where vagal tone is reduced relative to sympathetic:parasympathetic balance. In patients with ABSSSI and CABP, omadacycline has demonstrated a low potential to induce clinically significant increases in HR, BP, or QTc. No differences in cardiac AEs were observed within the omadacycline treatment group nor between the linezolid or moxifloxacin treatment groups.

4.5 Liver Safety

The liver safety findings are summarized for the pooled data from the 3 pivotal Phase 3 studies in ABSSSI and CABP. Overall, 5.4% of omadacycline patients, 4.9% of linezolid patients, and 7.2% of moxifloxacin patients had hepatic AEs of interest during the pivotal Phase 3 studies. The incidences of all hepatic AEs of interest, including increased ALT and increased AST, were similar between the omadacycline and comparator groups. In the omadacycline group, all hepatic AEs of interest were mild or moderate in severity, except in 1 omadacycline patient who had a severe TEAE of hypoalbuminemia. A total of 5 patients had hepatic TEAEs that resulted in discontinuation of test article, which included hepatic failure following a cardiac arrest in 1 (0.1%) omadacycline patient (serious TEAE; not related to test article; event resolved on Day 29), and laboratory-associated TEAEs (eg, AST, ALT,) in 2 (0.2%) omadacycline patients and 2 (0.5%) moxifloxacin patients. All hepatic AEs were either resolving or resolved without sequelae during or following completion of treatment, except in 2 omadacycline patients (TEAE of ALT increased which was considered mild in severity in 1 patient and not related to test article and TEAEs of ALT and AST increased which were considered mild in severity and not related to test article in another patient). Although these patients were considered recovered/resolved with sequelae by the investigator, no additional AEs of sequelae were reported.

The incidences of post-baseline elevations of ALT or AST by 3 × ULN, 5 × ULN, and 10 × ULN with omadacycline were similar to comparators in all patients (Appendix Table 54, page 111), patients who had normal values at Baseline, and patients who had abnormal values at Baseline. Increases in total bilirubin to > 2 × ULN were similar between treatment groups.

Elevations in ALT and AST were mostly asymptomatic, transient, of low magnitude, resolved following the completion of therapy, and did not result in discontinuation.

No patient met the criteria for Hy's law as defined in FDA guidance.[61]

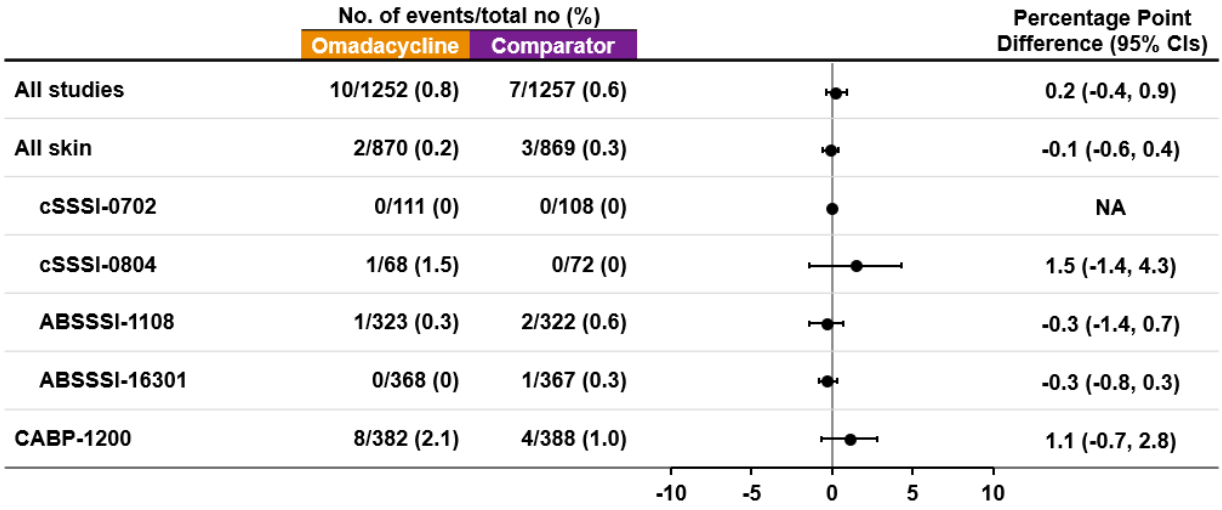
The use of tetracyclines has been associated with hepatic AEs, characterized, in general, as low frequency and low magnitude elevations of liver enzymes. The effects of omadacycline appear to be similar to that of linezolid and moxifloxacin and older tetracyclines.[62,63] Hepatic AEs occurred at similar with omadacycline compared with linezolid or moxifloxacin treatment and treatment discontinuations were infrequent. Elevations in liver enzymes observed in patients who received omadacycline were generally asymptomatic, of low magnitude and transient (ie, reversible to baseline values during or following completion of treatment).

4.6 Mortality

4.6.1 Mortality Across the Clinical Development Program

Across the omadacycline clinical development program, there were 10 (0.8%) omadacycline and 7 (0.6%) comparator patients who died. Among the comparator deaths, 4 (1.0%) occurred on moxifloxacin and 3 (0.4%) occurred on linezolid. Importantly the 95% CIs across all studies range from -1.4 to 4.3, and are similar between the studies. These data suggest a low and consistent rate and no difference from comparators.

Figure 10. Forest Plot of Mortality in All Phase 2 and 3 Omadacycline Studies



95% CI was constructed based on the Clopper-Pearson method or Exact confidence intervals
CABP = community-acquired bacterial pneumonia, CAP = community-acquired pneumonia, CI = confidence interval.

4.6.1.1 Mortality in ABSSSI

In all of the skin infection studies, the mortality rate was 0.2% for omadacycline versus 0.3% for linezolid. In OASIS-1 and OASIS-2, a total of 4 deaths occurred (1 omadacycline, 3 linezolid).

A single death in the omadacycline group of the OASIS-1 study was due to an opiate overdose. No deaths occurred in the omadacycline group in OASIS-2.

The 3 deaths in the linezolid group in OASIS-1 and OASIS-2 were due to cardiac failure (1 patient in OASIS-1), illicit drug overdose (1 patient in OASIS-2), and cardiac arrest (1 patient in OASIS-2).

The causes of death for the 4 patients who died in the OASIS-1 and OASIS -2 studies are summarized in Table 39 and individual mini-narratives are provided in Appendix Section 7.2, page 118.

Table 39. Fatal Adverse Events in OASIS-1 and OASIS-2

Case#	Study	Relative Day of Death	Age	Fatal Adverse Event Preferred Term	Immediate Cause of Death
OMC9	OASIS-1	2	67	Opiate Overdose	Illicit Drug Overdose
LZD1	OASIS-1	9	43	Cardiac Arrest	Cardiac Arrest
LZD2	OASIS-1	12	88	Cardiac Failure	Myocardial Infarction
LZD3	OASIS-2	91	62	Death	Illicit Drug Overdose

Mortality Summary in ABSSSI

Mortality rates between omadacycline and linezolid are similar and low in frequency. Randomization promotes comparability among treatment groups but does not protect against chance of small numerical differences.

4.6.1.2 Mortality in CABP

In OPTIC, 12 deaths occurred (8 omadacycline patients, 4 moxifloxacin patients). Of those 12 deaths, 11 occurred within 30 days of study treatment (8 omadacycline patients and 3 moxifloxacin patients). There was a single moxifloxacin patient who died at day 71. The rate difference between the treatment groups is 1.1% with 95% CI from -0.7 to 2.8 which encompasses the point estimates observed in both treatment groups.

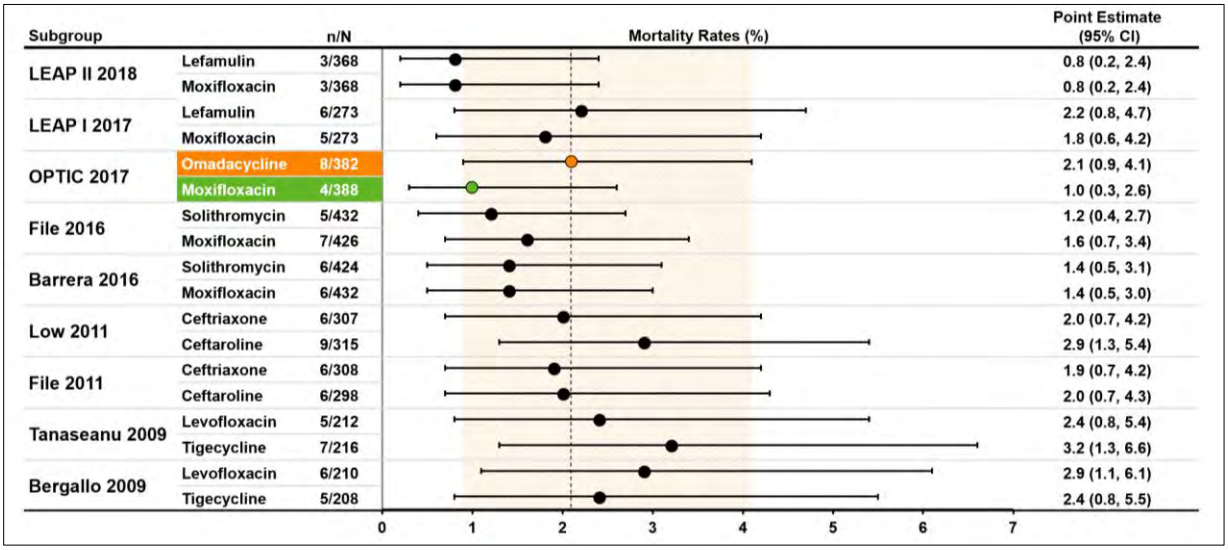
Because of the small numerical difference of 8 omadacycline versus 4 moxifloxacin deaths, the sponsor undertook a detailed examination of the deaths to determine if there was a possible causal relationship to omadacycline treatment.

A review of the literature as it relates to contemporary randomized registration CAP/CABP Phase 3 studies including studies that utilized moxifloxacin as the active comparator was performed.

Figure 11 shows a forest plot of randomized pivotal Phase 3 clinical studies in CAP/CABP since 2009. This includes randomized clinical studies of CAP/CABP for tigecycline,[64,65] ceftaroline,[66,67] solithromycin[60,68] and lefamulin[69,70] in addition to the OPTIC trial. The circles represent the point estimate for the observed mortality rate and the horizontal bar represents the 95% exact confidence interval for the point estimate in each treatment group for each randomized clinical study. The shaded region outlines the bounds of the 95% CI for the OPTIC study omadacycline mortality point estimate.

The literature search and supporting forest plot show that the mortality rates in the range of 0.8% to 3.2% are consistent with contemporary clinical trial experience with antimicrobial therapy in patients suffering CABP of demonstrated or presumed bacterial origin, with an illness severity requiring initial treatment with iv agents. The omadacycline mortality rate of 2.1% and the moxifloxacin mortality rate of 1.0% were both consistent with those observed in the contemporary randomized Phase 3 CABP studies.

Figure 11. Forest Plot of Contemporary CAP / CABP Clinical Studies, including OPTIC



95% CI was constructed based on the Clopper-Pearson method or Exact confidence intervals.

4.6.1.3 Causes of Death in CABP

The causes of death for the 12 patients who died in the OPTIC study are summarized in Table 40. The deaths were due to progression or complications of the pneumonia (septic shock, respiratory failure), cardiac causes including myocardial infarction, vascular causes including cerebrovascular accident and ruptured thoracic aortic aneurysm, and malignancy (lung and pancreas).

In order to more fully understand the mortality events in the OPTIC study, a detailed review of the individual cases was conducted with a focus on demographic and baseline factors, potential for lack of efficacy, pathogens, TEAE imbalances, and the timing of events. Brief by-patient narratives for the 12 patients who died are provided in Appendix 7.3, page 120.

Table 40. Fatal Adverse Events in OPTIC

Case#	Relative Day of Death	Age	PORT Class	Fatal Adverse Event Preferred Term	Cause of Death
OMC1	2	67	II	Septic shock	Progression of pneumonia
OMC2	2	76	III	Cardio-respiratory arrest	Sudden cardiac death
OMC3	2	66	IV	Acute myocardial infarction	Myocardial infarction
OMC4	9	72	IV	Aortic aneurysm rupture	Thoracic aneurysm rupture
MOX1	9	85	III	Acute respiratory failure	Progression of pneumonia
MOX2	9	83	IV	Cardiac failure	Myocardial infarction
OMC5	13	68	IV	Cerebrovascular accident	Cerebrovascular accident
OMC6	20	90	IV	Cardiogenic shock	Myocardial infarction
MOX3	20	82	IV	Lung neoplasm	Malignant neoplasm progression
OMC7	25	74	IV	Acute respiratory failure & Multi-organ failure	Progression of pneumonia
OMC8	30	86	IV	Pneumonia & ARDS	Secondary pneumonia
MOX4	71	72	III	Pancreatic Carcinoma	Malignant neoplasm progression

ARDS = acute respiratory distress syndrome, MOX = moxifloxacin, OMC = omadacycline.

The causes of death in the OPTIC study, as noted in the table above, are consistent with the causes described in observational studies and randomized registration studies in the CAP/CABP population. Mortensen et. al. examined both the immediate ("disease process, injury, or complication immediately preceding death") and underlying cause ("disease or injury that initiated the cascade of morbid events leading directly to death") of CAP mortality in over 2200 inpatients and outpatients.[71] Pneumonia-related mortality was 53% (immediate or underlying cause of death or if the pneumonia played a major role in the patient's death) and 85% of those deaths were observed in the Pneumonia Patient Outcomes Research Team (PORT) Risk Class IV or V categories. Respiratory failure (38%), cardiac conditions including cardiac arrhythmia and congestive heart failure (13%), and progression of presenting infectious condition including pneumonia and sepsis/bacteremia (11%) were the most frequent immediate causes of death. Neurologic conditions (29%), malignancies (24%), cardiac ischemia (14%), and incident pneumonia (10%) were the most frequent underlying cause of CAP mortality. A more recent prospective study by Waterer et al.[72] and the causes of death reported in contemporary randomized registration studies for CAP/CABP (Cerexa Studies P903-08 and P903-09;[73] Cempra Studies 300 and 301[74]) supports the analysis by Mortensen.[71]

4.6.1.4 Mortality-Associated Safety Analyses

In order to determine if there was a numerical trend for specific mortality-associated TEAEs (TEAEs with the outcome of death) that could represent a potential biologically plausible relationship to treatment assignment, "mortality-associated TEAEs by Preferred Terms" were examined in the large subpopulation of OPTIC patients who survived. Appendix Table 61 (page 118) demonstrates that the number of mortality-associated TEAEs by Preferred Terms in patients who survived were similar and very low in frequency. Similar number of events were

observed between omadacycline and moxifloxacin for all of these mortality-associated TEAE preferred terms including terms related to progression of pneumonia, cardiac events, vascular events and neoplasm. These analyses provide supportive data that there does not appear to be an AE seen more frequently that could be associated with omadacycline treatment in the patients who died.

In order to determine if the omadacycline patients in the OPTIC study who died had significant changes in HR, Appendix Figure 12 (page 118) shows that changes in HR for patients who died were of small magnitude (≤ 10 bpm) and well within the observed population based median values for HR change in patients treated with either omadacycline (who survived) or moxifloxacin (who survived or died).

4.6.1.5 Mortality in OPTIC - Discussion

The demographic and baseline factors for the omadacycline-treated patients who died describe an elevated potential risk of mortality (age over 65, PORT Risk Class IV, with underlying cardiovascular and pulmonary comorbidities).

The PORT Risk Classification estimates the potential rate of all-cause 30 day mortality. The PORT Risk Class is derived from the patient's age, gender, comorbidities, and vital signs and laboratory abnormalities upon presentation. All were a PORT Risk Class III or higher, and 6 of 8 omadacycline patients who died and 2 of 4 moxifloxacin patients who died were PORT Risk Class IV (Table 41).

Table 41. PORT Risk Class Including Patients Who Died in OPTIC

PORT Risk	OMC Deaths[a]	MOX Deaths[a]	OMC Mortality Rate by PORT Risk Class	MOX Mortality Rate by PORT Risk Class	30-Day All-Cause Mortality Range[b]
I	0	0	0	0	0.1-0.4%
II	1[c]	0	1.8%	0	0.6-0.7%
III[c]	1	2	0.4%	0.9%	0.9-2.8%
IV[c]	6	2	5.9%	1.7%	8.2-9.3%
V	0	0	0	0	27.0-31.1%
Total	8	4	2.1%	1.0%	

MOX=moxifloxacin, OMC=omadacycline, PORT=Pneumonia Outcomes Research Team.

[a] Actual PORT Risk Class, not as randomized.

[b] From Fine et. al., N Engl J Med 1997[75]

[c] On recalculation, PORT Risk determined be at least PORT III.

Based upon PORT Risk Class in OPTIC, the point estimates for omadacycline-and moxifloxacin-treated patients fall within the expected mortality ranges published for PORT Risk Class in hospitalized CABP patients.

The sponsor also investigated whether there were any omadacycline-related HR, QTc or TEAE mechanism(s) that could explain the small numerical differences in mortality (Appendix Table 59, page 116). These analyses demonstrate:

- The absence of excessive HR responses in the omadacycline patients who died
- The absence of an increase in QTcF in omadacycline patients across the ABSSSI and CABP populations studied (Appendix Table 58, page 116)
- The absence of cardiac TEAE imbalances for myocardial infarction, myocardial ischemia, cerebrovascular accident, heart failure, tachyarrhythmias, (Table 37) in the OPTIC study and across the integrated safety database
- The absence of any imbalance in mortality-associated TEAEs (Appendix Table 61, page 118) in omadacycline-treated versus moxifloxacin-treated patients who survived

Based upon these analyses, a biologically plausible or clinically associated causal relationship to treatment with omadacycline was not identified.

Overall, high rates of clinical efficacy were observed in the OPTIC study with no differences observed between omadacycline and moxifloxacin. Patients who died were considered failures. Since a lack of efficacy could result in increased mortality, additional analyses were conducted to determine whether efficacy was decreased in important subgroups. : 1) higher probability of mortality (eg, PORT Risk Class; Table 27), 2) higher rate of severity (eg, SMART-COP; Table 27), and 3) baseline bacteremia (Table 24). Subgroup population analyses demonstrated similar efficacy between omadacycline and moxifloxacin.

To assess whether insufficient ECR to either antibiotic therapy could result in the observed numerical difference in mortality, achievement of early clinical stability criteria was analyzed in the omadacycline and moxifloxacin treatment groups. These data demonstrated a high and similar percentage of patients in both treatment groups that successfully achieved early clinical stability. These high percentages are consistent with the high level of efficacy observed at the ECR assessment.

To determine if there was a differential level of achievement of clinical stability based upon PORT Risk class, analyses were conducted in these subgroups. The attainment of clinical stability for omadacycline and moxifloxacin patients by PORT Risk Class appeared similar to the ECR responses by PORT Risk Class (Table 41), suggesting no clinically appreciable nor differential delay in ECR based upon treatment assignment. These observations are also consistent with the low incidence of individual clinical cases in which only 2 omadacycline patients (OMC1 and OMC7) and only 1 moxifloxacin patient (MOX1) died due to progression of the incident pneumonia.

In order to determine if there was a specific pathogen that could be associated with the deaths, examination of the cases where there were pathogens isolated were conducted. No consistent pathogen was associated with the progression of the incident pneumonia to death. Two of the 4 patients with a baseline pathogen died due to progression of the pneumonia (OMC1 and OMC7). OMC1 died of pneumococcal sepsis and OMC7 died of progression of a multi-pathogen Gram-negative infection. *H. influenza* was identified at baseline in 3 omadacycline patients however OMC1 clinical course is most consistent with pneumococcal sepsis and OMC4 died of an aortic aneurysm rupture. OMC7 had *H. influenzae* and *E. coli* identified at baseline; however, the patient died of progression of a multi-pathogen Gram-negative infection including a gram

negative bacteria (*Proteus spp.)* intrinsically resistant to omadacycline. In addition, one patient (OMC3) had a baseline pathogen of *Pseudomonas aeruginosa*, which is intrinsically resistant to omadacycline.

Mortality Safety Summary

Overall, 17 deaths (10 omadacycline, 3 linezolid, 4 moxifloxacin) were reported in the Phase 2 and 3 studies. The mortality rates observed in the ABSSSI studies (1 omadacycline, 3 linezolid) were similar and low frequency. The mortality rates observed in OPTIC (8 omadacycline, 4 moxifloxacin) for both treatment arms were consistent with reported mortality rates in prior CAP/CABP randomized clinical studies. Randomization promotes comparability among treatment groups but does not protect against the chance of small numerical differences.

Further, the causes of death in OPTIC were consistent with identified causes of mortality in patients hospitalized with CABP. There were no specific TEAE imbalances observed that identified a specific AE that was directionally increased relative to omadacycline treatment. The mortality outcomes appear related to the underlying cardiovascular and pulmonary co-morbidities or progression of the presenting pneumonia without apparent biologic plausibility or causal assignment to omadacycline treatment identified.

4.7 Safety Conclusions

The following conclusions are based on the results of the safety analyses:

- Overall, omadacycline was safe and well tolerated.
- Rates of TEAEs, serious TEAEs, and treatment discontinuations were similar to comparator in the ABSSSI and CABP indications.
- Nausea and vomiting were the most frequent TEAEs with higher rates with omadacycline in OASIS-2 associated with the oral loading dose period on Day 1 and 2. In the pivotal Phase 3 studies, all nausea and vomiting TEAEs were mild or moderate in severity except in 1 omadacycline and 1 linezolid patient. Nausea and vomiting was not treatment limiting as only 4 omadacycline (0.4%) discontinued treatment for nausea and vomiting.
- Diarrhea occurred at a lower rate than comparators and no TEAEs associated with *C. difficile* infection occurred in omadacycline-treated patients.
- A review of all cardiac-related safety data available in ABSSSI and CABP patients demonstrate the low potential of omadacycline to be associated with: 1) increased HR; 2) increased QTc; 3) cardiac arrhythmias; or 4) other clinically significant cardiovascular AEs.
- Liver transaminase changes were transient, low-magnitude increases that were generally asymptomatic and resolved following treatment completion.
- The overall mortality rates between omadacycline and comparators are similar. Mortality in the CABP trial was extensively reviewed, and the rates and cause of mortality are consistent with contemporary CABP Phase 3 clinical studies. The mortality outcomes appeared related to underlying cardiovascular and pulmonary co-morbidities or progression of the presenting pneumonia without apparent biologic plausibility or causal assignment to omadacycline treatment identified.

5 BENEFIT RISK DISCUSSION

Omadacycline has been studied in a comprehensive and robust clinical development program and has demonstrated efficacy and safety in comparison to linezolid in ABSSSI and moxifloxacin in CABP. In this development program, 1,947 patients were exposed to omadacycline, including 1,073 patients exposed to omadacycline in the pivotal Phase 3 studies.

5.1 Benefits

Omadacycline was engineered to circumvent the clinically relevant mechanisms of tetracycline-specific resistance, namely ribosomal protection and efflux. There is no cross resistance with other classes of antibiotics which offers a therapeutic option for physicians who encounter resistance via those other mechanisms of action. Similarly, if resistance to omadacycline should emerge, it will not challenge resistance profiles of antibiotics outside of the tetracycline class based on the lack of cross-resistance. *In vitro*, a low propensity for the development of resistance has been demonstrated.

Omadacycline has in vitro activity against drug-resistant pathogens such as macrolide and penicillin resistant *S. pneumoniae* and MRSA that are encountered in the treatment of CABP and ABSSSI, respectively. Its spectrum of in vitro activity against Gram-positive, many Gram-negative, anaerobes, and atypical pathogens suggest that it would be an appropriate option for the empiric treatment of CABP and many ABSSSI infection types when either resistance or contraindications to guidance-driven antibiotic options limit the use of these agents.

In 2 pivotal Phase 3 studies in patients with ABSSSI, omadacycline was determined to be non-inferior to the gold standard comparator linezolid. Clinical success rates were high at the ECR primary endpoint assessment, as well as at the investigator-assessed PTE endpoint, thus demonstrating robust early (ie, ECR clinical response) and durable (ie, IACR PTE assessment) efficacy.

In the pivotal Phase 3 study OPTIC, omadacycline was determined to be non-inferior to the gold standard comparator moxifloxacin. Clinical success rates were high at the ECR primary endpoint assessment as well as at the later investigator-assessed PTE endpoint, again demonstrating robust early and durable efficacy. Additional subgroup, and symptom-based analyses demonstrate the robustness of the primary efficacy assessment. Similar rates of clinical success were observed at the ECR and PTE assessment between PORT Risk Class and treatment groups.

Omadacycline has been developed as a once-daily antibiotic, with both iv and po formulations and a spectrum of activity to treat patients with community-acquired bacterial infections, particularly when antibiotic resistance is of concern or for patients who cannot be prescribed other antibiotics. As a monotherapy available in both iv and po formulations, omadacycline affords physicians treating ABSSSI and CABP the flexibility of initiating iv treatment in an inpatient setting and beginning or completing oral-only treatment in an outpatient setting based on individual patient characteristics and evaluation of the infection at the point of care.

Adjustments in omadacycline dosing are not required. No dosing adjustments are required in patients based on age or gender or in patients with hepatic or renal impairment or in those undergoing dialysis. Omadacycline is not metabolized by the liver and is not an inhibitor or inducer of major cytochrome P450 enzymes, making clinically relevant drug-drug interactions through hepatic mechanisms unlikely. Omadacycline is not a substrate or inhibitor of most major drug transporters. Although po omadacycline is a substrate for P-gp, concomitant administration of po omadacycline with P-gp inhibitors does not require monitoring or dose adjustment.

Clostridium difficile infection has been reported with use of nearly all antibacterial agents; however, use of tetracyclines may be associated with less CDI compared to other classes of antibiotics.[76,23] The potential for less CDI is also supported by low omadacycline MIC, high intraluminal gut concentrations due to biliary excretion, and positive results in a hamster CDI model and the in-vitro gut model. Among all patients who have received omadacycline in Phase 1, Phase 2 or Phase 3 studies, no cases of *C. difficile*-associated infection was reported. Further clinical data will need to be analyzed to affirm these preliminary observations that the potential for a lower risk for CDIs with omadacycline treatment. The potential for a lower risk of CDI may benefit patients at high risk for CDI (eg, diagnosis of ABSSSI or CABP following a recent episode of CDI).

5.2 Risks

The favorable safety and tolerability profile of omadacycline has been well characterized in the entirety of the 27 all clinical studies conducted to date. Omadacycline is safe and well tolerated when administered in accordance with the proposed labeling. The identified risks of omadacycline from the Phase 3 clinical development program are consistent with the known safety profile of older generation tetracyclines.

The most common TEAEs reported with omadacycline treatment include nausea and vomiting. These gastrointestinal events were the only TEAEs reported in more than 5% of omadacycline-treated patients in the pooled Phase 3 studies. All events were of mild or moderate intensity, and only 4 of 1073 (0.4%) omadacycline-treated patients discontinued treatment because of nausea and/or vomiting.

Elevations in liver transaminases observed in patients who received omadacycline were generally asymptomatic, of low magnitude, and transient (ie, reversible during or following completion of treatment). Hepatic AEs occurred at similar or lower frequencies with omadacycline than with comparators and treatment discontinuations were rare. No cases of Hy's Law were identified.

Omadacycline has been studied for the acute, short-term treatment of adults with community-acquired ABSSSI and CABP. No data are available on pediatric use, use in severely immunocompromised patients, or long-term or chronic use of omadacycline.

Other potential risks for omadacycline include those associated with older generation tetracycline class of antibiotics. Important risks include teratogenicity, tooth staining in children < 8 years of age, and calcium binding. Accordingly, careful measures are in place to avoid administration of omadacycline during conception, pregnancy or in children < 8 years of age.

Although there is no information on the presence of omadacycline in human milk, serum concentrations of tetracycline in breastfed infants are low and short term use (7 to 10 days) of tetracycline antibiotics is not contraindicated in lactating women.

The development of bacterial resistance to omadacycline (and any other antibacterial agent) has not been observed to date in any bacterial isolates obtained in the clinical studies conducted in patients with skin infections or CABP. There have been few clinical failures of treatment in these studies and hence, few post-treatment isolates for testing. Nevertheless, clinical surveillance studies must be conducted in a diligent fashion as this product enters the clinic. Because the potential for emergence of resistance exists for any antibacterial therapy, this will remain a potential risk for omadacycline that will be followed closely.

5.3 Conclusions

Omadacycline is a next generation tetracycline that retains activity against bacteria that carry classical tetracycline resistance mechanisms, circumvents the 2 known clinical important tetracycline resistance mechanisms. The tetracycline-specific mechanism of action and the lack of cross-resistance to other antibiotics classes allows omadacycline to treat infections caused by bacteria with other clinically important mechanisms of bacterial resistance that continue to be problematic for patients and treating physicians.

The data and accompanying analyses provided in this briefing book support the conclusions that:

- Omadacycline demonstrated substantial evidence of efficacy for the treatment of ABSSSI in Phase 3 studies.
- Omadacycline demonstrated substantial evidence of efficacy for the treatment of CABP in a large Phase 3 study
- Omadacycline was safe and well-tolerated with an AE profile similar to older generation tetracyclines.
- There were similar rates of TEAEs, vital sign changes, and laboratory changes across the 3 pivotal Phase 3 studies.
- The overall mortality rates between omadacycline and comparators are similar. Mortality in the CABP trial was extensively reviewed, and the rates and causes of mortality are consistent with recent clinical trial experience. The mortality outcomes appeared related to the underlying cardiovascular and pulmonary co-morbidities or progression of the presenting pneumonia with no known biologic plausibility or causal assignment to omadacycline treatment identified.

Omadacycline represents an important new treatment option for ABSSSI and CABP for physicians when patients may have a resistant organism or cannot be cannot be prescribed currently available antibiotic therapies. The totality of the efficacy, safety and tolerability data support a positive benefit:risk profile for this NDA.

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7 APPENDIX

7.1 Supplemental Tables and Figure

Table 42. Activity of Omadacycline Against Common Gram-positive Bacterial Pathogens[a]

Species	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)[b]
Staphylococcus aureus (MSSA)	1206	0.12	0.12
Staphylococcus aureus (MRSA)	942	0.12	0.12
Coagulase–negative staphylococci[c]	320	0.12	0.5
Enterococcus faecalis (VSE)	607	0.06	0.12
Enterococcus faecalis (VRE)	29	0.06	0.12
Enterococcus faecium (VSE)	74	0.06	0.12
Enterococcus faecium (VRE)	167	0.06	0.25
Streptococcus pneumoniae	1012	0.06	0.12
Streptococcus pneumoniae (PRSP)	33	0.06	0.12
Streptococcus pyogenes	286	0.06	0.06
Streptococcus agalactiae	261	0.12	0.12
Viridans group streptococci[d]	106	0.06	0.12
Staphylococcus saprophyticus (MR)	7	--	Range: 0.06 - 0.25

MIC_{50} = minimum inhibitory concentration for at least 50% of the isolates tested for a given species or genus,
MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates tested for a given species or genus,
MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*,
PRSP = penicillin-resistant *Streptococcus pneumoniae*, VRE = vancomycin-resistant *Enterococcus*,
VSE = vancomycin-sensitive *Enterococcus*.

[a] Jones et al. Surveillance Report 2017 (study 17-PAR-05). Data on file.

[b] The MIC range was reported when < 10 strains were tested.

[c] Organisms include: *S. auricularis* (16), *S. capitis* (182), *S. caprae* (18), *S. carnosus* (1), *S. chromogenes* (1), *S. cohnii* (20), *S. epidermidis* (2,178), *S. equorum* (1), *S. haemolyticus* (369), *S. hominis* (399), *S. intermedius* (4), *S. lugdunensis* (191), *S. pasteuri (1)*, *S. pettenkoferi* (9), *S. pseudintermedius* (1), *S. pseudintermedius / intermedius / delphini* (2), *S. saprophyticus* (61), *S. schleiferi* (12), *S. sciuri* (7), *S. simulans* (29), *S. succinus* (1), *S. warneri (*82), *S. xylosus* (30), Unspeciated coagulase-negative staphylococci (1,313).

[d] Organisms include: *Streptococcus acidominimus* (2), *S. alactolyticus* (1), *S. anginosus* (288), *S. anginosus* group (52), *S. australis* (4), *S. bovis* group (73), *S. constellatus* (89), *S. cristatus* (8), *S. equinus* (2), *S. gallolyticus* (65), *S. gordonii* (37), *S. infantarius* (4), *S. infantis* (3), *S. intermedius* (36), *S. lutetiensis* (5), *S. massiliensis* (1), *S. mitis* (2), *S. mitis* group (357), *S. mitis/ oralis* (20), *S. mutans* (17), *S. oralis* (74), *S. parasanguinis* (61), *S. pasteurianus* (1), *S. salivarius* (84), *S. salivarius* group (5), *S. salivarius/ vestibularis* (9), *S. sanguinis* (70), *S. thermophilus* (1), *S. vestibularis* (16).

Table 43. Activity of Omadacycline Against Common Gram-negative Bacterial Pathogens[a]

Species	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)[b]
Haemophilus influenzae	4,683	1	2
Moraxella catarrhalis[c]	408	0.25	0.25
Citrobacter freundii[c]	86	1	4
Escherichia coli	14,091	1	2
Enterobacter aerogenes[c]	248	1	4
Enterobacter cloacae	2,703	2	>4
Klebsiella pneumoniae	6,792	2	>4
Morganella morganii[c]	175	4	32
Proteus mirabilis[c]	463	16	>32
Proteus vulgaris[c]	60	8	16
Providencia stuartii[c]	41	16	>32
Salmonella spp.	249	2	4
Serratia marcescens[c]	364	4	8
Pseudomonas aeruginosa[c]	1986	32	> 32
Acinetobacter baumannii	2,754	2	8
Burkholderia cepacia species complex[d]	8	--	Range: 0.5 - 4
Stenotrophomonas maltophilia	1,023	2	8

MIC_{50} = minimum inhibitory concentration for at least 50% of the isolates tested for a given species or genus,
MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates tested for a given species or genus.

[a] Jones et al. Surveillance Report 2017 (study 17-PAR-05). Data on file.
[b] The MIC range was reported when < 10 strains were tested.
[c] Jones et al. Surveillance Report 2009. Data on file.
[d] JMI Microbiology Visualization Platform, Surveillance data, 2016. Data on file.

Table 44. Activity of Omadacycline Against Anaerobic and Atypical Bacterial Pathogens

Class	Species	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)[a]	Reference
Anaerobic Pathogens	*C. difficile*	27	0.06	0.06	[b]
		21	0.25	0.5	[c]
	C. perfringens	100	1	4	[b]
		22	4	16	[c]
	Peptostreptococcus spp.	22	0.12	1	[c]
	B. fragilis	100	1	2	[b]
		21	0.5	4	[c]
	B. thetaiotaomicron	100	0.5	8	[b]
		21	1	4	[c]
	B. vulgatus	21	0.12	1	[c]
	B. ovatus	15	0.5	8	[c]
	Prevotella spp.	22	0.5	2	[c]
	P. asaccharolytica	21	0.25	0.5	[c]
	Anaerobic Gram-positive cocci	101	0.12	0.25	[b]
Atypical pathogens	*Legionella pneumophila*	12	2	4	[d]
	L. pneumophila (all serogroups)	25	0.25	0.25	[e]
		100	0.25	0.25	[f]
	Mycoplasma. pneumoniae	8	N/A	Range: ≤ 0.015 - 0.06	[d]
		20	0.12	0.25	[g]
	Mycoplasma. hominis	20	0.03	0.06	[g]
	Ureaplasma parvum	10	0.5	1	[g]
	Ureaplasma urealyticum	10	1	2	[g]

MIC_{50} = minimum inhibitory concentration for at least 50% of the isolates tested for a given species or genus,
MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates tested for a given species or genus.

[a] The MIC range was reported when < 10 strains were tested.
[b] Clinical Microbiology Institute Report 594, 2007. Data on file.
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Table 45. Overview of the Phase 2 and Phase 3 Omadacycline Clinical Studies

Protocol No. Start/Stop Dates	Study Design	No. of Patients (Safety Population)	Regimens: Omadacycline	Regimens: Comparator	Primary Efficacy Outcome
Studies in cSSSI					
CSSI-0702 Jul 2007/Jan 2008	Phase 2, randomized, evaluator-blinded	OMC = 111 Linezolid = 108	100 mg iv q24h 200 mg po q24h	600 mg iv q12h 600 mg po q12h	Investigator's assessment of clinical response at TOC visit
CSSI-0804 Apr 2009/Apr 2010	Phase 3, randomized, evaluator-blinded	OMC = 68 Linezolid = 72	100 mg iv q24h 300 mg po q24h	600 mg iv q12h 600 mg po q12h	Investigator's assessment of clinical response at TOC visit
Studies in ABSSSI					
OASIS-1 (ABSI-1108) Jun 2015/May 2016	Phase 3, double-blind, active comparator-controlled	OMC = 329 Linezolid = 326	100 mg iv q12h × 2 then 100 mg iv q24h 300 mg po q24h	600 mg iv q12h 600 mg po q12h	Early Clinical Response at 48 to 72 h after first dose; Investigator's assessment of clinical response at PTE (EMA)
OASIS-2 (ABSI-16301) Aug 2016/Jun 2017	Phase 3, double-blind, active comparator-controlled	OMC = 368 Linezolid = 367	450 mg po q24h × 2 then 300 mg po q24h	600 mg po q12h	Early Clinical Response at 48 to 72 h after first dose (FDA); Investigator's assessment of clinical response at PTE (EMA)
Study in CABP					
OPTIC (CABP-1200) Nov 2015/Feb 2017	Phase 3, double-blind, active comparator-controlled	OMC = 386 Moxifloxacin = 388	100 mg iv q12h ×2 then 100 mg iv q24h 300 mg po q24h	400 mg iv q24h 400 mg po q24h	Early Clinical Response at 72 to 120 h after first dose (FDA); Investigator's assessment of clinical response at PTE (EMA)

ABSSSI = acute bacterial skin and skin structure infection, CABP = community-acquired bacterial pneumonia, cSSSI = complicated skin and skin structure infections, EMA = European Medicines Agency, FDA = Food and Drug Administration, ITT = intent-to-treat, iv = intravenous, OMC = omadacycline, po = per oral, PTE = post therapy evaluation, q12h = every 12 h, q24h = every 24 h, TOC = test of cure.

Table 46. Demographic and Baseline Characteristics in ABSSSI Studies OASIS-1 and OASIS-2 (Safety Population)

	Study ABSI-1108			Study ABSI-16301		
Characteristics	**Omadacycline (N = 323)**	**Linezolid (N = 322)**	**All Patients (N = 645)**	**Omadacycline (N = 368)**	**Linezolid (N = 367)**	**All Patients (N = 735)**
Gender, n (%)						
Female	120 (37.2)	109 (33.9)	229 (35.5)	126 (34.2)	147 (40.1)	273 (37.1)
Male	203 (62.8)	213 (66.1)	416 (64.5)	242 (65.8)	220 (59.9)	462 (62.9)
Race, n (%)						
White	294 (91.0)	300 (93.2)	594 (92.1)	327 (88.9)	341 (92.9)	668 (90.9)
Black or African American	16 (5.0)	8 (2.5)	24 (3.7)	22 (6.0)	13 (3.5)	35 (4.8)
Asian	1 (0.3)	2 (0.6)	3 (0.5)	3 (0.8)	5 (1.4)	8 (1.1)
American Indian or Alaska Native	7 (2.2)	5 (1.6)	12 (1.9)	7 (1.9)	3 (0.8)	10 (1.4)
Native Hawaiian or Other Pacific Islander	1 (0.3)	3 (0.9)	4 (0.6)	3 (0.8)	0	3 (0.4)
Other	4 (1.2)	4 (1.2)	8 (1.2)	6 (1.6)	5 (1.4)	11 (1.5)
Ethnicity, n (%)						
Hispanic or Latino	84 (26.0)	91 (28.3)	175 (27.1)	154 (41.8)	156 (42.5)	310 (42.2)
Not Hispanic or Latino	235 (72.8)	229 (71.1)	464 (71.9)	214 (58.2)	211 (57.5)	425 (57.8)
Not reported/unknown	4 (1.2)	2 (0.6)	6 (0.9)	0	0	0
Age (years)						
Mean (SD)	46.9 (15.45)	46.6 (15.30)	46.8 (15.36)	42.8 (12.72)	44.5 (13.11)	43.7 (12.94)
Median	48.0	46.0	47.0	41.0	46.0	43.0
Min, max	19, 88	18, 90	18, 90	18, 86	20, 84	18, 86
Categorical age (years) n (%)						
18 - 45	146 (45.2)	154 (47.8)	300 (46.5)	213 (57.9)	183 (49.9)	396 (53.9)
> 45 - 65	141 (43.7)	136 (42.2)	277 (42.9)	141 (38.3)	164 (44.7)	305 (41.5)
> 65	36 (11.1)	32 (9.9)	68 (10.5)	14 (3.8)	20 (5.4)	34 (4.6%)

Table 46. Demographic and Baseline Characteristics in ABSSSI Studies OASIS-1 and OASIS-2 (Safety Population)

	Study ABSI-1108			Study ABSI-16301		
Characteristics	**Omadacycline (N = 323)**	**Linezolid (N = 322)**	**All Patients (N = 645)**	**Omadacycline (N = 368)**	**Linezolid (N = 367)**	**All Patients (N = 735)**
BMI (kg/m^2)						
n	323	321	644	368	367	735
Mean (SD)	27.98 (6.330)	28.14 (6.233)	28.06 (6.278)	27.91 (6.472)	27.93 (6.556)	27.92 (6.510)
Median	26.99	26.62	26.86	26.71	26.54	26.64
Min, max	16.9, 53.6	16.2, 54.7	16.2, 54.7	16.3, 71.3	16.7, 54.1	16.3, 71.3
CrCL (local lab), n (%)						
n	323	321	644	365	363	728
Normal renal function (> 80 mL/min)	277 (85.8)	276 (86.0)	553 (85.9)	343 (94.0)	340 (93.7)	683 (93.8)
Mild renal impairment (> 50 - 80 mL/min)	32 (9.9)	35 (10.9)	67 (10.4)	21 (5.8)	17 (4.7)	38 (5.2)
Moderate renal impairment (30 - 50 mL/min)	12 (3.7)	9 (2.8)	21 (3.3)	1 (0.3)	6 (1.7)	7 (1.0)
Severe renal impairment (< 30 mL/min)	2 (0.6)	1 (0.3)	3 (0.5)	0	0	0

Age was calculated from the date of birth to the informed consent date.
P-values for differences between treatment groups were from Fisher's exact test (for categorical variables) or Wilcoxon Rank Sum test (for continuous variables).
For each categorical parameter, the denominator for the percentage was the number of patients who had that parameter assessed.
BMI = body mass index, CrCL = creatinine clearance, max = maximum, min = minimum, SD = standard deviation.

Table 47. Overall Clinical Response at the PTE Visit Based on Investigator Assessments in OASIS-1 and OASIS-2 (CE-PTE Populations)

Efficacy Outcome	Omadacycline n (%)	Linezolid n (%)	Difference	95% CI Without Stratification[a]	95% CI With Stratification[b]
OASIS-1					
CE-PTE	(N = 269)	(N = 260)			
Clinical success	259 (96.3)	243 (93.5)	2.8	(-1.0, 6.9)	(-0.9, 7.1)
Clinical failure	10 (3.7)	17 (6.5)	-	-	-
OASIS-2					
CE-PTE	N = 284	N = 292			
Clinical success	278 (97.9)	279 (95.5)	2.3	(-0.6, 5.6)	(-0.5, 5.8)
Clinical failure	6 (2.1)	13 (4.5)			

Difference was observed difference in overall clinical success rate at PTE between the omadacycline and linezolid groups.

Overall clinical response at PTE was based on the investigator assessment at the EOT and PTE visits.

Percentages were based on the number of patients in each treatment group.

CE = clinically evaluable; CI = confidence interval; ME = microbiologically evaluable; PTE = post therapy evaluation.

[a] 95% CI was constructed based on the Miettinen and Nurminen method without stratification.

[b] 95% CI was adjusted for type of infection and geographic region based on the Miettinen and Nurminen method with stratification, using Cochran-Mantel-Haenszel weights as stratum weights. The 4 geographic regions were combined into 1 group. Infection type was not combined.

Table 48. Early Clinical Success 48 to 72 h After the First Dose of Test Article by Baseline Pathogen From the ABSSSI Site or Blood Culture in Greater Than or Equal to 6 Patients in OASIS-1 and OASIS-2 (micro-mITT Population)

	OASIS-1		OASIS-2		Pooled OASIS-1 and OASIS-2	
Baseline Pathogen	**Omadacycline (N = 228) n/N1 (%)**	**Linezolid (N = 227) n/N1 (%)**	**Omadacycline (N = 276) n/N1 (%)**	**Linezolid (N = 287) n/N1 (%)**	**Omadacycline (N = 504) n/N1 (%)**	**Linezolid (N = 514) n/N1 (%)**
Gram-positive organisms (aerobes)						
Staphylococcus aureus	138/156 (88.5)	131/151 (86.8)	194/220 (88.2)	194/233 (83.3)	332/376 (88.3)	325/384 (84.6)
MRSA	62/69 (89.9)	44/50 (88.0)	97/104 (93.3)	95/107 (88.8)	159/173 (91.9)	139/157 (88.5)
MSSA	77/88 (87.5)	87/102 (85.3)	101/120 (84.2)	103/130 (79.2)	178/208 (85.6)	190/232 (81.9)
Staphylococcus lugdunensis	6/6 (100.0)	3/3 (100.0)	4/5 (80.0)	0	10/11 (90.9)	3/3 (100.0)
Streptococcus anginosus group	39/47 (83.0)	27/37 (73.0)	54/57 (94.7)	36/45 (80.0)	93/104 (89.4)	63/82 (76.8)
Streptococcus anginosus	8/8 (100.0)	4/7 (57.1)	27/27 (100.0)	17/20 (85.0)	35/35 (100.0)	21/27 (77.8)
Streptococcus intermedius	11/12 (91.7)	14/18 (77.8)	21/23 (91.3)	18/24 (75.0)	32/35 (91.4)	32/42 (76.2)
Streptococcus constellatus	18/25 (72.0)	7/14 (50.0)	8/9 (88.9)	7/7 (100.0)	26/34 (76.5)	14/21 (66.7)
Enterococcus faecalis	9/10 (90.0)	12/13 (92.3)	7/8 (87.5)	8/12 (66.7)	16/18 (88.9)	20/25 (80.0)
VSE	9/10 (90.0)	12/13 (92.3)	6/7 (85.7)	6/10 (60.0)	15/17 (88.2)	18/23 (78.3)
Beta hemolytic streptococcus	10/16 (62.5)	20/22 (90.9)	26/33 (78.8)	15/19 (78.9)	36/49 (73.5)	35/41 (85.4)
Group A *or Streptococcus pyogenes*	8/11 (72.7)	17/18 (94.4)	24/29 (82.8)	13/16 (81.3)	32/40 (80.0)	30/34 (88.2)
Streptococcus mitis	6/6 (100.0)	3/4 (75.0)	1/1 (100.0)	0	7/7 (100.0)	3/4 (75.0)
Streptococcus sanguinis	2/2 (100.0)	6/6 (100.0)	1/1 (100.0)	0	3/3 (100.0)	6/6 (100.0)
Gram-positive organisms (anaerobes)						
Peptostreptococcus species	9/10 (90.0)	5/6 (83.3)	2/3 (66.7)	2/3 (66.7)	11/13 (84.6)	7/9 (77.8)
Finegoldia magna	4/4 (100.0)	5/5 (100.0)	2/3 (66.7)	0/1 (0.0)	6/7 (85.7)	5/6 (83.3)
Clostridium species	7/7 (100.0)	8/9 (88.9)	9/9 (100.0)	11/13 (84.6)	16/16 (100.0)	19/22 (86.4)
Clostridium perfringens	1/1 (100.0)	4/5 (80.0)	5/5 (100.0)	9/9 (100.0)	6/6 (100.0)	13/14 (92.9)
Gram-negative organisms (aerobes)						
Enterobacteriaceae	16/18 (88.9)	14/16 (87.5)	18/20 (90.0)	17/24 (70.8)	34/38 (89.5)	31/40 (77.5)
Enterobacter cloacae	7/9 (77.8)	4/5 (80.0)	5/5 (100.0)	5/6 (83.3)	12/14 (85.7)	9/11 (81.8)
Escherichia coli	2/2 (100.0)	3/3 (100.0)	4/4 (100.0)	1/1 (100.0)	6/6 (100.0)	4/4 (100.0)
Klebsiella pneumoniae	6/6 (100.0)	4/5 (80.0)	4/5 (80.0)	5/6 (83.3)	10/11 (90.9)	9/11 (81.8)

Table 48. Early Clinical Success 48 to 72 h After the First Dose of Test Article by Baseline Pathogen From the ABSSSI Site or Blood Culture in Greater Than or Equal to 6 Patients in OASIS-1 and OASIS-2 (micro-mITT Population)

	OASIS-1		OASIS-2		Pooled OASIS-1 and OASIS-2	
Baseline Pathogen	**Omadacycline (N = 228) n/N1 (%)**	**Linezolid (N = 227) n/N1 (%)**	**Omadacycline (N = 276) n/N1 (%)**	**Linezolid (N = 287) n/N1 (%)**	**Omadacycline (N = 504) n/N1 (%)**	**Linezolid (N = 514) n/N1 (%)**
Gram-negative organisms (anaerobes)						
Prevotella species	13/15 (86.7)	8/10 (80.0)	8/8 (100.0)	5/5 (100.0)	21/23 (91.3)	13/15 (86.7)
Prevotella denticola	2/2 (100.0)	1/1 (100.0)	5/5 (100.0)	1/1 (100.0)	7/7 (100.0)	2/2 (100.0)
Prevotella melaninogenica	6/7 (85.7)	5/6 (83.3)	2/2 (100.0)	3/3 (100.0)	8/9 (88.9)	8/9 (88.9)

N1 = number of patients in the micro-mITT population in the treatment group with the Baseline pathogen. Percentages were based on N1, the number of patients with the indicated pathogen.

Patients with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Patients with the same pathogen identified from both the blood and primary ABSSSI cultures were counted only once.

ABSSSI = acute bacterial skin and skin structure infection, micro-mITT = microbiological modified intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*, VSE = vancomycin-susceptible enterococci.

Table 49. Overall Clinical Success at PTE Visit Based on Investigator's Assessment by Baseline Pathogen From the ABSSSI Site or Blood Culture in Greater Than or Equal to 6 Patients in OASIS-1 and OASIS-2 (micro-mITT Population)

	OASIS-1		OASIS-2		Pooled OASIS-1 and OASIS-2	
Baseline Pathogen	**Omadacycline (N = 228) n/N1 (%)**	**Linezolid (N = 227) n/N1 (%)**	**Omadacycline (N = 276) n/N1 (%)**	**Linezolid (N = 287) n/N1 (%)**	**Omadacycline (N = 504) n/N1 (%)**	**Linezolid (N = 514) n/N1 (%)**
Gram-positive organisms (aerobes)						
Staphylococcus aureus	130/156 (83.3)	126/151 (83.4)	182/220 (82.7)	186/233 (79.8)	312/376 (83.0)	312/384 (81.3)
MRSA	57/69 (82.6)	43/50 (86.0)	89/104 (85.6)	85/107 (79.4)	146/173 (84.4)	128/157 (81.5)
MSSA	74/88 (84.1)	84/102 (82.4)	97/120 (80.8)	103/130 (79.2)	171/208 (82.2)	187/232 (80.6)
Staphylococcus lugdunensis	6/6 (100.0)	2/3 (66.7)	4/5 (80.0)	0	10/11 (90.9)	2/3 (66.7)
Streptococcus anginosus group	35/47 (74.5)	26/37 (70.3)	49/57 (86.0)	33/45 (73.3)	84/104 (80.8)	59/82 (72.0)
Streptococcus anginosus	7/8 (87.5)	5/7 (71.4)	24/27 (88.9)	16/20 (80.0)	31/35 (88.6)	21/27 (77.8)
Streptococcus intermedius	10/12 (83.3)	14/18 (77.8)	18/23 (78.3)	16/24 (66.7)	28/35 (80.0)	30/42 (71.4)
Streptococcus constellatus	16/25 (64.0)	9/14 (64.3)	8/9 (88.9)	5/7 (71.4)	24/34 (70.6)	14/21 (66.7)
Enterococcus faecalis	9/10 (90.0)	12/13 (92.3)	8/8 (100.0)	9/12 (75.0)	17/18 (94.4)	21/25 (84.0)
VSE	9/10 (90.0)	12/13 (92.3)	7/7 (100.0)	7/10 (70.0)	16/17 (94.1)	19/23 (82.6)
Beta hemolytic streptococcus	13/16 (81.3)	19/22 (86.4)	22/33 (66.7)	11/19 (57.9)	35/49 (71.4)	30/41 (73.2)
Group A or *Streptococcus pyogenes*	8/11 (72.7)	16/18 (88.9)	20/29 (69.0)	9/16 (56.3)	28/40 (70.0)	25/34 (73.5)
Streptococcus mitis	6/6 (100.0)	4/4 (100.0)	1/1 (100.0)	0	7/7 (100.0)	4/4 (100.0)
Streptococcus sanguinis	2/2 (100.0)	6/6 (100.0)	1/1 (100.0)	0	3/3 (100.0)	6/6 (100.0)
Gram-positive organisms (anaerobes)						
Peptostreptococcus species	9/10 (90.0)	6/6 (100.0)	3/3 (100.0)	2/3 (66.7)	12/13 (92.3)	8/9 (88.9)
Finegoldia magna	4/4 (100.0)	5/5 (100.0)	3/3 (100.0)	0/1 (0.0)	7/7 (100.0)	5/6 (83.3)
Clostridium species	7/7 (100.0)	8/9 (88.9)	8/9 (88.9)	9/13 (69.2)	15/16 (93.8)	17/22 (77.3)
Clostridium perfringens	1/1 (100.0)	4/5 (80.0)	4/5 (80.0)	7/9 (77.8)	5/6 (83.3)	11/14 (78.6)
Gram-negative organisms (aerobes)						
Enterobacteriaceae	14/18 (77.8)	11/16 (68.8)	16/20 (80.0)	19/24 (79.2)	30/38 (78.9)	30/40 (75.0)
Enterobacter cloacae	7/9 (77.8)	3/5 (60.0)	4/5 (80.0)	6/6 (100.0)	11/14 (78.6)	9/11 (81.8)
Escherichia coli	2/2 (100.0)	3/3 (100.0)	4/4 (100.0)	1/1 (100.0)	6/6 (100.0)	4/4 (100.0)
Klebsiella pneumoniae	4/6 (66.7)	2/5 (40.0)	4/5 (80.0)	4/6 (66.7)	8/11 (72.7)	6/11 (54.5)
Proteus mirabilis	2/2 (100.0)	1/1 (100.0)	1/2 (50.0)	6/7 (85.7)	3/4 (75.0)	7/8 (87.5)

Table 49. Overall Clinical Success at PTE Visit Based on Investigator's Assessment by Baseline Pathogen From the ABSSSI Site or Blood Culture in Greater Than or Equal to 6 Patients in OASIS-1 and OASIS-2 (micro-mITT Population)

Gram-negative organisms (anaerobes)						
Prevotella species	11/15 (73.3)	7/10 (70.0)	6/8 (75.0)	4/5 (80.0)	17/23 (73.9)	11/15 (73.3)
Prevotella melaninogenica	4/7 (57.1)	4/6 (66.7)	2/2 (100.0)	3/3 (100.0)	6/9 (66.7)	7/9 (77.8)

N1 = number of patients in the micro-mITT population in the treatment group with the Baseline pathogen. Percentages were based on N1, the number of patients with the indicated pathogen.
Patients with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Patients with the same pathogen identified from both the blood and primary ABSSSI cultures were counted only once.
ABSSSI = acute bacterial skin and skin structure infection, ECR = Early Clinical Response, micro-mITT = microbiological modified intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*, PTE = post therapy evaluation, VSE = vancomycin-susceptible enterococci.

Table 50. Abnormal Vital and Laboratory Signs at Baseline in OPTIC (ITT Population)

Characteristics	Omadacycline N = 386 n (%)	Moxifloxacin N = 388 n (%)
Fever (> 38.0°C [100.4°F])		
Yes	182 (47.2)	177 (45.6)
No	204 (52.8)	211 (54.4)
Hypothermia (< 36.0°C [95.5°F])		
Yes	15 (3.9)	11 (2.8)
No	371 (96.1)	377 (97.2)
Hypotension (SBP < 90 mm Hg)		
Yes	30 (7.8)	38 (9.8)
No	356 (92.2)	350 (90.2)
HR > 90 bpm		
Yes	163 (42.2)	132 (34.0)
No	223 (57.8)	256 (66.0)
RR > 20 breaths/min		
n	357	361
Yes	312 (87.4)	319 (88.4)
No	45 (12.6)	42 (11.6)
Hypoxemia (PaO2 < 60 mm Hg by ABG)		
n	255	257
Yes	113 (44.3)	111 (43.2)
No	142 (55.7)	146 (56.8)
Hypoxemia (oxygen saturation < 90% by pulse oximetry)		
n	375	371
Yes	102 (27.2)	117 (31.5)
No	273 (72.8)	254 (68.5)
Hypoxemia ([PaO_2 < 60 mm Hg by ABG] or [oxygen saturation < 90% by pulse oximetry])		
n	386	387
Yes	180 (46.6)	181 (46.8)
No	206 (53.4)	206 (53.2)
Elevated total WBC count (> 12,000 cells/mm3)		
n	385	388
Yes	123 (31.9)	118 (30.4)
No	262 (68.1)	270 (69.6)
Leukopenia (WBC < 4,000 cells/mm3)		
n	385	388
Yes	10 (2.6)	10 (2.6)
No	375 (97.4)	378 (97.4)
Elevated immature neutrophils (> 15% bands)		
n	217	233
Yes	25 (11.5)	26 (11.2)
No	192 (88.5)	207 (88.8)

Table 50. Abnormal Vital and Laboratory Signs at Baseline in OPTIC (ITT Population)

Characteristics	Omadacycline N = 386 n (%)	Moxifloxacin N = 388 n (%)
Elevated total WBC count (> 12,000 cells/mm^3) or leukopenia (WBC < 4,000 cells/mm^3) or elevated immature neutrophils (> 15% bands)		
n	385	388
Yes	146 (37.9)	144 (37.1)
No	239 (62.1)	244 (62.9)

Percentages were based on the number of patients who had the specific parameter assessed.
ABG = arterial blood gas, bpm = beats per min, CABP = community-acquired bacterial pneumonia, HR = heart rate, ITT = intent-to-treat, PaO_2 = partial pressure of arterial oxygen, RR = respiratory rate, SBP = systolic blood pressure, WBC = white blood cell.

Table 51. Patients With Pathogens Identified at Baseline From Blood Specimens, Respiratory Specimens, UATs, and/or Serology in Greater Than or Equal to 1% of the Population in OPTIC (microITT Population)

Baseline Pathogen	Omadacycline (N=204) n (%)	Moxifloxacin (N=182) n (%)
Gram-Positive Bacteria (aerobes)	61 (29.9)	56 (30.8)
Streptococcus pneumoniae [1]	43 (21.1)	34 (18.7)
MDR	7 (3.4)	6 (3.3)
PSSP	26 (12.7)	22 (12.1)
Macrolide Resistant	10 (4.9)	5 (2.7)
Staphylococcus aureus	11 (5.4)	11 (6.0)
MSSA	11 (5.4)	10 (5.5)
Other	10 (4.9)[a]	19 (10.4)[b]
Streptococcus mitis	3 (1.5)	5 (2.7)
Gram-Negative Bacteria (aerobes)	79 (38.7)	69 (37.9)
Haemophilus influenzae	32 (15.7)	16 (8.8)
Haemophilus parainfluenzae	18 (8.8)	17 (9.3)
Other	17 (8.3)[c]	22 (12.1)[d]
Klebsiella pneumoniae	13 (6.4)	13 (7.1)
Escherichia coli	6 (2.9)	7 (3.8)
Pseudomonas aeruginosa	3 (1.5)	5 (2.7)
Atypical Pathogens [2]	118 (57.8)	106 (58.2)
Mycoplasma pneumoniae	70 (34.3)	57 (31.3)
Legionella pneumophila [3]	37 (18.1)	37 (20.3)
Chlamydophila pneumoniae	28 (13.7)	28 (15.4)
Atypical Pathogens [4]	73 (35.8)	64 (35.2)
Mycoplasma pneumoniae	35 (17.2)	29 (15.9)
Legionella pneumophila [3]	29 (14.2)	28 (15.4)
Chlamydophila pneumoniae	15 (7.4)	14 (7.7)

Note: Percentages are calculated based on N. Subjects with the same pathogen from a blood specimen, respiratory

Table 51. Patients With Pathogens Identified at Baseline From Blood Specimens, Respiratory Specimens, UATs, and/or Serology in Greater Than or Equal to 1% of the Population in OPTIC (microITT Population)

Baseline Pathogen	Omadacycline (N=204) n (%)	Moxifloxacin (N=182) n (%)

specimen, urinary antigen test, and/or serology are counted only once for that pathogen. Subjects are counted only once in the overall tabulation of Gram-Positive Bacteria (Aerobes), Gram-Negative Bacteria (Aerobes) and Atypical Pathogens if they have more than one respective pathogen at baseline. Subjects with both MRSA and MSSA or with any combination of MDRSP, PSSP, and Macrolide Resistant are counted once in overall tabulation. Respiratory specimens include sputum, bronchoalveolar lavage and pleural fluid specimens.

MDR = multi-drug resistant, MDRSP = multidrug-resistant *S. pneumoniae*, microITT = microbiological intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*, N = Number of subjects in the microITT population, n = Number of subjects within a specific category, PSSP = penicillin-susceptible *S. pneumoniae*.

[1] Overall tabulation of *Streptococcus pneumoniae* includes identification from urinary antigen only, which will not have susceptibility data.

[2] Defined as in the Statistical Analysis Plan which considers an indeterminate convalescent serology result as positive

[3] *Legionella pneumophila* may be detected from culture, serology and/or urinary antigen test.

[4] For identification by serology, considers only a positive convalescent serology result as positive.

Per the Statistical Analysis Plan (SAP), a positive serology result consisted of:

a positive baseline or PTE IgM serology result, OR

a negative baseline and indeterminate PTE IgG serology result, OR

a negative baseline and positive PTE IgG serology result

Tables were also generated that considered only a positive convalescent serology result as positive, which is the more stringent criterion described in the package inserts

[a] β-Hemolytic streptococcus (2), *Streptococcus agalactiae* (2), *Streptococcus constellatus* (1), *Streptococcus mitis* group (1), *Streptococcus oralis* (1), *Streptococcus salivarius* (1), *Streptococcus sanguis* II (2).

[b] Includes MRSA (1), β-Hemolytic streptococcus (3), *Streptococcus agalactiae* (3), *Streptococcus anginosus* (1), *Streptococcus constellatus* (1), *Streptococcus gordonii* (1), *Streptococcus mitis* group (2), *Streptococcus parasanguinis* (2), *Streptococcus salivarius* (3), *Streptococcus sanguinis* (2).

[c] *Acinetobacter junii* (1), *Acinetobacter lwoffii* (1), *Enterobacter cloacae* (2), *Haemophilus haemolyticus* (1), *Haemophilus parahaemolyticus* (2), *Klebsiella oxytoca* (1), *Moraxella catarrhalis* (4), *Morganella morganii* (1), *Neisseria meningitidis* (1), *Proteus mirabilis* (2), *Serratia marcescens* (1).

[d] *Acinetobacter baumannii* (1), *Acinetobacter baumannii* complex (1), *Citrobacter braakii* (1), *Citrobacter freundii* (1), *Citrobacter youngae* (1), *Enterobacter cloacae* (4), *Haemophilus parahaemolyticus* (2), *Klebsiella oxytoca* (4), *Moraxella catarrhalis* (1), *Neisseria meningitidis* (1), *Proteus mirabilis* (2), *Pseudomonas putida* (1), *Stenotrophomonas maltophilia* (2).

Table 52. Clinical Response at ECR, EOT, and PTE in Subjects with Bacteremia in OPTIC (ME-EOT and ME-PTE Populations)

	PORT Risk Class II		PORT Risk Class III		PORT Risk Class IV		All	
Early Clinical Response in the ME-EOT Population								
	OMC (N=26)	**MOX (N=21)**	**OMC (N=123)**	**MOX (N=109)**	**OMC (N=44)**	**MOX (N=42)**	**OMC (N=193)**	**MOX (N=172)**
Bacteremic patients	1	2	7	9	5	7	13	18
Clinical Success	1 (100.0)	1 (50.0)	6 (85.7)	8 (88.9)	3 (60.0)	7 (100.0)	10 (76.9)	16 (88.9)
Clinical Failure or Indeterminate	0	1 (50.0)	1 (14.3)	1 (11.1)	2 (40.0)	0	3 (23.1)	2 (11.1)
Clinical Failure	0	1 (50.0)	0	1 (11.1)	1 (20.0)	0	1 (7.7)	2 (11.1)
Indeterminate			1 (14.3)	0	1 (20.0)	0	2 (15.4)	0
Investigator Assessment of Clinical Response at EOT in the ME-EOT Population								
	OMC (N=26)	**MOX (N=21)**	**OMC (N=123)**	**MOX (N=109)**	**OMC (N=44)**	**MOX (N=42)**	**OMC (N=193)**	**MOX (N=172)**
Bacteremic patients	1	2	7	9	5	7	13	18
Clinical Success	1 (100.0)	1 (50.0)	6 (85.7)	9 (100.0)	5 (100.0)	5 (71.4)	12 (92.3)	15 (83.3)
Clinical Failure or Indeterminate	0	1 (50.0)	1 (14.3)	0	0	2 (28.6)	1 (7.7)	3 (16.7)
Clinical Failure	0	1 (50.0)	1 (14.3)	0	0	2 (28.6)	1 (7.7)	3 (16.7)
Overall Clinical Response at PTE in the ME-PTE Population								
	OMC (N=25)	**MOX (N=22)**	**OMC (N=119)**	**MOX (N=107)**	**OMC (N=44)**	**MOX (N=40)**	**OMC (N=188)**	**MOX (N=169)**
Bacteremic patients	1	2	6	9	5	6	12	17
Clinical Success	1 (100.0)	1 (50.0)	5 (83.3)	9 (100.0)	5 (100.0)	4 (66.7)	11 (91.7)	14 (82.4)
Clinical Failure or Indeterminate	0	1 (50.0)	1 (16.7)	0	0	2 (33.3)	1 (8.3)	3 (17.6)
Clinical Failure	0	1 (50.0)	1 (16.7)	0	0	2 (33.3)	1 (8.3)	3 (17.6)

ME = microbiologically evaluable, MOX = moxifloxacin, OMC = omadacycline, PORT = Pneumonia Outsomes Research Team; PTE = post-therapy evaluation.

Table 53. Summary of TEAEs of Interest in the Phase 3 ABSSSI and CABP Studies (Pooled Safety Population)

Adverse Events of Interest Category/Preferred Term	Omadacycline (N = 1073) n (%)	Linezolid (N = 689) n (%)	Moxifloxacin (N = 388) n (%)
Blood Urea Increased	1 (0.1)	0	0
Blood urea increased	1 (0.1)	0	0
Cardiac Arrest	4 (0.4)	1 (0.1)	1 (0.3)
Cardiogenic shock	2 (0.2)	0	1 (0.3)
Cardiac arrest	1 (0.1)	1 (0.1)	0
Cardio-respiratory arrest	1 (0.1)	0	0
Cardiac Failure	6 (0.6)	2 (0.3)	5 (1.3)
Cardiac failure	3 (0.3)	1 (0.1)	3 (0.8)
Cardiogenic shock	2 (0.2)	0	1 (0.3)
Acute pulmonary oedema	1 (0.1)	0	0
Cardiac failure congestive	0	1 (0.1)	1 (0.3)
Hepatic congestion	0	0	1 (0.3)
Right ventricular failure	0	0	1 (0.3)
Ischemic Heart Disease	3 (0.3)	1 (0.1)	4 (1.0)
Acute myocardial infarction	2 (0.2)	0	0
Myocardial ischaemia	1 (0.1)	1 (0.1)	2 (0.5)
Angina pectoris	0	0	2 (0.5)
Tachyarrhythmias	6 (0.6)	0	1 (0.3)
Atrial fibrillation	5 (0.5)	0	1 (0.3)
Atrial flutter	1 (0.1)	0	0
Sinus tachycardia	1 (0.1)	0	0
Clostridium difficile Infection	0	0	8 (2.1)
Clostridium difficile colitis	0	0	1 (0.3)
Clostridium difficile infection	0	0	6 (1.5)
Pseudomembranous colitis	0	0	1 (0.3)
Diarrhoea	26 (2.4)	20 (2.9)	31 (8.0)
Diarrhoea	26 (2.4)	20 (2.9)	31 (8.0)
Esophageal Disorders	1 (0.1)	0	0
Oesophagitis	1 (0.1)	0	0
Nausea	160 (14.9)	60 (8.7)	21 (5.4)
Nausea	160 (14.9)	60 (8.7)	21 (5.4)
Pancreatitis	1 (0.1)	0	1 (0.3)
Pancreatitis chronic	1 (0.1)	0	0
Pancreatic pseudocyst	0	0	1 (0.3)
Vomiting	89 (8.3)	27 (3.9)	6 (1.5)
Vomiting	89 (8.3)	27 (3.9)	6 (1.5)
Extravasation Events	38 (3.5)	25 (3.6)	5 (1.3)
Infusion site extravasation	28 (2.6)	19 (2.8)	0
Infusion site pain	7 (0.7)	6 (0.9)	1 (0.3)
Peripheral swelling	5 (0.5)	1 (0.1)	0
Infusion site erythema	2 (0.2)	0	2 (0.5)
Infusion site irritation	1 (0.1)	0	0

Table 53. Summary of TEAEs of Interest in the Phase 3 ABSSSI and CABP Studies (Pooled Safety Population)

Adverse Events of Interest Category/Preferred Term	Omadacycline (N = 1073) n (%)	Linezolid (N = 689) n (%)	Moxifloxacin (N = 388) n (%)
Infusion site swelling	1 (0.1)	1 (0.1)	0
Skin induration	1 (0.1)	0	0
Infusion site inflammation	0	1 (0.1)	2 (0.5)
Fungal Infections	11 (1.0)	6 (0.9)	5 (1.3)
Oral candidiasis	5 (0.5)	1 (0.1)	1 (0.3)
Vulvovaginal mycotic infection	3 (0.3)	5 (0.7)	0
Fungal skin infection	1 (0.1)	0	0
Oesophageal candidiasis	1 (0.1)	0	1 (0.3)
Vulvovaginal candidiasis	1 (0.1)	0	0
Oral fungal infection	0	0	1 (0.3)
Respiratory moniliasis	0	0	2 (0.5)
Headache	31 (2.9)	21 (3.0)	5 (1.3)
Headache	31 (2.9)	21 (3.0)	5 (1.3)
Hypersensitivity Reactions	20 (1.9)	12 (1.7)	10 (2.6)
Pruritus	8 (0.7)	1 (0.1)	1 (0.3)
Rash	6 (0.6)	3 (0.4)	5 (1.3)
Urticaria	3 (0.3)	0	0
Dermatitis	1 (0.1)	1 (0.1)	0
Hypersensitivity	1 (0.1)	1 (0.1)	4 (1.0)
Rash pustular	1 (0.1)	1 (0.1)	0
Swelling face	1 (0.1)	1 (0.1)	0
Angioedema	0	1 (0.1)	0
Bronchospasm	0	0	1 (0.3)
Drug eruption	0	1 (0.1)	0
Infusion site urticaria	0	0	1 (0.3)
Pruritus generalised	0	1 (0.1)	0
Rash generalized	0	1 (0.1)	0
Liver Related Investigations, Signs and Symptoms	58 (5.4)	34 (4.9)	28 (7.2)
Alanine aminotransferase increased	42 (3.9)	25 (3.6)	18 (4.6)
Aspartate aminotransferase increased	33 (3.1)	24 (3.5)	14 (3.6)
Gamma-glutamyltransferase increased	15 (1.4)	8 (1.2)	8 (2.1)
Blood bilirubin increased	5 (0.5)	1 (0.1)	3 (0.8)
Blood alkaline phosphatase increased	3 (0.3)	1 (0.1)	4 (1.0)
Hypoalbuminaemia	2 (0.2)	0	3 (0.8)
Hepatic enzyme increased	1 (0.1)	0	0
Hepatic congestion	0	0	1 (0.3)
Biliary System Related Investigations, Signs and Symptoms	7 (0.7)	2 (0.3)	6 (1.5)
Blood bilirubin increased	5 (0.5)	1 (0.1)	3 (0.8)
Blood alkaline phosphatase increased	3 (0.3)	1 (0.1)	4 (1.0)

Table 53. Summary of TEAEs of Interest in the Phase 3 ABSSSI and CABP Studies (Pooled Safety Population)

Adverse Events of Interest Category/Preferred Term	Omadacycline (N = 1073) n (%)	Linezolid (N = 689) n (%)	Moxifloxacin (N = 388) n (%)
Vestibular Disorders	9 (0.8)	6 (0.9)	4 (1.0)
Dizziness	7 (0.7)	6 (0.9)	4 (1.0)
Vertigo	2 (0.2)	0	0

Coding of SOC and PT based on MedDRA Version 17.1.
A TEAE was defined as an AE with a start date/time on or after the date/time of the first dose of active test article.
If a patient had more than 1 TEAE with the same PT or within the same SOC, the patient was counted only once for that PT or SOC, respectively.
Percentages were based on the number of patients in each treatment group. Patients may have been counted in more than 1 row. The SOC terms were sorted.
alphabetically, then PTs were sorted within each SOC term by decreasing frequency of the TEAEs of the omadacycline group.
ABSSSI = acute bacterial skin and skin structure infection, AE = adverse event, CABP = community-acquired bacterial pneumonia, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

Table 54. Summary of Liver Chemistry Elevation for Patients With Any Baseline Values in OASIS-1, OASIS-2, and OPTIC (Pooled Safety Population)

Lab Parameter (SI unit)	Parameter	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
ALT (U/L)				
Any value at Baseline, N1		1031	659	381
Meeting criterion at post-Baseline	> 3 × ULN	44 (4.3)	27 (4.1)	17 (4.5)
	> 5 × ULN	22 (2.1)	5 (0.8)	4 (1.0)
	> 10 × ULN	9 (0.9)	3 (0.5)	1 (0.3)
AST (U/L)				
Any value at Baseline, N1		1040	661	379
Meeting criterion at post-Baseline	> 3 × ULN	38 (3.7)	27 (4.1)	12 (3.2)
	> 5 × ULN	20 (1.9)	7 (1.1)	4 (1.1)
	> 10 × ULN	6 (0.6)	1 (0.2)	2 (0.5)
Total bilirubin (µmol/L)				
Any value at Baseline, N1		1041	666	381
Meeting criterion at post-Baseline	> 1.5 × ULN	11 (1.1)	3 (0.5)	7 (1.8)
	> 2 × ULN	6 (0.6)	1 (0.2)	4 (1.0)

Baseline was defined as the value closest to but prior to the initiation of test article administration.

Percentages were based on number of patients with baseline values within normal limits and at least 1 post-baseline assessment (N1). For combined lab parameters, percentages were based on number of patients with baseline values within normal limits values and at least 1 post-baseline assessment for each of the parameters in the combination (N1).

Values from local labs and unscheduled visit were also included.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, SI unit = international system of units, ULN = upper limit of normal.

Table 55. Summary of Serious Treatment-Emergent Adverse Events in OASIS-1 and OASIS-2 (Pooled Safety Population)

System Organ Class Preferred Term	Omadacycline (N=691) n (%)	Linezolid (N=689) n (%)
Subjects with at least one serious TEAE	16 (2.3)	13 (1.9)
Cardiac disorders	0	2 (0.3)
Cardiac arrest	0	1 (0.1)
Cardiac failure	0	1 (0.1)
General disorders and administration site conditions	2 (0.3)	1 (0.1)
Drug withdrawal syndrome	1 (0.1)	0
Non-cardiac chest pain	1 (0.1)	0
Death	0	1 (0.1)
Hepatobiliary disorders	1 (0.1)	0
Cholecystitis acute	1 (0.1)	0
Infections and infestations	12 (1.7)	5 (0.7)
Subcutaneous abscess	3 (0.4)	0
Wound infection	3 (0.4)	1 (0.1)
Cellulitis	2 (0.3)	2 (0.3)
Bacteraemia	1 (0.1)	0
Gastroenteritis rotavirus	1 (0.1)	0
Hepatitis C	1 (0.1)	0
Staphylococcal bacteraemia	1 (0.1)	0
Sepsis	0	3 (0.4)
Injury, poisoning and procedural complications	2 (0.3)	1 (0.1)
Joint dislocation	1 (0.1)	0
Overdose	1 (0.1)	1 (0.1)
Nervous system disorders	1 (0.1)	0
Hemiparesis	1 (0.1)	0
Psychiatric disorders	0	1 (0.1)
Drug abuse	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.1)	2 (0.3)
Acute respiratory failure	1 (0.1)	0
Chronic obstructive pulmonary disease	0	1 (0.1)
Pulmonary embolism	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.1)
Angioedema	0	1 (0.1)

Coding of PT based on MedDRA Version 17.1.
Percentages are calculated relative to the treatment group N. Patients may be counted in more than one row.
A TEAE is defined as an AE with a start date/time on or after the date/time of the first dose of active test article.
If a patient has more than one TEAE with the same PT or within the same SOC, the patient is counted only once for that PT or SOC, respectively.
SOC terms are sorted alphabetically then PTs are sorted within each SOC term by decreasing frequency of the TEAEs of the omadacycline group.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event.

Table 56. Summary of Serious Treatment-Emergent Adverse Events in OPTIC (Safety Population)

System Organ Class Preferred Term	Omadacycline (N=382) n (%)	Moxifloxacin (N=388) n (%)
Subjects with at least one serious TEAE	23 (6.0)	26 (6.7)
Cardiac disorders	5 (1.3)	2 (0.5)
Acute myocardial infarction	2 (0.5)	0
Cardiogenic shock	2 (0.5)	1 (0.3)
Cardiac arrest	1 (0.3)	0
Cardiac failure	1 (0.3)	1 (0.3)
Cardio-respiratory arrest	1 (0.3)	0
Tachycardia	1 (0.3)	0
Pericardial effusion	0	1 (0.3)
Right ventricular failure	0	1 (0.3)
Gastrointestinal disorders	0	1 (0.3)
Colitis	0	1 (0.3)
General disorders and administration site conditions	1 (0.3)	0
Multi-organ failure	1 (0.3)	0
Hepatobiliary disorders	2 (0.5)	1 (0.3)
Cholecystitis acute	1 (0.3)	0
Hepatic failure	1 (0.3)	0
Hepatic congestion	0	1 (0.3)
Infections and infestations	8 (2.1)	16 (4.1)
Influenza	3 (0.8)	0
Pneumonia	2 (0.5)	6 (1.5)
Cellulitis	1 (0.3)	0
Infectious pleural effusion	1 (0.3)	1 (0.3)
Septic shock	1 (0.3)	2 (0.5)
Atypical mycobacterial pneumonia	0	1 (0.3)
Clostridium difficile colitis	0	1 (0.3)
Clostridium difficile infection	0	2 (0.5)
Hiv infection	0	1 (0.3)
Infective exacerbation of bronchiectasis	0	1 (0.3)
Lung abscess	0	1 (0.3)
Pneumonia viral	0	1 (0.3)
Injury, poisoning and procedural complications	0	1 (0.3)
Bladder injury	0	1 (0.3)
Metabolism and nutrition disorders	1 (0.3)	0
Decreased appetite	1 (0.3)	0
Musculoskeletal and connective tissue disorders	1 (0.3)	0
Back pain	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5)	6 (1.5)
Lung neoplasm	2 (0.5)	2 (0.5)
Adenocarcinoma	0	1 (0.3)
Chronic lymphocytic leukaemia	0	1 (0.3)
Colon cancer metastatic	0	1 (0.3)

Table 56. Summary of Serious Treatment-Emergent Adverse Events in OPTIC (Safety Population)

System Organ Class Preferred Term	Omadacycline (N=382) n (%)	Moxifloxacin (N=388) n (%)
Pancreatic carcinoma	0	1 (0.3)
Nervous system disorders	2 (0.5)	0
Cerebrovascular accident	2 (0.5)	0
Psychiatric disorders	1 (0.3)	0
Anxiety	1 (0.3)	0
Renal and urinary disorders	0	2 (0.5)
Renal failure acute	0	2 (0.5)
Respiratory, thoracic and mediastinal disorders	8 (2.1)	3 (0.8)
Pleural effusion	3 (0.8)	0
Acute respiratory distress syndrome	2 (0.5)	0
Acute respiratory failure	2 (0.5)	3 (0.8)
Acute pulmonary oedema	1 (0.3)	0
Vascular disorders	1 (0.3)	1 (0.3)
Aortic aneurysm rupture	1 (0.3)	0
Peripheral ischaemia	0	1 (0.3)

Coding of PT based on MedDRA Version 17.1.
Percentages are calculated relative to the treatment group N. Patients may be counted in more than one row.
A TEAE is defined as an AE with a start date/time on or after the date/time of the first dose of active test article.
If a patient has more than one TEAE with the same PT or within the same SOC, the patient is counted only once for that PT or SOC, respectively.
SOC terms are sorted alphabetically then PTs are sorted within each SOC term by decreasing frequency of the TEAEs of the omadacycline group.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event.

Table 57. Summary of Cardiac Events of Interest by PT in OPTIC (Safety Population)

PT	Omadacycline N = 382 n (%)	Moxifloxacin N = 388 n (%)
Acute myocardial infarction	2 (0.5)	0
Acute pulmonary edema	1 (0.3)	0
Angina pectoris	0	2 (0.5)
Atrial fibrillation	3 (0.8)	1 (0.3)
Atrial flutter	1 (0.3)	0
Cardiac arrest	1 (0.3)	0
Cardiac failure	3 (0.8)	3 (0.8)
Cardiac failure congestive	0	1 (0.3)
Cardiogenic shock	2 (0.5)	1 (0.3)
Cardio-respiratory arrest	1 (0.3)	0
Myocardial ischemia	1 (0.3)	2 (0.5)
Right ventricular failure	0	1 (0.3)
Sinus tachycardia	0	0

Coding of PT based on MedDRA Version 17.1.
A TEAE was defined as an AE with a start date/time on or after the date/time of the first dose of active test article. If a subject had more than 1 TEAE with the same category or PT, the subject was counted only once for that category or PT.
Categories were defined and sorted as in the identification of AEs of interest appendix in the SAP. The PTs within each category were sorted by descending frequency of omadacycline group. Percentages were calculated relative to the treatment group N.
AE = adverse event, HR = heart rate, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SAP = Statistical Analysis Plan, TEAE = treatment-emergent adverse event.

Table 58. Absolute and Change From Baseline in ECG in OASIS-1, OASIS-2, and OPTIC (Pooled Safety Population)

	Omadacycline (N = 1073)			Linezolid (N = 689)			Moxifloxacin (N = 388)		
ECG Parameter (unit)	**Value at Baseline**	**Value at EOT**	**Change From Baseline**	**Value at Baseline**	**Value at EOT**	**Change From Baseline**	**Value at Baseline**	**Value at EOT**	**Change From Baseline**
HR (beats/min)									
n	1029	946	931	672	593	583	362	332	327
Mean (SD)	79.9 (15.30)	77.0 (13.19)	-2.9 (14.78)	76.7 (13.27)	74.5 (13.21)	-2.1 (13.23)	84.3 (17.40)	75.8 (13.82)	-8.6 (16.59)
Median	78.0	76.0	-2.0	75.0	73.0	-2.0	81.5	74.0	-7.0
Min, max	38, 150	42, 150	-72, 87	46, 120	45, 124	-47, 41	51, 167	48, 146	-101, 44
QTcF (msec)									
n	1029	944	929	672	593	583	362	332	327
Mean (SD)	412.7 (24.39)	415.6 (22.45)	2.6 (18.08)	410.1 (22.48)	415.3 (22.79)	4.6 (17.81)	416.5 (24.76)	425.0 (23.21)	8.7 (22.99)
Median	413.0	415.0	2.0	409.0	414.0	4.0	416.0	424.0	8.0
Min, max	342, 517	343, 541	-105, 74	345, 514	349, 548	-57, 141	350, 523	366, 549	-108, 84

Baseline was defined as the value closest to but prior to the initiation of test article administration.
ABSSSI = acute bacterial skin and skin structure infection, CABP = community-acquired bacterial pneumonia, ECG = electrocardiogram, EOT = end of treatment, HR = heart rate, max = maximum, min = minimum, QTcF = QT interval corrected for heart rate using Fridericia's formula.

Table 59. QTcF Absolute and Change From Baseline Over Time in OPTIC (Safety Population)

			Omadacycline (N = 382)		Moxifloxacin (N = 388)	
Visit/ Dose	**Time Point**		**Actual Value**	**Change from Baseline**	**Actual Value**	**Change from Baseline**
Baseline		N	355		362	
		Mean (SD)	415.6 (24.19)		416.5 (24.83)	
		Median	415.0		416.0	
		Min, Max	353, 517		350, 523	
Dose 1	30 minutes prior to infusion	N	340		341	
		Mean (SD)	415.0 (24.30)		416.5 (25.21)	
		Median	415.0		416.0	
		Min, Max	353, 517		350, 523	
Dose 1	30-90 minutes after infusion	N	349	347	355	355
		Mean (SD)	416.4 (25.58)	0.8 (16.92)	422.6 (26.64)	5.8 (15.82)
		Median	415.0	-1.0	421.0	5.0
		Min, Max	355, 593	-41, 170	330, 549	-116, 80

Table 59. QTcF Absolute and Change From Baseline Over Time in OPTIC (Safety Population)

Visit/ Dose	Time Point		Omadacycline (N = 382)		Moxifloxacin (N = 388)	
			Actual Value	Change from Baseline	Actual Value	Change from Baseline
Dose 3	30 minutes prior to infusion	N	332	331	337	337
		Mean (SD)	416.4 (24.26)	1.4 (18.55)	420.5 (26.11)	4.3 (22.04)
		Median	415.5	1.0	421.0	4.0
		Min, Max	354, 504	-52, 126	217, 504	-220, 62
Dose 3	30-90 minutes after infusion	N	333	332	336	335
		Mean (SD)	416.8 (24.56)	1.8 (18.14)	427.1 (24.07)	11.1 (17.57)
		Median	414.0	2.0	427.0	10.0
		Min, Max	351, 520	-65, 61	353, 493	-61, 66

Baseline was defined as the value closest to but prior to the initiation of test article administration.
ECG = electrocardiogram, EOT = end of treatment, max = maximum, min = minimum, QTcF = QT interval corrected for heart rate using Fridericia's formula, SD = standard deviation.

Table 60. Clinically Notable Values for Heart Rate and Systolic BP at Any Post-Baseline Time Point in OPTIC (Safety Population)

Clinically Notable Criteria	Omadacycline (N = 382) n (%)	Moxifloxacin (N = 388) n (%)
Subjects with HR value at any post-Baseline visit	382	388
HR ≥ 120 bpm	21 (5.5)	22 (5.7)
Subjects with HR value at Baseline and any post-Baseline visit	382	388
HR ≥ 120 bpm and increase of ≥ 15 bpm	5 (1.3)	8 (2.1)
Subjects with systolic BP value at any post-Baseline visit	382	388
Systolic BP ≥ 180 mmHg	11 (2.9)	8 (2.1)
Subjects with systolic BP value at Baseline and any post-Baseline visit	382	388
Systolic BP ≥ 180 mmHg and increase of ≥ 20 mmHg	6 (1.6)	6 (1.5)

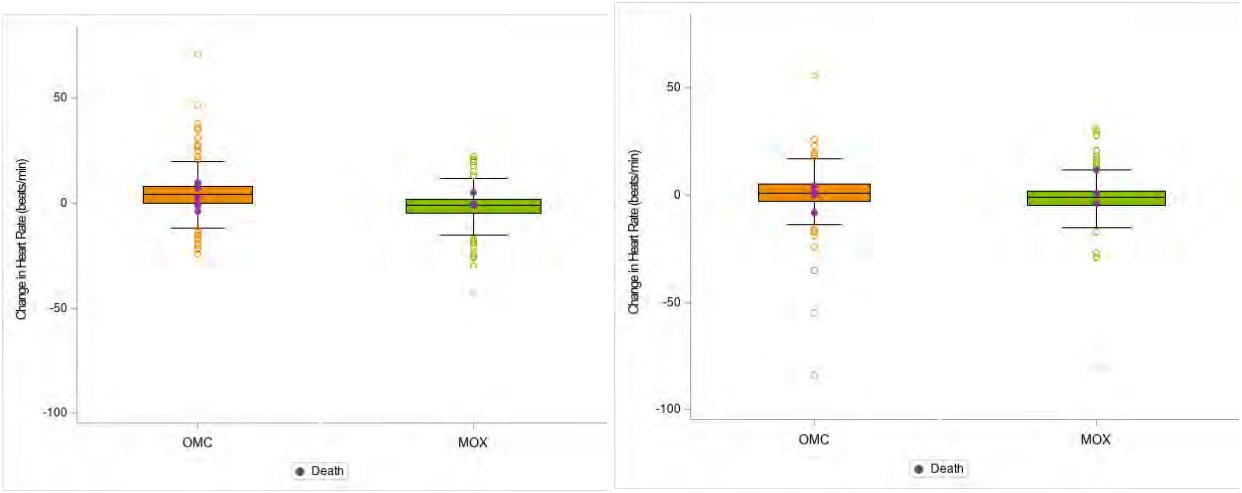
Baseline was defined as the value closest to but prior to the initiation of test article administration.
Percentages were based on the number of subjects with the specific parameter assessed.
BP = blood pressure, bpm = beats per minute.

Table 61. Summary of Mortality-associated TEAEs[a] by PT in Patients Who Did Not Die in OPTIC (Safety Population)[b]

Preferred term	OMC N=374	MOX N=384
Acute Myocardial Infarction	1	0
Cardiogenic Shock	1	1
Cardiac Failure	3	2
Cardio-respiratory arrest	0	0
Pneumonia	3	7
Septic Shock	0	2
Acute Respiratory Distress Syndrome	1	0
Acute Respiratory Failure	1	2
Aortic Aneurysm Rupture	0	0
Multi-Organ Failure	0	0
Cerebrovascular Accident	1	0
Lung Neoplasm	7	2
Pancreatic Carcinoma	0	0

MOX=moxifloxacin, OMC=omadacycline, TEAE = treatment-emergent adverse event.
*Preferred terms reported at any time with an outcome of death
**Safety population minus the patients who died in each treatment group

Figure 12. Change in Heart Rate on Dose 1 and Dose 3 by Treatment in OPTIC



OMC = omadacycline, MOX = Moxifloxacin.

7.2 OASIS-1 and OASIS-2 Individual Patient Narratives

Patient OMC9

AE Preferred Term: Death
A 60-year-old male with a relevant medical history of iv heroin use was treated as an outpatient with a single dose of iv omadacycline for a wound infection. During the iv administration, he

vomited, and study treatment was discontinued. He did not return for follow-up visits despite numerous attempted contacts and was considered lost to follow-up. Approximately 6 months later, the investigator received notification from the county medical examiner that the patient had died the day after his study visit. The suspected cause of death was opiate overdose. While outside of the study window for follow-up, the investigator became aware of the death and reported it to the sponsor.
Sponsor Assessment of Cause of Death: Illicit drug overdose

Patient LZD1

AE Preferred Term: Cardiac Arrest
A 43-year-old male with a pastmedical history of acute renal failure andrhabdomyolysis, and hypertension treated with lisinopril was treated as an outpatient with 5 days of iv linezolid and 2 days of oral linezolid for a wound infection. One day after the last dose of linezolid, he was short of breath on exertion. The following day, he was found partially responsive with agonal breathing. He was unresponsive upon emergency medical services arrival and resuscitating measures were unsuccessful. He was declared dead in the emergency room due to cardiac arrest. The investigator suspected a pulmonary embolism however an autopsy was not performed.
Sponsor Assessment of Cause of Death: Cardiac arrest. The absence of a post-mortem examination limits the ability to understand the pathophysiology of the observed cardiac arrest

Patient LZD2

AE Preferred Term: Cardiac Failure
An 88-year-old male with a history of cardiac failure, atrial fibrillation, and cerebrovascular insufficiency was hospitalized for a lower leg infection. He was treated with 7 days of iv linezolid and discharged from the hospital. Following discharge, he died at home due to cardiac failure. No signs and symptoms were noted on the day of the event, and the patient did not receive any medical care from emergency medical services. An autopsy was not performed and the death was attributed to decompensation of his pre-existing chronic cardiac insufficiency.
Sponsor Assessment of Cause of Death: Cardiac failure. Given the age of the patient and history of cardiac failure and atrial fibrillation, cardiac failure followed by death is not unexpected.

Patient LZD3

AE Preferred Term: Death
A 62-year-old female with a relevant medical history of heroin and marijuana use was treated as an outpatient with 10 days of oral linezolid for a wound infection caused by iv drug use. Approximately 3 months after stopping study treatment, she died. Following investigation and autopsy with the local coroner's office, it was determined that the cause of death was acute heroin, methamphetamine, tramadol, alprazolam, and diphenhydramine intoxication. The death certificate also indicated that the patient suffered from pulmonary emphysema, hypertension, and atherosclerotic cardiovascular disease which was not reported in medical history. While outside of the study window for follow-up, the investigator became aware of the death and reported it to the sponsor.
Sponsor Assessment of Cause of Death: Illicit drug overdose

7.3 OPTIC Individual Patient Narratives

Patient OMC1
AE Preferred Term: Septic Shock
A 67-year-old male with a history of congestive heart failure, COPD, diabetes mellitus, hypertension, congestive heart disease, and autopsy evidence of arteriosclerosis, prior myocardial infarction, cor pulmonale, and left ventricular hypertrophy. PORT Risk Class II (but upon Sponsor review of clinical data, PORT Risk Class III), right lower lobe (RLL) infiltrate by chest x-ray, sputum culture = *S. pneumoniae* + *H. influeunzae*; blood culture = *S. pneumoniae*. All pathogens were susceptible to omadacycline by proposed breakpoints. He received a single dose of test article, several hours after which his condition deteriorated rapidly, requiring admission to the intensive care unit, mechanical ventilation and vasopressor support. He was diagnosed with septic shock and despite aggressive treatment, including rescue treatment with a dose of moxifloxacin, he progressed to multi-organ failure and died 11 hours after randomization. Autopsy showed right middle lung pneumonia, severe COPD, severe cor pulmonale (secondary to pulmonary hypertension secondary to severe COPD), left ventricular hypertrophy (secondary to long-standing hypertension) and widespread atherosclerosis.
Sponsor Assessment of Cause of Death: Progression of pneumonia - The rapid deterioration on Day 1 suggested that the patient died to the overwhelming pneumococcal sepsis and that omadacycline, and moxifloxacin provided as rescue therapy, could not have prevented this outcome.

Patient OMC2
AE Preferred Term: Cardio-respiratory Arrest
A 76-year-old male with hypertension and a former smoking history. PORT Risk Class III, RLL infiltrate, sputum/blood cultures = negative. The patient received 3 doses of omadacycline. On Study Day 2, at some point after the third dose (and during placebo infusion used for blinding), the patient had an unwitnessed cardiorespiratory arrest. No clinically relevant changes in vital signs or ECG in any of the assessments prior to the unwitnessed arrest occurred.
Sponsor Assessment of Cause of Death: Sudden cardiac death – Since pneumonia is associated with cardiac events, a sudden cardiac death in a patient with known cardiac risk factors (age, hypertension, smoking) is not unexpected. Untreated pneumonia and omadacycline are unlikely contributors to the sudden cardiac event since vital signs were stable and no clinically relevant ECG changes were noted (eg, QTc prolongation, HR increases) prior to the event.

Patient OMC3
AE Preferred Term: Acute myocardial infarction
A 66-year-old male former smoker with a history of COPD and tuberculosis. PORT Risk Class IV, RUL infiltrate, sputum culture = *K. pneumoniae* and *P. aeruginosa*. (*K. pneumoniae* susceptible to omadacycline based on proposed breakpoints, and *Pseudomonas aeruginosa* intrinsically resistant to omadacycline). On Study Day 2, before administration of omadacycline, he developed severe dyspnea and cyanosis and an ECG revealed lateral wall ischemia with progression over the day to cardiogenic shock. Study medication was stopped. Troponin I was negative; however, a serial troponin I was not performed. A repeat chest x-ray showed more prominent consolidation of the pneumonic infiltrates, most likely of cardiac origin. He died later that day despite mechanical ventilation and pressor support. No clinical relevant changes in vital

signs or ECG in any of the assessments prior to the myocardial infarction occurred.
Sponsor Assessment of Cause of Death: Myocardial infarction - Since pneumonia is associated with cardiac events, myocardial infarction with subsequent death in a patient with known cardiac risk factors (age, smoking history) is not unexpected. The contribution of a potentially untreated pneumonia (i.e. the role of *Pseudomonas aeruginosa*, intrinsically resistant to omadacycline) at baseline is unlikely as since vital signs were stable and no clinically relevant ECG changes were noted (eg, QTc prolongation, HR increases) prior to the event.

Patient OMC4
AE Preferred Term: Aortic aneurysm rupture
A72-year-old male with a history of congestive heart failure, atrial fibrillation, diabetes, COPD, overweight, and tobacco use. The patient also had a large thoracic aortic aneurysm noted at enrollment. PORT Risk Class IV, right upper lobe (RUL) infiltrate with pleural effusion, sputum culture = *H. influenzae* (susceptible to omadacycline based on proposed breakpoints); blood culture = negative. The patient received omadacycline for 8 days and was considered a clinical success at early clinical response. A chest X-ray performed on Day 7 showed persistent severe large thoracic aortic aneurysm and right pleural effusion; right apical cavity pneumonia with possible pulmonary abscess; and increasing opacity in the right upper lobe compatible with worsening of pneumonia. Prior to dosing on Day 9 he developed dyspnea and severe chest pain which was rapidly followed by loss of consciousness and death in 5 minutes; he was diagnosed clinically with a ruptured thoracic aorta aneurysm. No clinical relevant changes in ECG in any of the assessments prior to the myocardial infarction occurred. The patient had decreased oxygen saturation (80-90%) throughout treatment.
Sponsor Assessment of Cause of Death: Thoracic aneurysm rupture – The patient had a known pre-existing large thoracic aneurysm. The clinical symptoms and rapid death are consistent with an aneurysm rupture or dissection.

Patient OMC5
AE Preferred Term: Cerebrovascular accident
A 68-year-old male with a history of congestive heart failure, hypertension, diabetes mellitus, obesity (by body mass index [BMI]), COPD and tobacco use. PORT Risk Class IV, RLL infiltrate, negative sputum/blood cultures. At baseline prior to first dose and during the study, the patient had new-onset atrial fibrillation identified. The patient received omadacycline for 7 days, was a clinical success at ECR and EOT and was discharged on Day 7 with atrial fibrillation. On study day 13, the patient experienced decreased consciousness, dyspnea, edema, peripheral cyanosis, tachypnea and hypotension. The patient was re-admitted with a clinically suspected cerebrovascular accident. He died later that day despite aggressive resuscitative efforts. No clinical relevant changes in vital signs or ECG in any of the assessments prior to the myocardial infarction occurred
Sponsor Assessment Cause of Death: Cerebrovascular accident – The patient had new onset atrial fibrillation on presentation and case records are without any documentation of treatment with systemic anticoagulation on discharge. The risk for cerebrovascular accident with atrial fibrillation without systemic anticoagulation treatment is well known. Lack of efficacy and safety concern related to omadacycline do not appear likely given the timing of events

Patient OMC6
AE Preferred Term: Cardiogenic shock

A 90-year-old female with history of chronic bronchitis, hypertension, diabetes mellitus, severe aortic valve stenosis, aortic insufficiency and mitral regurgitation, and myocardial infarction. PORT Risk Class IV (V per database), RLL infiltrate, sputum/blood cultures = negative. The patient received omadacycline for 13 days for CABP. She was discharged from the hospital on Day 7. Protocol efficacy assessments determined that the patient was a clinical success at ECR, EOT, and PTE. On study Day 15, 2 days after PTE, she experienced angina and was diagnosed with a non-ST-segment elevation myocardial infarction, and 5 days after that she developed cardiogenic shock and died. No clinical relevant changes in vital signs or ECG in any of the assessments prior to the myocardial infarction occurred

Sponsor Assessment Cause of Death: Myocardial infarction - The patient was an early clinical success and had a clinical diagnosis of myocardial infarction upon re-admission to the hospital approximately a week after the last dose of omadacycline. A myocardial infarction followed by cardiogenic shock in a patient with known cardiac risk factors (age, prior myocardial infarction, hypertension, diabetes mellitus) complicated by aortic stenosis, leading to death, is not unexpected.

Patient OMC7

AE Preferred Term: Acute respiratory failure and Multi- organ failure A 74-year-old female with history of hypertension, status post myocardial infarction, alcohol abuse, current smoker, a 10-day history of "flu" with grey sputum production. PORT Risk Class IV, right middle lobe (RML), and RLL infiltrates, sputum culture = *H. influenzae* and *E. coli* (both susceptible to omadacycline based on proposed breakpoints; blood cultures = negative. The patient's respiratory condition declined quickly after study enrollment requiring intubation on Study Day 2. BAL on Study Day 3 was performed and cultures identified omadacycline susceptible *H. influenzae* and *K. pneumoniae* (susceptible to omadacycline based on proposed breakpoints). On Study Day 4 and 5, *Proteus mirabilis* (intrinsically resistant to omadacycline), was also identified in an endotracheal aspirate and the blood. Treatment with omadacycline was stopped after Day 4. By Study Day 5, respiratory failure had progressed to multi-system organ failure. On study day 18, *P. mirabilis* and *E. faecalis* was cultured from urine. Despite continued aggressive care, including appropriate alternative antibiotic therapy (meropenem) which began on Study Day 5, the respiratory failure and multi-system organ failure progressed and the patient died on Study Day 25.

Sponsor Assessment Immediate Cause of Death: Progression of pneumonia –The patient had two baseline pathogens that are susceptible to omadacycline based on proposed breakpoints. Post-baseline, isolation of additional bacteria including a *Proteus mirabilis*, intrinsically resistant to omadacycline occurred. The subject died of a progression of pneumonia despite additional appropriate therapy for the bacteria isolated.

Patient OMC8

AE Preferred Term: Pneumonia and Acute respiratory distress syndrome

An 86-year-old female with a history of arteriosclerosis and hyperthyroidism. PORT Risk Class IV, left lower lobe infiltrate with pleural effusion by CT scan, sputum/blood cultures = negative. She was treated for 9 days with omadacycline. Protocol efficacy assessments determined that the patient was a clinical success at ECR and EOT and the patient was discharged from the hospital on Day 12. On study Day 18, the patient was hospitalized with a new contralateral RLL pneumonia (Baseline CT scan of the chest on enrollment into OPTIC, demonstrated no infiltrates in the RLL; thus this was a de novo contralateral RLL pneumonia). BAL cultures grew

Acinetobacter and *Candida* species. Despite anti-infective therapy (ceftriaxone, ciprofloxacin, colistin, gentamicin, fluconazole), repeated pleurocenteses, and general supportive care, the patient developed acute respiratory distress syndrome (ARDS) on Study Day 22 and subsequently died on Study Day 30. The cause of death was reported as ARDS, which was a consequence of the RLL pneumonia.
Sponsor Assessment Immediate Cause of Death: Secondary pneumonia – The patient was an early clinical success and the patient was re-hospitalized with a secondary pneumonia. The documented absence of a baseline RLL infiltrate by CT scan and subsequent development of RLL pneumonia suggests a new pneumonia which was not a recurrence of the incident pneumonia

Patient MOX1
AE Preferred Term: Acute respiratory failure
A 85-year-old female with a history of hypertension, atrial fibrillation, and ischemic stroke. PORT Risk Class III (recalculated to IV), RLL and left upper lobe infiltrates, sputum/blood cultures = *negative*. After 3 days of treatment, she had worsening dyspnea with bronchospasm, hypoxia, progression of bilateral pulmonary infiltrates on chest x-ray; study treatment was discontinued and alternate antibacterial therapy (meropenem, clindamycin) was administered. Despite additional treatment including mechanical ventilation and pressor support, her respiratory condition continued to deteriorate, eventually resulting in respiratory and circulatory failure.
Sponsor Assessment Immediate Cause of Death: Progression of pneumonia – The patient had progression of pneumonia despite appropriate therapy.

Patient MOX2
AE Preferred Term: Cardiac failure
A 83-year-old male without reported past medical history. PORT Risk Class IV, RML and RLL infiltrates, sputum culture = *negative*; blood culture = *E. coli*. *E. coli* bacteremia persisted through Study Day 3. Protocol efficacy assessments determined that the patient was a clinical success at ECR. On Study Day 7, there were new ECG findings that were suggestive of a recent myocardial infarction and new prolonged QTcF of 489 milliseconds. Troponin was elevated (0.54 ng/mL). On Study Day 9, the patient developed "severe possible heart failure", study treatment was stopped, and the patient died the same day.
Sponsor Assessment Cause of Death: Myocardial infarction – Following pneumonia, a documented myocardial infarction and subsequent death is not unexpected.

Patient MOX3
AE Preferred Term: Lung neoplasm
A 82-year-old male with multiple comorbidities including hypertension, Parkinson's disease, COPD. PORT Risk Class IV, RUL and RML infiltrates, sputum culture = *H. influenzae (considered "negative" due to poor sputum sample quality)*. He was treated for 14 days. Protocol efficacy assessments determined that the patient was a clinical failure at ECR, but was a clinical success at end of treatment. At the end of treatment, radiologic evaluation showed improvement in CABP but revealed a tumor in the upper lobe of the right lung. On Study Day 16, needle biopsy via bronchoscopy made the diagnosis of small-cell lung cancer. The patient died on Study Day 20. Autopsy confirmed metastatic small-cell lung cancer.

Sponsor Assessment Immediate Cause of Death: Malignant neoplasm progression – The patient was an early clinical success but died due to underlying malignancy.

Patient MOX4
AE Preferred Term: Pancreatic carcinoma
A 72-year-old female with multiple comorbidities including hypertension, coronary artery disease, and diabetes mellitus. PORT Risk Class III, left lower lobe and ligular infiltrates, sputum culture = *H. parainfluenzae;* blood cultures = negative. Protocol efficacy assessments determined that the patient was a clinical success at ECR and end of treatment. On Study Day 7, patient developed icterus; laboratory testing showed new significantly elevated serum transaminases, bilirubin, and alkaline phosphatase (ALP). Subsequent evaluation led to the diagnosis of pancreatic cancer. Treatment was stopped after 8 days and the patient was transferred to another hospital for further management. She died on Study Day 71, due to the pancreatic cancer.
Sponsor Assessment Cause of Death: Malignant neoplasm progression - The patient was an early clinical success but died due to underlying malignancy