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APPLICATION NUMBER:

209816Orig1s000
209817Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209816 209817
Priority or Standard	Priority
Submit Date(s)	February 02, 2018
Received Date(s)	February 02, 2018
PDUFA Goal Date	October 02, 2018
Division/Office	DAIP/OAP
Review Completion Date	October 02, 2018
Established Name	Omadacycline
(Proposed) Trade Name	NUZYRA
Pharmacologic Class	Tetracycline
Code name	PTK 0796; MK2764; BAY 73-7388
Applicant	Paratek Pharmaceuticals Inc.
Formulation(s)	IV and Oral
Dosing Regimen	**Acute Bacterial Skin and Skin Structure Infections:** Loading dose of 200-mg intravenous (IV) infused over 60 minutes on the 1st day or 100-mg infused over 30 minutes, twice on the 1st day; or a loading dose of orally administered tablets of 450 mg on the 1st day; followed by 100 mg IV infused daily or 300 mg oral tablets daily. **Community-Acquired Bacterial Pneumonia:** Loading dose of 200-mg IV infused over 60 minutes on the 1st day or 100-mg infused over 30 minutes, twice on the 1st day; followed by 100 mg IV infused daily or 300 mg oral tablets daily.
Applicant Proposed Indication(s)/Population(s)	Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults Community-Acquired Bacterial Pneumonia (CABP) in adults
Regulatory Action	Approval
Indication(s)/Population(s) (if applicable)	Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in adults Community-Acquired Bacterial Pneumonia (CABP) in adults

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
BMD	Bone mineral density
BPCA	Best Pharmaceuticals for Children Act
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
Clin-Pharm	Clinical-Pharmacology
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAIDS	Division of AIDS
DAIP	Division of Anti-infective Products
DMC	data monitoring committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
mITT-E	modified intent-to-treat
micro-ITT	microbiological intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	per “os” or by mouth
PP	per protocol
PPI	patient package insert
PeRC	Pediatric Review Committee
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
Pharm-Tox	Pharmacology-Toxicology
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
TEADR	treatment emergent adverse reaction
USPI	US prescribing information
WHO	World Health Organization

1 Executive Summary Office Level Concurrence

In NDAs 209816 and 209817, the Applicant has provided substantial evidence of effectiveness of omadacycline (NUZYRA), intravenous injection and oral tablets, for the treatment of ABSSSI and CABP. Two adequate and well-controlled trials in ABSSSI showed noninferiority of omadacycline to linezolid, and in one adequate and well-controlled trial in CABP, omadacycline was noninferior to moxifloxacin. In the CABP trial, there was an imbalance in mortality rates with 8 deaths (2%) in the omadacycline group and 4 (1%) in the moxifloxacin group. Nausea/vomiting and infusion site reactions were reported more often with omadacycline than with the comparators. The Applicant will be required to conduct an additional trial in CABP to further evaluate the finding of an imbalance in mortality in the CABP clinical trial.

1.1. Product Introduction

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness from two adequate and well-controlled Phase 3 clinical trials in ABSSSI (Studies ABSI-1108 and ABSI-16301) and data from one adequate and well-controlled Phase 3 trial in CABP (Study CABP-1200) to support approval of omadacycline for the treatment of ABSSSI and CABP caused by susceptible isolates of the designated bacteria.

ABSSSI Indication

The Applicant has submitted data from two adequate and well-controlled clinical trials in ABSSSI. The efficacy endpoint in both trials was clinical success at the early clinical response (ECR) timepoint, defined as ≥20% reduction in lesion size in the modified intent-to-treat population (mITT) within 48-72 hours after the first dose of study therapy.

Omadacycline was noninferior, to linezolid in the mITT population using a 10% noninferiority (NI) margin. Clinical success rates were comparable between the two treatment groups with 84.8% success in the omadacycline group and 85.5% in the linezolid group, with a treatment difference and 95% CI of -0.7 (-6.3, 4.9) in trial ABSI1108, and 87.5% for the omadacycline group and 82.5% for the linezolid group, with a treatment difference and 95% CI of 5 (-0.2, 10.3) in trial ABSI16301. In both trials, clinical response was sustained at the post therapy evaluation (PTE) visit, 7 to 14 days after completing treatment. Clinical success at PTE was based on survival after completion of study treatment without receiving any alternative antibacterial therapy, without any unplanned major unplanned surgical intervention between end of treatment (EOT) and PTE visits, and sufficient resolution of infection such that further antibacterial therapy was not needed.

CABP Indication

The Applicant submitted data from one adequate and well-controlled clinical trial in CABP (Study CABP1200). The efficacy endpoint was clinical success at the ECR timepoint in the intent to treat population (ITT) population, assessed 72 to 120 hours after the first dose of study therapy. Clinical success was defined as survival with improvement in at least two of four symptoms (cough, sputum production, chest pain, dyspnea) from baseline without deterioration in any of these symptoms, with no receipt of antibacterial treatment either as a rescue for CABP or as a treatment for other infections that may be effective for CABP, and no discontinuation of study treatment due to adverse event (AE). Omadacycline was noninferior to moxifloxacin in the ITT population using a 10% NI margin. Clinical success rates were similar in both treatment groups (81.1% omadacycline, 82.7% moxifloxacin [95% CI]: -1.6 [-7.1, 3.8]). Successful clinical response was also assessed by the investigator at the PTE visit, 5 to 10 days after the last dose of study drug and was defined as survival with improvement in signs and symptoms of CABP, based on the clinician's judgment, to the extent that further antibacterial therapy is not necessary. Overall clinical success rates were similar between the treatment groups at the PTE visit. An increase in mortality was observed in the single CABP trial. A warning describing the imbalance is included in the product labeling and the Applicant is required to conduct a trial in CABP, postmarketing to further assess this finding. A single trial in CABP was considered adequate to support the indication, as efficacy of omadacycline was demonstrated in two ABSSSI trials.

1.3. Benefit-Risk Assessment

This portion intentionally left blank. Next section to follow Benefit Risk Assessment Summary: **1.3.1. ABSSSI**

1.3.1. ABSSSI

Benefit-Risk Summary and Assessment for ABSSSI

In NDAs 209816 and 209817, the Applicant is seeking approval of omadacycline for the treatment of ABSSSI and CABP in adults due to designated susceptible organisms. Omadacycline is a tetracycline class antibacterial drug and is available as IV and oral formulations.

There are few oral treatment options available for patients with infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). As the spectrum of activity of omadacycline includes MRSA, it provides another oral option for patients for the treatment of ABSSSI.

These NDAs provide substantial evidence for the effectiveness of omadacycline in ABSSSI. Results from two adequate and well-controlled clinical trials in ABSSSI demonstrated noninferiority (NI) of omadacycline compared to linezolid in the mITT population at the early clinical response evaluation (48 to 72 hours after initiation of treatment). One trial evaluated an IV to oral switch (Study ABSI-1108) regimen, and the other trial evaluated an oral-only treatment (Study ABSI- 16301). In both trials, the pre-specified NI margin of 10% was met in the mITT population. The clinical response was sustained at a later time point in both trials at the PTE visit, 7 to 14 days after the last dose.

The safety database for omadacycline consisted of 1947 patients treated with varying doses of omadacycline, with 1073 patients who received the proposed dose and duration of omadacycline (IV/oral), for the treatment of ABSSSI/ CABP. The most frequent adverse drug reactions in the ABSSSI trials were nausea, vomiting, infusion site reactions, transaminase elevations, headache, insomnia, and diarrhea. Serious adverse events reported in the ABSSSI trial were consistent with those seen with the tetracycline class.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ABSSSI are relatively common and are an important cause of inpatient hospitalizations and ambulatory care visits in the United States and worldwide. The incidence of ABSSSI	ABSSSI are common and serious infections.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	requiring hospitalization or clinic visits is increasing.[2,3] • ABSSSI include cellulitis/erysipelas, wound infection, and major cutaneous abscess. Gram-positive microorganisms account for the majority of ABSSSI: *S. aureus*, (methicillin-sensitive), MRSA, and beta-hemolytic Streptococcus species, particularly *S. pyogenes*.	
Current Treatment Options	• Current treatments that are approved for the treatment of ABSSSI in the US include β-lactams, lipopeptides, fluoroquinolones, oxazolidinones, glycopeptides, and tetracyclines. • Few oral options exist for the treatment of skin infections that have activity against causative pathogens such as MRSA. The emergence of antimicrobial resistance among bacterial pathogens worldwide limits treatment options for ABSSSI caused by resistant pathogens.	Approved therapies are available as either intravenous or intravenous and oral formulations; however, there is a need for new antibacterial drugs with activity against MRSA, in particular oral treatments.
Benefit	• The clinical efficacy of omadacycline was demonstrated in two adequate and well-controlled clinical trials for the treatment of ABSSSI. • In both trials, clinical response was comparable between the treatment groups with 84.8% success in omadacycline group and 85.5% in linezolid group, with a treatment difference of -0.7% and 95% CI (-6.3%, 4.9%) in Study ABSI1108; and 87.5% success in the omadacycline group and 82.5% in the linezolid group, with a treatment difference of 5% and 95% CI (-0.2%, 10.3%) in Study ABSI16301. Clinical response was sustained at a later time point in both trials.	Omadacycline was noninferior to an acceptable comparator linezolid in two adequate and well-controlled trials. As omadacycline is available as parenteral and oral formulations, patients do not need to be switched to a different therapy for oral step-down. It also provides for another oral treatment option for treatment of MRSA infections.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety of IV and oral omadacycline was examined primarily in the safety data from 1,073 patients treated in the two Phase 3 trials in ABSSSI and a single Phase 3 trial in CABP. The Phase 3 trials include a total of 705 patients who received the IV-oral omadacycline regimen, as well as 368 patients who received the oral-only omadacycline regimen for the treatment of ABSSSI. • The most frequent adverse reactions were nausea, vomiting, infusion site reactions, alanine aminotransferase increased, headache, insomnia, and diarrhea.	Safety concerns associated with omadacycline use in ABSSSI are adequately addressed in product labeling. Routine post-marketing pharmacovigilance will suffice.

This portion intentionally left blank. Next section to follow 1.3.2. Benefit-Risk Summary and Assessment for CABP

1.3.2. CABP

Benefit-Risk Summary and Assessment for CABP

Community acquired bacterial pneumonia (CABP) is a leading cause of hospitalization and death among adults in the United States. The overall mortality rate for CABP is in the range of 1 to 2 %, however, for severely ill patients 30-day mortality rates up to 23% have been reported.[17]

These NDAs (NDA 209816 and 209817) provide substantial evidence for the effectiveness of omadacycline in CABP. Results from a single adequate and well-controlled randomized trial in CABP demonstrated noninferiority to the comparator drug, moxifloxacin in the ITT population at the early clinical response evaluation (ECR at 72 to 120 hours after initiation of treatment). The clinical success rates were 81.1% and 82.7%, in the omadacycline and moxifloxacin groups respectively, with a treatment difference of -1.6% and 95% CI (-7.31%, 3.8%). The clinical response was sustained at a later time point at the PTE visit, 5 to 10 days after the last dose of study drug. Subgroup analyses showed a numerically lower clinical response rates in omadacycline-treated patients with high risk for poor prognosis (e.g., age ≥ 65 years, PORT Risk Class IV, and underlying comorbidities e.g., COPD/asthma, diabetes mellitus). Success rates were also lower at ECR in the micro-ITT population and those with documented baseline cultures positive for *S. pneumoniae* or *H. influenzae*.

There was an imbalance in 30-day all-cause mortality, with eight deaths (2.1%) in the omadacycline group as compared to 3 deaths (0.8%) in the moxifloxacin group. Although causality has not been established, this imbalance in a randomized controlled trial where treatment groups were well balanced is concerning. The risk factors that were observed to be associated with the mortality were, age > 65 years, PORT Risk Class IV, underlying COPD /asthma and diabetes mellitus. The most frequent adverse drug reactions in the CABP trial were transaminase elevations, insomnia, nausea, vomiting, and headache. No noteworthy differences in non-fatal safety events were seen across subgroups defined by gender, race, geographic region, renal or hepatic impairment.

Overall, the benefit-risk assessment of omadacycline for the treatment of CABP is favorable. While an imbalance in mortality was observed, the reason(s) for the increased mortality could not be discerned. In terms of efficacy in the overall population, the efficacy of omadacycline was comparable to that of moxifloxacin. However, in some subgroups such as age ≥ 65 years, PORT Risk Class IV, patients with chronic lung diseases (COPD/asthma), patients with diabetes or those with bacteremia, the point estimates for efficacy did not favor omadacycline. These were post hoc subgroup analyses based on rather small numbers and so no definitive conclusions can be drawn. In addition, there is concern with a deficit in the efficacy of the tetracycline class of

antibacterial drugs with regard to certain serious infections such as, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia. Labeling for tigecycline, a tetracycline includes a Boxed Warning regarding the increased risk of mortality seen in a meta-analysis of clinical trials that included a variety of infections. The finding of mortality imbalance will be communicated in labeling. The Applicant will conduct a second adequate and well-controlled trial in CABP as a post marketing requirement (PMR) to further evaluate the observed mortality imbalance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CABP is a leading cause of hospitalization and death from infectious diseases among adults in the United States. • Most common bacterial organisms causing CABP include *S. pneumoniae, H. influenzae, S. aureus, M. catarrhalis, K. pneumoniae, C. pneumoniae, M. pneumoniae, and L. pneumophila*. Incidence rates of CABP increases with increasing age. • The overall mortality rate for CABP is in the range of 1 to 2 %, however, for those ill enough to require hospitalization and intensive care management, 30-day mortality rates up to 23% have been reported. The risk for mortality in CABP rises with increasing age, increased severity of pneumonia, and presence of comorbidities such as diabetes, cardiorespiratory disease, malignancy, neurological disease, and hypotension.	CABP is a serious infection characterized by recognizable clinical signs, symptoms and laboratory abnormalities, and associated with significant rates of hospitalization and death.
Current Treatment Options	• There are many FDA-approved antibacterial drugs of various classes used in the treatment of CABP including β-lactam drugs, fluoroquinolones, macrolides, vancomycin, and linezolid. • The selection of antimicrobial drugs for empiric therapy is based upon a number of factors, including known adverse reactions and patient co-morbidities and potential for known	Increasing rates of antibacterial resistance are seen in CABP pathogens, in the US and worldwide. Toxicity profiles of available antibacterial drugs could often limit their use for the treatment of CABP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or anticipated antibacterial resistance.	
Benefit	• Efficacy of omadacycline for the treatment of CABP was demonstrated in a single adequate and well-controlled NI trial compared to moxifloxacin. • Approximately 60% of patients in each group were characterized as PORT Risk Class III and about 26% as PORT Risk Class-IV. • Omadacycline was noninferior to moxifloxacin with results within the prespecified 10% NI margin in the ITT population at the early clinical response evaluation (ECR, 72 to 120 hours after initiation of treatment). Clinical success rates in omadacycline were 81.1% and 82.7%, in the omadacycline and moxifloxacin groups respectively, with a treatment difference of -1.6% and 95% CI (-7.31%, 3.8%). • Clinical response was sustained at a later time point at post-therapy evaluation (PTE, 5 to 10 days after the last dose of study drug) visit in the ITT population. • Numerically lower clinical success rates were observed in omadacycline-treated patients with risk factors predictive of higher severity of illness (e.g., age ≥ 65 years, PORT Risk Class IV, patients with chronic lung diseases such as, COPD/asthma, patients with diabetes or those with bacteremia), and patients in the micro-ITT population as compared to the moxifloxacin group. • No dose adjustment is needed for patients with renal or hepatic impairment.	Effectiveness of omadacycline for treatment of CABP was demonstrated in an adequate, well-controlled trial. Omadacycline was noninferior to moxifloxacin with results within prespecified 10% NI margin. Although, subgroup analyses showed a numerically lower response rate in omadacycline-treated patients with higher severity of illness there are limitations in these post-hoc subgroup analyses due to small sample sizes.
Risk and Risk Management	• The safety database is comprised of 1947 patients treated with varying doses of omadacycline, with 1073 patients who received proposed dose and duration of omadacycline (IV and oral combined), for the treatment in ABSSSI and CABP	An imbalance in mortality in CABP trial was seen with more deaths in the omadacycline-treated patients. Risk factors that were observed to be associated with mortality

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	trial. • No significant differences in non-fatal adverse events, SAEs or adverse events leading to treatment discontinuations were seen between treatment groups, or across different subgroups of patients as defined by gender, race, geographic region, and renal or hepatic insufficiency. • There was an imbalance in 30-day all-cause mortality, with eight deaths (2.1%) in the omadacycline group as compared to 3 deaths (0.8%) in the moxifloxacin group. • As reported in the literature, 30-day mortality risk for patients with baseline PORT Risk Class-III (PORT score between 71-90) is ~0.9%, and for PORT Risk Class-IV (PORT score between 91-120) is ~9.3%.[38]	were, PORT Risk Class-IV, age > 65 years, underlying COPD /asthma and diabetes mellitus. It is possible that this difference could be due to a "chance" finding. However, such a finding of increased mortality in a randomized controlled trial is concerning. However, the finding of lower point estimates in some subgroups such as age ≥ 65 years, PORT Risk Class IV, patients with chronic lung diseases (COPD/asthma), patients with diabetes or those with bacteremia and the known deficit in efficacy of the tetracycline class of antibacterial drugs with regard to certain serious infections such as, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia do raise concern about the finding of mortality imbalance. This finding of mortality imbalance will be communicated to healthcare providers through product labeling, including a warning. The Applicant will be required to conduct another adequate and well controlled, clinical trial in CABP to evaluate the safety and efficacy of omadacycline, (b) (4) as a PMR.

1.4. Patient Experience Data

Patient reported outcome (PRO) instrument developments for the indications of CABP or ABSSSI are underway but not yet qualified by FDA. However, the clinical outcome assessments of the primary efficacy endpoints of improvement in symptoms captures the patient's experience of symptom improvement in CABP, and lesion size reduction for ABSSSI captures the patient's experience that lesion size is improving. These have been documented in concept elicitation studies as part of PRO qualitative research using open-ended interviews with individual patients (the applicant is not directly involved in these PRO development efforts).

X	The patient experience data that was submitted as part of the application include:			Section
	X	Clinical outcome assessment (COA) data, such as		Section 7.2, Study endpoints
			Patient reported outcome (PRO) – not yet qualified	
			Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.2, Study endpoints

2 Therapeutic Context

2.1. Analysis of Condition

The proposed indications in these NDAs are acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP).

2.1.1. Acute bacterial skin and skin structure infections

Acute bacterial skin and skin structure infections are one of the leading causes of infection-related emergency room visits and hospital admissions in United States and worldwide. [1] The incidence of ABSSSI requiring hospitalization or clinic visits is increasing.[2,3] A cross-sectional analysis of data from the US Healthcare Cost and Utilization Project National Inpatient Sample

[1] Agency for Healthcare Research and Quality, 2011 National Statistics: All ED visits. Available at: http://hcupnet.ahrq.gov.

[2] *Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibacterial prescribing for skin and soft-tissue infections. Arch Intern Med. 2008 Jul 28; 168 (14):1585-91.*

[3] *May L, Mullins P, Pines J. Demographic and treatment patterns for infections in ambulatory settings in the United States, 2006-2010. Acad Emerg Med. 2014 Jan;21 (1):17-24.*

reported an estimated 17% increase in hospitalizations for ABSSSI between 2005 and 2011[4,5]. The overall cost to hospitals associated with ABSSSI exceeds 6 billion dollars per year with an average cost of $8,000 per hospitalized patient[6] and costs ofoutpatient treatments are less.[7]

ABSSSI include cellulitis/erysipelas, wound infection, and major cutaneous abscess. Common bacterial pathogens causing ABSSSI are *S. pyogenes* and *S. aureus* including methicillin-resistant *S. aureus*. Less common causes include other *Streptococcus* species, *Enterococcus faecalis*, or Gram-negative bacteria. The FDA ABSSSI guidance, defines ABSSSI as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration).[8] The minimum area of involvement of 75 cm^2 is chosen to select patients with acute bacterial skin infections for which a reliable control drug treatment effect can be estimated.[9,10,11,12] ABSSSI trials exclude patients with necrotizing fasciitis or diabetic foot infections as such infections require more complex regimens. Because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses, patients with major cutaneous abscesses should not comprise more than 30 percent of the clinical trial population.

2.1.2. **Community acquired bacterial pneumonia**

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[4] *Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. PLoS One. 2015 Nov 24;10(11):e0143276.*

[5] *Edelsberg J, Taneja C, Zervos M, Haque N, Moore C, Reyes K, et al. Trends in US hospital admissions for skin and soft tissue infections. Emerg Infect Dis. 2009 Sep;15(9):1516-18.*

[6] *LaPensee K, Fan W. Economic burden of hospitalization with antibacterial treatment for ABSSSI in the US: an analysis of the Premier Hospital Database. 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Washington DC; 2012.*

[7] Talan DA Salhi BA Moran GJ et al. . Factors associated with decision to hospitalize emergency department patients with skin and soft tissue infection. West J Emerg Med 2015; 16:89–97.

[8] https://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf

[9] Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); October 2013. https://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf

[10] Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibacterials in the management of community-acquired skin abscesses in the pediatric patient. Ann Emerg Med. 2010 May; 55(5):401-7.

[11] Rajendran PM, Young DM, et al. Antibacterial use in the treatment of soft tissue abscesses: a survey of current practice. Surg Infect (Larchmt). 2007 Apr;8 (2):237-8.

[12] Lee MC, Rios AM, et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant Staphylococcus aureus. Pediatr Infect Dis J. 2004 Feb; 23(2):123-7.

Community acquired pneumonia (CAP) is a leading cause of hospitalization and death from infectious diseases among adults in the United States[13]. Annual incidence of hospitalization for CAP is about 24.8 cases per 10,000 adults based on a population-based surveillance study in United States[14], and the medical cost of care exceeds $10 billion[15]. Community acquired bacterial pneumonia (CABP) is the subgroup of CAP, which is caused by bacterial pathogens. CABP is an acute infection in a patient who has acquired the infection in the community, as distinguished from hospital-acquired (nosocomial) bacterial pneumonia. Most common bacterial organisms causing CABP include *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. Incidence rates of CABP increases with increasing age.[16,17] The overall mortality rate for CABP is in the range of 1 to 2 %, however, about 80% of CABP patients are treated as an outpatient. For those ill enough to require hospitalization, 30-day mortality rates up to 23% have been reported.[17]

The pathogenic mechanisms and host defenses in patients with pneumonia have been well established.[18,19]

The diagnosis of CABP generally requires the demonstration of an infiltrate on chest radiograph in a patient with a clinically compatible syndrome described above (e.g., fever, dyspnea, cough, and sputum production). Microbiologic testing of a sputum sample is often not performed and is instead reserved for hospitalized patients and for selected outpatients in whom test results would change the management. Therefore, empiric therapy with an antibacterial drug that has an appropriate spectrum of therapy for likely bacterial pathogens is crucial for the treatment of CABP. The diagnostic testing for a specific organism is recommend when, based on clinical or epidemiologic data, pathogens that would not respond to usual empiric antibacterial regimens are suspected. Pretreatment blood cultures are positive for a pathogen in 7 to 16 percent of hospitalized patients.[20,21,22] Bacteremia is uncommon in CABP, but if it occurs *S. pneumoniae*

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[13] US Centers for Disease Control and Prevention. Fast Stats: leading causes of death. http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed March 24,2018

[14] Jain S, Self WH, Wunderink RG et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. NEJM 2015; 373: 415-27

[15] Pfuntner A, Wier LM, Steiner C; Agency for Healthcare Research and Quality. Costs for hospital stays in the United States. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb168-Hospital-Costs-United-States-2011.jsp. Accessed March 24,2018

[16] Marrie TJ, Huang JQ. Epidemiology of community-acquired pneumonia in Edmonton, Alberta: an emergency department-based study. Can Respir J 2005; 12:139.

[17] File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med 2010; 122:130.

[18] Donowitz GR. Acute Pneumonia. In Bennet D, editor. Principles and Practice of Infectious Diseases. 7th Edition. Churchill Livingstone Elsevier; 20 I 0. 64;89 I 916.

[19] Chaudhuri N, Whyte M, Sabroe I. Reducing the toll of inflammatory lung disease. Chest 2007; 131: 1550 6.

[20] Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. Respir Med 2001; 95:78.

accounts for two-thirds of the positive blood cultures. Newer tests such as polymerase chain reaction (PCR) for detecting *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* have been approved by the FDA.

Predictors of mortality in CABP

Appropriate antibacterial therapy has also been associated with lower mortality. [23,24]

A number of prediction tools or prognostic models have been developed to help with the decision for treatment of the patient with CABP as an outpatient or in the hospital. The two best known are Pneumonia Severity Index (PSI) and CURB-65. Both assign points to patients based on various criteria. The PSI uses 20 variables and relegates patients to 1 of 5 categories, while CURB-65 uses only 5 variables and puts patients in 1 of 3 categories. Patients admitted to hospital wards initially who subsequently worsen have a lower survival rates than equally ill patients who were initially cared for in ICU setting; up to 45% of patients with CAP who ultimately required ICU admission and died were initially admitted to a non- ICU setting. [25] Pneumonia may exacerbate an underlying disease, such as obstructive lung disease, congestive heart failure, or diabetes mellitus, which, by themselves, may require hospital admission. [26 27] Transfer to the ICU for delayed respiratory failure or delayed onset of septic shock is associated with increased mortality. [28]

The PSI score is based on gender, age, nursing home residence, comorbidities, physical examination findings, laboratory values, and radiographic findings. It is widely used for predicting 30-day mortality (Table below).[29] The PSI stratifies patients into 5 mortality risk classes, and its ability to predict mortality has been confirmed in subsequent studies.

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[21] Chalasani NP, Valdecanas MA, Gopal AK, et al. Clinical utility of blood cultures in adult patients with community-acquired pneumonia without defined underlying risks. Chest 1995; 108:932.

[22] Falguera M, Trujillano J, Caro S, et al. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. Clin Infect Dis 2009; 49:409.

[23] Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients, *Chest* , 1999, vol. 115 (pg. 462-74)

[24] Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, Gudiol F. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia, Arch Intern Med , 2004, vol. 164 (pg. 502-8)

[25] Ewig S, de Roux A, Bauer T, et al. Validation of predictive rules and indices of severity for community acquired pneumonia, Thorax , 2004, vol. 59 (pg. 421-7)

[26] Arnold FW, Ramirez JA, McDonald LC, Xia EL. Hospitalization for community-acquired pneumonia: the pneumonia severity index vs clinical judgment, Chest , 2003, vol. 124 (pg. 121-4)

[27] Marras TK, Gutierrez C, Chan CK. Applying a prediction rule to identify low-risk patients with community-acquired pneumonia, Chest , 2000, vol. 118 (pg. 1339-43)

[28] Leroy O, Santre C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit, Intensive Care Med , 1995, vol. 21 (pg. 24-31)

[29] Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with communityacquired

Table 2-1 Pneumonia PORT Risk Classification and Scoring Interpretation for the Prediction of 30-day mortality

Risk	PORT Risk Class	Points	Predicted Mortality
Low	I	0-50	0.1%
Low	II	51-70	0.6%
Low	III	71 to 90	0.9%
Moderate	IV	91 to 130	9.3%
High	V	>130	27.0%

2.2. Analysis of Current Treatment Options

2.2.1. Acute bacterial skin and skin structure infection

Current treatments that are approved for the treatment of ABSSSI in the US include β-lactams (e.g., ceftaroline), lipopeptides (e.g., daptomycin), fluoroquinolones (e.g., delafloxacin), oxazolidinones (e.g., linezolid), glycopeptides (e.g., vancomycin), and tetracyclines (e.g., tigecycline). Few oral options exist for the treatment of skin infections that have appropriate activity against *S. aureus*, including MRSA, and β-hemolytic streptococci. Oral β-lactams (e.g., amoxicillin-clavulanate) and fluoroquinolones, with the exception of delafloxacin, have no or limited MRSA activity, respectively. Clindamycin resistance in *S. aureus* is common. High rates of both clindamycin and tetracycline resistance are present in β-hemolytic streptococci. Trimethoprim-sulfamethoxazole, with low rates of resistance, has been associated with side effects (e.g., rash, gastrointestinal [GI], laboratory abnormalities) especially at higher doses.

Products currently approved for the treatment of ABSSSI and complicated skin and skin structure infections are presented in a tabular format in Appendix 15.5.1.

2.2.2. Community-acquired bacterial pneumonia

Treatment of CABP in adults who require hospitalization

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pneumonia, N Engl J Med , 1997, vol. 336 (pg. 243-50)

Initial treatment regimens for hospitalized patients with CABP are mostly empiric. A limited number of pathogens are responsible for the majority of cases for which a pathogen is known, but in most cases a pathogen is not identified. The most commonly detected bacterial pathogen is *Streptococcus pneumoniae*. Other common pathogens include *Haemophilus influenzae*, the atypical bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp), oropharyngeal aerobes and anaerobes (in the setting of aspiration).

Treatment recommendations from US IDSA and American Thoracic Society guidelines is listed in Appendix 15.5.2. Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogen(s) and knowledge of local susceptibility patterns. Other factors for consideration of specific antimicrobials include pharmacokinetics-pharmacodynamics parameter of the drug, compliance, safety, and cost. Once the etiology of CABP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen.

Patients are usually switched from intravenous to oral therapy when they are hemodynamically stable, demonstrate some clinical improvement (in fever, respiratory status, white blood count), and are able to take oral medications. Duration of treatment in patients with CABP who have a good clinical response within the first two to three days of therapy should generally be 5-7 days. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection.[30]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Omadacycline is a new molecular entity (NME) which is not marketed in the United States

3.2. Summary of Presubmission/Submission Regulatory Activity

The phase 3 clinical development of omadacycline was initiated in 2008. Following the publication of the guidance document from FDA, *Antibacterial Drug Products: Use of Non-Inferiority Studies to Support Approval,* the applicant halted phase 3 clinical development because the trial designs might not support a finding of non-inferiority. Following the

[30] https://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_By_Organ_System-81567/Lower/Upper_Respiratory/Community-Acquired_Pneumonia

publication of draft guidance documents for CABP and ABSSSI, the applicant re-initiated phase 3 clinical development based on the guidance document recommendations for trial designs.

Omadacycline was granted a QIDP designation for treatment of CABP, ABSSSI, complicated urinary tract infections (cUTI), and uncomplicated urinary tract infections (uUTI). Omadacycline was granted Fast Track Designation for indications CABP, ABSSSI and cUTI. As such, it received a priority review designation for these NDAs.

On April 29, 2013 a meeting was held between the Applicant and the Agency, in which general agreement was reached on the design of the ABSSSI and CABP studies, including an agreed upon noninferiority margin of 10% for the Phase 3 ABSSSI and CABP trials. At this meeting, the Agency also agreed that a single adequate and well controlled ABSSSI trial and a single adequate and well controlled CABP trial would be acceptable and support an NDA for both indications. Study ABSI-1108 and Study CABP-1200 were subsequently initiated and both trials were conducted under agreed to Special Protocol Assessments (SPAs).

4. Significant Issues from Other Review Disciplines

4.1. Pertinent to Clinical Office of Scientific Investigations (OSI)

Following sites were chosen for inspection and audit – Site # 254 (Study ABSI1108), Site # 608, 606, and 636 (Study ABSI 16301), in U.S.; Site #140 (Study ABSI1108) in Romania; Site # 307 (Study CABP1200) in Bulgaria and Site # 313 (Study CABP 1200) in Hungary.

OSI audit revealed GCP deficiencies at Site #606. A Form FDA 483 was issued by OSI at Site 606 in Study PTK-0796-ABSI-16301 (Soledad Lee; Buena Park, CA), due to the GCP deficiencies which were also identified by the sponsor and reported in the NDA. The Sponsor had stopped enrollment at this site. This site enrolled patients in the oral only ABSSSI trial (Study ABSI 16301); 7 patients in each of the treatment arms. All patients were recorded clinical success at ECR, EOT and PTE visits. No subjects were discontinued from either study treatment arms and no adverse events were reported by patients from either study treatment arms at site #606. A sensitivity analysis excluding the 14 patients from this site was consistent with the results from primary analysis. Thus, exclusion or inclusion of patients from this study site had no impact on the study results. Efficacy for Study ABSI16301 will be reported excluding subjects from this site.

For all remaining sites, no significant deficiencies were observed, and a Form FDA 483 was not issued; study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. Except for Site 606, the data from all inspected sites appeared reliable as reported in the NDA per OSI review. All audited data were acceptably verifiable against source records and case report forms (CRFs).

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

Omadacycline has been developed as an oral (tablet) formulation (NDA 209816) and as an intravenous formulation (NDA 209817).

The tablet formulation, omadacycline 150 mg, is supplied as a yellow, diamond-shaped, immediate release film-coated tablet containing 150 mg of omadacycline (equivalent to 196 mg omadacycline tosylate) debossed with OMC on one side and 150 on the other side. All excipients are compendial. The Applicant proposed a 60 mL, white, high density polyethylene (HDPE) bottle, with child resistant closure with (b) (4) desiccant and (b) (4) as the container closure system. (b) (4)

The clinical formulation used in the pivotal clinical trial is the same as the proposed commercial drug product, except for minor changes in tablet color and shape. The NDA provided comparative dissolution profile data to support bridging of the drug products used in the phase 3 clinical studies and the commercial tablets. The manufacturing site of the drug product-batches used in the phase 3 clinical and registration-stability studies is the same as the proposed commercial site. Results of the stability studies support a 24 months expiration date at the following proposed storage conditions: Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15 - 30°C (59°F to 86°F)" [see USP Controlled Room Temperature].

The IV formulation, omadacycline for injection 100 mg, is supplied as a sterile lyophilized powder in a single-dose colorless glass vial containing 100 mg of NUZYRA (equivalent to 131 mg omadacycline tosylate). The powder needs to be further diluted for intravenous infusion. All excipients are compendial.

The drug product is rendered sterile (b) (4). A biowaiver request was not needed for the proposed drug product because the formulation and manufacturing processes of the proposed commercial drug product are reported to be the same as those of the clinical trial product. Additionally, the manufacturing site of the clinical batches is the same as the site proposed for the manufacturing of the commercial batches. The stability studies results support a 24 months expiration date at the following proposed storage conditions: Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15 - 30°C (59°F to 86°F)" [see USP Controlled Room Temperature].

Both NDA 209816 and NDA 209817 are recommended for Approval from the Product Quality perspective. All Product Quality aspects including facilities are found acceptable. For details of the review findings, refer to the Integrated Quality Assessment (IQA) for each NDA.

Drug Product Composition for the Tablet Formulation

Ingredient	Amount per 150 mg Film-Coated Tablet (mg)	Function	Reference to Standards
Tablet core			
(b) (4)			
Omadacycline tosylate[a]	196.350	Active	Paratek in - house
Lactose monohydrate[a]	(b) (4)		NF / Ph. Eur.
Microcrystalline cellulose			NF / Ph. Eur.
Crospovidone			NF / Ph. Eur.
Sodium stearyl fumarate			NF / Ph. Eur.
Sodium bisulfite			FCC grade
(b) (4)			
Colloidal silicon dioxide,		(b) (4)	NF / Ph. Eur.
(b) (4)			
Total tablet core weight	(b) (4)		
Film-coating[b]			
(b) (4)			Paratek in - house USP / Ph. Eur.
Total film-coated tablet weight	774.000		

FCC = Food Chemicals Codex, NF = National Formulary, Ph. Eur. = European Pharmacopoeia, USP = United States Pharmacopeia.

a (b) (4)

b

c

d

Drug Product Composition for the IV Formulation

Ingredient	Amount per 100 mg IV (mg)[a]	Function	Reference to Standards
Omadacycline tosylate[b]	130.9	Active	Paratek in - house
Sucrose	100.0	(b) (4)	NF / Ph. Eur.
(b) (4)			(b) (4)
Total	(b) (4)	N/A	N/A

N/A = Not Applicable, NF = National Formulary, Ph. Eur. = European Pharmacopoeia, q.s = quantity sufficient, USP = United States Pharmacopeia.

a (b) (4)

b

c

d

e

f

This portion intentionally left blank. Next section to follow is Non-Clinical Pharmacology and Toxicology

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Secondary and safety pharmacology studies have shown that omadacycline binds the M2 muscarinic receptor and has inhibitory and antagonistic effects at that receptor. Omadacycline was not considered to significantly affect parameters measured in the Irwin test in rats at doses up to 44.7 mg/kg, and it did not alter the convulsive threshold of pentylenetetrazole in rats at 10 mg/kg while a small but statistically significant anticonvulsive effect was seen at 25 and 50 mg/kg. No respiratory effects were observed in monkeys studied under conscious or anesthetized conditions at doses up to 40 mg/kg and 90 mg/kg, respectively. Omadacycline did not affect renal function in the rat between 0-24 hours post-dose at doses up to 44.7 mg/kg.

Omadacycline demonstrated the potential to cause cardiac perturbation in several in vitro assays and nonclinical studies. These effects were believed to be via inhibition of Na+/K+-ATPase. Omadacycline demonstrated the potential in vitro to cause irreversible inhibition of human Na+/K+-ATPase (IC_{50} = 0.29 to 0.52mM depending on the amount of K+ available). Omadacycline also demonstrated a potential to cause cardiac depolarization in isolated rabbit Purkinje fibers and guinea-pig papillary muscles at the highest concentration tested (300 mcM), with effects on action potential being partially reversible upon washout. In dog Purkinje fibers, a small prolongation of action potential was seen at 10 mcg/mL omadacycline, with effects on resting membrane potential, upstroke amplitude and maximum rate of depolarization at 100 and 250 mcg/mL. In the study in conscious cynomolgus monkeys, increases in arterial blood pressure (systolic, diastolic and mean) and heart rate were noted at all doses (5, 20 and 40 mg/kg) and were reversible after up to 4.5 hours. A clinical thorough QT study was conducted to determine clinical relevance and potential for concern relative to these findings.

Repeat-dose GLP-compliant general toxicology studies of oral and IV administration were conducted in rats and cynomolgus monkeys for up to 13 weeks, with recovery periods.

In 13-week studies in monkeys, loose stools and/or emesis were seen at all doses (by both routes of administration), as was the presence in multiple tissues of Perls' stain negative pigment considered to be related to the test article (omadacycline) or its degradation products. At higher doses, decreased body weight, evidence of regenerative hemolytic anemia, vacuolar degeneration of cardiomyocytes and/or renal tubular epithelium, and/or death were observed. In the oral toxicology study, lymphoid depletion was noted, as were clinical pathology changes indicative of inflammation (increased neutrophils, fibrinogen) or hepatocellular leakage (increased AST, ALT, ALP and/or bilirubin), electrolyte changes associated with vomiting, and/or altered renal function (increased BUN, creatinine, phosphorus, magnesium). Most findings, with the exception of pigment deposition in multiple tissues, resolved during the 4-week recovery periods.

In 13-week studies in rats, deaths were seen at the highest dose after both IV and oral administration. After oral administration, dose-related decreases in body weight and food consumption, clinical signs of rales at all doses and decreased activity and hunched posture were observed at the high dose. Increased reticulocytes were evident at the mid- and high doses, and neutrophilia, increased bilirubin and serum transaminases were seen at the high dose, consistent with mild regenerative hemolytic anemia, inflammation and/or stress, and hepatocellular leakage. Sperm motility was decreased at the high dose but was reversible. Pathology findings were limited to discoloration and follicular pigment in the thyroid at the mid- and high doses that persisted at the end of the recovery period. After IV administration, findings included clinical signs (salivation and yellow/brown discoloration of teeth), dose-related changes in hematology (decreased red blood cell parameters, increased reticulocytes, with compensatory increased hematopoiesis in the spleen and bone marrow), clinical chemistry (decreased glucose, increased AST and total bilirubin) and organ weights (increased spleen and adrenal, and decreased testis weights, correlating to increased hematopoiesis, adrenal cortical hypertrophy, and atrophy of the seminiferous tubular epithelium in the testes with oligospermia/aspermia in the epididymides, respectively). Additional post-mortem findings after IV administration included findings at the catheter tip (endothelial hyperplasia/erosion, intimal thickening, vascular inflammation/necrosis/hemorrhage, thrombus, and deposits of basophilic material), bone and tooth discoloration, and deposition of iron-containing brown pigment in the liver and kidneys and non-iron containing brown pigment in the proximal tubular epithelium of the kidney, thyroid gland, and macrophages in the thymus and lymph nodes and Kupffer cells of the liver. Most changes, except for those observed in the testes, were at least partially reversible at the end of the 4-week recovery period.

Similar findings across toxicology studies involved hematopoiesis (decreased red blood cell parameters and increased reticulocytes in rat and monkey IV and oral studies; increased spleen weights and increased extramedullary hematopoiesis) that appeared to be reversible, gastrointestinal effects (cecum distended with feces, focal ulceration and/or hyperplasia of the non-glandular stomach in one oral toxicology study in rats, emesis, diarrhea, and fecal changes in oral and IV toxicology studies in monkeys), adrenal changes (increased weights in IV studies in rats and monkeys, hypertrophy or hyperplasia of the adrenal of the cortex, generally reversible), lymphoid depletion of the thymus, spleen, lymph nodes, and/or bone marrow in IV studies in rats and monkeys (generally reversible), clinical pathology findings related to the liver (increased AST, ALT, and/or bilirubin in IV rat and monkey studies, with histologic correlates in one rat and one monkey study, generally reversible), histopathologic changes in the heart in IV monkey studies (cardiac myofiber degeneration or myocardial vacuolar degeneration; not seen in recovery animals), atrophy/degeneration of seminiferous tubules in the testes with associated decreases in sperm numbers and motility (at least partially reversible), renal tubule degeneration in the monkey kidney, non-iron containing (Perl's stain negative) brown pigment deposited in multiple tissues (considered to be study drug or metabolite) in both species after oral or IV dosing, and iron-containing (Perl's stain positive) pigment deposition consistent with hemosiderin as a result of erythrocyte breakdown.

NOAEL doses in the 13-week studies are shown below with nonclinical and clinical toxicokinetic exposure data:

Species	Dose	AUC (mcg*hr/mL)	
Rat	5 mg/kg/day IV	$AUC_{0\text{-}24\ hr}$ on Day 1 Males: 8.41 Females: 4.93	$AUC_{0\text{-}24\ hr}$ on Day 91 Males: 8.61 Females: 3.74
Cynomolgus monkey	5 mg/kg/day IV	$AUC_{0\text{-}24\ hr}$ on Day 1 Males: 4.22 Females: 4.32	$AUC_{0\text{-}24\ hr}$ on Day 91 Males: 3.49 Females: 4.20
Human	100 mg IV	12.14	
Rat	300 mg/kg/day PO	$AUC_{0\text{-}24\ hr}$ on Day 1 Males: 8.32 Females: 5.28	$AUC_{0\text{-}24\ hr}$ on Day 76 Males: 7.10 Females: 5.79
Cynomolgus monkey	200 mg/kg/day PO	$AUC_{0\text{-}24\ hr}$ on Day 1 Males: 30.5 Females: 31.5	$AUC_{0\text{-}24\ hr}$ on Day 71 Males: 56.8 Females: 54.1
Human	300 mg PO	11.16 (steady state)	

Most studies in a battery of genetic toxicity tests of omadacycline were negative, although attempts to assess mutagenicity in bacterial reverse mutation assays were unsuccessful due to excessive toxicity to the test bacteria. However, a chromosomal aberrations assay in Chinese Hamster Ovary cells did demonstrate some clastogenic and aneugenic activity in vitro, and positive findings for mutagenicity were noted in the mouse lymphoma assay.

In a battery of developmental and reproductive toxicology tests, no effect of IV omadacycline tosylate was observed on female fertility, while, in males, increased seminal vesicle weights, and reduced or absent sperm motility were seen at doses > 5 mg/kg/day in the absence of effects on fertility (NOAEL = 20 mg/kg/day). In two embryo-fetal development studies in rats at doses ranging from 5 to 80/60 mg/kg/day, findings included, dose-dependent reduction in fetal body weights at all doses (correlating with delayed ossification at doses > 5 mg/kg/day) reductions in average number of ossified caudal vertebrae and hindlimb phalanges at doses > 5 mg/kg/day, and increased post-implantation loss and/or increased incidence of fetal external malformations at the highest doses. A fetal NOAEL in rats was not determined. In an embryo-fetal development study in rabbits, one abortion, increased post-implantation loss, and decreased average numbers of live fetuses were reported at the high dose. Malformations and variations in the heart and vessels, diaphragm, and lungs, skeletal malformations (cervical, thoracic, and lumbar vertebrae), and incomplete or delayed ossification were reported to be treatment-related (NOAEL = 5 mg/kg/day). In a pre- and post-natal development study in rats, no effects were noted post-weaning in behavioral or reproductive assessments (NOAEL = 30 mg/kg/day).

From a Pharmacology/Toxicology standpoint, this application is approvable. The nonclinical data support the safety of the proposed clinical use. Adverse effects seen in the toxicology studies were generally monitorable and/or were consistent with known effects of the drug class. Clinical trials provided data to support the safety of human exposures that were greater than those seen in toxicology test species at NOAEL doses. Positive findings in two of the five valid genetic toxicity tests may be of minimal concern due to the short duration of treatment with omadacycline (7-14 days). While the fertility and embryonic development study in female rats did not test to maternal toxicity, the NOAEL (high dose) was approximately twice the clinical dose after normalization for total body surface area.

Referenced INDs, NDAs, BLAs, DMFs

IND 73431
IND 75928

Pharmacology

Primary pharmacology

Omadacycline (PTK-0796) is a tetracycline class antibacterial. As a class, tetracyclines bind to the bacterial ribosome 30S subunit and inhibit binding of aminoacyl-transfer ribonucleic acid, blocking bacterial protein synthesis.

Details of primary pharmacology studies conducted with omadacycline can be found in the Nonclinical Microbiology Section 8.1.

Secondary Pharmacology

The Applicant's nonclinical overview indicates that omadacycline at 9.38 mcM exhibited significant binding to the muscarinic M_2 receptor (**Study no. P000949-7**). In a follow-up study (**Study no. RD-2011-50427**), inhibition of the M_2 receptor was confirmed (IC_{50} = 4.25 mcM), as well as antagonism against the M_2 receptor (IC_{50} = 25 mcM).

Safety Pharmacology

The following safety pharmacology studies (with one noted exception) were reviewed in the original IND 75928 by Drs. Wendy Schmidt and Theresa Allio.

Cardiac effects

Effects on multiple ion channel currents were examined in **Study report no. PH-33756, AT01846**, including the hERG K^+ current, the inward rectifier K^+ current I_{K1}, the Na^+/K^+ ATPase pump current, and the human cardiac Na^+ current I_{Na} in transfected or wild-type HEK293 and RBL2H3 cells. Concentration-dependent inhibition of hERG current was observed, with an IC_{50} of 4mM, and of the human cardiac Na^+ channel, with and IC_{50} of 1.5 mM. IC_{50} values for positive controls were in the nM range. These effects were partially or nearly completely reversible on washout. Significant inhibition of the Na^+/K^+ ATPase channel was observed that was comparable to the positive control and irreversible. Concentration-dependent hERG

inhibition was demonstrated again in **Study report no. DHIZ1004.** Effects were significant at 250 mcg/mL and greater, with an IC_{25} of approximately 166 mcg/mL.

In **Study report no. PH-33789**, the effect of omadacycline on action potentials in isolated rabbit Purkinje fibers and guinea pig papillary muscles was investigated. Due to its structural similarity, minocycline was included for comparison. Omadacycline demonstrated depolarization of the resting potential (significant at 300 mcM) and extension of APD_{20} at 100 mcM (as did minocycline at 300 mcM). Partial reversibility was seen on washout.

Effects of omadacycline on action potential in dog isolated Purkinje fibers were evaluated in **Study report no. DHIZ1005**. Prolongation of action potential duration was noted at 10 mcg/mL and higher concentrations, while resting membrane potential, upstroke amplitude and maximum rate of depolarization were also affected at 100 and 250 mcg/mL.

Effects of omadacycline on Guinea pig Langendorff preparations were examined in **Study no. 1016**. No delays in ventricular repolarization, alteration of ventricular or atrio-ventricular conductivity, or alterations in inotropy or lusiotropy were reported.

An electrophysiology study in rabbit sinoatrial node preparations (**Study no. 1170195**) has not been previously reviewed. The study report indicates that omadacycline had no significant stimulatory or inhibitory effects on action potential parameters at concentrations up to 0.422 mM (235 mcg/mL). However, at concentrations of 8-390 mcM, effects consistent with omadacycline's inhibition of M_2 receptors were seen.

Cardiovascular and Respiratory effects

Two in vivo monkey studies investigated effects of omadacycline after IV infusion. In conscious cynolmogus monkeys (**Study no.** (b) (4) **N104421**), mild transient increases in heart rate and arterial blood pressure were seen in all treated animals (5, 20, and 40 mg/kg). No effects on ECG, or on respiratory rate, tidal volume, or minute volume were reported. In anesthetized cynomolgus monkeys (**Study no. DDCD1071**), no toxicologically significant effects of omadacycline (30 or 90 mg/kg) on arterial blood pressure, heart rate, ECG, respiratory rate, tidal volume, or minute volume were reported.

Central Nervous System effects

Study no. T 5073672 evaluated the effect of intravenously administered omadacycline on seizure threshold of pentylenetetrazol-induced seizures in rats. No effect was seen at the lowest dose, 10 mg/kg, while a small but statistically significant anti-convulsive effect was seen at 25 and 50 mg/kg.

Study no. (b) (4) **22126** examined the effect of intravenously administered doses of 8.9, 22.4, and 44.7 mg/kg omadacycline on a modified Irwin screen in rats. No toxicologically significant effects were reported.

Renal effects

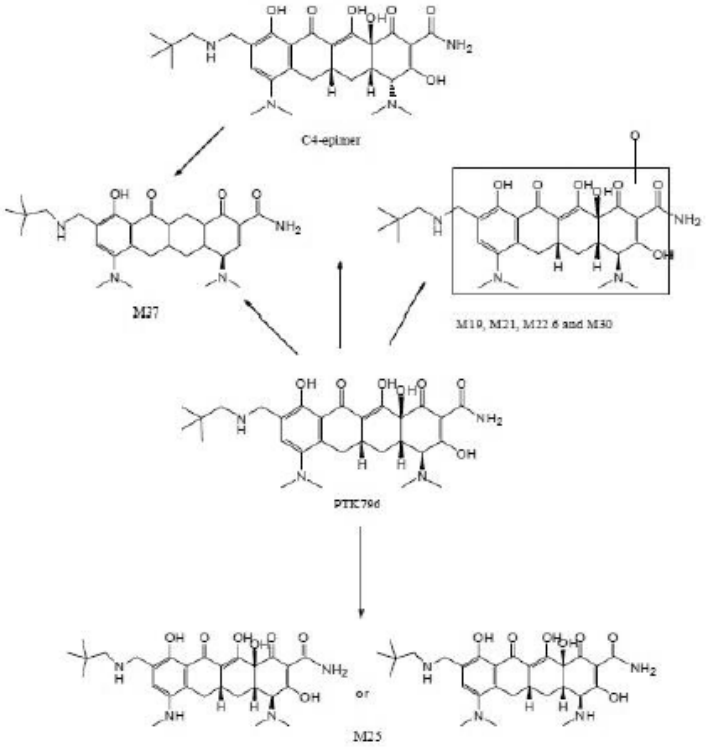
Renal function in rats administered IV doses of8.9, 22.4, or 44.7 mg/kg omadacycline was evaluated in **Study no.** (b) (4) **22235**. No effects of omadacycline in the first 24 hours post-dose were reported on urine volume, electrolyte or creatinine concentrations, NAG, or osmolality values.

5.2. ADME/PK

Type of Study	Major Findings
Absorption	
	Study no. 1000137A compared PK of a single IV dose of 5 mg/kg (base-equivalent) to that of a single oral dose of 90 mg/kg (base-equivalent) in rats: Following a 5 mg/kg IV dose of [^{14}C]omadacycline: • At 5 min, mean total radioactivity concentrations in blood was 4110 ngEq/mL (3170 ngEq/mL in plasma), followed by a rapid decline to ~18% at 4 hours and ~3% at 24 hours. The decline in plasma concentrations was similar, but, blood radioactivity concentrations declined more slowly at later time points. • Terminal elimination half-life was ~118 hours in blood and ~119 hours in plasma • PK analysis of omadacycline plasma concentration-time data resulted in a CL value of 1200 mL/h/kg with a Vss of 6.89 L/kg and a 4.6 hour half-life Following a 90 mg/kg PO dose of [14C]omadacycline: • The radioactivity Cmax (172 ngEq/mL) was attained between 0.25 and 2 hours. Mean Cmax of unchanged compound (47.5 ng/mL) was reached 0.5 hours post PO dose. • The rate of absorption was rapid and extent of absorption was estimated to be 2.93% based on PO to IV ratio of dose-normalized AUCt of radioactivity in plasma. The absolute bioavailability (unchanged drug) was estimated to be 0.23%. **Study no. PH-34172** examined the plasma pharmacokinetics of a single IV dose (30 minute infusion) of 2.58 or 9.03 mg/kg omadacycline in cynomolgus monkeys: • After single IV infusion (duration: 30 min) of 2.58 and 9.03 mg/kg omadacycline to fasted male cynomolgus monkeys, mean AUC∞ values for unchanged compound were 9.18 and 30.5 mg·h/L, respectively. • At the end of IV infusion, mean Cmax values were 1.86 and 6.86 mg/L. • The mean (of the 2 doses) CL was 0.289 L/h/kg and mean Vss was 5.65 L/kg. • The terminal plasma elimination t½ values were 20.7 hours (2.58 mg/kg) and 13.5 hours (9.03 mg/kg). **Study no. R1000204** examined the pharmacokinetics following a single oral dose of 5 mg/kg omadacycline in cynomolgus monkeys:

Type of Study	Major Findings
	• Following a single 5 mg/kg PO dose of omadacycline to monkeys, the mean (±SD) Cmax was 113 ± 42 ng/mL, occurring at 3 h (tmax), and AUC∞ was 1460 ± 624 (ng*h/mL). In **Study no. 07-3735-G2**, comparison of single 10 mg/kg nasogastric doses of omadacycline HCl and omadacycline tosylate demonstrated similar PK parameters between male and female monkeys and no significant exposure differences between the two salts administered. **Study no. R1000159** compared pharmacokinetic parameters following single oral 90 mg/kg doses in rats under fed and fasting conditions. Exposure in fed animals was approximately twice that in fasted animals, but due to the small number of animals and the high degree of variability, no definitive conclusions could be drawn.
Distribution	
	Study no. R1000512: Plasma protein binding was low in vitro, independent of concentration (10-10000 ng/mL), with no major species differences observed. Mean free unbound values in plasma were: rat (73.9 ± 12.1%) ≤ monkey (78.8 ± 7.26%) ≈ human (78.7 ± 9.72%) ≤ mouse (84.7 ± 5.31%). QWBA studies in Long-Evans (pigmented) rats (**Study no. 1000137b** and **Study no. PH-33888**): Following a single PO 90 mg/kg dose of [^{14}C] omadacycline to pigmented rats, radioactivity in blood and tissues was low, presumably due to poor absorption. • Peak tissue concentrations were observed at 1-7 h post dose in tissues which showed measurable radioactivity. Concentrations in tissues were higher than in blood, except in brain, spinal cord and eye. At 24 h post dose, the radioactivity in blood and most tissues were all below the LLOQ, but substantial radioactivity remained in bone mineral. • The highest tissue-to-blood (t/b) ratios calculated using AUC values (t/b > 5) were reported in bone mineral, harderian gland, liver, spleen and salivary gland. • Lower radioactivity (t/b of 1-5) was observed in bone marrow, kidney (cortex, pelvis and medulla), thymus, heart, adrenal cortex, lung, thyroid gland and pancreas. After a 5 mg/kg IV dose in pigmented rats, drug-related radioactivity widely and rapidly distributed into most tissues. • The radioactivity concentration in most tissues was higher than

Type of Study	Major Findings
	blood within 24 hours post dose. At 0.083 hours post-dose, the radioactivity concentration in bile was 100 times that of blood but was not measurable at 24 hours. The highest t/b was observed in bone mineral, thyroid gland and Harderian gland at 24 hours post-dose. Brain, spinal cord, eye, white fat, brown fat and seminal vesicles showed the lowest t/b at both 5 minutes (t/b<1) and 24 hours (t/b<3) post-dose. • While in orally dosed pigmented rats, radioactivity was not measureable in the uveal tract, after an IV dose, the uveal tract t/b value was ~ 5 at 5 minutes, and radioactivity was not measurable at 24 hours. This supports a lack of binding of omadacycline to melanin in uveal tract. • Drug-related radioactivity distribution was low to the central nervous system (brain and spinal cord) and moderate to the testis. Qualitative WBA in Wistar (albino) rats was performed after administration of a single 3 mg/kg IV dose (over 30 minutes). • Two hours after IV infusion, most organs and tissues, as well as blood, showed moderate to low radioactivity concentrations. Radioactivity was homogenously distributed to almost all organs and tissues, but no penetration across the blood/brain barrier was noted in the observation interval. In some organs, heterogeneous distribution patterns were detected, e.g., in liver, kidneys (papilla > cortex, outer and inner medulla), mucosa of the gastrointestinal tract, testes, epididymides, coagulation gland, spleen, adrenals, bone and skin. • Twenty-four hours after IV infusion, the highest radioactivity was located in intestinal contents, with moderate concentrations in compact bone, coagulation gland, Cowperian gland, mucous glands of the tongue, incisors and pharyngeal mucosa. In most organs and tissues, including blood, residual radioactivity was low. • After two days, moderate radioactivity persisted in compact bone, Cowperian gland, coagulation gland, and intestinal contents. Low residual radioactivity was detectable in bone marrow, thyroid, incisors, nasopharyngeal mucosa and mucous glands of the tongue, preputial gland, prostate, testes, epididymides, and skin. All other organs and tissues were below the autoradiographic detection limit.
Metabolism	
	• Primarily eliminated unchanged by renal, fecal, and biliary routes

Type of Study	Major Findings
	in rats and monkeys • No metabolism in vitro in rat, dog, monkey, or human microsomes (**Study no. R1000343**) or hepatocytes (**Study no. 1100197**) • Minimal in vivo metabolism; predominantly omadacycline and its C4-epimer in plasma in rats (**Study no. 1000137A**) o Proposed metabolic scheme: **Figure 1: Proposed metabolic scheme for omadacycline based on analysis of plasma, urine, and feces samples in rats dosed IV with [^{14}C]omadacycline**  o The predominant circulating component in plasma after IV or oral dosing was unchanged omadacycline and its C4-epimer. o The major fecal metabolite in the rats was M25 (15.7% of IV dose, not detected PO), a desmethyl derivative, followed by M37 (1.7% of IV dose, 7% of PO dose). o After IV administration, less than 1% of the dose was recovered in urine as M25, M30 and M37. • In rats, metabolites (M19, M21, M22.6, M25) collectively accounted for 1.3% of the dose in bile and 2% of the dose in urine

Type of Study	Major Findings
	(**Study no. R1000163**). • In monkeys, omadacycline was the primary compound found in plasma with a few minor metabolites detected (**Study no. PH-34172**). • Omadacycline was not a substrate for the major CYP isoforms, UGT1A1, or Flavin monooxygenase (FMO) enzymes (**Study no. 1100197**).
Excretion	
	• After IV administration to rats, the majority (approximately 80%) of the dose was recovered in bile and feces, with more than half of that being in bile, and the remainder in urine (approximately 30%). After oral administration to rats, most (approximately 120%) of the radioactivity was recovered in the feces (**Study no. 1000137A**). • In bile duct-cannulated rats (**Study no. R1000163**), excretion of the radioactive dose was complete by 48 hours post-dose. Approximately 30%, 42%, and 35% of the radioactive dose was recovered in bile, urine, and feces, respectively. • After IV administration to monkeys (**Study no. PH-33788**), approximately 36% of the dose was recovered in urine and 30% recovered in feces.
TK data from general toxicology studies *Include study type and number; e.g. one-month and 3-month toxicology studies in rats;*	<u>Rat</u> **Study no. 70668 -** 13-week IV toxicology study in rats *T1/2*: 2.28-9.44 hours *Accumulation*: There was no sign of accumulation over time. *Dose-proportionality*: On Days 1 and 91, exposure ($AUC_{0\text{-}24\ hr}$) increased in a dose-related and slightly more than dose-proportional manner

Type of Study	Major Findings

Group Number	Dose Level (mg/kg/day)	Gender of Animals	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)	CL (L/hr/kg)	$V_{d,ss}$ (L/kg)
Day 1								
2	5	Female	2.28	0.12	3.55	4.93	1.11	2.81
		Male	3.47	0.12	2.86	8.41	0.655	2.83
3	15	Female	3.71	0.12	7.67	14.0	1.07	4.22
		Male	4.07	0.12	9.81	17.1	0.868	3.60
4	45	Female	3.14	0.12	31.2	82.9	0.54	1.87
		Male	5.52	0.12	54.1	75.9	0.574	2.77
Day 91								
2	5	Female	2.79	0.28	1.39	3.74	1.13	4.01
		Male	5.19	0.12	3.76	8.61	0.56	3.19
3	15	Female	6.26	0.12	7.91	13.8	1.02	6.44
		Male	4.71	0.12	13.6	25.8	0.567	3.32
4	45	Female	6.58	0.12	39.0	54.4	0.782	4.65
		Male	9.44	0.28	51.3	89.2	0.442	4.24

Study no. 0970656 - 13-week oral toxicology study in rats
T1/2: not provided
Accumulation: There did not appear to be significant accumulation.
Dose-proportionality: Exposure increased in an approximately dose-proportional manner

Dose (mg/kg/day)	Study Day	Gender	AUC0-24h±SE (ng*h/mL)	AUC0-24h±SE/Dose (ng*h/mL)/ (mg/kg/day)	Cmax (ng/mL)	Cmax/Dose (ng/mL)/ (mg/kg/day)	Tmax (h)
100	1	Male	1740±217	17.4±2.17	261	2.61	0.5
		Female	1680±150	16.8±1.50	277	2.77	0.5
	9	Male	3310±524	33.1±5.24	581	5.81	1.0
		Female	2380±364	23.8±3.64	484	4.84	1.0
	76	Male	1750±NC	17.5±NC	266	2.66	0.5
		Female	1460±134	14.6±1.34	297	2.97	0.5
300	1	Male	8320±797	27.7±2.66	1040	3.47	1.0
		Female	5280±760	17.6±2.53	751	2.50	0.5
	9	Male	6780±797	22.6±2.66	853	2.84	0.5
		Female	6910±1290	23.0±4.30	3000	10.0	0.5
	76	Male	7100±424	23.7±1.41	1330	4.43	0.5
		Female	5790±440	19.3±1.47	1090	3.63	1.0
750	1	Male	39100±12200	52.1±16.3	23900	31.9	0.5
		Female	14600±1770	19.5±2.36	2130	2.84	0.5
	9	Male	23200±NC	30.9±NC	2440	3.25	1.0
		Female	10400±953	13.9±1.27	2330	3.11	0.5
	76	Male	16400±NC	21.9±NC	3270	4.36	1.0
		Female	30100±NC	40.1±NC	2470	3.29	1.0

NC:Not Calculable

Type of Study	Major Findings
	Monkey **Study no. 30205 -** 13-week IV toxicology study in cynomolgus monkeys *T1/2*: 9.51-12.85 hr on Day 1, increased with dose and on Day 91 *Accumulation*: Slight accumulation at all doses (5, 15, 30 mg/kg/day) *Dose-proportionality*: $AUC_{0\text{-}24\ hr}$ increased approximately proportional to dose, but Cmax values increased in a greater than dose-proportional manner

Group Number	Dose Level (mg/kg/day)	Gender of Animals	$t_{1/2}$ (h)	C_{max} (µg/mL)	T_{max} (h)	CL (L/h/kg)	$V_{d,ss}$ (L/kg)	$AUC_{0\text{-}24h}$ (µg·h/mL)
Day 1								
2	5	Male	9.51	4.09	0.12	0.35	4.22	12.27
		Female	10.86	5.12	0.12	0.33	4.32	12.70
3	15	Male	11.53	14.68	0.12	0.33	4.85	36.87
		Female	10.02	16.40	0.12	0.34	4.19	36.77
4	30	Male	12.85	59.22	0.18	0.25	3.62	95.40
		Female	12.66	44.08	0.18	0.28	4.31	81.50
Day 91								
2	5	Male	14.34	4.72	0.17	0.19	3.49	19.03
		Female	9.13	4.34	0.12	0.33	4.20	13.12
3	15	Male	10.71	16.50	0.17	0.31	4.07	41.17
		Female	14.12	21.47	0.12	0.25	4.40	46.97
4	30	Male	22.10	51.73	0.12	0.19	4.85	98.15
		Female	16.35	58.76	0.15	0.18	3.42	124.44

Study no. 0970655 - 13-week oral toxicology study in cynomolgus monkeys
T1/2: not provided
Accumulation: Exposure was considered to be similar on Day 1 and on later sampling days, however, inter-animal variability was high and may have masked any accumulation effect.
Dose-proportionality: Exposure was approximately dose-proportional between 50 and 200 mg/kg/day but was less than dose-proportional between 200 and 600 mg/kg/day.

Type of Study	Major Findings

Dose (mg/kg/day)	Study Day	Gender	AUC0-24h (ng*h/mL)		AUC0-24h/Dose (ng*h/mL)/(mg/kg/day)		Cmax (ng/mL)		Cmax/Dose (ng/mL)/(mg/kg/day)		Tmax (h)		n
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
50	1	Male	6270	3800	126	76.5	514	391	10.3	7.79	3.0	0.0	3
		Female	9650	1780	193	35.1	816	187	16.3	3.73	3.0	0.0	3
	8	Male	14800	7570	296	152	961	360	19.2	7.18	4.3	2.3	3
		Female	12200	1650	244	32.1	842	92.9	16.9	1.87	3.0	0.0	3
	22	Male	10800	6140	217	123	714	380	14.3	7.59	3.0	0.0	3
		Female	14900	4920	297	97.8	989	319	19.8	6.36	3.0	0.0	3
	71	Male	13600	4220	271	84.1	1350	701	27.0	14.0	2.3	1.2	3
		Female	14900	3580	298	70.5	1040	295	20.9	5.90	3.0	0.0	3
200	1	Male	30500	13200	153	66.0	1800	645	9.00	3.23	4.3	2.3	3
		Female	31500	10800	158	53.8	2060	748	10.3	3.75	5.7	2.3	3
	8	Male	57700	21300	288	107	3740	1520	18.7	7.58	4.3	2.3	3
		Female	41600	12700	208	63.8	2130	528	10.7	2.64	4.3	2.3	3
	22	Male	64400	27800	322	139	3610	1750	18.1	8.77	4.3	2.3	3
		Female	38600	4950	193	24.5	2360	313	11.8	1.56	5.7	2.3	3
	71	Male	56800	16900	284	84.2	3380	978	16.9	4.89	5.7	2.3	3
		Female	54100	22200	271	111	3250	1240	16.3	6.19	5.7	2.3	3
600	1	Male	128000	228000	214	379	22900	44800	38.2	74.8	2.4	2.8	5
		Female	46500	26100	77.4	43.3	10200	10000	17.1	16.8	1.5	1.4	5
	8	Male	123000	90400	205	151	6630	4120	11.1	6.86	4.6	2.2	5
		Female	66700	29300	111	48.9	4350	1440	7.24	2.39	2.5	2.7	5
	22	Male	62600	20100	104	33.4	3740	731	6.23	1.22	3.0	0.0	4
		Female	62100	18000	103	29.9	4630	2040	7.71	3.41	2.5	1.1	5
	71	Male	109000	49900	182	83.4	6380	3420	10.6	5.71	7.0	0.0	4
		Female	81500	16900	136	28.3	4990	1630	8.31	2.72	4.5	3.0	4

There were no significant gender differences in either species.

TK data from reproductive toxicology studies

Rat

AUC: 17.10 mcg*hr/mL on Day 1 and 16.04 mcg*hr/mL on Day 14 in males in a separate study ($AUC_{0\text{-}inf}$; **Study no. 22206**, 14-day IV toxicology study) at the 20 mg/kg/day dose that was the male NOAEL in the rat fertility study, but did show reduced sperm counts and motility

AUC: 13.81 mcg*hr/mL on Day 1 and 12.71 mcg*hr/mL on Day 14 in non-pregnant females in a separate study ($AUC_{0\text{-}inf}$; **Study no. 22206**) at the 20 mg/kg/day dose that was the female NOAEL for fertility, but did show significantly lower numbers of corpora lutea, implantation sites, and average number of viable embryos

AUC: 6.80 mcg*hr/mL on Day 1 and 5.77 mcg*hr/mL on Day 14 in non-pregnant females in a separate study ($AUC_{0\text{-}inf}$; **Study no. 22206**) at the 10 mg/kg/day dose that was associated with delayed ossification in the rat embryo-fetal development study (no fetal NOAEL was demonstrated) *Reviewer's comment: This study was not performed using the tosylate salt of omadacycline and was not performed in pregnant females, which could demonstrate different pharmacokinetics.*

Rabbit

AUC: 14.1 mcg*hr/mL on Gestation Day (GD) 7 and 14.8 mcg*hr/mL on GD 19 at 5 mg/kg/day (the fetal NOAEL, although there were 2 litters at that dose with one fetus each that had vertebral alterations)

5.3. Toxicology

5.3.1. General Toxicology

General toxicology studies were reviewed under INDs 73431 and IND 75928. Thirteen-week studies are summarized here, and shorter-term toxicology studies and are summarized below under "General toxicology; additional studies." The test article in the four 13-week studies was the tosylate salt of omadacycline.

Study no. 70668: PTK 0796 Tosylate: A 13-Week Intravenous Infusion Toxicity Study Followed by a 4-Week Recovery Period in Wistar Rats

(Reviewed by Dr. Kelly Brant)

PTK 0796 Tosylate was administered by intravenous infusion (over a 15-min period) daily for 13-consecutive weeks with a 4-week recovery period to Wistar rats (10 rats/sex/group Main Study Group; 5 rats/sex/group Recovery Group) at doses of 0 (vehicle), 5, 15, and 45 mg/kg/day. No treatment-related changes in body weight, feed consumption, ocular findings, or urinary parameters were reported. Administration of PTK 0796 Tosylate at a dose level of 5 mg/kg/day was well tolerated and did not result in any noteworthy findings. Administration of PTK 0796 Tosylate at doses of 15 and/or 45 mg/kg/day produced clinical signs (salivation and yellow/brown discoloration of teeth), changes in hematology, clinical chemistry and organ weights. The majority of these changes were dose-related and correlated with microscopic findings consisting of atrophy of the seminiferous tubular epithelium in the testes; oligospermia/aspermia in the epididymides (at 45 mg/kg/day); deposition of iron-containing brown pigment in the liver and kidneys consistent with increased erythrocyte turnover; and non-iron containing brown pigment consistent with a possible metabolite of PTK 0796 in the proximal tubular epithelium of the kidney, follicular epithelium and lumen of the thyroid gland, and macrophages in the thymus and lymph nodes and Kupffer cells of the liver. Increased hematopoiesis in the spleen and bone marrow hypercellularity (at 15 and/or 45 mg/kg/day) were considered to be compensatory to increased erythrocyte turnover. All changes, except for those observed in the testes, were either completely or partially reversible at the end of the 4-week recovery period.

No sex-related differences in TK parameters were noted following administration of PTK 0796 at any of the dose levels. Following the 1st dose, C_{max} for PTK 0796 was reached approximately 7 minutes post-start of the 15-minute infusion with values ranging from 2.86 to 54.1 mcg/mL for males and from 3.55 to 31.2 mcg/mL for females, with $AUC_{0\text{-}24h}$ ranging between 8.41 to 75.9 mcg·h/mL (males) and 4.93 to 82.9 mcg·h/mL (females). Over the entire dose range, exposure ($AUC_{0\text{-}24h}$ and C_{max}) to PTK 0796 generally increased in a dose-related and slightly more than dose-proportional manner following the 1st and 91st doses. There were no indications of PTK 0796 Tosylate accumulation from Day 1 to Day 91.

Based on the parameters evaluated in this study, the No-Observed-Adverse-Effect Level (NOAEL) of PTK 0796 Tosylate administered to rats for 13-weeks was considered to be 5 mg/kg/day. At that dose, AUC was 4.93 mcg*hr/mL in females and 8.41 mcg*hr/mL in males on Day 1 and 3.74 mcg*hr/mL in females and 8.61 mcg*hr/mL in males on Day 91.

Study no. 0970656: 13-week oral (gavage) toxicity study in rats with a 4-week recovery period

This study was conducted to evaluate general toxicity and potential for effects on male fertility. Ten animals/sex/dose were administered oral doses of 100, 300, or 750 mg/kg/day PTK796. Five males and two females in the high dose group were found dead or euthanized in moribund condition; the causes of death in these animals were undetermined. Decreases in body weight and food consumption were apparent in a dose-related manner, but only appeared significant at the high dose. Clinical signs included rales at all doses and decreased activity, piloerection, and hunched posture at the high dose; at the end of the recovery period, rales persisted in one high dose animal. Clinical pathology findings included increased reticulocytes at the mid- and high doses, neutrophilia at the high dose, and increases in serum transaminases and bilirubin at the high dose. No pathology findings were associated with deaths in the early decedents. At the end of treatment, pathology findings were limited to discoloration and microscopic follicular pigment in the thyroid glands of mid- and high dose males and females that persisted at the end of the recovery period.

A statistically significant and reversible decrease observed in sperm % motility in high dose males relative to controls but was not correlated to any histological findings.

The no-observable-adverse-effect-level (NOAEL) was concluded to be 300 mg/kg/day for PTK796 in rats in view of the mortality, clinical pathology changes, thyroid gland effects, and effects on the male reproductive system observed at 750 mg/kg/day. At the 300 mg/kg/day dose, AUC was 8.32 mcg*hr/mL in males and 5.28 mcg*hr/mL in females on Day 1, 6.78 mcg*hr/mL in males and 6.91 mcg*hr/mL in females on Day 9, and 7.10 mcg*hr/mL in males and 5.79 mcg*hr/mL in females on Day 76.

Study no. 30205: PTK0796 Tosylate: A 13-week intravenous infusion toxicity study followed by a 4-week recovery period in cynomolgus monkeys

Doses of vehicle, 5, 15, or 30 mg/kg/day PTK 0796 tosylate were administered by 15-minute intravenous infusion to cynomolgus monkeys (3/sex) once daily for 13 consecutive weeks. An additional 2/sex in the control and high dose groups underwent a 4-week recovery period.

The dose levels of 5 and 15 mg/kg/day appeared to be well tolerated. Findings at those doses included increased incidence of loose stool (as compared to controls) and the presence of brown pigment and/or Perls' stain negative material in various tissues (possibly representing degradation products of PTK 0796 tosylate) and/or Perls' stain positive material in the spleen (suggesting the presence of hemosiderin, most likely from the breakdown of erythrocytes).

The high dose, 30 mg/kg/day, resulted in increased incidence of loose stool, pallor, dehydration, hypothermia, and decreased appetite, decreased body weight or body weight gain, changes in hematology (decreases in red blood cell parameters with increased MCV, MCH, and reticulocyte counts, likely indicative of regenerative hemolytic anemia), minimal to moderate vacuolar degeneration of the cardiomyocytes and the renal tubular epithelium, as well as the presence of brown pigment and/or Perls' stain negative material (possibly representing degradation products of PTK 0796 tosylate) in various tissues and/or Perls' stain positive material (suggesting the presence of hemosiderin, most likely from the breakdown of erythrocytes) in the liver and spleen.

By end of the 4-week recovery period, most changes (including HCT, MCV and MCH values, and reticulocyte counts) in the 30 mg/kg/day animals were reversed. However, the brown pigment and/or Perls' stain negative material persisted in the 30 mg/kg/animals.

The No Observed Adverse Effect Level (NOAEL) was considered to be 5 mg/kg/day PTK 0796 tosylate, although findings at 15 mg/kg/day appeared to be limited to the significant presence of test article-related pigment in tissues. The NOAEL dose was associated with mean $AUC_{0\text{-}24h}$ values of 12.27-12.70 mcg*hr/mL on Day 1 and 13.12-19.03 mcg*hr/mL on Day 92.

Study no. 0970655: 13-week oral (gavage) toxicity study in monkeys with a 4-week recovery period

Groups of 3 monkeys per sex were administered vehicle, 50, 200, or 600 mg/kg/day PTK796 by oral gavage. An additional 2 per sex in the vehicle and high dose groups underwent a 4-week recovery period.

Two high dose animals were euthanized in extremis on Day 22 (male) and on Day 69 (female). Myocardial vacuolar degeneration considered to have probably contributed to the demise of these animals. Transmission electron microscopy of the female's heart confirmed vacuolar degeneration and mitochondria with ultrastructural changes and the presence of autophagic vacuoles.

In study animals that survived until termination, clinical signs at all doses were primarily related to the gastrointestinal system (diarrhea/soft feces, discolored feces, emesis). Abdominal distension was noted at the mid- (one female) and high doses (all animals) and reversed during the recovery period. Body weight and food consumption were decreased at the high dose but were not seen in recovery animals. Increased heart rate was seen at the mid- and high doses; this was considered to be due to stress, but test article contribution could not be ruled out. Clinical pathology changes were seen at the high dose, consisting of findings indicative of inflammatory changes (increased neutrophils, fibrinogen), increased reticulocyte count, hepatocellular leakage (increased AST and/or ALT; also increased ALP and bilirubin in the male early decedent), electrolyte changes resulting from vomiting (decreased sodium and chloride),

and findings related to altered renal function in the female early decedent (increased BUN, creatinine, phosphorus and magnesium).

Post-mortem findings included pigment accumulation in macrophages or parenchymal cells in widespread tissues at the mid- and/or high doses. Minimal pigment was also seen in liver, pituitary gland, lymph nodes and spleen at the low dose. After a 4-week recovery period, pigment accumulation persisted at the same levels in heart, liver, thyroid and testes. Decreased pigment levels were observed in other tissues. Lymphoid depletion in the thymus was observed at the mid- and high doses but was not seen after the recovery period.

The NOAEL was considered to be the mid-dose, 200 mg/kg/day (mean $AUC_{0\text{-}24h}$ = 56800 (male) or 54100 (female) ng*hr/mL on Day 71).

General toxicology; additional studies

Toxicology studies submitted to and reviewed under the original IND 75928 were conducted using the omadacycline free base or HCl salt. These included:

- single dose studies of the HCl salt in the mouse and the rat, both by IV bolus ((b) (4) **Reports #21954 and #21953**, respectively) and by IV infusion ((b) (4) **Reports #22870 and #22871**, respectively)
- a 7-day IV dose range-finding (DRF) toxicology study of the HCl salt in the rat ((b) (4) **Report Number 21879**, non-GLP)
- a 7-day IV maximum tolerated dose (MTD) toxicology study of the HCl salt in cynomolgus monkeys ((b) (4) **Report Number 21982**, non-GLP)
- a GLP-compliant 14-day IV toxicology study of the HCl salt in the rat ((b) (4) **Report Number 22206**)
- a GLP-compliant 14-day IV toxicology study of the HCl salt in cynomolgus monkeys ((b) (4) **Report Number 22193**)
- a GLP-compliant 4-week IV toxicology study of the HCl salt in rats (**Study no. 1116-004**)
- a GLP-compliant 4-week IV toxicology study of the HCl salt in cynomolgus monkeys (**Study no. 1116-007**)
- a GLP-compliant oral dose range-finding toxicology study of the HCl salt in rats (**Study no. 1116-009**; single dose followed by 7 days repeated dosing)
- a GLP-compliant oral dose range-finding toxicology study of the HCl salt in cynomolgus monkeys (**Study no. 1116-010**; single dose followed by 7 days repeated dosing)
- a 15-day GLP-compliant oral toxicology study of the free base in rats (**Study no. TT #06-0024**)
- a 15-day GLP-compliant oral toxicology study of the free base in rhesus monkeys (**Study no. TT #06-1046**
- a 37-day GLP-compliant IV toxicology study in rats (**Report no. PH-33758, Study no. T2073877**)

The following table from the review of the original submission of IND 75928 summarizes most of these studies:

Toxicology parameters for PTK0796				
Species	Duration	NOAEL (mg/kg)	LLD (mg/kg)	HED of NOAEL (mg/kg)
Intravenous				
Mouse (CD-1)	1X, bolus	<26.8	62.5	2.2
	1X, 15 min	50	100	4.0
Rat (SD)	1X, bolus	<26.8	62.5	4.3
	1X, 15 min	25	>100	4.0
	DX7, 15 min	20	>50	3.2
	DX14, 15 min	20	>40	3.2
Rat (Wistar)	DX28, 15 min	15	45	2.4
Monkey (Cynomolgus)	DX7, 15 min	??50	>50	16.2
	DX15, 15 min	40	>40	13.0
	DX28, 15 min	15	45	4.9
ORAL				
Rat (SD)	DX7, gavage	800	>800	130
Monkey	DX7, gavage	<25	>400	8

The reviewers of the original IND submission (Drs. Wendy Schmidt and Theresa Allio) noted that the primary organs of toxicity were those of the hematopoietic system (anemia in the rat), liver (increased transaminases, increased total bilirubin, minimal to mild histopathologic changes indicative of bile stasis), and gastrointestinal tract (diarrhea in the monkey), and that effects typical of minocycline (omadacyline is a derivative of minocycline) also were observed after treatment with omadacycline (discoloration of the thyroid, bone, spleen, liver and lung;, and testicular degenerative effects). The monkey showed soft/mucoid feces at all dose levels. The reviewers noted that the dose-response by the intravenous route (especially in the 28-day monkey study) suggests a rather steep lethality curve: no toxicity at 15 mg/kg with 50% mortality at 45 mg/kg, and no clear-cut cause of death. Another concern of the original reviewers was that the numbers of animals tested (5 rats/group, 3 monkeys/group) were barely adequate to make a determination of toxicity.

A 2-week IV toxicology study of omadacycline in rats, reviewed under IND 75928 by Dr. Theresa Allio, compared effects and toxicokinetics in animals administered the HCl salt to those in animals administered the tosylate salt.

ITR Study Number 70388: PTK 0796 HCl and PTK 0796 Tosylate: A 14-Day Intravenous Infusion Toxicity Study in Wistar Rats

This study was performed in order to compare the safety and toxicokinetics profile of PTK0796 Tosylate and PTK0796 HCl salts. Doses of 0, 5, 15, 45, mg/kg/day were administered by IV infusion for 14 days to 10 Wistar rats/sex/dose group in 0.9% NaCl for injection as 10 ml/kg infused over 15 minutes, with satellite toxicokinetics animals.

Findings were similar between the two salts, consisting of:

- increased reticulocytes on Day 15 at 15 and 45 mg/kg/day for both test articles
- increased total bilirubin on Day 15 at 45 mg/kg/day for both test articles
- pale material at the infusion sites at all doses of PTK0796 Tosylate and at the high dose of PTK0796 HCl
- dark discoloration of the thyroid at 15 and 45 mg/kg/day PTK0796 Tosylate and at 45 mg/kg/day PTK0796 HCl (previously noted to be consistent with effects of minocycline)

Toxicokinetics (Day 1 and 14): Tmax was 0.117 h for nearly all doses for both test articles, only females treated with 45 mg/kg/day tosylate salt showed a different value (0.750 h). Cmax and AUC increased in a dose dependent manner without significant accumulation seen with multiple dosing with either compound. Exposures were not significantly different between males and females. The table below summarized concentrations measured for each of the two test articles:

Dose group	Nominal time	Reported concentration ng/ml (observed range)	
		PTK 0796 Tosylate	PTK 0796 HCL
5 mg/kg	2h post dose day 1	394-677	NA
	8h post dose day 1	88.8-152	NA
	24h post dose day 1	< LLQ	NA
	2 h post dose day 14	470 – 729	NA
	8h post dose day 14	107 - 173	NA
	24h post dose day 14	<LLQ	NA
15 mg/kg	2h post dose day 1	1370 - 1850	NA
	8h post dose day 1	287 - 677	NA
	24h post dose day 1	< LLQ – 81.0	NA
	2h post dose day 14	1390 - 1830	NA
	8h post dose day 14	218 – 670	NA
	24h post dose day 14	21.6 – 68.5	NA
45 mg/kg	2h post dose day 1	3850 - 5110	4060 - 5310
	8h post dose day 1	994 - 1350	1130 - 1990
	24h post dose day 1	78.0 - 378	<LLQ - 225
	2 h post dose day 14	291 - 4200	1080 - 6760
	8h post dose day 14	949 - 1960	1150 - 2450
	24h post dose day 14	< LLQ - 534	< LLQ - 238

The safety and pharmacokinetic profiles for the two PTK0796 salts were considered to be similar. The reviewer concluded that the NOAEL was the mid-dose, 15 mg/kg/day.

Other studies described in the application as using the tosylate salt of omadacycline as the test article included:

- a single dose IV infusion (15 minutes) toxicity study in the Wistar rat
- a non-GLP 4-day dose escalation oral toxicology study (“sighting cycle”) in cynomolgus monkeys (**Study no. 1070481**)
- a 2-week non-GLP oral toxicology study in rats (**Study no. 1070326**); the test article is not specified in the report as being the tosylate salt
- a 2-week non-GLP oral toxicology DRF study in cynomolgus monkeys (**Study no. 1070051**); the test article is not specified in the report as being the tosylate salt

These do not appear to have been previously reviewed other than as summaries submitted to an annual report.

Study no. 1070326: 2-week oral (gavage) dose range-finding toxicity study in rats

Five IGS Wistar Hannover rats/sex/dose group were administered doses of 0, 100, 300, or 1000 mg/kg/day once daily for 15 days by oral gavage. At 1000 mg/kg/day, PTK796 was associated with piloerection (4/5 animals), rales (2/5 animals), and feces with apparent compound (5/5 animals) in females. High dose males and females had an increase in absolute reticulocyte counts, suggesting accelerated turnover or shortened life span of red blood cells (RBCs). Increased neutrophil and/or platelet counts and increased globulin suggestive of inflammation were seen in males at ≥ 300 mg/kg/day. Increases in AST and/or ALT at the mid- (females only) and high doses were suggestive of hepatocellular leakage. Of the clinical chemistry findings reported, only the ALT increases in high dose animals were statistically significant. Adrenal weights were increased in high dose males, correlating with the microscopic finding of cortical hypertrophy (in 4/5 high dose males). The cecum was distended with feces in most animals at the high dose. Focal ulceration and/or hyperplasia of the non-glandular mucosa in the stomach were reported in 3 of 5 high dose males. The mid-dose, 300 mg/kg/day, was considered to be the NOAEL.

After single and multiple doses of PTK796, the plasma exposure appeared to increase in a less than dose-proportional manner between 100 and 300 mg/kg/day on both Days 1 and 14 and in a more than dose-proportional manner between 300 and 1000 mg/kg/day on Day 1. There was no evidence of accumulation at 100 and 300 mg/kg/day for up to 14 days. However, after multiple doses at 1000 mg/kg/day, the plasma exposure was decreased on Day 14 relative to that observed on Day 1. Toxicokinetic parameters for this study are shown below:

Dose	Study Day	Gender	AUC0-24	AUC0-24/dose	Cmax	Cmax/Dose	Tmax
100	1	Male	2100	21.0	244	2.44	1.00
		Female	1800	18.0	241	2.41	0.500
	14	Male	1980	19.8	301	3.01	1.00
		Female	2140	21.4	276	2.76	0.500
300	1	Male	3590	12.0	405	1.35	3.00
		Female	5080	16.9	927	3.09	0.500
	14	Male	4460	14.9	473	1.58	0.500
		Female	3140	10.5	477	1.59	0.500
1000	1	Male	42500	42.5	3450	3.45	1.00
		Female	33800	33.8	2470	2.47	1.00
	14	Male	19800	19.8	1250	1.25	7.00
		Female	14000	14.0	1690	1.69	0.500

Units for each parameter: Dose = mg/kg/day, AUC0-24 = ng.h/mL, AUC0-24 /Dose = (ng.h/mL)/(mg/kg/day), Cmax = ng/mL, Cmax /Dose = (ng/mL)/(mg/kg/day), Tmax = h

Study no. 1070051: 2-week oral (gavage) dose range-finding toxicity study in monkeys

Doses in this study were 0, 10, 30, and 100 mg/kg/day. Groups consisted of one cynomolgus monkey per sex, except for the high dose group, which included 2 animals/sex. Findings were limited to soft feces or diarrhea in mid- and high dose animals. The fecal effects were manageable by supplementation with Metamucil® wafers as directed by the study veterinarian.

After a single dose of PTK796, the plasma exposure in male and female monkeys showed an approximately dose proportional increase. After repeated doses at 10 and 30 mg/kg/day, the plasma exposure was similar to that after a single dose. However, after multiple doses at 100 mg/kg/day for up to 15 days, the plasma exposure was lower than that seen after a single 100 mg/kg dose. No gender differences were noted. Toxicokinetic parameters in this study are shown below:

Dose (mg/kg/day)	Study Day	Animal #	Gender	AUC0-24 (ng*h/mL)	AUC0-24/dose (ng*h/mL) / (mg/kg/day)	Cmax (ng/mL)	Cmax/Dose (ng/mL) / (mg/kg/day)	Tmax (h)
10	1	2001	M	1240	124	85.6	8.56	3.00
		2501	F	1850	185	114	11.4	7.00
	15	2001	M	1270	127	119	11.9	1.00
		2501	F	1700	170	180	18.0	1.00
30	1	3001	M	4280	143	331	11.0	3.00
		3501	F	8710	290	605	20.2	3.00
	15	3001	M	5260	175	368	12.3	3.00
		3501	F	4280	143	331	11.0	3.00
100	1	4001	M	25600	256	1820	18.2	7.00
		4002	M	17400	174	967	9.67	7.00
		4501	F	13300	133	798	7.98	7.00
		4502	F	14600	146	890	8.90	7.00
	15	4001	M	7200	72.0	527	5.27	3.00
		4002	M	9970	99.7	781	7.81	3.00
		4501	F	6930	69.3	544	5.44	3.00
		4502	F	7840	78.4	1040	10.4	1.00

Study no. 1070481: An oral (gavage) sighting cycle dose toxicity study in male monkeys

PTK796 was administered PO as a solution in purified water. Escalating doses of 200, 600 and 1000 mg/kg/day were administered to a group of three male cynomolgus monkeys on Days 1-4, 8-11 and 22-25, respectively. Test article-related clinical signs (soft feces, diarrhea, emesis) were seen in monkeys treated at all doses tested. Over the dose range tested, exposure to PTK796 increased with dose in a less than proportional manner. Since variability was high at the high dose (1000 mg/kg/day), exposure at that dose was considered to be similar to the exposure at 600 mg/kg/day. Toxicokinetic parameters in this study are shown below:

Dose (mg/kg/day)	Study Day	AUC0-24h±SD (ng*h/mL)	AUC0-24h/Dose±SD (ng*h/mL)/(mg/kg/day)	Cmax±SD (ng/mL)	Cmax /Dose±SD (ng/mL)/(mg/kg/day)	Tmax (hour)
200	3	27000±5240	135±26.1	2550±1870	12.8±9.38	3.5
600	10	53400±5360	89.0±8.96	5490±1560	9.16±2.63	0.7
1000	24	65800±18900	65.8±18.9	7620±2990	7.62±2.99	1.7

5.3.2. Genetic Toxicology

In vitro genetic toxicology studies and the mouse micronucleus assay were reviewed under the original IND submission by Drs. Wendy Schmidt and Theresa Allio.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study number (b) (4) Report # 21784, MRL TT #025530: PTK0796: Testing for mutagenic activity with Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 and Escherichia coli WP2uvrA

Key Study Findings:

- PTK0796 was toxic to the bacterial lawn at concentration as low as 5ug/plate, this assay was not suitable for investigation of genotoxicity potential.

GLP compliance: Yes, OECD
Test system: *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537; *E. coli* WP2uvrA
Study is valid: No

Study number Bayer HealthCare AG report # PH-33546, MRL TT #04-5559: BAY 73-73888: Salmonella microsome test—plate incorporation and preincubation method

Key Study Findings:

- The test article was too toxic to the bacterial lawn to be adequately tested. However, at the low levels tested, the sponsor claimed no mutagenic effect was observed.

GLP compliance: Yes, OECD
Test system: *S. typhimurium* TA 98, TA 100, TA 102, TA 1535, TA 1537
Study is valid: No

Study number (b) (4) Report # (b) (4), MRL TT #03-5553: Bacterial reverse mutation assay

Key Study Findings:

- The study was not valid due to toxicity to the bacterial lawn (highest concentration without complete ablation of background lawn was 50 mcg/plate). No remarkable changes in the number of revertants were observed except with the positive controls.

GLP compliance: Yes, US, UK, Japan, and OECD
Test system: S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537 and E. coli strain WP2 uvrA
Study is valid: No

In Vitro Assays in Mammalian Cells

Study number (b) (4) Report # 22081, MRl TT #03-5529: PTK0796: Mouse lymphoma cell mutation assay

Key Study Findings:

- In the dose-ranging study, all concentrations of omadacycline HCl at or above 50 µg/mL were completely toxic to the L5178Y cells.
- PTK0796 displayed marginal mutagenic activity in the presence of S9 activation, which was higher than historical controls.

- There was a lack of consistency in trend of small to large colony ratios in the replicate assays.
- The original review stated that PTK0796 was not considered to be mutagenic in this assay, but the findings of mutagenic activity outside of the range of historical controls support the findings as positive for mutagenicity.

GLP compliance: Yes, US, UK, Japan, and OECD
Test system: Mouse lymphoma L5178 Y cells tk+/tk-; clone-3.7. 2C, +/- S9
Study is valid: Yes

Study number (b) (4) Report # 22188, MRL TT #02-5528: PTK0796: Chromosomal aberrations assay with Chinese Hamster Ovary cell cultures in vitro.
Key Study Findings:

- PTK0796 (hydrochloride salt) displayed weak clastogenic activity in the 6-hour incubation with S9 activation. The aberrations were primarily chromatid gaps, breaks and fragments, with an aberration frequency of 0.05 to 0.15 in the 250 and 350 mcg/mL cultures relative to controls.
- There was some evidence that PTK0796 may also increase the incidence of polyploid cells in the 22-hour incubation without S9 activation at 100 mcg/mL relative to controls (mean of 4 in the treated group compared to 1 in the control group).
- These results suggest that PTK0796 possesses some clastogenic and aneugenic activity in vitro.

GLP compliance: Yes, OECD
Test system: Chinese Hamster Ovary (CHO) cells, +/-S9
Study is valid: Yes

Study number Bayer HealthCare AG Report # PH-33633, MRL TT # 04-5560: BAY 73-7388: In vitro chromosome aberration test with Chinese Hamster V79 cells
Key Study Findings:

- BAY 73-7388 (free base) was not considered to be clastogenic in this study.

GLP compliance: Yes, OECD
Test system: Chinese Hamster V79 cells, +/- S9
Study is valid: Yes

<u>In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)</u>

Study number (b) (4) Report # (b) (4), MRL TT #03-5554: Mammalian erythrocyte micronucleus test
Key Study Findings:

- 6/15 males and 6/15 females in the 150 mg/kg dose group died prematurely, so bone marrow was only analyzed for 4 animals/sex at this dose at the 48 hour timepoint.
- PTK0796 (hydrochloride salt) was considered negative in this in vivo mouse micronucleus assay.

GLP compliance: Yes, US, UK, Japan, and OECD
Test system: ICR mice 5/sex/dose/timepoint, single IP doses of 0, 5, 50, or 150 mg/kg; all four groups evaluated at 24 hours; control and high dose only analyzed at 48 hours
Study is valid: Yes

The following was the only genetic toxicology study using the toluenesulfonate (tosylate) salt of omadacycline and is reviewed here for the first time.

Study no. 0970653: Rat bone marrow micronucleus test after intravenous administration
Key Study Findings:

- There was no statistically significant difference between the mean micronucleus frequencies in the treated groups and the negative control group, suggesting that the test article had no clastogenic and/or aneugenic potential *in vivo* under the test conditions used.

GLP compliance: Yes, OECD
Test system: HanRcc:WIST(SPF) rats, bone marrow polychromatic erythrocytes; The rats were treated intravenously twice with an interval of approximately 24 hours between administrations, and bone marrow was sampled 48 hours after the first application. Doses were 8, 25 and 80 mg/kg/day (in terms of the free base) PTK796. The high dose was determined to be the MTD in a dose-range finding study.
Study is valid: Yes; the mean percentage of micronucleated polychromatic erythrocytes (MPE) in the positive control (cyclophosphamide, 10 mg/kg/day) group was clearly higher than the negative control value.

Other Genetic Toxicity Studies

Three reports of computational assessments of potential impurities were submitted to the NDA:

1. Study 0919411: *In silico* prediction of potential mutagenic properties
The following table adapted from the study report summarizes the findings:

Compound	Likelihood to be mutagenic	Genotoxicity test recommended	Comment
			(b) (4)

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(b) (4)

These appear to be reasonable conclusions.

5.3.3. Carcinogenicity

Not applicable

5.3.4. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were previously reviewed under INDs 73431 and 75928 and are summarized below.

Fertility and Early Embryonic Development

Reproductive and developmental toxicology studies were previously reviewed under INDs 73431 and 75928 and are summarized below.

Study no. CUA00012: Intravenous Fertility and General Reproduction Toxicity Study of PTK 0796 Tosylate in Rats

Twenty-five rats/sex/dose group were administered doses of vehicle, 5, 10, or 20 mg/kg/day of PTK 0796 tosylate once daily by IV infusion via the tail vein. Males were treated for 28 days prior to cohabitation and throughout a 21-day cohabitation period. Females were treated from 15 days prior to cohabitation through gestation day (GD) 7. Findings in these animals included swelling at the injection site at the high dose, and decreased food consumption and decreased weight gain in females at the high dose during the first week of dosing.

In males, terminal observations included large seminal vesicles with fluid in one high dose animal, significantly increased seminal vesicle weights at 10 and 20 mg/kg/day, and low or no sperm motility at 20 mg/kg/day. Nevertheless, there was no effect of PTK0796 on male fertility parameters.

In females, fertility parameters were similar to controls. However, at necropsy, high dose animals were found to have significantly lower numbers of corpora lutea, implantation sites, and average number of viable embryos. Post-implantation loss was significantly increased at 20 mg/kg/day.

Protocol deviations included infusion times that were shorter or longer than prescribed in 1-3 treated animals in a given group on most treatment days. The study did not test to maternal toxicity. However, the IV doses did exceed clinical IV doses after normalization for total body surface area, and this drug is a member of a drug class for which there has been a great deal of clinical experience. The protocol deviations were not considered to have affected the outcome of the study.

Embryo-Fetal Development

Study no. CUA00007: Intravenous developmental toxicity study of PTK 0796 HCl in rats

Twenty-five presumed pregnant Crl:CD(SD) rats per group were administered IV doses of 0 (Vehicle), 5, 10, and 20 mg/kg/day from GD 7 through GD 18.

The only clinical sign attributed to intravenous administration of PTK 0796 HCl was purple discoloration at the injection site. The finding was observed in all groups but was more prevalent in the 20 mg/kg/day group (incidence was 2, 3, 4, and 8 of 25 animals in the 0, 5, 10, and 20 mg/kg groups, respectively). No test article related changes were reported in body weight, feed consumption, or necropsy observations. The study was insufficient, since it did not test to maternal toxicity. The high dose, 20 mg/kg/day would be equivalent to a clinical dose of 3.3 mg/kg, or 200 mg for a 60 kg patient. Dosing was not high enough to support safety for patients receiving 200 mg/day but weighing less than 60 kg.

Pregnancy occurred in 23 to 25 dams in the four treatment groups. Fetal body weights (total, male and/or female) were significantly reduced in a dose-dependent manner in the 5, 10 and 20 mg/kg/day dosage groups, relative to vehicle controls and correlated with delayed ossification at 10 and 20 mg/kg/day. No gross external, soft tissue, or skeletal alterations were reported. Reductions in average number of ossified caudal vertebrae and hindlimb phalanges reported in 10 and 20 mg/kg/day groups were considered to be related to treatment.

The maternal NOAEL was determined to be the high dose, 20 mg/kg/day. The study did not included doses that tested to maternal toxicity or that were a multiple of the proposed clinical dose. A fetal NOAEL was not determined; findings were limited to dose-related decreased fetal body weights (3-6% less than controls) and delayed ossification in the caudal vertebrae and hindlimb phalanges.

The rat embryo-fetal development study was repeated in order to include doses testing to maternal toxicity. The following study was reviewed by Dr. Kelly Brant.

Study no. 20116248: An Embryo-Fetal Development Study of PTK 0796 Tosylate by Intravenous Infusion in Rats

Pregnant Crl:CD Sprague Dawley rats were administered intravenous doses of PTK 0796 Tosylate once daily from gestation day (GD)6 through GD17 at 0 (vehicle), 20, 40, or 80 mg/kg/day. Due to unexpected mortality (2 females) and adverse clinical signs consistent with an adverse immune response following the first dose, the high dose of 80 mg/kg/day was lowered after the first day of dosing to 60 mg/kg/day for the duration of the dose period (hereinafter referred to as 80/60 mg/kg/day). Females assigned to Main Study group were euthanized on GD21 and females assigned to the TK satellite group were euthanized after final blood collection on GD12.

PTK 0796 Tosylate-related clinical observations and injection site reactions were observed at 80/60 mg/kg/day, along with a significant reduction in maternal body weight gain. Test article related clinical signs included decreased activity, hunched posture, erected/ungroomed fur, labored breathing, prostration, and soft, swollen muzzle, abdomen, forepaw, and/or hindpaw. Maternal no-adverse-effect level (NOAEL) for PTK 0796 Tosylate was determined to be 40 mg/kg/day (C_{max} of 18800 ng/mL and AUC_{0-t} of 50800 hr*ng/mL), based on mortality at 80 mg/kg/day and clinical signs at 80/60 mg/kg/day.

No placental abnormalities were detected and mean numbers of corpora lutea and sex ratios were similar among all dose groups. The mean number of early and late resorptions were significantly higher in the 80/60 mg/kg/day dose group compared with controls ($p \leq 0.01$), resulting in higher post-implantation loss and lower mean number of fetuses. PTK 0796 Tosylate-related lower fetal body weights at ≥ 20 mg/kg/day were observed along with an increased incidence of fetal external malformations at 80/60 mg/kg/day. Coincident with reductions in fetal body weight, administration of PTK 0796 Tosylate also caused delays in skeletal ossification at ≥ 20 mg/kg/day. Therefore, the developmental NOAEL could not be established based on lower fetal body weights at all doses.

Study no. CUA00009: Intravenous Developmental Toxicity Study of PTK 0796 HCl In Rabbits

Twenty timed-mated female rabbits per group were administered vehicle, 5, 10, or 20 mg/kg/day PTK 0976 HCl once daily by IV infusion via the marginal ear vein on gestation days (GD 7-19). Early maternal deaths occurred at the high dose, and one doe aborted. Clinical signs were limited primarily to injections site swelling and fecal changes at all doses. High dose dams lost approximately 1% of their body weight during the first 3 days of dosing, then gained weight, but at a lower rate than controls. Body weight gains recovered after cessation of dosing. Feed consumption was decreased in the 10 and 20 mg/kg/day groups during dosing and persisted in the early post-dosing period in the high dose group.

Post-implantation loss, average litter size and average numbers of live fetuses were significantly decreased at the high dose. Percentages of litters with alterations and fetuses per litter with any alteration were increased at the high dose.

Malformations and variations in the heart and vessels, diaphragm, and lungs in the 10 and 20 mg/kg/day groups appeared to be related to test article administration. These included ventricular septal defects (VSDs) in the heart in 1 and 2 litters in the 10 and 20 mg/kg/day dose groups, respectively, blood vessel alterations at 20 mg/kg/day, including persistent truncus arteriosis, distended pulmonary artery, and absent or misplaced innominate or subclavian artery, and small or absent lung lobes in the 10 and 20 mg/kg groups, with diaphragmatic hernia in one 10 mg/kg fetus.

Skeletal malformations were found in litters from dams treated with 5 mg/kg/day and 20 mg/kg/day and consisted of changes to cervical, thoracic, and lumbar vertebrae (including

hemivertebra, fused centrum, bifid centrum). Most skeletal variations were seen in control and treated groups and were not considered to be related to treatment. However, incomplete ossification in the sternum and pelvis in a 20 mg/kg litter was considered to be related to treatment. The report also indicates that the incidence of supernumerary ribs, with associated increases and decreases in the numbers of thoracic and lumbar vertebrae, respectively, was statistically significantly increased in the 20 mg/kg group and may be related to maternal toxicity.

The average number of ossified fore- and hind-limb phalanges was significantly reduced ($p \leq 0.01$) in the 20 mg/kg/day dose group, relative to the vehicle control group values. Delays in ossification were considered to be treatment-related.

The report concluded that the maternal NOAEL was 10 mg/kg/day. It also indicated that the fetal NOAEL was 10 mg/kg/day, citing that reduced fetal body weight at that dose was still within the historical control range. However, since lung malformations and cardiac VSDs were found in a dose-related incidence at 10 and 20 mg/kg/day and were considered to be test article-related, the fetal NOAEL would be better estimated as 5 mg/kg/day (maternal AUC was 14.1 mcg*hr/mL on GD 7 and 14.8 mcg*hr/mL on GD 19.

Prenatal and Postnatal Development

The following study was reviewed by Dr. Kelly Brant.

A Developmental and Perinatal/Postnatal Reproduction Study of PTK 0796 Tosylate by Intravenous Infusion in Rats, Including a Postnatal Behavioral/Functional Evaluation (Study no. 20116247)

Key Study Findings

- No test article-related effects were observed on maternal toxicity or reproductive function. Offspring showed no effects of treatment on behavioral or reproductive parameters.
- The NOAEL for F_0 reproductive toxicity, F_1 developmental toxicity was 30 mg/kg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle), 7.5, 15, or 30 mg/kg/day; once daily
Route of administration:	Intravenous infusion via lateral tail vein
Formulation/Vehicle:	0.9% Sodium Chloride Injection, USP
Species/Strain:	Crl:CD (SD) Sprague-Dawley rats (from (b) (4))

Number/Sex/Group:	22
Satellite groups:	None
Study design:	Pregnant females (F_0) were dosed daily from gestation day (GD) 6 through lactation day (LD) 20 (rats delivering litter) or GD24 (rats that did not deliver a litter). F_0 data included mortalities, clinical signs, body weights and body weight gains, food consumption, and necropsy observations. Dams were euthanized on LD 21. F_1 generation males and females were weaned and 2/sex/litter were selected resulting in 22 pups/sex for study continuation. F_1 data included mortalities, clinical signs, pre- and post-weaning body weights, food consumption, behavioral assessments (bone measurement and changes in neurobehavior as evaluated by passive avoidance, motor activity, acoustic startle, and water maze testing), reproductive parameters (sexual maturation, estrous cycling, and cohabitated for assessment of reproductive function), and necropsy observations. F_1 generation rats were euthanized on post-partum day 89 (following behavioral assessment), days 117-119 (following assessment of reproductive parameters in males), or GD 13 (following assessment of reproductive parameters in females).
Deviation from study protocol affecting interpretation of results:	No - several F_0 animals administered 30 mg/kg/day PTK 0796 Tosylate exhibited injection site reactions (swelling and tail discoloration) and were given a dosing holiday between LD12 and LD15 and continuing until euthanasia (LD20). The dosing holiday is unlikely to affect interpretation of the study results given it occurred late in the dosing period, lactational exposure in pups is presumed to be minimal based on the poor oral bioavailability of the test article in rats, and the pups are expected to be consuming solid food by postpartum day 14.

Observations and Results

Generation	Major Findings
F0 Dams	None
F1 Generation	None
F2 Generation	N/A

5.3.5. Other Toxicology Studies

Local Tolerance

(b) (4) Report Number 22807: PTK0796: Local Tolerance and Irritation Test in Rabbits

A local tolerance study was performed in NZW rabbits. The nonclinical overview indicates that the test article in this study was the HCl salt, but this is not confirmed in the study report. Five groups of 4 male rabbits each were treated *via* intravenous injection to the marginal ear veins. A dose volume of 3 mL was administered using an infusion pump over 30 minutes (infusion rate 0.1 mL/min). Each rabbit received one injection in each ear as follows:

Group	Site/Treatment		Animal
	Left marginal ear vein ($10\ mg.ml^{-1}$ PTK0796)	Right marginal ear vein	
1	PTK0796 in D5W	D5W	1-4
2	PTK0796 in PlasmaLyte 148	PlasmaLyte 148	5-8
3	PTK0796 in 0.45% saline	0.45% saline	9-12
4*	PTK0796 in 0.45% saline	0.45% saline	13-16
5	PTK0796 in Lactated Ringers' Solution (0.45% saline)	Lactated Ringers' Solution (0.45% saline)	17-20

* In error 0.45% saline was used as the vehicle in the preparation of the solutions for Group 4. Four animals were added to the study, allocated to Group 5 and treated with Lactated Ringers' Solution (0.45% saline).

Infusions were administered first to the right ear (vehicle) and were made to the left ear approximately 2 hours later. Injection sites were examined at 1, 3-4, and 24 hours after administration. The sites were scored on a scale of 0-4 for evidence of erythema and edema, and any local reactions were recorded. Erythema was noted in one animal at 1 hour (very slight, 1) and at 24 hours (well-defined, 2) and another animal at 24 hours (very slight, 1) in the PTK0796/D5W ear. In the remaining PTK0796-treated ears, very slight erythema (1) was noted in 0-2 animals at 24 hours post-injection. Erythema findings in vehicle treated ears were similar in incidence and severity. No edema was noted in any ear.

Twenty-four hours after completion of dosing, animals were sacrificed, and the injection sites were examined. At necropsy, the ear was dark or reddened in ears from two animals receiving PTK0796 in D5W and in the ear of one animal receiving PlasmaLyte 148, correlating with findings of perivascular hemorrhage on microscopic examination.

Histological findings of mild to moderate intimal proliferation, fibrin thrombus formation, necrosis and perivasculitis were recorded at the needle tip. Arteritis was recorded in one animal, and focal ulceration in two animals, also at the needle tip. These were considered to be consistent with needle trauma at the site of injection. There were no toxicologically significant differences in histological changes at the needle end point, between ears given vehicle with PTK0796 or vehicle alone, or between groups given different vehicles.

Intravenous administration of PTK0796 was considered to be well tolerated in the rabbit ear vein when given in D5W, PlasmaLyte 148, 0.45% Saline or Lactated Ringers' Solution (0.45% saline).

Phototoxicity

(b) (4) Study Number 8223219 (Sponsor Reference No. 0970657): Evaluation of *in vitro* phototoxicity on Balb/c 3T3 fibroblasts using the Neutral Red Uptake assay

PTK796 (tosylate salt) was assayed for phototoxicity to Balb/c 3T3 fibroblast cells using the Neutral Red Uptake assay. Cells were treated with a range of concentrations of PTK796 (up to 1000 mcg/mL) or positive control chemical (chlorpromazine, CPZ), as well as vehicle (1% dimethyl sulphoxide in PBS) and untreated (PBS) controls.

After irradiation and incubation, cytotoxicity was assessed by the Neutral Red Uptake assay. Based on findings of cytotoxicity in radiated and non-irradiated cells at the highest concentrations of PTK796 in the range-finder experiment, the highest concentration tested in the main experiments was reduced to 128 mcg/mL in the absence of UV-vis and 64 mcg/mL in the presence of UV-vis.

In Experiment 1, treatment of cultures with PTK796 resulted in a decrease in cell survival, both in the absence and in the presence of UV-vis light. Cytotoxicity, as indicated by a decrease in Neutral Red uptake, was observed at the highest two concentrations tested in the absence of UV-vis (64 and 128 mcg/mL) and the highest two concentrations tested in the presence of UV-vis (32 and 64 mcg/mL). The IC50 and PIF calculations are given below:

Table 1-1 IC_{50} and PIF calculations – Experiment 1

Test article	IC_{50} absence of UV-vis (μg/mL)	IC_{50} presence of UV-vis (μg/mL)	PIF Value
PTK796	67.0	17.4	3.9
Chlorpromazine	21.2	1.03	20.6*

* Positive control response was acceptable (IC_{50} absence of UV-vis between 7 and 90 μg/mL, IC_{50} presence of UV-vis between 0.1 and 2 μg/mL, PIF > 6).

In Experiment 2, treatment of cultures with PTK796 resulted in a decrease in cell survival, both in the absence and in the presence of UV-vis light. Cytotoxicity, as indicated by a decrease in Neutral Red uptake, was observed at the highest two concentrations tested in the absence of UV-vis (64 and 128 mcg/mL) and the highest concentration tested in the presence of UV-vis (64 mcg/mL). The IC50 and PIF calculations are given below:

Table 1-2 IC_{50} and PIF calculations – Experiment 2

Test article	IC_{50} absence of UV-vis (μg/mL)	IC_{50} presence of UV-vis (μg/mL)	PIF Value
PTK796	65.4	33.8*	1.9
Chlorpromazine	33.8	1.69	20.0*

* Positive control response was acceptable (IC_{50} absence of UV-vis between 7 and 90 μg/mL, IC_{50} presence of UV-vis between 0.1 and 2 μg/mL, PIF > 6).

The PIF value of Experiment 2 is reported to indicate no phototoxic potential but is stated to be close to the cut-off for a 'probable phototoxic' result, which provides support for the outcome of Experiment 1.

It was concluded that, under the conditions employed in this study, PTK796 was "probably phototoxic" in this *in vitro* test system when tested up to the limit of toxicity, according to the OECD guideline. However, the report states that the IC_{50} values under irradiation were only obtained at concentrations above 17 mcg/mL, and that PTK796 did not fulfil the criteria for a clear phototoxic response (PIF >5). The report states that the result may be of questionable biological relevance. Since the OECD guideline, as described in the report, supports a conclusion of "probably phototoxic," and since phototoxicity is a known class effect of tetracyclines, it is appropriate that the results of this test be considered to be "probably phototoxic." Class labeling for tetracycline antibacterial drugs will be used for omadacycline.

Potential for induction of allergic reactions

The Applicant conducted a single IV dose toxicology study in dogs reportedly to assess potential to induce allergic reactions. This study was reviewed in the original IND 75928 by Drs. Wendy Schmidt and Theresa Allio.

Study Number: CUA W-0108: A Study To Evaluate The Acute Effects Of A Test Article When Administered By Intravenous Injection To Beagle Dogs

Groups of Beagle dogs were administered 10 mg/kg PTK0796 as a slow IV bolus injection of 1 mL/kg over 1 minute formulated in Plasmalyte 148 or Lactated Ringers' solution. Additional animals were scheduled to receive 5 mL/kg IV formulated in Plasmalyte 148 or Lactated Ringers' solution administered as a 30-minute infusion, but dosing was terminated early due to severe adverse reactions. The positive control was 0.4 mg/kg levofloxacin as a slow IV bolus. Observations were obtained post-treatment, and histamine levels were determined at 1, 3, 5, 10, and 20 minutes, and at 1, 2, and 4 hours post-administration.

Omadacycline was positive for effects consistent with an allergic reaction. Findings included erythema, edema, salivation, vocalization, and/or vomiting in all animals treated with PTK0796. Erythema and salivation were seen in animals treated with levofloxacin.

Clinical adverse events were more severe with a 30-minute infusion rather than a 1 minute IV bolus. Histamine levels correlated with the severity of the clinical signs. Histamine levels peaked 1 minute after infusion in females and at 10 to 20 minutes after infusion in males. Histamine levels were much lower in animals that received PTK0796 by infusion compared to those receiving it by slow IV bolus. There was no apparent difference seen between formulations and histamine response.

Impurity qualification

The Applicant's nonclinical overview and written summary state that impurities and degradants in both the IV and oral formulations were either below the ICH qualification threshold or were qualified in nonclinical toxicology studies of at least 14 days duration. Impurities are discussed in the Quality section of the application. For potential organic related substances in the omadacycline tosylate drug substance (degradation products and process impurities), the application states that all are well controlled or not detected in the final drug substance. Of the known related substances, the following are proposed to be specified at the listed acceptance criteria:

- (b) (4) ≤ (b) (4) % w/w
- ≤ % w/w
- ≤ % w/w
- ≤ % w/w
- ≤ % w/w
- ≤ % w/w
- ≤ % w/w
- ≤ % w/w
- ≤ % w/w
- individual unidentified impurity ≤ % w/w
- Total impurities ≤ % w/w

Since the ICH Q3A threshold for identification is 0.1% of the drug substance, it is unclear how the acceptance criteria of an individual unidentified impurity could be ≤ (b) (4) % w/w . Of the individual impurities that meet the criteria for identification, all but two have acceptance criteria that are ≥ (b) (4) % of the drug substance and should be qualified in toxicology studies per ICH Q3A. The application states that impurities meeting the qualification threshold were qualified in nonclinical toxicology studies of at least 14 days duration. The following tables were provided in the Quality section of the application:

Table 2. Initial Qualification of Specified Related Substances

Known Related Substances	Batch No.	Level of Degradant (% a/a)	Level of Degradant Based on Freebase (% w/w)	Level of Degradant Based on Tosylate (% w/w)	Study No.	Study Type
(b) (4)	80240001			(b) (4)	1116-007	28-day IV monkey
	80240001				1116-007	28-day IV monkey
	MFC6559/I				22193	14-day IV monkey
	80240001				1116-007	28-day IV monkey
	80240001				1116-007	28-day IV monkey
	80240001				1116-007	28-day IV monkey
	74550[a]				5002516	14-day IV rat
	C-026848-CRS01[a]				5002516	14-day IV rat
	INV-2-02516-30a[a]				5002516	14-day IV rat
	RB-604-49[a]				5002516	14-day IV rat

[a] Related substances were spiked directly into the sample to qualify the specific limits that are referenced in the table here.

Table 3. Updated Qualification of Specified Related Substances

Known Related Substances	Batch No.	Level of Degradant (% a/a)	Level of Degradant (% w/w)	Level of degrade based on tosylate (% w/w)	Study No.	Study Type
(b) (4)	80240001			(b) (4)	1116-007	28-day IV monkey
	80240001				1116-007	28-day IV monkey

After calculation of the animal dose of each impurity at the NOAEL and conversion to an equivalent clinical dose, each is expressed as a percentage of the daily clinical omadacycline dose (100 mg IV). The following acceptance criteria were proposed:

Table 4. Qualified Related Substance Levels and Proposed Drug Substance Acceptance Criteria

Specified Related Substances	% Qualified Based on Tosylate Table 2 and Table 3 above	Proposed Acceptance Criteria in Omadacycline Drug Substance
(b) (4)	On Release and Stability	
	(b) (4) % w/w	≤ (b) (4) % w/w
	% w/w	≤ % w/w
	% w/w	≤ % w/w
	% w/w	≤ % w/w
	% w/w	≤ % w/w
	% w/w	≤ % w/w
	(b) (4)	
	(b) (4) % w/w	≤ % w/w
	% w/w	≤ % w/w
	% w/w	≤ % w/w

The quality section of the application indicates that inorganic impurities and residual solvents are either not present or are below the ICH limits for the drug substance.

For the oral drug product (tablet), acceptance criteria were proposed for six of the specified impurities in the drug substance as shown in the table below from the Quality section of the application.

Table 2. Qualified Related Substance Levels and Proposed Omadacycline Tablet Acceptance Criteria on Release and Stability

Specified Related Substances	% Qualified based on free base (% a/a)	% Qualified based on free base (w/w)	Proposed Acceptance Criteria Omadacycline Tablet, 150mg
(b) (4)	(b) (4) a/a	(b) (4) % w/w	≤ (b) (4) % w/w
	a/a	% w/w	≤ % w/w
	a/a	% w/w	≤ % w/w
	a/a	% w/w	≤ % w/w
	a/a	% w/w	≤ % w/w
	a/a	% w/w	≤ % w/w

Proposed acceptance criteria are ≤ (b) (4)% w/w for individual unidentified impurities and ≤ (b) (4)% for total impurities. The application does not describe how the amounts listed in the above table as being qualified toxicologically were determined, and they do not all appear to be consistent with those listed in the previous table for the drug substance. However, the following comparison of the qualified daily human equivalent doses to the daily dose based on the proposed acceptance criteria generally supports the choice of those acceptance criteria.

Impurity	Qualified IV Human Equivalent Dose (HED)	Clinical IV dose based on Drug Product (tablet) acceptance criteria*	Clinical PO dose based on Drug Product (tablet) acceptance criteria*
(b) (4)			

*Based on an IV omadacycline dose of 100 mg/60 kg/day (1.67 mg/kg/day) or oral omadacycline dose of 300 mg/60kg/day (5 mg/kg/day)

The application indicates that the (b) (4) impurity will be controlled as an individual unidentified impurity with an acceptance criterion of not more than (b) (4)% w/w, which is below the qualification threshold for the drug product (ICH Q3B). This would correspond to a clinical IV dose of (b) (4) mg/kg and a clinical PO dose of (b) (4) mg/kg, which would be consistent with the qualified IV HED and with ICH M7.

Nevertheless, only the acceptance criteria for (b) (4) and (b) (4) exceed the (b) (4)% threshold for qualification in the drug product as described in ICH Q3B, and these appear to be supported based on this reviewer's calculations. The oral dose for (b) (4) at the acceptance criteria for the oral formulation slightly exceeds the qualified HED for IV administration but may be offset by lower bioavailability.

There were no concerns stated for genetic toxicity of impurities, with the exception of one impurity that had an equivocal structural alert for genetic toxicity (see in silico reports described under "Other Genetic Toxicity Studies"). The Applicant states that that impurity ((b) (4)) is being controlled as per ICH M7 (see above). The application states that literature references indicate that the similar structure to that impurity is present in

approved [redacted] that were negative in the Ames assay. Most of the potentially genotoxic impurities (PGIs) were considered not genotoxic based on structural alerts shared with [redacted] citing negative Ames tests for that compound. Others share a structural alert with omadacycline, which was toxic to the test bacteria, so a valid Ames test could not be conducted. In the mouse lymphoma assay (MLA), positive findings for omadacycline were seen, but control of PGIs to levels consistent with ICH Q3 A/B would likely be sufficient.

Positive toxicology alerts for two [redacted] derivatives of omadacycline are summarized below.

Study 1119337: *In silico* prediction of potential toxicological properties
(see review under "Other Genetic Toxicity Studies")

Computation assessment of [redacted] were performed.
The results of the SAR assessment included:

- [redacted] are predicted to show mutagenicity based on the [redacted]. Both alerts are also determined for PTK796
- MCASE determines a biophore for skin sensitization for [redacted]. However, the same biophore is also seen for PTK769. The MCASE predictions are uncertain due to several unknown fragments. Two biophores for skin sensitization are found one of which is also seen for PTK796. The MCASE predictions are uncertain due to several unknown fragments.
- Alerts for hepatotoxicity of tetracycline and precursor of [redacted] are found for the [redacted] impurity, which are, however, also detected for PTK796. MCASE using the 14 FDA modules for the prediction of liver side effects detects a biophore for abnormal liver function. The same biophore is also determined for PTK796. The MCASE predictions are uncertain due to two unknown fragments (including [redacted] moiety).
- Alerts for hepatotoxicity of tetracycline and precursor of [redacted] are found for the [redacted], which are, however, also detected for PTK796. MCASE using the 14 FDA modules for the prediction of liver side effects detects a biophore for abnormal liver function and hepatitis. The prediction for hepatitis is inconclusive due to the concomitant detection of a deactivating fragment. The same biophores are also determined for PTK796."

In general, this computational assessment supported a similar toxicological profile for both of these impurities to that of omadacycline. The report did stipulate, however, that the predictive value of the calculations performed for [redacted] is reduced due to the lack of coverage of the [redacted] moiety in the MCASE databases.
In the absence of any discussion of these specific compounds in the nonclinical section of the application, the relevance of this assessment is unclear, although one or both may be related to

the [redacted] (b) (4) discussed under "ADME." No metabolites were reported for clinical patients (See Clinical Pharmacology Section 6.2)

Overall, the safety evaluation of the identified impurities and metabolites appears to support the proposed use of the drug product.

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6. Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Clinical Pharmacology IV, Division of Pharmacometrics) reviewed the information contained in the NDAs for omadacycline oral tablets and IV infusion. The clinical pharmacology information submitted in the applications supports the approval of omadacycline for CABP and ABSSSI, administered by either an intravenous (IV) infusion route or orally as a tablet.

Table 6-1 Summary of OCP's Recommendations & Comments on Key Review Issues

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal or supportive evidence of effectiveness</td><td>The evidence of effectiveness of omadacycline in patients with ABSSSI was provided by two Phase 3 trials for ABSSSI (ABSI-1108, ABSI-16301) and in patients with CABP by one Phase 3 trial (CABP-1200).</td></tr>
<tr><td>General dosing instructions</td><td>The proposed dosage regimen of omadacycline is as follows:
<table>
<tr><th>Loading Doses</th><th>Maintenance dose</th></tr>
<tr><td>200 mg intravenous infused over 60 minutes on the 1st day.
Or

100-mg infused over 30 minutes, twice on the 1st day.</td><td>100 mg intravenous once daily infused over 30 minutes.
Or
300 mg (2 x 150 mg Tablets) orally once daily.</td></tr>
<tr><td>450 mg (3 x 150 mg Tablets) orally once a day on the 1st and 2nd day.</td><td>300 mg (2 x 150 mg Tablets) orally once daily.</td></tr>
</table>
Treatment duration is 7-14 days. Patients should fast for 4 hours before oral dosing. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours.</td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>No dose adjustment is needed in patients with renal or hepatic impairment.</td></tr>
<tr><td>Labeling</td><td>The Clinical Pharmacology review team has specific content and formatting change recommendations that will be communicated to the applicant during labeling discussions.</td></tr>
</table>

Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed tablet formulation was used in Phase 3 trials (ABSI-1108, ABSI-16301, CABP-1200).

Source: NDA 209816 and 209817

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Summary of the clinical pharmacokinetics of omadacycline

Absorption	The absolute bioavailability of a single 300 mg dose of omadacycline tablets (2 × 150 mg) was 34.5 %. Omadacycline exposure (AUC) following administration of a single 300 mg oral tablet dose was comparable to that following a single 100 mg IV dose. Peak plasma concentrations are achieved within about 2.5 hours after oral administration. Rate and extent of absorption (C_{max} and AUC) of omadacycline is reduced under fed conditions.
Distribution	Mean (SD) plasma protein binding is 21.3 (9.7) %. The mean (%CV) steady state volume of distribution of omadacycline is 190 (27.7) L.
Elimination	Estimated mean (%CV) half-life is 16 (21.7) h. Mean (%CV) systemic clearance is 9 (25.2) L/h. The renal clearance across studies ranged from 2.4 to 3.3 L/h.
	Metabolism No metabolism *in vitro* in human liver microsomes and hepatocytes. No major systemic metabolites observed in plasma, urine or feces up to 7 days following oral administration.
	Excretion Following administration of 300-mg oral [^{14}C] omadacycline, biliary excretion was the dominant route of elimination, with 77.5% to 84.0% radioactivity recovered in feces and approximately 10.7 to 17.4% of the radioactivity excreted in urine as unchanged omadacycline.
Lung Penetration	Following IV administration of 100 mg omadacycline to healthy subjects, at steady state the AUC of omadacycline in alveolar cells (AC) was 26-fold higher than plasma AUC and the AUC of omadacycline in epithelial lining fluid (ELF) was 1.47-fold higher than plasma AUC.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Applicant's proposed dosage regimen for ABSSSI and CABP patients, shown below, is supported by the PK, efficacy, and safety data from the clinical trials submitted in the application.

200-mg of omadacycline for injection administered by IV infusion over 60 minutes on day 1 (or 100-mg administered by IV infusion over 30 minutes (b) (4) for the first two doses on day 1), followed by 100-mg administered intravenously once daily or 300-mg administered orally once daily.
450-mg of omadacycline tablets orally, once a day for the first 2 days, followed by 300-mg orally once daily.

Treatment duration is 7 to 14 days. Note that for ABSSSI, the proposed IV to oral and oral only dosage regimens were shown to be adequately effective. For CABP, only the proposed IV to oral dosage regimen was evaluated and was shown to be adequately effective; the oral only dosage regimen was not evaluated. (b) (4) see also section 6.3.2 for further details.
Patients should fast for at least 4 hours before oral dosing. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours.

Therapeutic Individualization

Extrinsic Factors (Effect of Food):
Relative to administration of omadacycline under fasting conditions, ingestion of a standard high-fat nondairy meal (855 calories; 59% calories from fat) and standard high-fat meal including dairy (985 calories; 60% calories from fat) 2-hours before administration of omadacycline decreased the rate (C_{max}) and extent of absorption (AUC) by 40% and 42%, and 60% and 63%, respectively. However, the rate and extent of absorption of omadacycline were not substantially decreased when a high-fat nondairy meal (800-1000 calories; 50% calories from fat) was ingested 4 hours pre-dose.

Following ingestion of either a light non-fat (300-350 calories; ≤5% calories from fat), or a standard low-fat (800-1000 calories; 30% calories from fat), or a standard high fat (800-1000 calories; 50% calories from fat) meal 2 hours post-dose, the AUC was 10 to 13% lower compared to fasted conditions, and C_{max} was not substantially altered. In addition, the T_{max} (range of 1.0-6.0 hours) in the fed state was comparable to that in fasted state (range of 1.5-4.0 hours). In general, regardless of the types of meal, C_{max} and AUC were affected by the timing of the meals.

Therefore, patients should be fasted for at least 4 hours before the dose of omadacycline and for at least 2 hours after the dose of omadacycline.

Outstanding Issues

(b) (4)

(see section 6.3.2 for details).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 6-2: General Pharmacology and Pharmacokinetic Characteristics

Pharmacology					
Mechanism of Action	Omadacycline is a novel semi-synthetic tetracycline antibacterial compound prepared by (b) (4). After entering bacteria, tetracyclines bind to the 30S subunit of the ribosome, thus inhibiting the binding of aminoacyl tRNA and blocking protein synthesis.				
Active Moieties	Omadacycline				
QT Prolongation	Omadacycline demonstrated no significant QTc prolongation effect after single IV doses of 100 mg or 300 mg in a thorough QTc study with a moxifloxacin positive control (Study PTK0796-TQTC-0803). However, increases in heart rate (16.9 to 21.6 bpm) were observed in the study.				
General Information					
Bioanalysis	Validated LC/MS/MS methods were used to determine omadacycline concentrations in human plasma, urine, feces, BAL (broncho alveolar lavage), AC (alveolar cells) and dialysate (See section 15.2).				
Healthy vs. Patients	In this application, PK samples were collected in both healthy adult volunteers and patients. For both IV and oral formulations, the overall exposure (AUC) of omadacycline was comparable between healthy volunteers and patients with CABP and ABSSSI.				
Drug exposure at steady state following the therapeutic dosing regimen		Oral tablet 450-mg Q24h on 1st and 2nd Day followed by 300-mg Q24h (Patients)	Oral tablet 300 mg Q24h, Day 1 to 5 [b] (Healthy subjects)	IV injection 100 mg Q12h Day 1, 100 mg Q24h, Day 2 to 4 (Healthy subjects)	IV to oral 200 mg IV Day 1, 300 mg PO Q24h Day 2 to 5 (Cystitis patients)
		Mean [a] (CV%)	Mean (CV%) N=23	Mean (CV%) N=41	Mean (CV%) Day1 N=11;

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>N=105</td><td></td><td></td><td>Day 5 N=10</td></tr>
<tr><td>AUC_{0-24h} (µg.h/mL)</td><td>Day 1: 9.8 (43.4)
Day 3: 8.8 (37.3)</td><td>Day 5: 9.26 (26.8)</td><td>Day 4: 12.1 (26.5)</td><td>Day 1: 16 (29);
Day 5: 13.2 (59.7)</td></tr>
<tr><td>C_{max} (µg/mL)</td><td></td><td>0.80 (25.9)</td><td></td><td>Day 5: 1.11 (58.8)</td></tr>
<tr><td>Median Tmax (h) (range)</td><td></td><td>2.5 (1 to 3)</td><td></td><td>Day 5: 3.0 (0 to 4)</td></tr>
<tr><td>CL or CL/F (L/h)</td><td>11.4 (27.2)</td><td></td><td>8.8 (25.2)</td><td>Day 1: 10.27 (15.1)</td></tr>
<tr><td>Vss or Vss/F (L)</td><td>234 (38.8)</td><td></td><td>189.8 (27.7)</td><td>Day 1: 167.6 (17.5)</td></tr>
<tr><td>T1/2(h)</td><td></td><td>16 (21.7)</td><td>15.5 (10.7)</td><td></td></tr>
</table>
[a] PopPK estimates
[b] These PK parameters do not takes into the account the effect of the Loading Dose.
</td></tr>
<tr><td>Dose Proportionality</td><td>For IV administration, omadacycline exposure increased in a dose proportional manner following single doses ranging from 25 mg to 600 mg (Study PTK0796-SDES-501). For oral administration of the to-be-marketed tablet, omadacycline exposure increased in an approximately dose proportional manner with once-daily dose administration ranging from 300 mg to 450 mg, and exposure was slightly less than dose proportional for doses ranging from 450 mg to 600 mg.</td></tr>
<tr><td>Accumulation</td><td>The accumulation ratio for the once daily oral dosing regimen ranged from 1.4 to 1.6 (Study PTK0796-MDPO-16105).
The accumulation ratio for IV dosing regimen of 200 mg IV Q24h ranged from 1.5 to 1.6 (Studies PTK0796-MDES-601).</td></tr>
<tr><td>Variability</td><td>For oral administration, the inter-subject variability (%CV) in C_{max} and AUC values at steady state for the 300-mg to-be-marketed tablet formulation in healthy subjects was 26 and 27%, respectively. (Study PTK0796-MDPO-16105).
For IV administration, the inter-subject variability (%CV) in C_{max} and AUC values at steady state for the IV to-be-marketed formulation administered to healthy subjects was 32% and 27%, respectively (Study PTK0796-BAL-15104).</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Bioavailability</td><td>The absolute bioavailability of the to-be-marketed 150 mg tablets at a dose of 300 mg was estimated to be 34.5% relative to administration of a single 100 mg IV dose (Study CPTK796A2104).</td></tr>
<tr><td>T_{max} Median (range)</td><td>2.5 h (1 to 4 hours)</td></tr>
</table>

Food effect	Food effect studies show that ingestion of a standard high-fat nondairy meal (855 calories; 59% calories from fat) and a standard high-fat meal including dairy (985 calories; 60% calories from fat) consumed 2 hours before administration of omadacycline decreased the rate (C_{max}) and extent of absorption (AUC) significantly. However, the rate and extent of absorption of omadacycline were not substantially decreased when a high-fat nondairy meal (800 to 1000 calories; 50% calories from fat) was ingested 4 hours pre-dose. Following ingestion of either a light non-fat (300 to 350 calories; ≤ 5% calories from fat), or a standard low-fat (800 to 1000 calories; 30% calories from fat), or a standard high fat (800-1000 calories; 50% calories from fat) meal 2 hours post-dose, the AUC and C_{max} were not substantially altered, as compared to fasting conditions. Therefore, patients should be fasted for at least 4 hours before the dose of omadacycline and for at least 2 hours after the dose of omadacycline (see **Table 6-6**).
Volume of Distribution	After IV dose, the mean (%CV) volume of distribution of omadacycline was 190 (27.7) L at steady state (Study PTK0796-BAL-15104).
Plasma Protein Binding	At omadacycline concentrations ranging from 0.01 to 10 µg/mL, the Mean (SD) protein binding, is 21.3±9.7 %, as determined by the equilibrium-dialysis method (Study 1000512).
Substrate transporter systems [*in vitro*]	Omadacycline is not a substrate of BCRP, MRP2, OAT1, OAT3, and OCT2 (Studies R1000026, 1000274, 1000027, 1000518). Omadacycline was not an OATP1B1 or OATP1B3 substrate at supra-therapeutic concentrations (5-13 fold higher than clinically relevant concentrations) tested in *in vitro* studies (Study 1000321). Omadacycline was shown to be a substrate of P-gp *in vitro* (Study R1000026).
Substrate transporter systems [*in vivo*]	Verapamil (P-gp inhibitor) causes slight increase in exposure of omadacycline in vivo, which is not clinically significant.
Elimination	
Half-life	The mean half-life for omadacycline ranges from 16-17 hours after single dose IV administration in healthy subjects. The mean half-life values for omadacycline in healthy subjects ranged from 13 to 17 hours following once-daily administration of oral doses over the dose range of 300 mg Q24h to 600 mg Q24h (Study PTK7096-MDPO-16105). The reported half-lives of omadacycline are consistent with the observation of the accumulation ratios of 1.4 to 1.6 following multiple IV and oral dose administration.
Metabolism	
Fraction metabolized (% dose)	No metabolites have been identified.
Primary metabolic pathway(s) [*in vitro*]	No metabolism
Excretion	

Primary excretion pathways % dose (SD)	After oral administration of [^{14}C]-omadacycline (300 mg), the total 7-day recovery of radioactivity averaged 95.5% of unchanged drug. A mean (SD) of 14.4% (2.3) of the dose was recovered in urine, and 81.1% (2.3) of the dose was eliminated in feces.
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	At clinically relevant concentrations, omadacycline does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 *in vitro* in human liver microsomes. Omadacycline also showed no apparent time-dependent *in vitro* inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5 at concentrations up to 50 µM. In human hepatocytes, omadacycline showed no potential for *in vitro* induction of CYP1A2, 2B6, 2C9, 2C19, 2C8, 3A4, 3A5 or UGT1A1 (Studies 1000061).
Inhibition/Induction of transporter systems	Omadacycline is not an *in vitro* inhibitor of the following transporters at clinically relevant concentrations: P-gp, MDR1, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2 (Studies 1000027, 1000028, 1000518 and 1000321).

Pharmacokinetic parameters are presented as mean (CV%) or median (range) unless otherwise noted; a= Approximately 150, 250, and 500 calories from protein, carbohydrate, and fat, respectively

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of efficacy of omadacycline for the treatment of ABSSSI was provided by two Phase 3 trials (Study -ABSI-1108 and Study-ABSI-16301) and primary evidence of efficacy of omadacycline for the treatment of CABP was provided by one Phase 3 trial (Study-CABP-1200). The exposure-response (E-R) analysis based on PK and efficacy data from the ABSSI Phase 3 trials provided supportive evidence of effectiveness of omadacycline. See section 15.2 for details.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed IV to oral, and oral only dosing regimens as shown below are acceptable for the general patient population with ABSSSI.

200-mg of omadacycline for injection administered by IV infusion over 60 minutes on day 1 (or 100-mg administered by IV infusion over 30 minutes (b) (4) for the first two doses on day 1) followed by 100-mg administered intravenously once daily or 300-mg administered orally once daily. Treatment duration is 7 to 14 days.

450 mg (3 x 150 mg Tablets) of omadacycline tablets orally, once a day for the first 2 days, followed by 300 mg (2 x 150 mg Tablets) orally once daily. Treatment duration is 7 to 14 days.

The IV to oral dosing regimen (100 mg IV Q12h × 2 then 100 mg IV Q24h with the option to switch to 300 mg PO daily after at least 3 days) was used in two Phase 3 studies (Study ABSI-1108 and CABP-1200). An oral only dosing regimen (450 mg PO Q24h × 2 then 300 mg PO Q24h) was used in one ABSSSI Phase 3 study ABSI-16301.

ABSSSI

The evidence of effectiveness for omadacycline in the treatment of ABSSSI has been demonstrated in both Phase 3 studies (refer to Section 7 for details). At the IV and oral doses studied, high clinical success rates (85 to 88%) and non-inferiority to the comparator (linezolid) demonstrated the adequacy of omadacycline exposure for efficacy. Using data from omadacycline-treated subjects, the E-R analyses for efficacy was carried out to demonstrate relationship between early clinical response (ECR) and free-drug plasma AUC:MIC ratio. The flat E-R relationship suggested that the omadacycline exposure in Phase 3 studies may have reached a plateau for efficacy. Based on these relationships, the lowest response was 80% for patients with AUC: MIC ratio below 12.5 (refer to section 15.4.2 for Pop PK and E-R analysis). The clinical response rates at ECR observed in studies ABSI-1108 and ABSI-16301 were similar, with high concordance between the ECR and post therapy evaluation (PTE) assessments. Similar clinical response rate with a 100 mg IV Q12h loading dose on Day 1 or a 450 mg PO daily loading dose on Days 1 and 2 (clinical success rate: 84.8% and 87.5%, respectively) supports either a 100 mg IV q12h loading dose on Day 1 or a 450 mg PO daily loading dose on Days 1 and 2.

CABP

The IV to oral dosing regimen (100 mg IV Q12h × 2 then 100 mg IV Q24h with the option to switch to 300 mg PO daily after at least 3 days) was used in Phase 3 study CABP-1200. The 450-mg oral loading dose was not evaluated in patients with CABP. In the CABP-1200, omadacycline demonstrated non-inferiority to moxifloxacin and had a clinical success rate of 81% for ECR assessment in the ITT population. In addition, exposure of omadacycline in ELF was 1.5-fold higher than in plasma and exposure of omadacycline in AC (alveolar cells) was 26-fold higher than in plasma. The IV to oral dosage regimen is acceptable from a Clinical Pharmacology perspective for CABP.

Since the proposed 450 mg oral loading dose (LD) regimen was not studied in CABP, the reviewer conducted an exposure (AUC) comparison for different loading doses; 100 mg IV q12h on Day 1 or 200 mg IV on Day 1, and 450 mg PO daily loading dose on Days 1 and 2 (**Figure 6-1**).

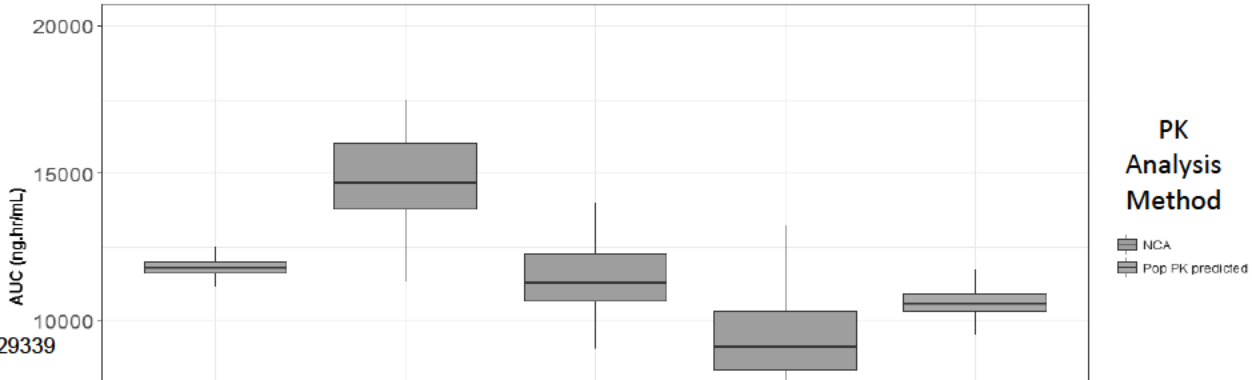

Figure 6-1: Exposure (AUC) comparison with 450 mg PO LD vs 200 mg IV LD
Source: Reviewer's analysis

The AUC of omadacycline at Day 1 following 200-mg IV LD is not comparable to omadacycline AUC with the 450 mg PO LD on Days 1 and 2. Therefore, the oral only dosage regimen with the 450 mg oral LD is not acceptable.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Based on the population pharmacokinetic analysis, the pharmacokinetics of omadacycline are not significantly impacted by age, sex, race, weight, or body mass index (see section 15.2) for details).

Hepatic Impairment

In a dedicated hepatic impairment Study # CPTK796A2201, omadacycline (PTK0796) exposures were similar between the subjects with hepatic impairment (regardless of Child-Turcotte-Pugh score) and the matched healthy subjects following IV or oral administration. The geometric mean ratio and 90% confidence intervals of AUC_{last}, AUC_{inf}, and C_{max} for all treatment groups are presented in Table 6-3 below. Hepatic impairment did not significantly impact omadacycline clearance following either IV or oral administration. We agree with the Applicant that no dose adjustment is needed for patients with mild, moderate and severe hepatic impairment.

Table 6-3: Geometric Mean Ratio Comparison of and 90% Confidence Intervals for Primary PK Parameters (Hepatic Impaired Subjects/Healthy Subjects)

	Group 1[1]		Group 2[2]		Group 3[3]
Parameter (unit)	100 mg IV PTK796	300 mg oral PTK796	50 mg IV PTK796	150 mg oral PTK796	50 mg IV PTK796
AUClast (hr*ng/mL)	0.90 (0.73, 1.11)	0.79 (0.50, 1.24)	0.85 (0.75, 0.97)	1.02 (0.75, 1.40)	1.08 (0.91, 1.27)
AUCinf (hr*ng/mL)	0.86 (0.69, 1.07)	0.79 (0.50, 1.24)	0.88 (0.78, 0.99)	1.02 (0.75, 1.40)	1.08 (0.91, 1.27)
Cmax (ng/mL)	1.42 (1.10, 1.84)	0.96 (0.64, 1.42)	1.02 (0.84, 1.25)	1.24 (0.94, 1.65)	1.08 (0.89, 1.31)

[1] Group 1: mild hepatic impairment vs. Matched healthy subjects.
[2] Group 2: moderate hepatic impairment vs. Matched healthy subjects.
[3] Group 3: Severe hepatic impairment vs. healthy subjects matched to group 2, receiving 50 mg IV PTK796.

Source: Table 14.2-1.5 and Table 14.2-1.6. CSR Study No. CPTK796A2201, page 49

Renal Impairment

In the mass balance study, CPTK796A2101, following oral administration of 300 mg [^{14}C]-omadacycline, approximately 14.4 % of total radioactivity was recovered in urine as unchanged omadacycline. These results suggest that renal excretion is not a major route of elimination for omadacycline.

In the dedicated renal impairment Study # PTK0796-RENL-15102 with a reduced design in subjects with end stage renal disease (ESRD), omadacycline was administered on two separate occasions; prior to dialysis and after dialysis.

The results of the statistical comparison of PK parameters for ESRD subjects on stable hemodialysis vs matched healthy control subjects are presented in Table 6-4. The results of the statistical comparison of PK parameters for ESRD subjects on stable hemodialysis with dosing before dialysis vs dosing after dialysis are presented in Table 6-5.

Table 6-4: Statistical Comparison of Pharmacokinetic Parameters for ESRD Subjects on Stable Hemodialysis vs Matched Healthy Control Subjects

PK Parameter	Cohort	Geometric Mean	Ratio of Geometric Mean (%)	90% Confidence Interval
$AUC_{0\text{-last}}$	Cohort 1 Period 1 (Test)	9210	103	85.8 - 124.3
(h*µg/L)	Cohort 2 (Reference)	8910		
$AUC_{0\text{-inf}}$	Cohort 1 Period 1 (Test)	10100	105	87.7 - 125.8
(h*µg/L)	Cohort 2 (Reference)	9610		
C_{max}	Cohort 1 Period 1 (Test)	1780	94.3	72.4 - 122.7
(µg/L)	Cohort 2 (Reference)	1880		
CL	Cohort 1 Period 1 (Test)	9.91	95.2	79.5 - 114.1
(L/h)	Cohort 2 (Reference)	10.4		

Source: Table 14.2.3.1 CSR: PTK0796-RENL-15102, page 48

Cohort 1 Period 1 (Test): ESRD subjects on stable hemodialysis (dosing after dialysis).
Cohort 2 (Reference): Healthy subjects.

Table 6-5: Statistical Comparison of Pharmacokinetic Parameters for ESRD Subjects on Stable Hemodialysis for dosing before dialysis (Test) vs dosing after dialysis (Reference)

PK parameter	Cohort	Geometric Mean	Ratio of Geometric Mean (%)	90% Confidence Interval
$AUC_{0\text{-last}}$	Period 2 (Test)	9090	98.8	94.8 - 102.9
(h*µg/L)	Period 1 (Reference)	9210		
$AUC_{0\text{-inf}}$	Period 2 (Test)	10000	99.5	96.1 - 103
(h*µg/L)	Period 1 (Reference)	10100		
C_{max}	Period 2 (Test)	2180	123	98.3 - 153.6
(µg/L)	Period 1 (Reference)	1780		
CL	Period 2 (Test)	9.95	100	97.1 - 104
(L/h)	Period 1 (Reference)	9.91		

Source: Table 14.2.3.2 CSR: PTK0796-RENL-15102, page 49
Cohort 1 Period 1 (Reference): Omadacycline 100 mg ESRD subjects on stable hemodialysis (dosing after dialysis);
Cohort 1 Period 2 (Test): Omadacycline 100 mg ESRD subjects on stable hemodialysis (dosing before dialysis).

Based on comparison of exposures, renal impairment did not have a significant effect on the overall extent of exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) of omadacycline, nor on its CL, Vss, or $t_{1/2}$. During dialysis, 7.9% of the omadacycline dose was recovered in the dialysate.
The review team concurs with the Applicant's proposal that no dose adjustment of omadacycline is needed in patients with renal impairment and ESRD patients on hemodialysis.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant evaluated the effect of food content and timing on the relative bioavailability of omadacycline following single oral dose administration with the to-be marketed oral tablet formulation in Study CPTK796A2103 and Study PTK0796-FDEF-15101 (Table 6-6).

Table 6-6: Geometric mean ratio (Fed/Fasted) and 90% confidence intervals for PK parameters

	$AUC_{0\text{-}\infty}$	C_{max}	T_{max} (h)
[a]High-fat (nondairy) meal 4 hours before dosing	83.3 (74.9, 92.7)	84.5 (75.8, 94.1)	Fasted: T_{max} (median) = 2.5 (1.5 to 4.0 hours) Fed: T_{max} (median) = 2.9 (1-6 hours)
[a]High-fat (nondairy) meal 2 hours before dosing	57.7 (51.8, 64.1)	60.1 (53.9, 66.9)	Fasted: T_{max} (median) = 2.5(1.5 to 4.0 hours) Fed: T_{max} (median) = 2.9 (1-6 hours)
[a]High-fat meal including dairy 2 hours before dosing	37.3 (33.6, 41.5)	40.6 (36.5, 45.2)	Fasted: T_{max} (median) = 2.5(1.5 to 4.0 hours); Fed: T_{max} (median) = 2.9 (1-6 hours)
[a]High fat meal 2 hours post-dose	87 (82, 92)	108 (100, 116)	Fasted: T_{max} (median) = 2.5 (1.5 to 4 hours); Fed: T_{max} (median) = 2.5 (1-3 hours)

[b] Low-fat meal 2 hours post-dose	88 (83, 93)	113 (106, 122)	Fasted: T_{max} (median) = 2.5 (1.5 to 4 hours); Fed: T_{max} (median) = 2.5 (1-3 hours)
[c]Light non-fat meal 2 hours post-dose	90 (85, 96)	108 (100, 116)	Fasted: T_{max} (median) = 2.5 (1.5 to 4 hours); Fed: T_{max} (median) = 2.5 (1-2.5 hours)

a= Approximately 150, 250, and 500 calories from protein, carbohydrate, and fat, respectively; *b* = low-fat meal (800-1000 calories; 30% calories from fat); c= *light non-fat (300-350 calories; ≤5% calories from fat);* Tmax: median (range)

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 rate (C_{max}) and extent of absorption (AUC) was reduced by 15% and 17% by a high-fat nondairy meal 4 hours before dosing, 40% and 42% by a high-fat nondairy meal 2 hours before dosing, and 59% to 63% for a high-fat dairy meal 2 hours before dosing compared to dosing in the fasted state. In another food effect study, the extent of absorption (AUC) of omadacycline was marginally reduced by 10 to 13%, while the rate of absorption (C_{max}) was not substantially altered by low-fat, standard non-fat, and the FDA high-fat meals when ingested 2-hours post-dose.

The exposure of omadacycline declines with food intake 4 hours before, or less than 2 hours after dosing. Therefore, to minimize the food effect omadacycline tablets should be taken in a fasting state for at least 4 hours prior to dosing and for at least 2 hours after dosing.

Drug-Drug Interactions (DDI)

CYP Enzyme Mediated DDIs:

In vitro metabolism studies have shown that omadacycline is not a substrate, inhibitor, or inducer of human metabolizing enzymes. Omadacycline does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5 activities at drug concentrations (50 µM) that are well above the C_{max} achieved at recommended dose.

In vitro studies showed that omadacycline was not a time dependent inhibitor of CYP1A1, CYP2A6, CYP2D6 and CYP3A4/5. Therefore, clinically significant DDIs due to inhibition of CYP-mediated metabolism of co-administered drugs by omadacycline are unlikely in humans. Please refer to section 15.2 for details.

In vitro, omadacycline was shown to be a weak inducer of CYP2C19 at a concentration 5 -fold higher than C_{max}, but not of CYP1A2, CYP2B6, CYP1B1, CYP2C8, CYP2C9 and UGT1A1 expression. Therefore, potential DDIs due to increased metabolism of co-administered drugs by omadacycline seems unlikely in humans. Please refer to section 15.2 for details.

Transporter-Mediated DDIs:

Based on results from *in vitro* studies, omadacycline is not an inhibitor of human BCRP, MRP2, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3-mediated transport; omadacycline is not a substrate of the transporters BCRP, MRP2, OAT1, OAT3 and OCT2 but is a potential substrate of P-gp. Omadacycline was not an OATP1B1 or OATP1B3 substrate at supra-therapeutic concentrations (5-13 fold higher than clinically relevant concentrations) tested in *in vitro* studies.

In study PTK0796-DDI-17106 the Applicant investigated the effect 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 AUC by approximately 18% and the C_{max} by 14%. The small increase in omadacycline exposure suggests that no dose adjustment is necessary when omadacycline is given with a known P-gp inhibitor.

Does the clinical pharmacology information support the proposed breakpoint?

The clinical pharmacology information submitted in this NDA cannot support the Applicant's proposed susceptibility breakpoint of (b) (4) in ABSSSI patients, and (b) (4) in CABP patients.

For the susceptibility breakpoints of other pathogens (not listed in **Table 6-7**) (b) (4) the reviewers defer to Clinical/Clinical Microbiology reviewers because there were no relevant clinical pharmacology data for these pathogens.

Table 6-7: Applicant Proposed Susceptibility Breakpoints for Omadacycline

	Minimum Inhibitory Concentrations (µg/mL)		
Pathogen	S	I	R
(b) (4)			

The results of our (probability of target attainment) PTA analyses in ABSSSI patients support the susceptibility breakpoint of 0.12 mcg/mL, 0.12 mcg/mL and 0.03 mcg/mL for *S. aureus, Streptococcus pneumoniae,* and *E. coli*, respectively. The results of our PTA analyses in CABP patients support the susceptibility breakpoint of 0.5 and 1 mcg/mL for *S. pneumoniae* and *H. influenzae* using *ELF AUC*, while the susceptible breakpoint of 0.12 and 0.5 mcg/mL for *S. pneumoniae* and *H. influenzae* using free-drug plasma AUC.

Probability of Target Attainment (PTA) for *S. aureus, S. pneumoniae* and *Enterobacteriaceae*

The PK/PD index for omadacycline is free AUC_{0-24}/MIC which is closely correlated to omadacycline antibacterial activity for *S. aureus, S. pneumoniae,* and *E. coli* based on neutropenic murine thigh infection models. The results from PK/PD studies in the neutropenic murine thigh infection model indicated mean values of AUC_{0-24}/MIC of 23.7, 33.3, and 64.3

were associated with net bacterial stasis for *S. aureus, S. pneumoniae* and *E. coli*, respectively (Table 6-8).

Table 6-8: Summary of AUC0-24/MIC ratio associated with stasis for omadacycline against *S. aureus, Streptococcus. pneumoniae* and *E. coli*

	S. aureus	*S. pneumoniae*	*E. coli*
N	10	5	4
MIC range (µg/mL)	0.25-0.5	0.06-0.12	0.5-1
Median (range)	21.9 (13.8-51.3)	31.2 (17.5-53.4)	64.7 (28.4-98.8)
Mean (SD)	23.7 (10.6)	33.3 (12.8)	64.1 (30.3)
25% quantile, 75% quantile	16.4, 24.7	24.2, 43.2	34.5, 93.2

PTA analyses were conducted for the mean of AUC_{0-24}/MIC ratios for net bacterial stasis using the proposed loading dose and maintenance dose for *S. aureus, Streptococcus pneumoniae,* and *E. coli* (Table 6-9).

Table 6-9: Percent Probabilities of PK-PD Target Attainment by MIC

S. aureus				
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	**Day 3[a]**	**Day 1[b]**	**Day 3[b]**
0.06	100	100	100	99.4
0.12	99.5	99.0	96.2	97.0
0.25	90.5	76.3	73.7	70.8
0.5	38.7	24.0	21.3	19.1
Streptococcus pneumoniae				
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	**Day 3[a]**	**Day 1[b]**	**Day 3[b]**
0.03	100	100	100	100
0.06	100	100	99.9	98.0
0.12	99.9	94.0	92.3	89.9
0.25	70.4	51.1	49.7	46.8
E. coli				
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	

	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
≤0.015	100	100	100	100
0.03	100	100	99.7	97.0
0.06	99.2	93.3	89.0	86.8
0.12	74.5	77.3	74.1	71.6

[a] Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. [b] Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.

Probability of Target Attainment (PTA) for *S. pneumoniae and H. influenzae*

The PK/PD index for omadacycline is free AUC_{0-24}/MIC which is closely correlated to omadacycline antibacterial activity for *S. pneumoniae* based on neutropenic murine pneumonia models and for *H. influenzae* based on in vitro infection models.

The results from PK/PD studies in the neutropenic murine pneumonia infection model indicated mean values of AUC_{0-24}/MIC of 13.6 and 12.3 were associated with 1 log_{10} CFU reduction for *S. pneumoniae* in plasma and ELF, respectively. However, for strain # 1293 PK/PD target value for plasma and ELF AUC/MIC was very high ranging from 180 to 200. The Applicant has not provided any explanation for this high PK/PD target in *S. pneumoniae* 1293. Almost 100% of the drug in plasma penetrated the ELF compartment in mice; therefore, the PK-PD targets are similar in plasma and ELF.

The results of in vitro PK/PD study indicated mean values of AUC_{0-24}/MIC of 8.3 was associated with 1 log10 CFU reduction for *H. influenzae*, respectively (Table 6-10).

Table 6-10: Summary of AUC0-24/MIC ratio associated with 1-log CFU kill for omadacycline against *S. pneumoniae* and *H. influenza*

	S. pneumoniae (Plasma)	*S. pneumoniae (ELF)*	*H. influenzae*
N	4	4	5
MIC range (µg/mL)	0.03-0.125	0.03-0.125	1.0-2.0
Mean (SD)	13.6 (6.9)*	12.3 (5.8)*	8.3 (2.7)
Median (range)	17.5 (6.1-180)	15.5 (6.0-200.6)	8.9 (5.4-11.6)
25% quantile, 75% quantile	8.5, 140	7.8, 154.8	5.6, 10.7

*PK/PD target in *S. pneumoniae* 1293 was excluded

PTA analyses were conducted for the mean of AUC0-24/MIC ratios for 1 log10 CFU using the proposed loading dose and maintenance dose for *S. pneumoniae* and *H. influenzae* (Table 6-11).

Table 6-11: Percent Probabilities of PK-PD Target Attainment by MIC

S. pneumoniae (plasma)	
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC
	Intravenous administration with PO

	switch	
	Day 1[a]	**Day 3[a]**
0.12	99.4	97.9
0.25	93.0	88.7
0.5	81.1	79.0
1	64.0	60.6
S. pneumoniae (ELF)		
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC	
	Intravenous administration with PO switch	
	Day 1[a]	**Day 3[a]**
0.12	100	100
0.25	100	100
0.5	99.9	97.1
1	87.4	74.5
H. influenza (Plasma)		
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC	
	Intravenous administration with PO switch	
	Day 1[a]	**Day 3[a]**
0.25	100	100
0.5	96.1	93.0
1	70.4	66.3
2	7.37	5.43
H. influenzae (ELF)		
MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC	
	Intravenous administration with PO switch	
	Day 1[a]	**Day 3[a]**
0.25	100	100
0.5	100	100
1	97.6	93.7
2	81.6	46.2

[a] Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2.

The FDA reviewer's analysis provides support for IV to PO dosing regimens with a loading dose and omadacycline susceptibility breakpoints for *S. pneumoniae* of 0.12 and 0.5 mcg/mL using plasma AUC and ELF AUCs, respectively.

For *H. influenzae*, the FDA reviewer found that the PTA ≥ 90% at MIC values of 0.5 and 1 µg/mL were achieved for IV to PO dosing regimens using plasma and ELF AUCs, respectively. (b) (4)

Regarding determination of susceptibility breakpoints, the MIC distributions in clinical trials and surveillance programs, nonclinical PK-PD target attainment data, and clinical data should all be taken into consideration. The ultimate determination of the omadacycline breakpoints will depend on the totality of information provided by each discipline. Please refer to the clinical microbiology section and clinical review section for further details on the breakpoint determinations.

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7. Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Trials

Table 7-1 Table Listing of Clinical Trials Relevant to omadacycline

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	Sample Size/Gender/Age/ Population	No. of Sites and Countries
Controlled phase-3 Trial(s) to Support Efficacy and Safety for the Indication of CABP					
Study CABP-1200	Phase 3, randomized (1:1), double-blind, active comparator-controlled, trial comparing Omadacycline (OMC) and moxifloxacin (MOX) in the treatment of adults with CABP (PORT Risk Class II, III, or IV)	**Investigational therapy:** OMC, 100 mg iv q12h (first 2 doses), followed by 100 mg iv q24h for at least 3 days with option to switch to oral tablets 300 mg po q 24h **Comparator therapy:** MOX, 400 mg iv q24h for at least 3 days with the option to switch to 400 mg po q24h Treatment duration was 7-14 days	The primary efficacy endpoints: ECR assessment (72 to 120 hr. after administration of first dose of study drug) in the ITT population. Secondary efficacy endpoint: Overall assessment of clinical response at PTE	Total: 774 (OMC = 386 MOXI = 388) Male (427), Female (347) Age 19 to 97 Years Patients with signs and symptoms of CABP	86 sites enrolled and randomized at least 1 patient. Most sites were located in the Eastern Europe, that enrolled ~ 80% of patients (82% and 78% in OMC and MOXI group, respectively); followed by Rest of World (including Latin America, Asia-Pacific, Israel, Turkey, and South Africa) which enrolled ~15% of patients (15% and 17% in OMC and MOXI, respectively); Western Europe accounted for 3% and 5% enrollment in OMC and MOXI group, respectively, and the United states , 0.25% and 0.5% in OMC and MOXI group, respectively)
Controlled phase-3 trials to Support Efficacy and Safety for Indication: ABSSSI					
Study ABSI-1108	Phase 3, randomized (1:1), double-blind, active comparator-	**Investigational therapy:** Multiple dose, OMC 100 mg iv q12 h for	Primary efficacy endpoints: ECR at 48 to 72 hours after the first dose of study drug	Total: 645 OMC = 323 LZD = 322	Total of 55 sites enrolled and randomized at least 1 patient; Eastern Europe had the most sites (25 sites), followed by

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	Sample Size/Gender/Age/ Population	No. of Sites and Countries
	controlled, multi-center study comparing omadacycline (OMC) and linezolid (LZD) for the treatment of adults with ABSSSI	two doses, followed by 100 mg iv q 24h OR 300 mg po q24h **Comparator therapy:** LZD 600 mg iv q12h, and LZD 600 mg po q12h Total treatment duration of 7 to 14 days.	in the mITT Population Secondary efficacy endpoint: Overall assessment of clinical response at PTE	Male = 416, Female = 229 Age 18 to 90 years	Western Europe (16), North America (11) and Latin America (3).
Study ABSI-16301	Phase 3, randomized, double-blind, double-dummy, comparator controlled multicenter study to compare the efficacy of OMC with LZD in adults with ABSSSI	**Investigational therapy:** OMC 450 mg po q24h, followed by OMC 300 mg po q24h **Comparator therapy:** LZD 600 mg po q12h Total treatment duration of 7 to 14 days.	Primary efficacy endpoints: ECR at 48 to 72 hours after the first dose of study drug in the mITT population	Total: 735 OMC = 368 LZD = 367 Male =462, Female =273, Age 18 to 86 years	This study was conducted in US only. A total of 33 sites enrolled and randomized at least 1 patient.
Additional phase-2 and 3 Studies to support safety					
Study PTK0796-CSSI-0804	A Phase 3 randomized, evaluator-blinded, study to compare the safety and efficacy of	**Investigational therapy:** OMC 100 mg q24h, iv And OMC 300 mg q24h,	Clinical response rates were summarized using both the investigator reported outcome and sponsor adjudicated	Total: 140 OMC = 68 LZD = 72	A total of 143 patients were enrolled at 6 investigation sites within the US.

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	Sample Size/Gender/Age/ Population	No. of Sites and Countries
	omadacycline (OMC) with Linezolid (LZD) in complicated skin and skin-structure infection (cSSSI)	po **Comparator therapy**: Multiple dose, LZD 600 mg q12h, iv and LZD 600 mg q12h, po	outcome for each population for EOT and TOC visits.	Male =93, Female =47 Age 18 to 82 years	
Study PTK0796-CSSI-0702	A phase-2 randomized, evaluator-blinded, study to compare the safety and efficacy of omadacycline with linezolid in cSSSI	**Investigational therapy**: Multiple dose, OMC HCl 100 mg q24h, iv And OMC freebase 200 mg q24h, po **Comparator therapy:** Multiple dose, LZD 600 mg q12h, iv And LZD 600 mg q12h, po	Clinical success rates in the modified ITT (mITT) population; mITT All patients who received at least 1 dose of study drug and who had at least 1 infecting pathogen isolated at the Baseline evaluation) and Clinical Evaluable (CE) populations	Total: 219 OMC = 111 LZD = 108 Male =123, Female =96 Age 19 to 80 years	This was a multicenter study conducted at 11 investigational sites across the United States (US); each investigational site enrolled and treated at least 1 eligible patient.
Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, PORT= Pneumonia Outcome research Team; AC = alveolar cells, ADME = absorption, distribution, metabolism, and excretion, CABP = community-acquired bacterial pneumonia, cSSSI = complicated skin and skin structure infections, ELF = epithelial lining fluid, ER = extended release, ESRD = end-stage renal disease, HCl = hydrochloride, iv = intravenous, LZD = linezolid, MOXI = moxifloxacin, OMC = omadacycline, PBO = placebo, PD = pharmacodynamics, PK = pharmacokinetics, po = oral, QTc = corrected QT interval, q12h = every 12 hours, q24h = every 24 hours, TIG = tigecycline, yrs. = years.					

7.1.2. Review Strategy

The review of clinical efficacy will primarily focus on the phase 3 trial (Study CABP-1200) for CABP indication, and two phase 3 trials (Study ABSI-1108 and Study ABSI-16301) for ABSSSI indication. Of note, the Applicant has also submitted results of clinical trials, conducted for the treatment of complicated skin and soft tissue infections (i.e., cSSSI). Because these trials differed from ABSSSI trials with regard to study design, dosing regimen and primary end points, they are not included in the pooled safety and efficacy analyses. Synopsis of these studies are presented briefly in Appendix 15.3.3.

In large part, for both indications, the clinical reviewer was responsible for the safety review and the statistical reviewer was responsible for the efficacy review. However, there were numerous analyses in this application for both indications, which were jointly conducted when the efficacy outcomes were entwined with safety outcomes, for instance, consideration of outcomes in patients with risk factors associated with mortality, outcomes in subgroups with risk factors, or outcomes in subgroups with relevant pathogens, sensitivity analysis based on receipt of prior antibacterial therapy, or those who discontinued therapy due to treatment emergent adverse events related to worsening of index infection or due to lack of efficacy.

Data Sources

The data sources for review included applicant study reports, data sets analyzed, and literature referenced. The data were provided electronically in SDTM and ADAM formats with codes. The full electronic path of these data is located at url: \\CDSESUB1\EVSPROD\NDA209816\0000\

Data and Analysis Quality

Quality and integrity review of the submitted data did not find any issues with regards to reproducibility of the primary analysis dataset from the original data source. It was possible to verify the randomized treatment assignments. The applicant submitted documentation of data quality control/assurance procedures per ICH E3, section 9.6; and ICH E6, section 5.1). The blinding/unblinding procedures were well documented as described in ICH E3, section 9.4.6. A final statistical analysis plan (SAP) was submitted and relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding. The level of effort needed to process the data was moderate.

The analyses conducted by the Applicant appeared generally consistent with the pre-specified statistical analysis plan. The reviewer was able to reproduce the primary and key secondary efficacy results from the submitted datasets. A few discrepancies were found during review such as the PORT score calculation, the clinical and statistical reviewers submitted information requests to Sponsor for a few deficiencies, clarification questions and additional analyses. There were some concerns reported in by the inspection team about a site in ABSI-16301 study, see Section 4.1. for details.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. ABSSSI Trial (Study ABSI-1108)

Trial Design and Endpoints

Study ABSI-1108 was a phase 3 randomized (1:1), double-blind, active comparator-controlled, multi-center study to compare the safety and efficacy of omadacycline IV/PO to linezolid IV/PO for treating adult patients with acute bacterial skin and skin structure infection (ABSSSI) that is known or suspected to be due to a Gram-positive pathogen(s).

Patient randomization was stratified across treatment groups by type of infection (wound infection, cellulitis/erysipelas or major abscess) and geographic region (North America, Latin America, Eastern Europe, and Western Europe). The number of patients with major abscess was limited to no more than 30% of randomized patients. All patients were expected to present with ABSSSI severe enough to require a minimum of at least 3 days of intravenous (IV) antibacterial drug treatment. After a minimum of 3 days of IV treatment, the investigator could switch the patient to oral (po) treatment based on evidence of improvement both systemically and at the primary site of infection. Patients were enrolled at a total of 55 sites globally (North America-11 sites, Eastern Europe-25 sites, Western Europe-16 sites, and Latin America-3 sites).

Patients participated in the study for approximately 30 days. Following Screening, eligible patients were randomly assigned to receive IV study drug with the option to switch to oral therapy after 3 days. Screening assessments, with the exception of the blood cultures, were performed within 24 hours prior to randomization. The blood culture was to be completed within the 24 hours prior to the first dose of study drug. Visits were conducted daily on Days 1 through 7. The Day 6 visit was optional for patients that had been switched to oral therapy and had been discharged from a hospital setting. A Day 10 visit was to be conducted for patients with treatment extending beyond 9 days, unless this visit coincided with the EOT Visit. EOT Visit was to be performed on the calendar day of, or within 2 days following the last dose of study drug administration. If a patient withdrew prematurely or terminated participation in the study before completion, the EOT Visit was to be conducted. PTE Visit was to be performed 7-14 days after the patient's last day of study therapy, and Final Follow-up assessment visit was conducted on Day 30-37 (after start of first infusion of study drug). The details of schedule of assessments and procedures is provided in Appendix 15.3.4

The study protocol was designed in accordance with the FDA guidance on developing antimicrobial drugs for the treatment of ABSSSI, in addition to the guidelines of the Infectious Diseases Society of America. The FDA guidelines recommend a primary endpoint (48 to 72 hours after the first dose of study drug) based on reduction in lesion area for a finding of non-inferiority.

Linezolid was chosen as an active comparator drug, since it is approved worldwide for the treatment of ABSSSI caused by Gram-positive pathogens and has an acceptable and well-defined safety profile. Additionally, linezolid can be administered IV and orally, and has FDA approval for the treatment of complicated and uncomplicated skin and skin structure infections (these indications fully encompass the ABSSSI indication) caused by Gram-positive pathogens including MRSA.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

Patients who were 18 years of age or older, had a qualifying skin and skin structure infection, and had evidence of a systemic inflammatory response 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 erythema, edema, or induration (at least 1 or more). The classification of qualifying skin and skin structure infection infections included the following:

- 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 inflammatory response within the 24 h prior to randomization was indicated by 1 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]).

Exclusion Criteria

The principal criteria for exclusion from the study were if : patient received 1 or more doses of a potentially effective systemic antibacterial treatment within 72 h prior to first dose of study drug; had, for any reason, used a topical antibacterial agent(s) with specific antibacterial activity continuously within 72 h prior to first dose of study drug, if applied to the skin for greater than or equal to 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 study drug; or had previously been treated with omadacycline or previously enrolled in this study.

Dosing Regimen Study ABSI-1108

Dosing schedule is shown in the table below.

Dosing regimen in ABSI-1108		
Study Day	**Omadacycline group**	**Linezolid group**
Day 1	100mg iv q12h (first 2 doses)	600mg iv q12h
Day 2-3	100mg iv q24h	600mg iv q12h
Day 4-EOT (7-14)	Continued the above treatment with option to switch to 300mg po q24h	Continued the above treatment with option to switch to 600mg po q12h

Prior and Concomitant treatment

At Screening visit, all patients were carefully evaluated, and a determination was made as to whether 1 or more procedures were indicated. When indicated, planned procedures were to be performed within 24 h and no later than 48 h after, the start of study drug.
Any non-study systemic antibacterial agent with a spectrum that is active against the known or potential infecting pathogen(s) responsible for the infection under study, except in cases of clinical failure. All treatments not specified as prohibited were permitted during the study.

7.2.2. ABSSSI Trial (Study ABSI-16301)

Study Design and Procedure

Study ABSI-16301 was a randomized (1:1), double-blind, and double-dummy, active comparator-controlled, phase 3 non-inferiority trial comparing omadacycline and linezolid, administered orally (also referred to as “po therapy” in this document), for the treatment of adult patients with ABSSSI that was known or suspected to be due to a Gram-positive pathogen(s). The number of patients with major abscess was limited to no more than 30% of randomized patients. Enrollment of patients who had received a single dose of an allowed short-acting antibacterial within the 72 h prior to randomization was permitted but was limited to no more than 25% of randomized patients. Patient randomization was stratified by type of infection (wound infection, cellulitis/erysipelas, or major abscess) and receipt of an allowed antibacterial therapy in the 72 h prior to randomization (again, not more than 25% of the patient population). Patients were enrolled at a total of 33 sites in the US.

Patients participated in the study for approximately 30 days. Following Screening, eligible patients were randomly assigned to receive po treatment with either omadacycline or linezolid. The expected total duration of treatment was 7 to 14 days. The schedule of all assessments performed in the study is provided in Appendix 15.3.4

Reviewer's Comment: Note that in study ABSI-1108, patients were excluded if they have received 1 or more doses of a potentially effective systemic antibacterial treatment within 72 h prior to first dose of study drug. In ABSI16301, a single dose of an allowed short-acting antibacterial within the 72 h prior to randomization was allowed but limited to no more than 25% of randomized patients.

Selection of Patients

The selection of patients in the Study ABSI16301 was identical to that of Study ABSI-1108 described above with the following exceptions: patients may have been eligible despite prior antibacterial therapy if they had been treated with a single dose of a short-acting antibacterial (i.e., 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 receipt of corticosteroids equivalent of greater than or equal to 40 mg of prednisone per day for more than 14 days in the 30 days prior to Screening was changed to receipt of systemic corticosteroids for more than 14 days in the 30 days prior to Screening.; The oxazolidinones, including tedizolid, were added to the compounds included in the exclusion criteria for patients with a history of hypersensitivity or allergic reaction; and the inability to tolerate oral medication (e.g., nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of oral medication).

Dosing Regimen Study ABSI-16301

Dosing regimen is shown in the table below.

Dosing regimen in ABSI-16301		
Study Day	**Omadacycline group**	**Linezolid group**
Day 1-2	450mg po q24h	600 mg po q12h
Day 3-EOT (7-14)	300mg po q24h	600mg po q12h

Prior and Concomitant Treatments

The treatments prohibited and permitted in the study were identical to those in Study ABSI-1108.

Efficacy Endpoints for ABSI 1108 and ABSI 16301 Trials

Primary Efficacy Endpoint for ABSI 1108 and ABSI 16301 Trials

The primary efficacy outcome was the percentage of patients with Clinical Success at ECR assessment (48 to 72 h after the first infusion of study drug in the mITT population). This endpoint was based on the lesion size reduction. To be classified as a responder for the primary endpoint, patients should be alive, with the primary lesion size reduced by ≥20% compared to

screening measurements, without receiving any rescue antibacterial therapy, and was not a clinical failure. Definition of clinical failure is presented in Appendix 15.3.23

Patients were considered to have an 'indeterminate' response if there was not enough information to determine if they met criteria for ECR. The Applicant pre-specified a 10% non-inferiority margin. The scientific justification for this margin based on the ECR endpoint is described in the FDA's draft guidance document.

Secondary Endpoints for Study ABSI 1108 and ABSI 16301 Trials

The secondary efficacy outcome was the overall assessment of clinical response at PTE based on the assessments at the EOT and PTE visits. Success was defined as survival after completion of a study drug regimen without receiving any alternative (rescue) antibacterial therapy other than study drug, without any unplanned major surgical intervention between EOT and PTE visits, sufficient resolution of infection such that further antibacterial therapy is not needed.

The primary efficacy analysis was conducted in the mITT population. Treatment differences in clinical success rates (omadacycline treatment group minus the linezolid treatment group) at ECR and its 95% confidence interval (CI) were calculated without stratification by Miettinen and Nurminen method. Non-inferiority was established if the lower limit of the two-sided 95% CI for the difference in the ITT population was not greater than the non-inferiority margin of 10%.

For ABSI-1108, the planned sample size of 632 patients was based on the response rate assumption of 82% for omadacycline and linezolid, and a statistical power of 90%. The trials did not plan to conduct interim efficacy analyses and did not provide for early stopping for futility or sample size modifications. An independent data monitoring committee monitored safety throughout the conduct of the trials and recommended continuing trials without any modifications.

For ABSI-16301, the planned sample size of 704 patients was based on the response rate assumption of 85% for omadacycline and linezolid, and a statistical power of 90%. No interim analysis of efficacy or safety was planned or performed.

Reviewers' Comment: Two ABSSSI trials were conducted that generally followed the recommendations in FDA's guidance document, Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment.31 The trials were designed as non-inferiority trials using the appropriate efficacy endpoint and a non-inferiority margin of 10%. Linezolid was used as the active control.

[31] https://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf

7.2.3. Statistical Analysis Plan for ABSSSI Trials (Study ABSI-1108 and ABSOI-16301)

The protocols defined several analysis populations. The intent-to-treat (ITT) population was comprised of all randomized patients. The safety population was comprised of randomized patients who received any amount of study drug. The modified intent-to-treat (mITT) population consisted of all randomized patients without a sole Gram-negative causative pathogen(s) at Screening. The microbiological modified intent-to-treat (micro-mITT) population consisted of patients in the mITT population who have at least 1 Gram-positive causative pathogen(s) at Screening. The clinically evaluable (CE) population consisted of all mITT patients who received study drug, had a qualifying ABSSSI, completed an outcome assessment, and meet all other evaluability criteria detailed in the SAP. The microbiologically evaluable (ME) population included patients in the CE population who have at least 1 Gram-positive causative pathogen(s) at Screening. Refer to Appendix 15.3.24. for individual definition of analysis population.

For ABSI-1108, the planned sample size of 632 patients was based on the response rate assumption of 82% for omadacycline and linezolid, and a statistical power of 90%. The trials did not plan to conduct interim efficacy analyses and did not provide for early stopping for futility or sample size modifications. An independent data monitoring committee monitored safety throughout the conduct of the trials and recommended continuing trials without any modifications.

For ABSI-16301, the planned sample size of 704 patients was based on the response rate assumption of 85% for omadacycline and linezolid, and a statistical power of 90%. No interim analysis of efficacy or safety was planned or performed.

7.2.4. Study Results (ABSSSI Trials)

Compliance with Good Clinical Practices

The Applicant reported that the phase 3 trials (CABP-1200, ABSI-16301 and ABSI-1108) were conducted in conformance with the International Council for Harmonisation (ICH) for Good Clinical Practice(GCP) standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human patients participating in biomedical research. The Applicant further reported that all analyses of data for these studies complied with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E9) and the Applicant's guidance documents and standards. The Applicant's statistical analyses were performed using SAS Version 9.3 (or higher). Refer to section 8 for additional details.

7.2.4.1 Patient Disposition and Protocol Violations

Patient Disposition

For Study ABSI1108, about 91% of subject randomized completed the study in both groups. The most frequent reason for discontinuation was lost to follow-up. About 89% subjects completed study treatment. The reasons for treatment discontinuation were physician decision, lost to follow-up, withdrawal by patient, other and AE; all occurred with similar frequencies. There were also 3 deaths observed.
For Study ABSI-16103, about 85% of subjects completed the study. The main reason for discontinuation was lost to follow-up, approximately 89% of omadacycline patients and 86% of the linezolid patients discontinued study treatment. Most common reason for this is the lost to follow-up. The other reasons included withdrawal by patient, physician decision and other reasons.

Patient disposition is summarized in Appendix 15.3.7 for Study ABSI1108 and Study ABSI16301, respectively.

Protocol Violations/Deviations

In Study ABSI-1108, major protocol deviations were uncommon, occurring in < 5% of all patients for each category. The most frequently reported deviations included visit scheduling/patient visit completion issues (4.6% of ITT patients) and missing endpoint assessments (3.2% patients). These major types of protocol deviations led to exclusion of such patients from the evaluable populations; however, these protocol deviations did not have a major impact on the efficacy assessment. In Study ABSI-16301, major protocol deviations occurred in < 10% of all patients for each category. The most commonly reported deviations included missing endpoint assessments (7.5% of all patients), visit scheduling issues (5.6% of all patients), and study treatment compliance issues (3.9% of all patients). Table summarizing protocol violation in Study ABSI1108 and ABSI16301 is listed in Appendix 15.3.7.

Reviewers' Comment: In a non-inferiority trial, poor trial conduct or compliance can drive the study results toward the alternative hypothesis of similarity between the treatment groups. Therefore, it is important to evaluate reasons for premature withdrawal of subjects from the study, premature discontinuation of study drug, and protocol violations. The discontinuations and associated reasons from study or study treatment were equally balanced between treatment arms. The most common major protocol deviation in ABSSSI trials were visit scheduling issues and endpoint assessment violations, which were balanced between the treatment groups and should not expected to impact the results of efficacy and safety evaluation.

7.2.4.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics in ABSI-1108 and ABSI-16301 for the mITT population are presented in the following Table 7-2.

Table 7-2 Demographic and Baseline Characteristics Study ABSI-1108 and ABSI-16301 Trials (mITT Population)

Baseline characteristic	Study ABSI-1108 (IV to PO)		Study ABSI-16301 (PO therapy)	
	Omadacycline (n = 316)	Linezolid (n =311)	Omadacycline (n =360)	Linezolid (n =360)
	n (%)	n (%)	n (%)	n (%)
Gender				
Male	199 (63.0)	208 (66.9)	210 (58.3)	215 (59.7)
Female	117 (37.0)	103 (33.1)	121 (33.6)	145 (40.3)
Race				
White	287 (90.8)	289 (92.3)	320 (88.9)	334 (92.8)
Black or African American	16 (5.1)	8 (2.6)	22 (6.1)	13 (3.6)
Asian	1 (0.03)	2 (0.06)	3 (1.0)	5 (1.4)
Other	12 (3.8)	12 (3.9)	15(4.2)	8(2.2)
Age (years)				
<65	280 (88.6)	279 (89.7)	344 (95.6)	339 (94.2)
>=65	36 (11.4)	32(10.3)	16 (4.4)	21(5.8)
Region				
North America	207 (65.5)	202 (65.0)	360 (100)	360 (100)
Eastern Europe	81 (25.6)	84 (27.0)	n/a	n/a
Western Europe	23 (7.3)	21 (6.8)	n/a	n/a
Latin America	5 (1.6)	4 (1.3)	n/a	n/a
Infection type				
Wound infection	102 (32.3)	104 (33.4)	210 (58.3)	214 (59.4)
Major abscess	91 (28.8)	89 (28.6)	64 (17.8)	62 17.2()
Cellulitis	123 (38.9)	118 (37.9)	86 (23.9)	84 (23.3)
Lesion area				
<=300 cm	160 (50.6)	147 (47.3)	162 (45.0)	185 (51.4)
>300 - 600	88 (27.8)	101 (32.5)	134 (37.2)	118 (32.8)
>600 - 1000	43 (13.6)	34 (10.9)	44 (12.2)	36 (10.0)
>1000	25 (7.9)	29 (9.3)	20 (5.6)	21 (5.8)
History of Diabetes				
Yes	20 (6.3)	30 (9.6)	14 (3.9)	31 (8.6)
No	296 (93.7)	281 (90.4)	346 (96.1)	329 (91.4)
History of hepatitis C				
Yes	95 (30.1)	89 (28.6)	116 (32.2)	125 (34.7)
No	221 (69.9)	222 (71.4)	244(67.8)	235(65.3)
Cr Cl (mL/min)				
<=50	9 (2.8))	7 (2.3)	18 (5.0)	17 (4.8)
>50	306 (96.8)	302 (97.1)	339 (95.0)	339 (95.2)

Baseline characteristic	Study ABSI-1108 (IV to PO)		Study ABSI-16301 (PO therapy)	
	Omadacycline (n = 316)	Linezolid (n =311)	Omadacycline (n =360)	Linezolid (n =360)
Missing	1(0.3)	2(0.6)	3(<1.0)	4(1.1)
Source: FDA Statistical analysis; CSR CrCL= creatinine clearance				

Reviewers' Comment: The trials were well-balanced in terms of baseline demographics and disease characteristics. The types of primary infections were balanced across treatment groups in both ABSSSI trials. In the global study (Study ABSI-1108), there were comparatively higher percentages of patients presented with cellulitis/erysipelas (~40%) as their primary ABSSSI infections. Whereas, in Study ABSI-16301, nearly 60% of primary infections were wound infections. This may be a reflection of the greater proportion of IV drug users with resulting wound infections, who were enrolled in the US study. In both trials, the majority of the primary infections occurred in the extremities (leg or arm).

7.2.4.3 Other Baseline Characteristics (ABSSSI Trials)

Table 7-3 below summarizes medical history relevant to ABSSSI infections in the mITT populations in Study ABSI-1108 and Study ABSI-16301.

Table 7-3 ABSSSI Relevant Medical History in Study ABSI-1108 and Study ABSI-16301 (m-ITT Population)

	Study ABSI-1108 (IV to PO)		Study ABSI-16301 (PO therapy)	
	Omadacycline (n = 316)	Linezolid (n =311)	Omadacycline (n =360)	Linezolid (n =360)
	n (%)	n (%)	n (%)	n (%)
Patients with ABSSSI relevant medical history	229	243	309	320
Recent trauma that resulted in the primary infection	183 (58)	205 (66)	270 (75)	260 (72)
Infection was the result of iv drug abuse	160 (51)	166 (53)	254 (71)	240 (67)
Patient had a prior ABSSSI	151 (48)	154 (50)	200 (56)	198 (55)
Hepatitis C*	94 (29)	90 (28)	116 (32)	125 (35)
Diabetes mellitus**	24 (7)	35 (11)	14 (3.9)	31 (8.6)
Relevant surgical procedure that resulted in the primary ABSSSI	8 (3)	3 (1)	2 (0.6)	3 (0.8)
Infection was the result of vascular insufficiency or edema	3 (1)	4 (1)	0	2 (0.6)
Peripheral artery disease	2 (0.6)	2 (0.6)	0	1 (0.3)
Concurrent secondary ABSSSI lesions	NA	NA	88 (24)	95 (26)

	Study ABSI-1108 (IV to PO)		Study ABSI-16301 (PO therapy)	
	Omadacycline (n = 316)	Linezolid (n =311)	Omadacycline (n =360)	Linezolid (n =360)
	n (%)	n (%)	n (%)	n (%)
Source: CSR, FDA Statistical Analysis * Included the MedDRA PTs "hepatitis C" and "chronic hepatitis C." ** Included events within the MedDRA high level term of "diabetes mellitus (including subtypes)."				

Clinical Reviewer's Comment: There was an overall lower proportion of patients reporting ABSSSI relevant medical history in Study ABSI-1108 (75%), as compared to Study ABSI-16301 (87%). Diabetes mellitus was comparable between the trials and between the treatment groups. In Study ABSI-1108, about 38% (n=242) patients were hospitalized and under in-patient care at the time of initiation of study drug while no patients were hospitalized for their skin infections at the start of the US study ABSI-16301. Additionally, in Study ABSI-16301, nearly 70% of patients reported that the qualifying ABSSSI was the result of IV drug abuse, and about 55% of all patients had at least 1 prior history of ABSSSI.

7.2.4.4 Baseline Pathogen Characteristics

The Baseline pathogenic organisms from the ABSSSI site or blood culture by genus and species is summarized for the micro-m ITT population in Appendix 15.3.9.

Few patients had bacteremia in either study. In Study ABSI-16301, 10 patients (2 omadacycline and 8 control group) and in Study ABSI-1108, 20 patients (11 omadacycline and 9 control group) had bacteremia at baseline.

Clinical Reviewer's Comment: The incidence and distribution of pathogens were similar between treatment groups in ABSSSI trials. In ABSI 1108 trial, a majority of patients were infected with aerobic Gram-positive pathogens which included S. aureus (68.4% omadacycline, 66.5% linezolid patients). Next common pathogen isolated was S. anginosus (20.6% omadacycline, 16.3% linezolid). In the S. aureus group, a slightly higher percentage of linezolid patients had MSSA as compared to omadacycline patients (38.6% omadacycline, 44.9% linezolid), while a higher percentage of omadacycline patients had MRSA as compared to linezolid patients (30.3% omadacycline, 22.0% linezolid).

In ABSI1108 trial, mono-microbial Gram-positive infection was present in 156 (68.4%) omadacycline patients and 171 (75.3%) linezolid patients in the micro-mITT population. Although patients with a sole Gram-negative pathogen(s) at baseline were excluded from the trial; however, Gram-negative pathogens were present as poly-microbial infections (Gram-negative aerobes: 28 (12.3%) omadacycline patients, 23 (10.1%) linezolid patients; Gram-negative anaerobes: 17 (7.5%) omadacycline patients, 13 (5.7%) linezolid patients). Patients who did not have a positive culture at baseline (e.g., patients with cellulitis for which it is

difficult to establish a microbial pathogen on culture of the leading edge of the skin infection), were still included in the ITT efficacy analyses.

In ABSI16301 trial, mono-microbial Gram-positive infection was present in 66.7% omadacycline, and 73.9% linezolid patients. Distribution of Gram positive pathogen was similar as seen in ABSI1108 trial with 79.7% omadacycline patients and 81.2% linezolid patients had S. aureus isolated from ABSSSI site. S. anginosus was isolated from 20.7% omadacycline, and 15.7% linezolid patients. Gram-negative pathogens were present in a subset of poly-microbial infections; 12.7% and 14.7% of omadacycline and linezolid patients, respectively, had a Gram-negative pathogen.

7.2.4.5 Efficacy Results

Primary Efficacy Endpoint

The next two tables (Table 7-4 and Table 7-5) summarize the primary efficacy analysis: ECR at 48-72 hours in the mITT population. In ABSI-1108, the response rates were 84.8% vs 85.5%, the treatment difference was -0.7% favoring the linezolid arm slightly, with a lower bound of -6.3% for the 95% CI. In ABSI-16301, the response rates were 87.5% and 82.5% respectively. The treatment difference is 5.0% favoring omadacycline, with a lower bound of -0.2%. Since both the lower bounds were above -10%, both trials met their primary objectives, demonstrating that omadacycline was non-inferior to linezolid.

Table 7-4 Table Primary Efficacy Analysis: ECR in Study ABSI-1108 (mITT population)

Primary Efficacy Analysis: ECR in Study ABSI-1108 (mITT population)			
Outcome	Omadacycline N = 316 n (%)	Linezolid N = 311 n (%)	% Difference (95%CI)
Clinical success	268 (84.8)	266 (85.5)	-0.7 (-6.3, 4.9)
Clinical failure + indeterminate	48 (15.2)	45 (14.5)	
Clinical failure	23 (7.3)	19 (6.1)	
Indeterminate	25 (7.9)	26 (8.4)	
Source: FDA Statistical Reviewer's Analysis Note: Clinical Success: early clinical response (ECR) assessed by ≥ 20% reduction in lesion size within 48 to 72 hours after the first dose. CI = confidence interval.			

In ABSI1108, clinical success, failure and indeterminate rates were comparable between the two treatment groups. Reasons for clinical failure at ECR included lack of reduction in lesion size by at least 20% from baseline (5.1% omadacycline, 4.5% linezolid), AE requiring discontinuation of study drug (1.6% omadacycline, 0.6% linezolid), discontinuation of study drug 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 under study (0.6% omadacycline, 0% linezolid). Of the patients who had an indeterminate outcome, most had an assessment

outside of the 48 to 72 hours' window (5.1% omadacycline, 5.8% linezolid) or were lost to follow-up or withdrew consent (2.8% omadacycline, 2.6% linezolid).

Table 7-5 Primary Efficacy Analysis: ECR in Study ABSI-16301 (mITT population)

Primary Efficacy Analysis: ECR in Study ABSI-16301 (mITT population)			
Outcome	Omadacycline N = 360 n (%)	Linezolid N = 360 n (%)	% Difference (95%CI)
Clinical success	315 (87.5)	297 (82.5)	5.0 (-0.2, 10.3)
Clinical failure + indeterminate	45 (12.5)	63 (17.5)	
Clinical failure	26 (7.2)	32 (8.9)	
Indeterminate	19 (5.3)	31 (8.6)	
Source: FDA Statistical Reviewer's Analysis; Note: Clinical Success: ECR assessed by ≥ 20% reduction in lesion size within 48 to 72 hours after the first dose. CI = confidence interval.			

Similarly, in ABSI-16301 trial, clinical success, failure and indeterminate rates were comparable between the two groups. Reasons for failure at ECR included lack of reduction in lesion size by at least 20% from baseline (5.8% in omadacycline, 7.2% in linezolid). In addition, discontinuation of treatments with need for rescue antibacterial therapy was uncommon at this early assessment time point (1.4% omadacycline, 1.7% linezolid). Of patients with 'Indeterminate' outcome at 48 to 72 hours, most had an assessment outside of the 48 to 72 hours' window (3.1% omadacycline, 5.6% linezolid) or were lost to follow-up or withdrew consent (2.2% omadacycline, 3.1% linezolid), causing those patients to fall in 'Indeterminate' category. Nevertheless, patients with 'Indeterminate' outcomes were considered 'clinical failure' in all analyses. The statistical reviewer and the clinical reviewer were able to reproduce and confirm the Applicant's primary endpoint efficacy analyses for these two trials.

FDA sensitivity analysis of primary efficacy after exclusion of patients from Study Site with GCP non-compliance (Site # 606): Study ABSI16301

Outcome	**Omadacycline N = 353 n/N (%)**	**Linezolid N = 353 n /N (%)**	**Difference (95% CI)**
Clinical Success at ECR	308/353 (87.3)	290/353 (82.2)	5.1 (-0.2, 10.5)
Clinical Success at PTE	296/353 (83.9)	284/353 (80.5)	3.4 (-2.3, 9.1))
Source: FDA Statistical Reviewer's Analysis;			

The revised analysis results were almost identical to the primary analysis which included patients from study site # 606. In general, it is preferred to exclude from the efficacy analyses the subgroup of patients who were enrolled at trial sites for which an inspection found deviations from Good Clinical Practice (e.g., illegible source records).

Secondary and other relevant endpoints

Analysis using the pre-specified key secondary endpoint of clinical status at PTE (success/failure/indeterminate) in the mITT population is presented in Table 7-6 and Table 7-7. This endpoint served to evaluate the maintenance of the clinical response achieved at 48-72 hours at later timepoint. FDA analyses were consistent with the Applicant's analyses.

In Study ABSI-1108, the response rates at this later endpoint were higher in the omadacycline group (86.1%) than in the comparator arm (83.6%). Similarly, in trial ABSI-16301, the response rates were also higher in the omadacycline group (84.2%) than in the comparator arm (80.8%).

Table 7-6 Overall Clinical Response at the PTE Visit Based on Investigator's Assessments for the mITT Population: Study ABSI-1108

Overall Clinical Response at the PTE Visit Based on Investigator's Assessments for the mITT Population: Study ABSI-1108			
Outcome	Omadacycline N = 316 n (%)	Linezolid N = 311 n (%)	% Difference (95% CI)
Clinical success	272 (86.1)	260 (83.6)	2.5 (-3.2, 8.2)
Clinical failure + indeterminate	44 (13.9)	51 (16.4)	
Clinical failure	20 (6.3)	27 (8.7)	
Indeterminate	24 (7.6)	24 (7.7)	
Source: FDA Statistical Reviewer's Analysis			

Table 7-7 Overall Clinical Response at the PTE Visit Based on Investigator's Assessments for the mITT Population: Study ABSI-16301

Overall Clinical Response at the PTE Visit Based on Investigator's Assessments for the mITT Population: Study ABSI-16301			
Outcome	Omadacycline N = 360 n (%)	Linezolid N = 360 n (%)	% Difference (95% CI)
Clinical success	303 (84.2)	291 (80.8)	3.3 (-2.2, 8.9)
Clinical failure + indeterminate	57 (15.8)	69 (19.2)	
Clinical failure	12 (3.3)	21 (5.8)	
Indeterminate	45 (12.5)	48 (13.3)	
Source: FDA Statistical Reviewer's Analysis *Note: Includes 14 patients (7 patient in each arm) from site #606. All patients had clinical success at ECR and PTE*			

In Study ABSI-16301, there were six patients in the omadacycline and eight patients in linezolid arms, respectively who had received a prior effective antibacterial therapy within 72 hours of enrollment. Of note, there were no patients who reported having received prior effective

antibacterial therapy within 72 hours of randomization in Study ABSI-1108, since this was an exclusion criterion in this trial.

Between both treatment groups, similar proportions of approximately 40% of patients had bedside incision and drainage as standard of care prior to the first dose, and about 10% of patients received bedside incision and drainage at some time from the first dose through ECR assessment.

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trial

Micro-MITT population

Clinical response rates at the ECR assessments were also evaluated in the micro-mITT population for ABSI-1108 and ABSI 16301 trials. The results of FDA analysis were identical with the Applicant's results. Table 7-8 and Table 7-9 summarizes outcome in micro-mITT population in ABSSSI trials.

Table 7-8 Clinical response at ECR for Study ABSI-1108 (micro-mITT population)

Clinical response at ECR for Study ABSI-1108 (micro-mITT population)			
ECR	Omadacycline n/N (%)	Linezolid n /N (%)	Difference (95% CI)
Clinical success	200/228 (87.7)	195/227 (85.9)	1.8 (-4.5, 8.2)
Clinical failure	28/228 (12.3)	32/227 (14.1)	
Source: FDA Statistical Reviewer's Analysis			

Table 7-9 Clinical response at ECR for Study ABSI-16301 (micro-mITT population)

Clinical response at ECR for Study ABSI-16301 (micro-mITT population)			
ECR	Omadacycline n/N (%)	Linezolid n/N (%)	Difference (95% CI)
Clinical success	244/276 (88.4)	238/287 (82.9)	5.5 (-0.3, 11.3)
Clinical failure	32/276 (11.6)	49/287 (17.1)	
Source: FDA Statistical Reviewer's Analysis			

Clinical success rates at ECR were comparable between treatment groups in both studies.

Subgroup Analysis

Proportion of Patients with success at ECR in Selected Subgroups in Study ABSI-1108 and Study ABSI16301 is presented in Table 7-10 and Table 7-11 below.

Table 7-10 Clinical success at ECR in selected Subgroups: Study ABSI-1108 (mITT population)

Clinical success at ECR in selected Subgroups: Study ABSI-1108 (mITT population)				
Subgroup	Omadacycline	Linezolid	Difference	95% CI
Gender				
Male	175/199 (88.0)	183/208 (88.0)	0.0	(-6.5, 6.4)
Female	93/117 (79.5)	83/103 (80.6)	-1.1	(-11.7, 9.7)
Age				
Age ≥65 years	29/36 **(80.6)**	28/32 **(87.5)**	**-6.9**	(-25.0, 11.7)
Age <65 years	239/280(85.4)	238/279(85.3)	0.1	(-5.9, 6.0)
Region				
North America	177/207 (85.5)	170/202 (84.2)	1.3	(-5.7, 8.4)
Eastern Europe	72/81 (88.9)	76/84 (90.5)	-1.6	(-11.6, 8.2)
Western Europe	14/23 (60.9)	18/21 (85.7)	-24.8	(-48.5, 1.9)
Latin America	5/5 (100.0)	2/4 (50.0)	50.0	(-10.0, 86.0)
Race				
White	241/287 (84.0)	247/289 (85.5)	-1.5	(-7.4, 4.4)
Black	14/16 (87.5)	7/8 (87.5)	0.0	(-27.7, 37.7)
Asian	1/1 (100)	2/2 (100)	0.0	
Other	12/12 (100.0)	10/12 (83.3)	17.0	(-10.6, 45.4)
Infection Type				
Wound infection	91/102 (89.2)	92/104 (88.5)	0.8	(-8.2, 9.7)
Major abscess	80/91 (87.9)	75/89 (84.3)	3.6	(-6.7, 14.2)
Cellulitis	97/123 **(78.9)**	99/118 **(83.9)**	**-5.0**	(-14.9, 4.9)
Lesion Size				
<=300 cm^2	142/160 (88.8)	130/147 (88.4)	0.3	(-6.9, 7.7)
>300 - 600 cm^2	74/88 (84.1)	84/101 (83.2)	0.9	(-10.1, 11.6)
>600 - 1000 cm^2	34/43 (79.1)	28/34 (82.4)	-3.3	(-20.9, 15.6)
>1000 cm^2	18/25 **(72.0)**	24/29 **(82.8)**	**-10.8**	(-33.6, 11.9)
Bacteremia	7/11 **(63.6)**	8/9 **(88.9)**	**-25.3**	(-57.9, 15.5)
History of diabetes				
Yes	16/20 **(80.0)**	26/30 **(86.7)**	**-6.7**	(-30.6, 14.2)
No	252/296(85.1)	240/281(85.4)	-0.3	(-6.1, 5.6)
History of hepatitis C				
Yes	82/95 (86.3)	76/89 (85.4)	1.0	(-9.4, 11.4)
No	186/221 (84.2)	190/222 (85.6)	-1.4	(8.2, 5.3)
CrCl* (ml/min)				
<=50	6/9 **(66.7)**	6/7 **(85.7)**	-19.05	(-56.3, 27.2)
>50	261/306 (85.3)	258/302 (85.4)	-0.1	(-5.8, 5.5)
Source: FDA Analysis * CrCl at baseline was missing for 1patient in omadacycline and 2 patients in linezolid				

Clinical Reviewers' Comment: Although not statistically significant, as shown in table above, in Study ABSI-1108, subgroup analyses showed numerical differences in clinical success rates at

ECR. Patients older than 65 years, patients with infection type 'cellulitis,' or lesion area ≥ 1,000 cm², those with creatinine clearance < 50 mL/min, or with diabetes mellitus, or patients with bacteremia, were noted to have a numerically lower success rates at ECR in the omadacycline group as compared to the linezolid, control group. Of note, the sample size in each subgroup is small and thus nominal confidence intervals are wide. Therefore, it is difficult to draw any strong conclusion from these small subgroups.

Table 7-11 Clinical success at ECR in selected Subgroups: Study ABSI-16301 (mITT population)

Clinical success at ECR in selected Subgroups: Study ABSI-16301 (mITT population)				
Subgroup	Omadacycline	Linezolid	Difference	95% CI
Gender				
Male	210/239 (87.9)	182/215 (84.7)	3.2	(-3.1, 9.8)
Female	105/121 (86.8)	115/145 (79.3)	7.5	(-1.7, 16.4)
Age				
Age >=65 years	15/16 (93.8)	12/21 (57.1)	37.7	(8.5, 59.3)
Age < 65 years	300/344 (87.2)	285/339 (84.1)	3.1	(-2.1, 8.5)
Race				
White	279/ 320 (87.2)	279/334 (83.5)	3.7	(-1.8, 9.1)
Black	20/22 (90.9)	7/13 (53.8)	37.1	(7.8, 64.2)
Asian	3/3 (100.0)	4/5 (80.0)	20.0	(-45.9, 64.8)
Other	12/15 (100)	10/8 (83.3)	17.0	(-10.6, 45.4)
Infection Type				
Wound infection	187/210 (89.0)	177/214 (82.7)	6.3	(-0.3, 13.1),)
Major abscess	60/64 (93.8)	55/62 (88.7)	5.0	(-5.4, 16.2)
Cellulitis	68/86 (79.1)	65/84 (77.4)	1.7	(10.8, 14.3)
Lesion Size				
<=300 cm	144/162 (88.9)	146/185 (78.9)	10.0	(2.2, 17.7)
>300 – 600	118/134 (88.1)	104/118 (88.1)	0.0	(-8.2, 8.4)
>600 – 1000	38/44 (86.4)	31/36 (86.1)	0.3	(-15.4, 17.1)
>1000	15/20 (75.0)	16/21 (76.2)	-1.2	(-28.0, 25.4)
Hepatitis at Baseline				
Yes	105/116 (90.5)	107/125 (85.6)	4.9	(-3.5, 13.4)
No	210/244 (86.1)	190/235 (80.9)	5.2	(-1.5, 12.0)
CrCl* (ml/min)				
<=50	1/1(100.))	5/6(83.3)	16.7	(-71.0, 59.2)
>50	312/356 (87.6)	291/350(83.1)	4.5	(-0.7, 9.8)
History of Diabetes				
Yes	11/14(78.6)	21/31(67.7)	10.8	(19.6, 34.9)
No	304/346(87.9)	276/329(83.9)	4.0	(-12.9,9.3)
Source: FDA Statistical Analysis *CrCl at baseline missing for 3 patients in omadacycline and 4 patients in linezolid				

In Study ABSI-16301 no significant differences were observed in the efficacy findings among the different subgroups as shown in Table above.

Clinical Response by Pathogen at ECR

When grouped by the Baseline pathogens (isolated from the ABSSSI site or blood culture), clinical success rates at ECR were generally similar in the two treatment arms in ABSSSI trials. Statistical analyses were conducted for each study as well as by pooling both trials and as individual trials. Pooled analysis is presented since response rates at ECR by baseline pathogen was similar when comparing two ABSSSI trials.

Clinical success rates at ECR by baseline pathogen in ABSSSI trials, presented individually and as Pooled analysis in Appendix 15.3.11.

Clinical Reviewer's Comment: Although not statistically significant, in pooled ABSSSI trials, at ECR, majority of patients had a numerically higher success rates in omadacycline group as compared to linezolid group for S. aureus (88.3% omadacycline and 84.6% linezolid) and Streptococcus anginosus Gr (89.4% omadacycline and 76.8% linezolid group). However, numerically lower success rates were observed for β-hemolytic streptococcus (73.5% omadacycline versus 85.4% linezolid group) and for Group A or S. pyogenes (80% omadacycline versus 88.2% linezolid group), which favored comparator for both of these pathogens. Notably, majority of these differences in success rates were driven by results from ABSI1108 trial. As noted previously, the small sizes in each subgroup limit any conclusions from being drawn.

Outcomes in patients with Bacteremia

Table 7-12 below summarizes clinical success at ECR and PTE in patients with Bacteremia in ABSSSI trials (mITT Population).

Table 7-12 Clinical Success at ECR and PTE in patients with Bacteremia in ABSSSI trials (mITT Population)

Clinical Success at ECR and PTE in patients with Bacteremia in ABSSSI trials (mITT Population)				
	Study ABSI-1108		**Study ABSI-16301**	
	Omadacycline	Linezolid	Omadacycline	Linezolid
	(N = 316)	(N = 311)	(N = 360)	(N = 360)
	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)
ECR	7/11 **(63.6)**	8/9 (**88.9)**	1/2 (50.0)	6/8 (75.0)
PTE	9/11 **(81.8)**	9/9 **(100.0)**	1/2 (50.0)	5/8 (62.5)
Source: CSR, FDA Analysis				

Clinical Reviewer's Comment: Overall, the clinical success rate was numerically lower in omadacycline patients with bacteremia as compared to linezolid patients. In Study ABSI1108, A total of 11 (3.3%) omadacycline and 9 (2.8%) linezolid patients had bacteremia, which included S. aureus (n = 6 [3 MRSA, 3 MSSA] omadacycline, n = 6 [2 MRSA, 4 MSSA] linezolid patients) and

Streptococcus pyogenes (n = 2 omadacycline, n = 2 linezolid). All of clinical failure in bacteremic patients were driven by Gr-B beta-hemolytic streptococcus, Gr-A S. pyogenes and S. viridans.

In Study ABSI16301, a total of 10 patients had bacteremia (2 omadacycline patients, 8 linezolid patients) at baseline. Of the 2 patients in the omadacycline group, 1 (50%) achieved clinical success at ECR, while 6 of the 8 (75%) patients in the linezolid group achieved clinical success.
Clinical success at ECR by baseline pathogen in bacteremic patients in ABSSSI trials is summarized in Appendix 15.3.11.

Overall Clinical Success in patients infected with *Staphylococcus aureus* at PTE by the pathogen's resistance profile in Study ABSI-1108 (micro-mITT Population) is summarized in Appendix 15.3.12.

Clinical Reviewer's Comment: Although resistance profiles were similar across treatment arms in study ABSI-1108, the clinical success rate appeared to be lower for omadacycline-treated patients with multi drug resistant S. aureus as compared to those infected with S. aureus resistant to only one antibacterial drug; or as compared to linezolid treated patients with the same resistance profile. This apparent difference was not observed in study ABSI-16301 and successful treatment outcomes were observed with both omadacycline and linezolid for the majority of S. aureus isolates in ABSSSI, regardless of resistance profile in Study ABSI16301.

Comparison of Clinical Response over Time in ABSSSI Trials is summarized in Appendix 15.5.13.

Concordance between ECR success and PTE success

Concordance between ECR and PTE success rates for study ABSI-1108, and ABSI 16301 is presented in Appendix 15.3.14.
In ABSI1108, there was a good concordance between ECR and PTE outcomes. Most (94% in omadacycline group and 90% in linezolid group) of the patients with 'clinical success' at ECR maintained their response. The percentages of patients who had clinical success at ECR but were reported as a 'clinical failure or indeterminate' at PTE visits were 6.3% (17/268) in the omadacycline group and 9.8% (26/266) in the linezolid group.8% in each treatment group. The percentages of patients who were determined as 'clinical failures or Indeterminate' at ECR and later deemed 'clinical success' at PTE by the investigators were 6.6% (21/316) omadacycline group and 6.4% (20/311) in the Linezolid group.

Similarly, In ABSI16301, there was a good concordance between ECR and PTE outcomes. Most (89% in the omadacycline group and 87% in the linezolid group) of the patients with 'clinical success' at ECR maintained their response. The incidence of patients who had clinical success at ECR but were reported as a 'clinical failure or indeterminate' at PTE visits were 11.3% (36/315) in the omadacycline group and 13.2% (39/297) in the linezolid group. The incidence of patients who were determined as 'clinical failures or Indeterminate' at ECR and later deemed 'clinical success' at PTE by the investigators were 6.7% (24/360) Omadacycline group and 9.2%(33/360) in the Linezolid group.

ABSSSI Trials Efficacy Conclusions

In summary, omadacycline is efficacious as indicated by the non-inferiority to linezolid for ECR in both studies. This finding was supported by analysis of the overall clinical response at the PTE visit, sensitivity analyses, and the concordance analysis. Subgroup analyses indicated numerical differences across some subgroups; however, these differences likely arose by chance and were not investigated further.

Of note, a subgroup analyses in ABSI-1108 showed numerical lower success rates in omadacycline group at ECR as compared to the linezolid control group (e.g. in patients older than 65 years, or patients with infection type cellulitis, or lesion area ≥ 1,000 cm², those with creatinine clearance < 50 mL/min, or with diabetes mellitus, or patients with bacteremia). However, the sample sizes of these subgroups are quite small, and it is possible that these numerical differences could arise by chance alone.

Study ABSI-16301 enrolled outpatients who likely had a lower severity of illness as compared to Study ABSI-1108, where a higher percentage of patients had fever, leukocytosis, SIRS, bacteremia, or leukocytosis/leukopenia at baseline. Additionally, about 37.5% of patients were hospitalized at the start of therapy in Study ABSI-1108, whereas none of the patients in Study ABSI-16301 required hospitalization for their ABSSSI at the start of therapy.

There was a GCP issue identified by OSI inspection, the inadequate attention to GCP at a site in studyABSI-16301. This issue was addressed via the exclusion of subjects from the impacted site. Conclusions for efficacy remained unchanged.

7.3.1. CABP Trial (Study CABP1200)

Trial Design and Endpoints

Study CABP 1200, was a Phase 3 trial in patients with CABP. It was initiated in November 6, 2015 and completed in February 17, 2017. The study was designed in accordance with the guidance on developing antimicrobial drugs for the treatment of CABP[32]. Patients with

[32] FDA guidance for industry, *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment,* https://www.fda.gov/downloads/drugs/guidances/ucm123686.pdf

diagnosis of CABP, who required hospitalization, were randomized 1:1, to omadacycline or moxifloxacin in a double-blind, and double-dummy fashion. Patient randomization was stratified by Pneumonia Outcomes Research Team (PORT) Risk Class (II or III/IV), receipt of an allowed antibacterial therapy in the 72 h prior to study treatment, and geographic region. Allotment of antibacterial therapy in the 72 h prior to study treatment was limited to 25% of the patients randomized. The number of patients randomized to Port Risk Class II was limited to no more than 15%. All patients were expected to present with CABP severe enough to require a minimum of at least 3 days of IV treatment, after which, the investigator was allowed to switch the patient to oral (po) treatment based on pre-specified criteria for clinical stability.

Globally 86 sites enrolled/randomized at least 1 patient. The majority of sites were in Eastern Europe, which accounted for 82.4% of enrollment. There was only 1 site in US which enrolled 3 patients. Other site locations included Western Europe (3% patients), North America (0.25% patients), and the Applicant-defined "Rest of the World", including Latin America, Asia-Pacific, Israel, Turkey, and South Africa 15% patients).

Inclusion and Exclusion Criteria

Key Inclusion criteria included male and female patients ≥18 years of age with PORT Risk Class II-IV with radiographically-confirmed pneumonia. The diagnosis of CABP required at least 3 symptoms (cough, production of purulent sputum, dyspnea, and pleuritic chest pain), and at least 2 abnormal vital signs of fever or hypothermia, hypotension with systolic blood pressure <90 mm Hg, heart rate > 90 beats/min, or respiratory rate > 20 breaths/min. Eligibility also required at least 1 clinical sign or laboratory finding associated with CABP (hypoxemia, physical examination findings of pulmonary consolidation),
an elevated total white blood cell (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).

Major exclusion criteria were found to be generally standard criteria for a CABP trial (see Appendix xx for the complete list of inclusion and exclusion criteria).

Dosing Regimen

The dosing regimen in CABP trial is shown below:

Study Day	Omadacycline group	Moxifloxacin group
Day 1	100mg iv q12h (first 2 doses)	400 mg iv q24h
Day 2-3	100mg iv q24h	400 mg iv q24h
Day 4-EOT (7-14)	Option to switch to 300mg po q24h, or continuation of IV treatment	Option to switch to po 400 mg q24h or continuation of IV treatment

Omadacycline placebo pills and moxifloxacin placebo pills were used to maintain the blinding.

Study visits included a baseline visit, an early clinical response (ECR) visit at 72-120 hours after the first dose of study drug, and evaluated based on the Investigators assessment on the same day or within 2 days following the last dose of study drug (EOT), and approximately 5 to 10 days after the last dose of study drug (PTE visit), and a follow-up telephone contact was to occur approximately 30 to 37 days after the first dose of study drug.

Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the successful response to therapy at the ECR assessment (72 to 120 hours after administration of the first dose of study drug) as described in the FDA's draft guidance document on developing drugs for treatment of CABP. This endpoint was based on the 4 symptoms of cough, sputum production, pleuritic chest pain, and dyspnea, each rated as absent, mild, moderate, or severe. To be classified as a responder for the primary endpoint, patients had to be alive were to have shown improvement of at least 1 level (i.e., severe to moderate, moderate to mild, mild to absent) from baseline on at least 2 out of the 4 symptoms and had no worsening by at least 1 level on other symptoms. In addition, responders could not have received antibacterial treatment either as a rescue for CABP or as a treatment for other infections that may be effective for CABP from the first dose of study drug to the ECR assessment and not discontinued due to AE. Patients not meeting all these criteria were classified as non-responders.

Secondary Efficacy Endpoint

The secondary efficacy outcome was the overall assessment of clinical response at PTE based on the assessments at the EOT and PTE visits. Success was defined as survival after completion of a study drug regimen without receiving any systemic antibacterial therapy other than study drug, 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, and not a failure at the EOT visit.

Statistical Analysis Plan

The protocol defined several analysis populations. The intent-to-treat (ITT) population was comprised of all randomized patients. The safety population was comprised of randomized patients who received any amount of study drug. The microbiological intent-to-treat (micro ITT) population was comprised of all patients in the ITT population who had at least 1 causative pathogen identified at Screening from culture of a respiratory specimen, culture of blood, or from a culture-independent method. Clinically evaluable (CE-PTE) population included patients in the ITT population who received study drug, had a qualifying CABP, had no prior or concomitant antibacterial therapy, an assessment of outcome that is not indeterminate, and sufficiently complied with the protocol and scheduled use of study drugs. Microbiological evaluable (ME-PTE) population consists of patients who are in both Micro ITT and CE-PTE.

The primary efficacy analyses were based on the intent-to-treat (ITT) population. Treatment differences in ECR success rates (omadacycline treatment group minus the moxifloxacin treatment group) and its 95% confidence interval (CI) were calculated by the Miettinen and Nurminen method, without stratification. Non-inferiority was established if the lower limit of the 95% CI for the difference in the ITT population was within the non-inferiority margin of 10%. A key secondary endpoint of investigator's overall assessment at the post therapy evaluation (PTE) was evaluated analogously to the primary endpoint. Similar secondary analyses in the micro ITT population were conducted. Other secondary analyses were for the PTE in the ITT, CE-PTE and ME-PTE, and all-cause mortality at Day 15 and 30 were summarized in the ITT population.

Statistical Reviewer's Comment; The planned sample size of 750 patients was based on the response rate assumption of 79% for omadacycline and moxifloxacin, a 10% non-inferiority margin, and a 1-sided alpha level of 0.025. With the planned sample size, there was 92% power to show non-inferiority. The trials did not include interim efficacy analyses and did not provide for early stopping for futility or sample size modifications. An independent data monitoring committee monitored safety and recommended continuing the trial without any modification following each meeting.

7.3.2. Study Results of the CABP Trial

7.3.2.1. Patient Disposition and Protocol Violations/Deviations

In the ITT population, 92% omadacycline patients and 93% moxifloxacin patients completed the study. Patient disposition and protocol violations are summarized in Appendix 15.5.8.

In a non-inferiority trial, poor trial execution, conduct or compliance can drive the study results toward a finding of non-inferiority. Therefore, it is important to evaluate reasons for premature withdrawal of patients from the study, premature discontinuation of study drug, and protocol violations. The exclusion criteria violations, and study procedure violations were equally balanced between the treatment groups in CABP trial and should not impact the results of efficacy and safety evaluation. Study randomization issues were also equally balanced between treatment groups and were caused by either due to incorrect stratification due to prior antibacterial use or incorrect stratification for PORT Risk class. There were a few mismatches in PORT scores between the IWRS used for randomization and actual PORT Risk scores. These miscalculations would not be expected to impact randomization protection for the overall study, as FDA still used stratified randomization classification for subgroup analyses. FDA analyses used original PORT scores assigned during randomization and stratification.

Analysis population and reason for exclusion from specific analysis population category for Study CABP-1200 is summarized in Appendix 15.3.5

7.3.2.2. Demographic Characteristics

The distributions of demographic variables were similar and well balanced between the two groups. Overall, 55.2% of patients were male and a majority of patients were White (91.9%) and not Hispanic or Latino (95.9%). Most patients were either between 45 to 65 years of age (42.2%) or > 65 years of age (41.9%); about 20.4% patients were > 75 years of age. The mean age was 61.5 years and mean Body mass index (BMI) was 27.33 kg/m2. A total of 82.8% of patients had normal renal function (defined as a CrCL of > 80 mL/minute) or mild renal impairment (defined as a CrCL of > 50 to 80 mL/minute).

Table 7-13 below summarizes demographic characteristics in the primary efficacy (ITT) population.

Table 7-13 Demographic characteristics of the primary efficacy analysis population (ITT)- Study CABP1200

Demographic characteristics of the primary efficacy analysis population (ITT)- Study CABP1200			
Demographic Parameters	Omadacycline N=386	Moxifloxacin N=388	*P value*
Categories	**n (%)**	**n (%)**	
Age			
<45 years	62 (16)	61 (16)	0.34
45 - 65 years	172 (45)	155 (40)	
> 65 years	152 (40)	172 (44)	
>75 years	75 (19)	83 (21)	
Mean Age of Population	***61 (15)***	***62 (15)***	
Min, max	19, 97	19, 94	
Sex/Gender			
Female	178 (46)	169 (44)	0.51
Male	208 (54)	219 (56)	
Race			
White	356 (92)	355 (92)	0.33
Asian	17 (4)	18 (5)	
Black or African American	11 (3)	7 (2)	
American Indian or Alaska Native	0	2 (0.5)	
Other	2 (0.5)	6 (1.5)	
Ethnicity			
Not Hispanic or Latino	372 (96)	370 (95)	0.73
Hispanic or Latino	10 (3)	14 (4)	
Unknown	4 (1)	4 (1)	
Region*			
Eastern Europe	318 (82.4)	301 (77.6)	
Western Europe	11 (2.8)	20 (5.1)	
Rest of World	56 (14.5)	65 (16.8)	
North America	1 (0.25)	2 (0.51)	

Demographic characteristics of the primary efficacy analysis population (ITT)- Study CABP1200			
Demographic Parameters	Omadacycline N=386	Moxifloxacin N=388	*P value*
Categories	**n (%)**	**n (%)**	
Source: FDA Analysis; *Following countries participated from Eastern Europe: Bulgaria, Georgia, Hungary, Latvia, Romania, Russia, Slovakia, Ukraine; Rest of the world: Brazil, Israel, Peru, Philippines, Taiwan, Turkey, South Africa; and Western Europe/North America: Croatia, Czech Republic, Greece, Mexico, Poland, Spain, and US.			

7.3.2.3. Baseline Disease Characteristics

7.3.2.4. Baseline Pathogen Characteristics

Table *7-14* summarize pathogen characteristics at baseline in CABP trial.

Table 7-14 **Baseline Pathogen Characteristics- Study CABP 1200 (micro-ITT population)**

Baseline Pathogen Characteristics- Study CABP 1200 (micro-ITT population)		
	Treatment Arm	
	Omadacycline	Moxifloxacin
BL-Pathogen Positive (micro-ITT)	**204 (53)**	**182 (47)**
Atypical Pathogen Only (excluding mixed atypical pathogens)	67 (33)	57 (31)
Mycoplasma pneumoniae	30 (15)	23 (13)
Legionella pneumophila	24 (12)	23 (13)
*Serology***	*22 (11)*	*21 (12)*
Urinary antigen	*5 (2.5)*	*7 (4)*
Chlamydophila pneumoniae	13 (6)	11 (6)
Typical Pathogen Only	86 (42)	76 (42)
*Streptococcus pneumoniae****	43 (21)	34 (19)
PSSP	26 (13)	22 (12)
Quinolone Resistant	None	None
Macrolide Resistant	10 (5)	5 (3)
MDRSP	7 (3)	6 (3)
Staphylococcus aureus	11 (5)	10 (5.5)
MRSA	None	None
MSSA	11 (5)	10 (5.5)
Haemophilus influenzae	32 (16)	16 (9)
Haemophilus parainfluenzae	18 (9)	17 (9)
Klebsiella pneumoniae	13 (6)	13 (7)
Moraxella catarrhalis	4 (2)	1 (0.5)
Source: IR request from Sponsor for "atypical only pathogen", excluding mixed **For identification by serology, considers only a positive convalescent serology result as positive. ***In addition to atypical pathogen, *S. pneumoniae* was isolated as a baseline pathogen from a		

Baseline Pathogen Characteristics- Study CABP 1200 (micro-ITT population)		
	Treatment Arm	
	Omadacycline	Moxifloxacin
BL-Pathogen Positive (micro-ITT)	204 (53)	182 (47)
positive UAT test in 11% of omadacycline patients and 9% of moxifloxacin patients. -Causative bacterial pathogens identified from: Culture of a resp. specimen, blood, or from UAT tests for S. pneumoniae or L. pneumophila, or positive serology for L. pneumophila, M. pneumoniae, or C. pneumoniae. -Patients with the same pathogen from a blood specimen, respiratory specimen, UAT, and/or serology were counted only once for that pathogen. MDRSP = multi-drug resistant *S. pneumoniae*; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; PNSSP = penicillin-non-susceptible *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*.		

Clinical Reviewer's Comment: The incidence and distribution of pathogen was similar between treatment groups except for H. influenzae, which was twice as high in omadacycline group. Multidrug resistant S. pneumoniae was isolated from only 3% of cases in each group (7 patients in omadacycline group and 6 patients in moxifloxacin group); there were no quinolone-resistant strains. Most patients with a poly-microbial infection had either a mixed Gram-negative mixed with atypical pathogen infection (21 (10%) in omadacycline and 17 (9%) in moxifloxacin group), or a Gram-positive mixed with atypical pathogen (14 (7%) in omadacycline group and 18 (10%) in moxifloxacin group) infection.

Bacteremia at Baseline

A total of 15 (7%) omadacycline and 18 (10%) moxifloxacin patients in the micro-ITT population had bacteremia. Overall, majority of patients with bacteremia had a positive blood culture with *Streptococcus pneumoniae* (73% omadacycline patients, and 61% moxifloxacin patients). Table 7-15 below summarizes patients with a positive blood culture identified at Baseline.

Table 7-15 Bacteremia at Baseline-Study CABP 1200 (micro-ITT Population)

Bacteremia at Baseline-Study CABP 1200 (micro-ITT Population)		
	Treatment Group	
	Omadacycline (N=204)	Moxifloxacin (N=182)
	n (%)	n (%)
Patients with bacteremia	**15 (7)**	**18 (10)**
Gram-positive bacteria (aerobes)	12 (80)	13 (72)
Streptococcus pneumoniae	11 (73)	11 (61)
PSSP	9 (60)	11 (61)
Macrolide-resistant	4 (27)	3 (17)
MDRSP	1 (7)	3 (17)
Streptococcus mitis	1 (7)	2 (11)
Staphylococcus aureus (MSSA)	1 (7)	0
Gram-negative bacteria (aerobes)	3 (20)	5 (28)
Escherichia coli	0	4 (22)

Acinetobacter baumannii	0	1 (6)
Acinetobacter lwoffii	1 (7)	0
Haemophilus influenzae	1 (7)	0
Klebsiella pneumoniae	1 (7)	0
Source: CSR		

Prior and Concomitant Antibacterial Medications

In the ITT population, any systemic antibacterial medication taken within 72 hours prior to the first dose of study drug occurred in about 23% of patients in each treatment groups. The most common reason for taking a systemic antibacterial medication within 72 hours prior to the first infusion of study drug was for current episode of CABP; these were single doses of short-acting antibacterials (i.e., the standard dosing regimen was more frequent than once per day) that were permitted per protocol in up to 25% of all patients randomized.

Receipt of Rescue antibacterial medications

Receipt of antibacterial medications by patients after randomization, and between first dose of study drug to EOT and PTE Visits is summarized in Appendix 15.3.16.

Clinical Reviewer's Comment: About 6% of patients in omadacycline group and 9% of patients in moxifloxacin group received concomitant antibacterial medications between the first dose of study drug and the EOT visit in clinically evaluable population (CE-EOT population); and 8% patients in omadacycline group and 11% of patients in moxifloxacin group received concomitant antibacterial medications between the first dose of study drug and the PTE visit in clinically evaluable population. The most common reason for concomitant therapy was "due to insufficient therapeutic effect of the study drug" in 4% omadacycline patients, 7% moxifloxacin patients at the EOT visit and 5% omadacycline patients, and 8% moxifloxacin patients at the PTE visit.*

Receipt of Systemic Corticosteroids

Receipt of systemic corticosteroids use from the first dose study drug through final follow up visit in Study CABP1200 is summarized in Appendix 15.3.6.

Clinical Reviewer's Comment: In this trial, about 18% in omadacycline group and 26% in moxifloxacin group received systemic corticosteroid therapy from the first dose study drug through final follow up visit. Overall randomization succeeded in balancing the treatment groups on key baseline factors and presenting symptoms of CABP. Study withdrawals, discontinuations from therapy, or protocol violations were found unlikely to have compromised results. The ITT population in this trial appeared appropriate for a CABP non-inferiority assessment due to adequate randomization, inclusion of patients with sufficient severity, high

rate of baseline symptoms present, minimization of prior therapy, high rate of microbiologically confirmed diagnoses.

7.3.2.5. Efficacy Results

Primary Efficacy Endpoint

Omadacycline met an efficacy finding of noninferiority with a lower bound of the two-sided 95% confidence interval (CI) being greater than the pre-specified NI margin of 10%.
The table below displays results for the primary efficacy analysis of ECR in ITT population.

Table 7-16 Primary Efficacy (ITT population)-CABP 1200

Primary Efficacy (ITT population)-CABP 1200			
Outcome	**Treatment Arms**		
	OMC N=386	**MOXI N=388**	***Diff/95%CI***
Clinical success	313 **(81.1)**	321 **(82.7)**	*-1.6 (-7.1, 3.8)*
Clinical failure + indeterminate	73 (18.9)	67 (17.3)	
Clinical failure	49 (12.7)	47 (12.1)	
Indeterminate	24* (6.2)	20 (5.2)	
Source: FDA statistical Reviewer's Analysis ** 4 of the 24 indeterminate responses in omadacycline arm withdrew consent after randomization; and never received the study drug.*			

This efficacy analysis result depended on the assumption that indeterminants were treatment failures. It is important to understand the reasons and subsequent consequences, to make sure such an interpretation of the indeterminates were credible in this trial.

FDA sensitivity analyses

A few patients who were characterized as "clinical success" at the ECR assessment later died during the trial. In the first sensitivity analysis, patients who died were recharacterized as "clinical failure" at the ECR assessment. This did not change the efficacy findings: 309/386 (80.1%) and 319/388 (82.2%) for the omadacycline and moxifloxacin groups, respectively, for a difference of -2.2% (95% CI: -7.7, 3.4).

In the second sensitivity analyses, ECR "indeterminate" were recharacterized by their PTE status, so ECR indeterminate who was a PTE success (failure) were regarded as ECR success (failure). However, those who were PTE indeterminates were classified different in the two

arms: as "failure" in omadacycline arm and as "success" in the Moxifloxacin arm. The results are summarized in Table below. The non-inferiority still holds, and we consider the efficacy results robust.

Table 7-17 Sensitivity analysis of Primary Efficacy endpoint (ITT population)-CABP 1200

Sensitivity analysis of Primary Efficacy endpoint (ITT population)-CABP 1200			
Outcome	Omadacycline n/N (%)	Linezolid n /N (%)	Difference (95% CI)
Clinical success at ECR	318/386 (82.4)	331/388 (85.3)	-2.9 (-8.2, 2.3)
Source: FDA statistical Analysis			

FDA Sensitivity Analysis Based on Receipt of Prior Antibacterial Therapy

An important post hoc clinically relevant sensitivity analysis is in the subgroup of patients who did not receive prior effective antibacterial therapy and therefore received study drugs as the sole antibacterial therapy for CABP, See Table below. In this subgroup omadacycline arm had a lower response rate, and the treatment difference is also lower than the overall population, but the lower bound of the 95% CI was -10.1%, very close to the protocol pre-specified margin of -10% and is within the -12.5% noninferiority margin recommended in the guidance on CABP. On the other hand, people who did take prior antibacterial therapy did better numerically in the omadacycline group. Statistical testing for treatment by prior antibacterial therapy had a p-value of 0.45, meaning there is no statistical evidence to suggest that the prior use of antibacterial therapy had an impact on the treatment differences observed in this trial.

Table 7-18 Proportion of Patients with Clinical Success at ECR Based on Receipt of Prior Antibacterial Drugs Within 72 Hours Prior to Randomization: Study CABP-1200 (ITT population)

Proportion of Patients with Clinical Success at ECR Based on Receipt of Prior Antibacterial Drugs Within 72 Hours Prior to Randomization: Study CABP-1200 (ITT population)			
	Treatment Arms		
Clinical Success at ECR	**Omadacycline N = 386 n/N1 (%)***	**Moxifloxacin N = 388 n/N1 (%)***	**% Difference (95%CI)**
Patients who did not receive prior antibacterial therapy	235/297 (79.1)	247/298 (82.9)	-3.8 (-10.1, 2.6)
Patients who received prior antibacterial therapy	78/89 (88%)	74/90 (82%)	5.4 (-5.3, 16.2)
Source: FDA Statistical Reviewer's Analysis ADSL, ADCM, ADEEFIN data sets; *number (n) with early clinical response (ECR)/ number (N1) in subgroup, (%)			

Subgroup analyses of the primary endpoint

As discussed in section 2.1.2, the Pneumonia Severity Index (PSI), developed from the PORT cohort study aids in risk stratification of patients with CABP.[33] **Table 7-19** summarizes subgroup analyses by PORT Risk Class, and age group.

Table 7-19 Proportion of Patients with Clinical Success at ECR Based on PORT RISK Class, and Age Group: Study CABP-1200 (ITT population)

	Omadacycline N = 386 n/N1 (%)*	Moxifloxacin N = 388 n/N1 (%)*	% Difference (95%CI)
PORT RISK Class**			
PORT-II	42/56 (75.0)	43/56 (76.8)	-1.8 (-17.8, 14.2)
PORT-III	203/241(84.2)	198/232 (85.3)	-1.1 (-7.7, 5.5)
PORT-IV	68/89 **(76.4)**	80/100 **(80.0)**	-3.6 (-15.6, 8.2)
Age Group			
< 65 years	190/223 (85.2)	177/205 (86.3)	-1.1 (-7.8, 5.6)
≥ 65 years	123/163 **(75.5)**	144/183 **(78.7)**	-3.2 (-12.2, 5.6)
< 75 years	248/301 (82.4)	253/300 (84.3)	-1.9 (-7.9, 4.1)
≥ 75 years	65/85 (76.5)	68/88 (77.3)	-0.8 (-13.5, 11.8)

Source: FDA Statistical analysis;
*number (n) with early clinical response (ECR)/ number (N1) in subgroup, (%)
** originally stratified PORT Risk classification

Reviewers' Comment: Although not statistically different, subgroup analyses by PORT Risk Class and age group showed a numerically lower response rates in omadacycline-treated patients with PORT Risk Class-IV or age ≥ 65 years. The sample size in subgroups is quite small and thus any strong conclusion about efficacy in these subgroups cannot be made from these small subgroups.

The following table displays clinical success at ECR in other subgroups of interest.

Table Subgroup Analyses of ECR rates in ITT Population (Study CABP1200)

	Treatment groups			
Subgroups	**Omadacycline**	**Moxifloxacin**	**Difference**	**95% CI**
	n/N (%)	**n/N (%)**		
Sex				

[33] Aujesky D, Fine MJ. The pneumonia severity index: a decade after the initial derivation and validation. Clin Infect Dis 2008;47: S133-9.

Male	174/208 (83.7)	178/219 (81.3)	2.4	(-4.9, 9.6)
Female	139/178 (78.1)	143/169 (84.6)	-6.6	(-14.8, 1.7)
Region				
Eastern Europe	201/249 (80.7)	206/248 (83.1)	-2.3	(-9.2, 4.5)
Western Europe and North America	75/91 (82.4)	73/92 (79.3)	3.1	(-8.6, 14.7)
Rest of World	37/46 (80.4)	42/48 (87.5)	-7.1	(-22.7, 8.2)
Race				
White	288/356 (80.9)	293/355 (82.5)	-1.6	(-7.4, 4.1)
Black	8/11 (72.7)	6/7 (85.7)	-13.0	(-48.0, 31.1)
Asian	16/17 (94.1)	16/18 (88.9)	5.2	(-18.2, 2.9)
Other	1/2 (50.0)	6/8 (75.0)	-25	(-79.3, 35.0)
Prior antibiotic therapy				
No	235/297 **(79.1)**	247/298 **(82.9)**	-3.8	(-10.1, 2.6)
Yes	78/89 (87.6)	74/90(82.2)	5.4	(-5.3, 16.2)
Clinically evaluable Patients	316/340 (92.9)	312/345 (90.4)	2.5	(-1.7,6.8)
CrCl				
≤50 mL/min	53/71 (74.7)	45/62 (72.6)	2.1	(-12.9, 17.3)
>50 mL/min	260/315 (82.5)	276/326 (84.7)	-2.1	(-7.9, 3.6)
Lung Infiltrate				
Multilobar	72/93 (77.4)	88/113 (77.9)	-0.5	(-1.2, 10.9)
Unilobar	241/293 (82.3)	233/275 (84.7)	-2.5	(-8.6, 3.7)
Subjects with bacteremia				
Yes	10/15 **(67)**	16/18 **(89)**	-22.2	(-50.2, 6.6)
No	153/189 (81.0)	140/164 (85.4)	-4.4	(-12.2, 3.6)
Pleural Effusion				
Yes	53/60 (88.3)	59/65 (90.8)	-2.4	(-14.3, 8.9)
No	250/326(76.7)	262/323(81.1)	-4.4	(-10.7, 18.5))
Mild to moderate COPD				
Yes	43/57 (75.4)	40/51 (78.4)	-3.0	(-18.9, 3.3)
Symptomatic asthma with wheezing				
Yes	14/18 (77.8%)	19/20 (95.0%)	-17.2%	(-41.6, 5.5)
COPD or asthma, or Chronic bronchitis or emphysema				
Yes	66/85 **(77.6)**	62/76 **(81.6)**	-3.9	(-16.4, 8.8)
No	247/301(82.6)	259/312(83.1)	-1.0	(-7.0, 5.1)
Diabetes				
Yes	48/63 **(76.2)**	61/71 **(85.9)**	-9.7	(-23.5, 3.6)
No	265/323 (82.0)	260/317 (82.0)	0.0	(-5.9, 6.0)
Source: FDA Analysis; Dataset ADEIFFN, ADSL Note: Rest of the World: Brazil, Israel, Peru, Philippines, Taiwan, Turkey, South Africa				

There was no statistically significant treatment difference by subgroup interactions for ECR rates. Some analyses showed numerical differences in ECR rates: Female patients, black patients, and patients with symptomatic asthma with wheezing were noted to have a numerically lower ECR in the omadacycline group as compared to the control group. In most cases the sample sizes of these subgroups are quite small. Statistical interaction testing indicated these differences could arise by chance.

Clinical Reviewer's Comment: Although not statistically significant, since sample sizes were too small, when looking at clinically important subgroups of interest, which were also observed to have higher mortality in CABP Trial, e.g. patients with lung disease (COPD/asthma), diabetes, showed numerical lower clinical success rate at ECR. Furthermore, a numerical lower cure rate was seen in patients with bacteremia (which was also observed in ABSSI1108 IV to oral switch trial).

Early Clinical Response by Baseline Pathogen in micro-ITT population

Another important sensitivity analysis is in the subgroup of patients who had documentation of a bacterial pathogen at baseline (micro-ITT population). **Error! Reference source not found.** below shows the ECR rates in the micro- ITT population and by relevant CABP bacterial pathogens.

Table 7-20 Early Clinical Response by Baseline Pathogens (micro-ITT population)

Early Clinical Response by Baseline Pathogens (micro-ITT population)					
Bacterial Pathogen	Omadacycline N = 204		Moxifloxacin N = 182		% Difference (95% CI)
	N1	Success at ECR (%)	N2	Success at ECR (%)	
Microbiological ITT	204	163 **(79.9%)**	182	156 **(85.7%)**	-5.8 (-13.3, 1.8)
Not in Microbiological ITT	182	150 (82.4%)	206	165 (80.1%)	2.3(-5.6, 10.1)
Gram-positive (aerobes)	61	51 (83.6)	56	49 (87.5)	
S. pneumoniae[*]	43	34 **(79.1)**	34	30 **(88.2)**	-9.2 (-25.8, 8.6)
S. aureus (methicillin susceptible)	11	10 (90.9)	10	8 (80.0)	
Gram-negative (aerobes)	79	62 (78.5)	69	58 (84.1)	
H. influenzae	32	22 **(68.8)**	16	14 **(87.5)**	-18.8 (-39.8, 8.7)
H. parainfluenzae	18	15 (83.3)	17	14 (82.4)	
K. pneumoniae	13	11 (84.6)	13	11 (84.6)	
Escherichia coli	6	4 (66.7)	7	6 (85.7)	
Atypical pathogens (including mixed[**] pathogens)	118	92 (78)	106	91 (86)	
M. pneumoniae[***]	70	54 (77)	57	49 (86)	-8.8 (-22.2, 5.2)
L. pneumophila[***]	37	31 (84)	37	32 (87)	-2.7 (-20.0, 14.5)
C. pneumoniae[***]	28	18 **(64)**	28	22 **(79)**	-14.3 (-37.0, 9.7)

Early Clinical Response by Baseline Pathogens (micro-ITT population)					
Bacterial Pathogen	Omadacycline N = 204		Moxifloxacin N = 182		% Difference (95% CI)
	N1	Success at ECR (%)	N2	Success at ECR (%)	
Source: IR response from Sponsor N1, number of omadacycline patients in subgroup; N2, number of moxifloxacin patients in subgroup.; Source of pathogens identified from blood specimens, respiratory specimens, urinary antigen tests, or serology.; *Includes either culture positive or positive convalescent serology **"mixed" patients had a culture positive for a gram-positive or gram-negative bacterial pathogen AND had a serological test "positive" for an atypical pathogen; Only positive convalescent serology was considered as "positive' result ***Identified only from serology.					

Clinical success rate at ECR in micro-ITT population (patients with documented pathogen at baseline in ITT population) was lower in omadacycline group as compared to moxifloxacin group. Conversely, non-micro-ITT patients performed numerically better in omadacycline treatment group.

Clinical Reviewer's Comment: When examining clinical success rates at ECR by key baseline causative pathogen in CABP, clinical success for patients with documented H. influenzae and S. pneumoniae were numerically lower in the omadacycline group as compared to the control group. A similar trend was seen at the PTE visit, although response rates were overall higher in both arms at the PTE assessment. Of note, 4 of 10 clinical failures in the omadacycline-treated patients with H. influenzae, had coinfection with either E. coli, S. pneumoniae, or P. mirabilis. One of the nine patients with S. pneumoniae, was coinfected with H. influenzae.
Clinical success rates were also numerically lower for atypical pathogens (in particular M. pneumoniae and C. pneumoniae) in omadacycline treatment group.

While analyzing key CABP pathogens excluding polymicrobial or mixed infections, numerical difference in clinical success rates between treatment group for these pathogens persisted (Table 7-21).

Table 7-21 Clinical Success at ECR visit by Baseline Pathogen-CABP 1200 (micro-ITT)

Clinical Success at ECR visit by Baseline Pathogen-CABP 1200 (micro-ITT) – Excludes polymicrobial and mixed infections		
	Omadacycline N = 204	Moxifloxacin N = 182
Pathogen		
S. pneumoniae	18/22 (81.8)	10/11 (90.9)
H. influenzae	15/16 (93.8)	4/4 (100)
S. aureus (MSSA**)	3/3 (100)	4/6 (66.7)

K. pneumoniae	2/3 (66.7)	5/7 (71.4)
Haemophilus parainfluenzae	6/7 (85.7)	5/7 (71.4)
Atypical Pathogens	57/68 (83.8)	50/55 (90.9)
Mycoplasma pneumoniae	32/39 (82.1)	22/23 (95.7)
Chlamydophila pneumoniae	8/11 (72.7)	10/12 (83.3)
Legionella pneumophila	17/18 (94.4)	18/20 (90.0)
Source: IR response from Sponsor Denominators are number of patients in each category; Numerators are number of clinical success at ECR **One moxifloxacin-treated patient had MRSA included here in the table		

Overall Investigator's Clinical response of success at PTE by baseline pathogen is summarized in Appendix 15.3.19.

ECR in patients with Bacteremia (CABP trial-micro-ITT)

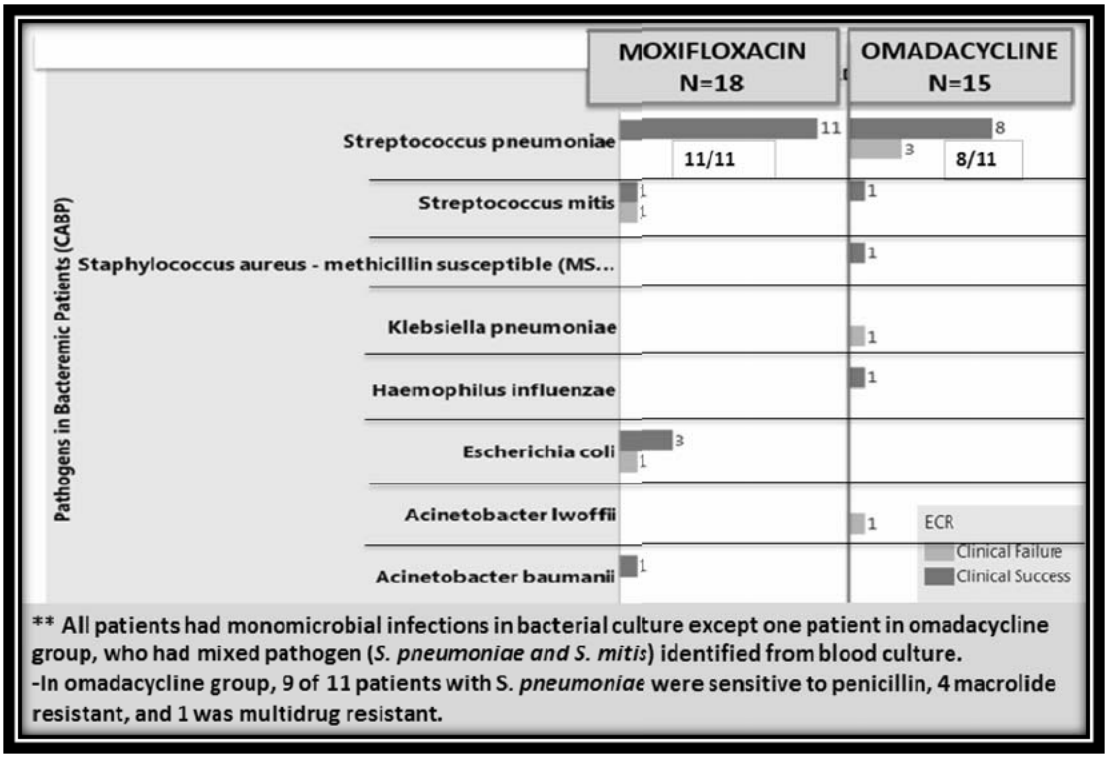
Table below summarizes outcome in bacteremic patients at ECR and PTE in CABP trial.

Table 7-22 Outcomes in patients with Bacteremia at ECR and PTE -CABP1200 (micro-ITT)

Outcomes in patients with Bacteremia at ECR and PTE -CABP1200 (micro-ITT)			
	Omadacycline N=204	**Moxifloxacin N=182**	**Difference (95% CI)**
ECR	**15**	**18**	**-**
Clinical success	10 ***(66.7)***	16 ***(88.9)***	-22.2 (-50.2, 6.6)
Clinical failure or indeterminate	5 (33.3)	2 (11.1)	
Clinical failure	2 (13.3)	2 (11.1)	
Indeterminate	3 (20.0)	0	
PTE	**15**	**18**	
Clinical success	11 ***(73.3)***	15 ***(83.3)***	-10.0 (-39.3, 18.8)
Clinical failure or indeterminate	4 (26.7)	3 (16.7)	
Clinical failure	3 (20.0)	3 (16.7)	
Indeterminate	1 (6.7)	0	
Source: CSR; FDA Statistical Reviewer's Analysis			

Figure 7-1 below shows outcome by pathogen at ECR in bacteremic patients.

Figure 7-1 Outcomes by Pathogen in patients with Bacteremia



Source: Clinical Reviewer's Analysis

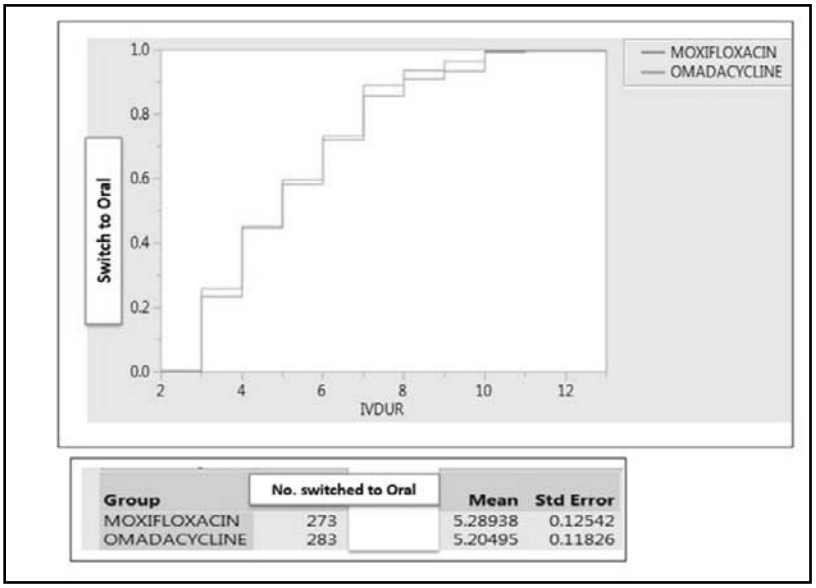
Clinical Reviewer's Comment: Lower clinical success rates were observed in patients with bacteremia in omadacycline group as compared to moxifloxacin group at ECR (66.7% omadacycline, and 88.9% moxifloxacin group). Notably, clinical success rates improved in omadacycline group, whereas deteriorated in moxifloxacin group at PTE timepoint (73.3% omadacycline, and 83.3% moxifloxacin group).

At ECR, 11 of 11 patients with S. pneumoniae bacteremia achieved clinical success in moxifloxacin group as compared to 8 of 11 patients in omadacycline group. All 3 failures were penicillin sensitive S. pneumoniae (PSSP).

Time to Clinical stability and switch to oral treatment-CABP Trial (ITT).

*Switch to oral treatment was compared between the treatment arms. Recall that switch to oral treatment involves criteria that correlates with the clinical stability in CABP patients in the trial, and these criteria were pre-specified in the protocol to be followed by the investigators. As shown in the analysis (*Figure 7-2*) below, time to switch to oral treatment was similar between the treatment arms. Mean days when patients were switched from IV to oral therapy was 5.2 days in both treatment arms.*

Figure 7-2 Time to Clinical stability and switch to oral treatment-CABP Trial (ITT)

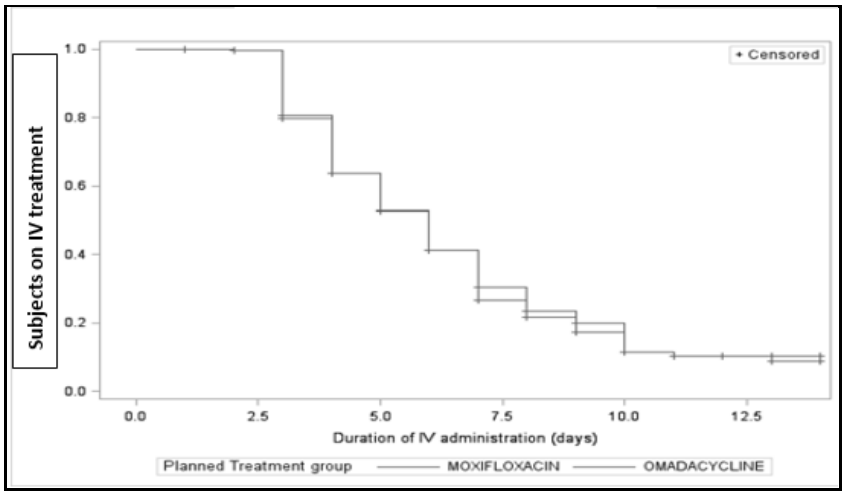


Group	No. switched to Oral	Mean	Std Error
MOXIFLOXACIN	273	5.28938	0.12542
OMADACYCLINE	283	5.20495	0.11826

Source: Clinical Reviewer's Analysis (JMP)

Comparison of duration on IV treatment in days:
The duration of IV treatment between omadacycline and moxifloxacin group was compared by FDA statistical reviewer using product limit Kaplan-Meier-Curves provided below.

Figure 7-3 Product Limit Kaplan-Meier-Curves for the Duration of iv Days



Source: FDA Statistical Reviewer's Analysis
Statistical Reviewer's Comment: The log rank test (p-value=0.61) demonstrated that there was no significant difference between the two curves with respect to the duration of IV days. The median days of IV duration was 6 days for both treatment groups.

Secondary Efficacy Analysis

Table 7-23 summarizes Overall Clinical Response at PTE.

Table 7-23 Overall Clinical Response at PTE (based on Investigator assessments at EOT and PTE)- Study CABP-1200 (ITT population)

	Treatment Arms		
Outcome at PTE	Omadacycline N = 386	Moxifloxacin N = 388	% Difference (95%CI)
Clinical success	338 (87.6)	330 (85.1)	2.5 (-2.4, 7.4)
Clinical failure + indeterminate	48 (12.4)	58 (14.9)	
Clinical failure	32 (8.3)	42 (10.8)	
Indeterminate	16 (4.1)	16 (4.1)	

Source: FDA Statistical Reviewer's Analysis and Applicant's Table 26, page 83 of clinical study report
Overall Clinical Response at the PTE Visit was a successful clinical response as assessed by the investigator 5 to 10 days after last dose.

In addition to primary endpoint of early clinical response, additional endpoint assessments were conducted. The number and percentages of subjects classified as clinical success, clinical failure, and Indeterminate by the Investigator's assessment at PTE in ITT population calculated for each treatment group as summarized in Table above. Overall clinical success rates were similar between the treatment groups at the PTE visit. The reviewer's analyses were consistent with the Applicant's analyses. In the ITT population, clinical success at PTE was 87.6% for omadacycline and 85.1% for moxifloxacin, with a difference of 2.5%, and 95% CI (-2.4, 7.4).

Analysis of CABP Signs Symptoms at EOT and PTE

The number and percentage of patients with resolution of all clinical symptoms that were present at baseline was evaluated for EOT and PTE visit. The proportion of patients who had resolution of all clinical symptoms was 45.7% in the omadacycline group and 42.2% in the moxifloxacin group at the EOT visit; and 74.5% omadacycline group, 75.4% moxifloxacin group at PTE visit. The proportion of patients with no new or worsening CABP symptoms were 97.6%, and 97.1% at EOT; 97.8%, and 99.2%, at the PTE visit, for omadacycline and moxifloxacin group respectively.

Concordance between ECR and PTE in CABP trial

The results of the concordance analysis of the primary efficacy outcome (ECR at 72 to 120 h) with the overall assessment of clinical response at the PTE visit (based on the investigator's assessment) are summarized in Appendix 15.4.18. FDA concordance analysis was similar to Applicant's analysis. There was a good concordance between ECR and PTE outcomes. Refer to Appendix 15.4.18 for details.

7.4. Integrated Review of Effectiveness

Data from two adequate and well-controlled trials in ABSSSI and one adequate and well-controlled trial in CABP demonstrate the effectiveness of omadacycline for the treatment of ABSSSI and CABP.

Study ABSI-1108 was conducted globally and evaluated initial IV treatment followed by oral treatment, while Study ABSI-16301 was conducted in the United States and evaluated the oral-only regimen. The results from each ABSSSI trial demonstrated that omadacycline was noninferior to linezolid with respect to the primary endpoint, reduction in lesion size of ≥ 20%, 48 to 72 hours after treatment initiation in the mITT population. The observed treatment effect at 48 to 72 hours appeared to be sustained at later time points evaluated. The clinical response was sustained through the key secondary endpoint of overall clinical response at the PTE visit. Sensitivity analyses in most of the relevant subgroups yielded similar results. Although in a few subgroups (e.g., patients older than 65 years, patients with infection type 'cellulitis,' or lesion area ≥ 1,000 cm², those with creatinine clearance < 50 mL/min, or patients with diabetes mellitus, or with bacteremia) in the IV to oral switch trial (Study ABSI1108) numerical differences in efficacy findings were observed, the sample sizes in these subgroups were too small and any conclusions about efficacy findings in subgroups could not be reached. The data support both an IV or PO induction dosage regimen for treatment of ABSSSI.

Efficacy of omadacycline for the treatment of CABP was demonstrated in Study CABP1200, where noninferiority of omadacycline compared to moxifloxacin was demonstrated with results within the prespecified 10% NI margin in the ITT population at the early clinical response evaluation. The results of secondary endpoint analyses were consistent with the primary endpoint and supported the primary efficacy analysis. While generally two adequate and well-controlled trials are required for each indication, the evidentiary standard for treatment of CABP was met by pairing the results of the successful ABSSSI trials with the results of the successful CABP trial. Subgroup analyses showed a numerically lower clinical response rates in omadacycline-treated patients with high risk for poor prognosis (e.g., age ≥ 65 years, PORT Risk Class IV, and underlying comorbidities e.g., COPD/asthma, diabetes mellitus). Success rates were also lower at ECR in the micro-ITT population and those with documented baseline cultures positive for S. pneumoniae or H. influenzae. However, there are limitations to these post-hoc subgroup analyses due to small sample sizes. Finally, the clinical data support only an IV induction dosage regimen for treatment of CABP, followed by a switch to oral therapy.

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8. Clinical Microbiology Review

8.1. Nonclinical Microbiology

8.1.1. Mechanism of Action

Omadacycline is a tetracycline antibacterial drug and exerts its effects by binding to the 30S subunit of the bacterial ribosome and blocking protein synthesis. Support for the mechanism of action was provided by whole-cell macromolecular synthesis assays [Draper 2014][34]. Control antibacterial drugs included rifampin (RNA synthesis inhibitor), ciprofloxacin (DNA synthesis inhibitor), and fosfomycin (peptidoglycan synthesis inhibitor). Omadacycline, like tetracyclines, inhibits protein synthesis (IC_{50} range <0.03 to 0.19 mcg/mL) (Table 8-1). The inhibition of protein synthesis by omadacycline was not impacted by the presence of tetracycline resistance mechanisms, efflux (*tet*K) or ribosome protection (*tet*M) in *S. aureus*.

Table 8-1 Antibacterial activity and macromolecular synthesis inhibition by omadacycline and comparators (Source reference: Draper 2014).

Compound	*S. aureus* Strain	Resistance Mechanism	MIC (µg/mL)	IC_{50} Protein Synthesis (µg/mL)	IC_{50} RNA Synthesis (µg/mL)	IC_{50} DNA synthesis (µg/mL)	IC_{50} PG synthesis (µg/mL)
Omadacycline	RN450	None	0.125	<0.03	>32	>32	11.6
	ATCC 29213	None	0.25	0.19	>32	>32	15.7
	RN4250	*tet*(K)	0.25	0.08	>32	>32	>32
	MRSA5	*tet*(M)	0.125	0.11	>32	>32	15.6
Tetracycline	RN450	None	< 0.06	0.04	31.4	25.7	8.8
	ATCC 29213	None	0.125	0.09	23.7	>32	7.6
	RN4250	*tet*(K)	32	13.8	32	>32	22.7
	MRSA5	*tet*(M)	>64	1.8	>64	>32	>32
Doxycycline	RN450	None	<0.06	0.02	>32	>32	3.3
	ATCC 29213	None	0.125	0.08	>32	>32	2.9
Rifampin	RN450	None	NT	0.01	0.01	>32	>32
	ATCC 29213	None	NT	<0.01	0.01	>32	>32
Ciprofloxacin	RN450	None	0.5	14.0	>32	0.4	>32
	ATCC 29213	None	0.5	>32	>32	0.3	>32
Fosfomycin	RN450	None	NT	>32	>32	>32	7.8
	ATCC 29213	None	NT	>32	>32	>32	11.9

Note: IC_{50} data represents the calculated concentration of drug that reduces activity in the assay by 50% relative to the no-drug control. ATCC = American Type Culture Collection, DNA = deoxyribonucleic acid, IC_{50} = concentration of drug producing 50% inhibition, MIC = minimum inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*, NT = not tested, PG = peptidoglycan, RNA = ribonucleic acid.

[34] Draper MP, Weir S, Macone A, Donatelli J, Trieber CA, Tanaka SK et al. Mechanism of action of the novel aminomethylcycline antibiotic omadacycline. *Antimicrob Agents Chemother.* 2014 58(3):1279-83.

The ribosomal protection protein Tet(O) interacts with the *E. coli* 70S ribosome and facilitates the release of bound tetracycline. Omadacycline was shown to inhibit protein synthesis in a cell-free system irrespective of the presence or absence of Tet(O), whereas tetracycline activity was significantly reduced in the presence of Tet(O) (Figure 8-1Figure 8-1 Effect of Tet(O) protein on the protein synthesis activity of omadacycline *in vitro*. Poly(U)-dependent Poly(Phe) synthesis (*in vitro* translation) was carried out in the presence or absence of purified Tet(O) added in a 1:1 molar ratio with ribosomes and various concentrations of either omadacycline or tetracycline. Percent activity relative to the control reaction (no omadacycline or tetracycline) is plotted. Source reference: Draper 2014.).

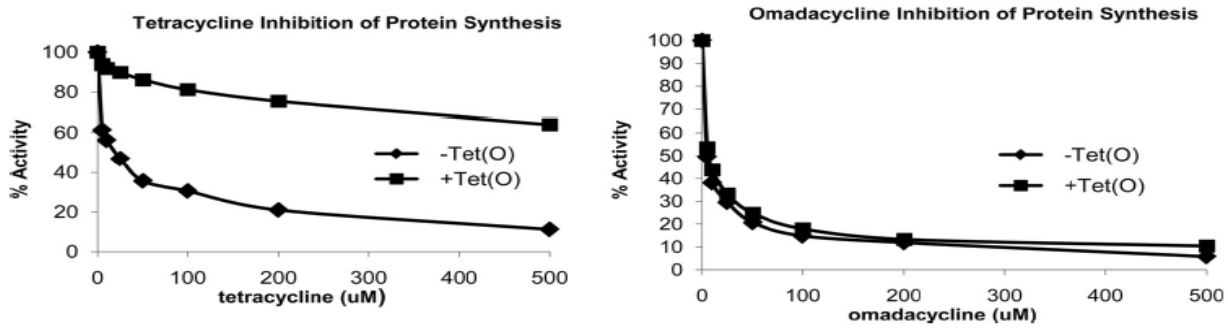


Figure 8-1 Effect of Tet(O) protein on the protein synthesis activity of omadacycline *in vitro*. Poly(U)-dependent Poly(Phe) synthesis (*in vitro* translation) was carried out in the presence or absence of purified Tet(O) added in a 1:1 molar ratio with ribosomes and various concentrations of either omadacycline or tetracycline. Percent activity relative to the control reaction (no omadacycline or tetracycline) is plotted. Source reference: Draper 2014.

Using the *in vitro* coupled prokaryotic transcription/translation inhibition system, the concentrations required for 50% inhibition (IC_{50}) of protein synthesis for tigecycline, omadacycline, minocycline and tetracycline were 1.4, 5.8, 8.7 and 16.3 □M, respectively (Study report RD-2010-50354).

The structural interaction of omadacycline with the ribosome was characterized by genetic analysis of 16S rRNA tetracycline resistance mutations and chemical probing using *E. coli* 70S ribosomes [Heidrich 2016][35]. Minimum inhibitory concentration (MIC) values for tetracycline, tigecycline, and omadacycline increased 4- to 8-fold in strains

[35] Heidrich CG, Mitova S, Schedlbauer A, Connell SR, Fucini P, Steenbergen JN, et al. The Novel Aminomethylcycline Omadacycline Has High Specificity for the PrimaryTetracycline-Binding Site on the Bacterial Ribosome. Antibiotics (Basel). 2016 Sep 22;5(4).

with mutations in the primary tetracycline binding site, suggesting that tigecycline and omadacycline bind to the primary tetracycline site. The chemical probing study using dimethyl sulfate and Fe^{2+} mediated Fenton cleavage to map the interaction of omadacycline on the 16S rRNA provides additional support for binding of omadacycline to the primary tetracycline binding site.

Functional assays that demonstrate activity of omadacycline against isolates expressing tetracycline resistance (ribosomal protection and efflux) were performed to further elucidate the structure activity relationship [Honeyman 2015][36]. The results of this study are summarized in Table 8-2. Omadacycline was active against Gram positive bacteria expressing tetracycline resistance due to ribosomal protection or efflux. The activity of omadacycline was comparable to tigecycline against Gram positive bacteria.

Table 8-2 Initial structure-activity relationships of omadacycline against tetracycline-resistant Gram-positive bacteria (Source reference: Honeyman 2015).

Strain	TET Resistant determinant	Mechanism type	MIC (mcg/mL)			
			OMC	TET	MIN	TIG
S. aureus RN450	wild type	None	0.25	<0.06	0.25	0.25
S. aureus MRSA 5	Tet M	Ribosome protection	0.25	32	2	0.25
S. aureus RN4250	Tet K	Efflux	0.25	>64	0.5	0.5
E. faecalis JH2-2	wild type	None	0.25	0.25	0.5	0.5
E. faecalis JH2-2 (pAM211)	Tet M	Ribosome protection	0.5	>64	16	0.5
E. faecalis JH2-2 (pMV158)	Tet L	Efflux	0.5	64	0.5	0.5
E. faecium 494	Tet M + L	Ribosome protection and efflux	0.5	>64	16	0.5
S. pneumoniae 157E	wild type	None	<0.06	<0.06	<0.06	<0.06
S. pneumoniae ATCC70090	Tet M	Ribosome protection	<0.06	32	8	<0.06

OMC = Omadacycline; TET = Tetracycline; MIN = Minocycline; TIG = Tigecycline

Clinical Microbiology Reviewer's Comment: Omadacycline was shown to bind to the 30s subunit of the bacterial ribosome and terminate protein synthesis in experiments of macromolecular synthesis, protein synthesis inhibition and competition with radiolabeled tetracycline, and transcription/translation cell free extract systems.

[36] Honeyman L, Ismail M, Nelson ML, Bhatia B, Bowser TE, Chen J et al. Structure-activity relationship of the aminomethylcyclines and the discovery of omadacycline. *Antimicrob Agents Chemother*. **2015** 59(11):7044-53.

Structure-activity studies demonstrate that omadacycline maintains activity in the presence of tetracycline-specific efflux (tet K and L) and ribosomal protection proteins (tet M) in Gram positive bacteria.

8.1.2. Activity *in vitro*

The *in vitro* activity of omadacycline has been evaluated in large scale surveillance studies in North America (NA), Europe (EU), Latin America and Asia-Pacific (ROW) regions during 2009, 2010, 2011, 2015, 2016 and in small scale surveillance studies. The large surveillance studies were performed by JONES Microbiology Institute (JMI), North Liberty, Iowa, using standard Clinical and Laboratory Standards Institute (CLSI) methods. The surveillance MIC data for pathogens associated with ABSSSI and CABP are summarized in Appendix 15.4 (Tables 15.4.1, 15.4.2, and 15.4.3).

With respective to Gram positive bacteria, omadacycline is active *in vitro* against methicillin susceptible *S. aureus* (MIC range = 0.03 -2.0 mcg/mL; MIC_{90} = 0.25 mcg/mL), methicillin resistant *S. aureus* (MIC range = 0.015 -8.0 mcg/mL; MIC_{90} = 0.5 mcg/mL), coagulase negative staphylococci (MIC range = 0.03 - 4.0 mcg/mL; MIC_{90} = 1.0 mcg/mL), vancomycin susceptible *E. faecalis* (MIC range = 0.03 - 4.0 mcg/mL; MIC_{90} = 0.5 mcg/mL), vancomycin resistant *E. faecalis* (MIC range = 0.015 - 2.0 mcg/mL; MIC_{90} = 0.5 mcg/mL), vancomycin susceptible *E. faecium* (MIC range = 0.03 - 1.0 mcg/mL; MIC_{90} = 0.25 mcg/mL), vancomycin resistant *E. faecium* (MIC range = 0.03 - 8.0 mcg/mL; MIC_{90} = 0.25 mcg/mL), *S. pneumoniae* (MIC range = 0.03 - 1.0 mcg/mL; MIC_{90} = 0.12 mcg/mL), S. agalactiae (MIC range = 0.03 – 0.5 mcg/mL; MIC_{90} = 0.12 mcg/mL), *S. anginosus* group (MIC range = 0.03 – 0.5 mcg/mL; MIC_{90} = 0.12 mcg/mL), *S. pyogenes* (MIC range = 0.03 – 0.5 mcg/mL; MIC_{90} = 0.06 mcg/mL), and viridans group streptococci (MIC range = 0.03 – 0.5 mcg/mL; MIC_{90} = 0.12 mcg/mL).

With respect to Gram negative bacteria, omadacycline is active *in vitro* against *E. coli* (MIC range = 0.12 – >4.0 mcg/mL; MIC_{90} = 2 mcg/mL). The omadacycline MIC_{90} value was 2-fold higher for *E. coli* ESBL producers compared to non-ESBL producers. For *K. pneumoniae*, the omadacycline MIC_{90} value was >4 mcg/mL (MIC range = 0.12 - >4 mcg/mL) and similar for *K. pneumoniae* ESBL producers. In smaller surveillance studies, omadacycline had lower activity against 154 ESBL and 26 carbapenemase producing *K. pneumoniae* with MIC ranges 1.0 – 32.0 mcg/mL and MIC_{90} values 8.0 to 16.0 mcg/mL. The activity of omadacycline was similar to tigecycline against *E. coli* but lower than tigecycline against *K. pneumoniae*. For *E. cloacae*, the omadacycline MIC_{90} value was >4 mcg/mL (MIC range = 0.5 - >4 mcg/mL). For *E. aerogenes*, the omadacycline MIC_{90} value was 4 mcg/mL (MIC range = 1-8 mcg/mL). For *Citrobacter* spp. including *C. fruendii*, the omadacyline MIC_{90} was 2 mcg/mL. Omadacycline is active against *H. influenzae* (MIC range = 0.06 – 16.0 mcg/mL; MIC_{90} = 2 mcg/mL) and *Moraxella catarrhalis* (MIC range = 0.06 – 0.5 mcg/mL; MIC_{90} = 0.25 mcg/mL). The omadacycline MIC_{90} against *Acinetobacter baumannii* and *Stenotrophomonas maltophila* were 8 mcg/mL. Omadacycline is not active against *P. aeruginosa*, *Proteus* spp, *Morganella* spp, and *Providencia* spp

Clinical Microbiology Reviewer's Comment: The omadacycline MIC range and MIC_{90} values in smaller surveillance studies were similar to that observed in the large surveillance studies. The activity of omadacycline is comparable to tigecycline against Gram-positive and Gram-negative bacteria.

Atypical bacteria

The omadacycline MIC range against 137 *L. pneumophila* isolates was 0.06-4 mcg/mL and the MIC_{90} values ranged from 0.25 to 4 mcg/mL (

Table 8-3). Omadacycline was active against 28 *Mycoplasma pneumoniae* isolates with an MIC range of ≤0.015 – 0.25 mcg/mL and MIC_{90} value of 0.25 mcg/mL. Omadacycline was active against 15 *C. pneumoniae* isolates with an MIC range of 0.03-0.5 mcg/mL and MIC_{90} values of 0.25 mcg/mL.

Table 8-3 Activity of omadacycline and comparator agents against atypical organisms.

Species	No. of Strains	Antibiotic	Minimum Inhibitory Concentration (MIC, µg/mL) MIC Range	MIC_{50}	MIC_{90}	Reference
L. pneumophila	12	Omadacycline	0.5 - 4	2	4	02-04-2016-Paratek9v3
		Tigecycline	0.12 - 1	0.25	0.5	
L. pneumophila (all serogroups)	25[a]	Omadacycline	0.06 - 1	0.25	0.25	25-006
		Doxycycline	0.06 - 1	1	1	
	100	Omadacycline	0.06 - 1	0.25	0.25	214-017D (study 2)
		Doxycycline	0.5 - 1	1	1	
M. pneumoniae	8	Omadacycline	≤0.015 - 0.06	N/A	N/A	02-04-2016-Paratek9v3
		Tigecycline	≤0.015 - 0.12	N/A	N/A	
	20	Omadacycline	0.12 - 0.25	0.12	0.25	Mycoplasma-Waites
		Doxycycline	0.12 - 0.5	0.25	0.5	
		Tetracycline	0.25 - 0.5	0.5	0.5	
M. hominis	20	Omadacycline	0.016 - 0.12	0.03	0.06	Mycoplasma-Waites
		Doxycycline	0.016 - 2	0.06	2	
		Tetracycline	0.03 - 32	0.12	16	
U. parvum	10	Omadacycline	0.25 - 1	0.5	1	Mycoplasma-Waites
		Doxycycline	0.06 - 4	0.12	4	
		Tetracycline	0.12 - 16	0.5	16	
U. urealyticum	10	Omadacycline	0.25 - 2	1	2	Mycoplasma-Waites
		Doxycycline	0.06 - 4	0.5	0.5	
		Tetracycline	0.12 - 16	1	2	
Ureaplasma spp.	20	Omadacycline	0.25-2	1	2	Mycoplasma-Waites
		Doxycycline	0.06 - 4	0.25	4	
		Tetracycline	0.12 - 16	1	16	
C. pneumoniae	15	Omadacycline	0.03 – 0.5	0.06	0.25	SUNY-Hammerschlag
		Doxycycline	0.06 – 0.25	0.12	0.12	

MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration against 90% of the isolates, N/A = not applicable, MIC_{50} and MIC_{90} values not calculated when less than 10 strains were tested, No. = number.

[a] Erythromycin-resistant

Data source is listed in the column "References".

Anaerobic Bacteria

The activity of omadacycline and comparators against anaerobes was determined using both broth microdilution and agar dilution methods and is shown in

Table 8-4 (Study 08-03-2016-Paratek10 and Study 594). The omadacycline MIC_{90} values for *Clostridium perfringens*, and *Bacteroides* spp. were 4-8 mcg/mL. The omadacycline MIC_{90} values against *Prevotella* spp., and *Porphyromonas asaccharolytica* were 2 mcg/mL, and 0.5 mcg/mL, respectively. The activity observed with omadacycline against anaerobes was similar to that observed with tigecycline.

Table 8-4 Activity of omadacycline and comparators against anaerobic bacteria

Species	No. of Strains	Antibiotic	Minimum Inhibitory Concentration (MIC, µg/mL) MIC Range	MIC_{50}	MIC_{90}	Reference
C. difficile	27	Omadacycline	0.06 – 0.12	0.06	0.06	Study 594
		Doxycycline	0.015 – 0.5	0.03	0.5	
	21	Omadacycline	0.25 - 8	0.25	0.5	08-03-2016-Paratek10
		Tigecycline	0.25 - 4	0.25	0.25	
C. perfringens	100	Omadacycline	0.06 - 8	1	4	Study 594
		Doxycycline	0.015 - 16	2	8	
	22	Omadacycline	0.12 - 16	4	16	08-03-2016-Paratek10
		Tigecycline	0.25 - >16	8	>16	
Peptostreptococcus spp.	22	Omadacycline	0.06 - 2	0.12	1	08-03-2016-Paratek10
		Tigecycline	0.06 - 4	0.12	2	
B. fragilis	100	Omadacycline	0.25 - 16	1	2	Study 594
		Doxycycline	0.06 - 16	8	8	
	21	Omadacycline	0.25 - 16	0.5	4	08-03-2016-Paratek10
		Tigecycline	0.5 - 8	0.5	2	
B. thetaiotaomicron	100	Omadacycline	0.06 - 32	0.5	8	Study 594
		Doxycycline	0.06 - >32	4	8	
	21	Omadacycline	0.12 - 16	1	4	08-03-2016-Paratek10
		Tigecycline	0.25 - 16	1	8	
B. vulgatus	21	Omadacycline	0.06 - 2	0.12	1	08-03-2016-Paratek10
		Tigecycline	0.12 - 2	0.25	1	
B. ovatus	15	Omadacycline	0.06 - >16	0.5	8	08-03-2016-Paratek10
		Tigecycline	0.03 - >16	0.5	8	
Prevotella spp.	22	Omadacycline	0.12 - 8	0.5	2	08-03-2016-Paratek10
		Tigecycline	0.06 - 16	1	4	
P. asaccharolytica	21	Omadacycline	0.06 - 2	0.25	0.5	08-03-2016-Paratek10
		Tigecycline	0.03 - 1	0.25	0.5	
Anaerobic Gram-positive cocci[a]	101	Omadacycline	0.015 - 1	0.12	0.25	Study 594
		Doxycycline	0.015 -8	1	4	

MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration against 90% of the isolates, No. = number.

[a] Organisms include: *A. prevotii* (6), *M. micros* (8), *F. magna* (10), *P. anaerobius* (50), *P. asaccharolyticus* (27)

Data source is listed in the column "References".

Activity against target pathogens with key resistance genotypes

The *in vitro* activity of omadacycline was assessed against strains of *S. aureus, H. influenzae*, and *S. pneumoniae* with resistance genes (Table 8-5, 216-036B Dubois2017). For the macrolide-resistant (*ermA*, *B* & *C* genotype; n=50) and ciprofloxacin-resistant (*gyrA* and *parC* genotype; n = 39) *S. aureus* strains, the omadacycline MIC range was 0.06 – 0.25 mcg/mL and MIC_{90} values were 0.25 mcg/mL. For the macrolide-resistant (*ermA*, *B* & *C* genotype; n = 129) and 48 ciprofloxacin-resistant (*gyrA* and *parC* genotype;

n = 48) *H. influenzae* strains, the omadacycline MIC range was 0.25 – 8 mcg/mL and MIC_{90} values were 2 mcg/mL. For the erythromycin-resistant (*erm*B and *mef*E genotype; n = 159) *S. pneumoniae* strains, the omadacycline MIC range was ≤ 0.008 to 0.5 mcg/mL and the MIC_{90} range was 0.06 - 0.12 mcg/mL. For the ciprofloxacin-resistant (*gyr*A and *par*C genotype; n = 38) *S. pneumoniae* strains, the omadacycline MIC range was ≤0.016 to 0.25 mcg/mL and the MIC_{90} was 0.12 mcg/mL.

Table 8-5 Activity against target pathogens with key resistance genotypes

			Minimum Inhibitory Concentration (MIC, µg/mL)		
Species	No. of Strains	Antibiotic	MIC Range	MIC_{50}	MIC_{90}
S. aureus (macrolide-resistant)[a]	50	Omadacycline	0.06 - 0.25	0.25	0.25
		Doxycycline	0.25 - 1	1	1
		Tigecycline	0.25 - 1	0.5	0.5
S. aureus (ciprofloxacin-resistant)[b]	39	Omadacycline	0.06 - 0.25	0.25	0.25
		Doxycycline	0.5 - 1	1	1
		Tigecycline	0.25 - 0.5	0.5	0.5
H. influenzae (macrolide-resistant)[a]	129	Omadacycline	0.25 - 8	1	2
		Doxycycline	0.12 - 8	0.25	4
		Tigecycline	0.06 - 4	0.25	1
H. influenzae (ciprofloxacin-resistant)[b]	48	Omadacycline	0.25 - 8	1	2
		Doxycycline	0.03 - 8	0.25	0.5
		Tigecycline	0.06 - 4	0.12	0.5
S. pneumoniae (erythromycin-resistant)[c]	105	Omadacycline	0.016 -0.5	0.06	0.12
		Doxycycline	0.06 - ≥16	≥16	≥16
		Tigecycline	0.06 - 1	0.25	0.25
S. pneumoniae (erythromycin-resistant)[d]	54	Omadacycline	≤0.008 – 0.25	0.06	0.06
		Doxycycline	0.12 - ≥16	4	≥16
		Tigecycline	0.016 – 0.5	0.25	0.25
S. pneumoniae (ciprofloxacin-resistant)[b]	38	Omadacycline	≤0.016 – 0.25	0.06	0.12
		Doxycycline	0.06 - ≥16	0.25	≥16
		Tigecycline	0.03 – 0.5	0.25	0.25

MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration against 90% of the isolates, No. = number.
[a] *erm*A, B & C genotype
[b] *gyr*A and *par*C genotype
[c] *erm*B genotype
[d] *mef*E genotype
Source: Study report: 216-036B Dubois2017

Clinical Microbiology Reviewer's Comment: Omadacycline was active in vitro against strains of S. aureus, H. influenzae, and S. pneumoniae with macrolide and ciprofloxacin resistance genes. The clinical significance of this finding is not known.

The activity of omadacycline was examined against tetracycline resistant *Enterobactericeae* isolates with tetracycline-specific efflux and ribosomal protection proteins. The omadacycline MIC_{90} for 32 *Enterobactericeae* isolates carrying the *tetA* gene was 16 mcg/mL (Table 8-6). Among the isolates with omadacycline MIC >4 mcg/mL, there were two *Enterobacter* spp. with MIC of 8 mcg/mL and seven *K.*

pneumoniae with MICs of 8 - >32 mcg/mL. The omadacycline MIC_{90} was 4 mcg/mL in 25 *Enterobactericeae* isolates expressing *tetB* (Table 8-7).

Table 8-6 Activity of omadacycline and comparator tetracyclines against 32 Enterobacteriaceae isolates carrying tetA.

Antimicrobial agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Range (µg/mL)	CLSI[a]		
				%S	%I	%R
Omadacycline	4	16	0.5 - >32			
Tetracycline	>16	>16	1 - >16	6.2	0.0	93.8
Doxycycline	>8	>8	0.5 - >8	21.9	15.6	62.5
Tigecycline	0.5	2	≤0.06 - 4	96.9	3.1	0.0[b]

CLSI = Clinical and Laboratory Standards Institute, FDA = Food and Drug Administration, I = intermediate, MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates, R = resistant, S = susceptible.

[a] Criteria as published by CLSI [2017].

(b) (4)

Organisms include: *C. freundii* (1), *E. aerogenes* (4), *E. cloacae* (1), *E. coli* (13), *K. oxytoca* (3), *K. pneumoniae* (10)

Table 8-7 Activity of omadacycline and comparator tetracyclines against 25 Enterobacteriaceae isolates carrying tetB.

Antimicrobial agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Range (µg/mL)	CLSI[a]		
				%S	%I	%R
Omadacycline	1	4	0.5 - 4			
Tetracycline	>16	>16	16 - >16	0.0	0.0	100.0
Doxycycline	>8	>8	8 - >8	0.0	8.0	92.0
Tigecycline	0.25	0.5	0.12 - 1	100.0	0.0	0.0 [b]

CLSI = Clinical and Laboratory Standards Institute, FDA = Food and Drug Administration, I = intermediate, MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates, R = resistant, S = susceptible.

[a] Criteria as published by CLSI [2017].

(b) (4)

Organisms include: *C. freundii* (4), *E. cloacae* (1), *E. coli* (10), *K. oxytoca* (5), *K. pneumoniae* (5)

Clinical Microbiology Reviewer's Comment: Tigecycline was more active than omadacycline against tetracycline resistant Enterobactericeae isolates.

8.1.3 Effects of Miscellaneous factors on activity

Data from an investigation of the comparative *in vitro* activity of omadacycline in broth, and broth plus surfactant and serum was included (Study P1141). In this study, the investigators determined the MIC and minimum bactericidal concentration (MBC) of omadacycline against clinical isolates of *S. aureus*, *S. pneumoniae*, *E. coli*, and *H. influenzae*, using Cation-Adjusted Mueller Hinton Broth (without additives, with 1% lung surfactant, and with 25-50% human serum) as the growth media. MIC and MBC determinations were made using CLSI procedures. The activity of omadacycline against *S. aureus* in the presence of broth, surfactant and serum, is summarized in Table 8-8.

Doxycycline and daptomycin were tested as comparators. The activity of omadacycline was not affected by the addition of either lung surfactant or human serum, in this study.

Table 8-8 Effect of bovine surfactant or serum on the activity of Omadacycline, Doxycycline, and Daptomycin.

Organism	N	Condition	Range MIC µg/mL		
			Omadacycline	Doxycycline	Daptomycin
S. aureus	6	Broth	0.125-0.5	≤0.06-4	0.25
		Surfactant	0.125-0.5	≤0.06-4	16
		Serum (50%)	0.25-0.5	0.5-16	2-4
S. pneumoniae	3	Broth	0.03-0.06	0.03-4	0.25
		Surfactant	0.03-0.06	0.03-4	4-16
		Serum (50%)	0.03	0.125-4	0.5-1
E. coli	6	Broth	0.5-4	0.5-32	N/A
		Surfactant	0.5-2	0.5-64	N/A
		Serum (50%)	0.25-2	1- >64	N/A
H. influenzae	6	Broth	0.5-4	0.5-4	N/A
		Surfactant	0.5-4	0.25-4	N/A
		Serum (50%)	0.5-4	1-8	N/A

MIC = minimum inhibitory concentration, N = number, N/A = not applicable.
Reference: P1141

Protein binding

In pharmacokinetic studies, approximately 20% of omadacycline was bound to plasma proteins.

Intracellular activity

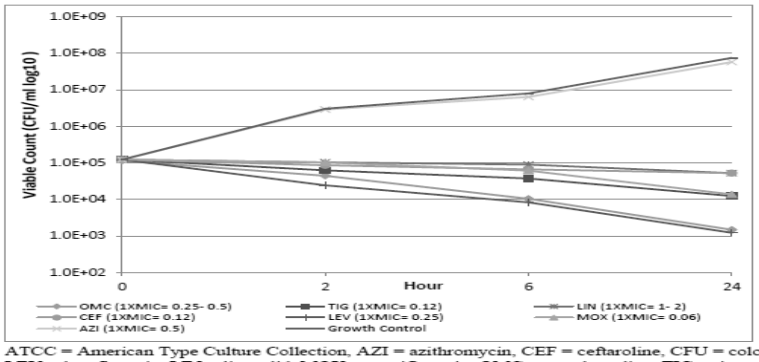
The intracellular activity of omadacycline was evaluated against *L. pneumophila* and *S. aureus* using human monocytes (Study 214-016D and Study 215-019B, Poster-551). The minimal extracellular concentration inhibiting the intracellular multiplication of bacteria (MIEC) was determined by exposing human monocytes (U937 cell line) with intracellular bacteria to antibacterial drugs for two or four days. A reduction of ≥50% of intracellular *L. pneumophila* was observed for all strains with an omadacycline mean MIEC/MIC ratio of 0.24 (Table 8-9).

Table 8-9 MIC, MIEC and MIC/MIEC Ratio of *Legionella pneumophila*.

			2 Days of Drug Exposure		4 Days of Drug Exposure	
L. pneumophila	Antibiotic	MIC (μg/mL)	MIEC[a] (μg/mL)	MIEC/MIC[b]	MIEC[c] (μg/mL)	MIEC/MIC[d]
All tested strains (N=5)	Omadacycline	0.25	0.06	0.24	0.06	0.24
	Doxycycline	1	0.5	0.5	0.5	0.5
	Azithromycin	0.5 and 0.06	0.5 and 0.06	1	ND	ND
	Moxifloxacin	0.008 and 0.004	0.004 and 0.002	0.5	0.004 and 0.002	0.5
Erythromycin-Resistant (N=3)	Omadacycline	0.25	0.06	0.24	0.06	0.24
	Doxycycline	1	0.5	0.5	1	1
	Azithromycin	0.5	0.5	1	0.5	1
	Moxifloxacin	0.008	0.004	0.5	0.004	0.5

MIC = minimum inhibitory concentration, MIEC = minimal extracellular concentration inhibiting the intracellular multiplication of bacteria, ND = not done.
[a] MIEC after 2 days of drug exposure
[b] MIEC/MIC ratio after 2 days of drug exposure
[c] MIEC after 4 days of drug exposure
[d] MIEC/MIC ratio after 4 days of drug exposure
Source: Poster-551

Omadacycline treatment resulted in ≥99% growth reduction of all intracellular *S. aureus* strains (MSSA n =2; MRSA n = 2) evaluated after 24 hours of antibacterial drug exposure (Figure 8-2). In these experiments, human monocytes, TPH-1 cell line was used. The intracellular activity of omadacycline was greater than tigecycline and azithromycin.



ATCC = American Type Culture Collection, AZI = azithromycin, CEF = ceftaroline, CFU = colony-forming units, LEV = levofloxacin, LIN = linezolid, MOX = moxifloxacin, OMC = omadacycline, TIG = tigecycline.
Activity against all tested strains: ATCC29213, ATCC25923, ATCC33591, ATCC43300
Reference: 215-019B

Figure 8-2 In vitro intracellular activity of omadacycline against *S. aureus* (N=4) with antibiotic from 0 to 24 hours of incubation.

Clinical Microbiology Reviewer's Comment: The intracellular activity studies demonstrate that omadacycline can penetrate monocytes resulting in a Log10 CFU reduction that was similar to levofloxacin.

Postantibiotic effect

Clinical isolates of *S. aureus* (n=2; 1 MRSA), *E. faecalis* (n=1), *E. faecium* (n=1; VRE), *S. pneumoniae* (n=2; 1 PRSP), and *E. coli* (n=1) were tested to determine the post antibiotic effect (PAE) after exposure of log-phase bacteria to 5-fold the MIC of omadacycline, tigecycline, or linezolid for 1 hour compared to an unexposed control (Poster 512). The

PAE for omadacycline was shorter than tigecycline against enterococci (Table 8-10). The PAE against gram positive bacteria (*S. aureus*, *S. pneumoniae* and enterococci) ranged from 2.0 to 3.3 hours.

Table 8-10 Post-Antibiotic Effect observed with omadacycline and comparators.

Organism	Phenotype	PAE (h)		
		Omadacycline	Tigecycline	Linezolid
S. aureus	MSSA	2.6	3.9	1.3
S. aureus	MRSA	2.2	2.5	1.0
S. pneumoniae	PSSP	3.3	3.2	2.2
S. pneumoniae	PRSP	2.3	3.6	1.5
E. faecalis	VSE	2.0	3.8	1.2
E. faecium	VRE	2.1	4.4	1.8
E. coli	N/A	1.4	1.4	N/A

MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*, N/A= not applicable, PAE = post-antibiotic effect, PRSP = penicillin-resistant *S. pneumoniae*, PSSP = penicillin-susceptible *S. pneumoniae*, VRE = vancomycin-resistant enterococci, VSE = vancomycin-susceptible enterococci.
Reference: Poster 512

Effect on gut flora

The effect of omadacycline on the gut microbiota and *C. difficile* germination, proliferation, and toxin production was examined using the triple stage chemostat containing pooled human fecal slurry from healthy volunteers (Study Wilcox Cdiff 2017). The model was challenged with 10^7 CFU/mL *C. difficile* spores (ribotype 027) on days 14 and 21. Omadacycline (430 mg/L) or moxifloxacin (43 mg/L) was instilled once daily, for 7 days from day 21. The model was observed for 3 weeks post-antimicrobial challenge (days 28-49). The addition of moxifloxacin resulted in decrease in $\log_{10}$ CFU/mL for *B. fragilis* group species (~4 $\log_{10}$ CFU/mL), *Enterococcus* spp. (~4 $\log_{10}$ CFU/mL) and *Lactobacillus* spp. (~3 $\log_{10}$ CFU/mL). Moxifloxacin also stimulated *C. difficile* infection and cytotoxin production. In contrast, omadacycline exposure caused decrease in gut flora bacteria [bifidobacteria (~8 $\log_{10}$ CFU/mL), *B. fragilis* group species (~8 $\log_{10}$ CFU/mL), *Lactobacillus* spp. (~6 $\log_{10}$ CFU/mL), *Enterococcus* spp. (~6 $\log_{10}$ CFU/mL), clostridia (~5 $\log_{10}$ CFU/mL) and Enterobacteriaceae (~5 $\log_{10}$ CFU/mL)]. However, there was no evidence of *C. difficile* germination, vegetative cell proliferation or toxin production with omadacycline exposure.

Bactericidal activity

The applicant conducted a study designed to investigate the possibility of bactericidal activity of omadacycline (the tetracyclines are generally considered bacteriostatic antimicrobials). The minimum bactericidal concentration (MBC) or the time-kill analysis were performed using CLSI approved methods (Study report 2462).

Minimum Bactericidal Concentration Studies

Omadacycline (like the tetracycline comparator, doxycycline) was bactericidal against some isolates of *S. pneumoniae*, but was bacteriostatic against all *S. aureus*, *E. coli*, *Enterococcus* species, *M. catarrhalis*, and *H. influenzae* (Table 8-11). The activity of omadacycline was not impacted by resistance phenotypes included in this study (i.e., ESBL for *E. coli*, MRSA, penicillin-resistance in *S. pneumoniae*).

Table 8-11 MIC and MBC values for Omadacycline (OMA) and doxycycline (DOX) against selected isolates

Species	Antibacterial agent	MIC (μg/mL)			
		MIC_{50}	MIC_{90}	MIN	MAX
E. coli (n=13)	OMA	2	4	0.5	4
	TIG	0.25	0.5	0.25	1
	DOX	8	64	1	64
	TSX	64	>64	0.06	>64
M. catarrhalis (n=10)	OMA	0.12	0.25	0.12	0.25
	TIG	0.12	0.12	0.06	0.25
	DOX	0.12	0.25	0.06	0.25
	TSX	0.12	0.25	0.12	0.5
	AZI	0.03	0.03	≤0.015	0.03
H. influenzae (n=11)	OMA	1	1	0.5	1
	TIG	0.25	0.5	0.12	1
	DOX	0.5	1	0.5	1
	TSX	2	8	≤0.03	8
	AZI	1	2	0.5	2
S. aureus (n=14)	OMA	0.25	0.25	0.25	0.5
	TIG	0.25	0.25	0.12	0.25
	DOX	0.12	0.12	0.12	0.5
	TSX	≤0.03	0.12	≤0.03	0.12
	AZI	1	>32	0.5	>32
	LZD	2	2	1	2
S. pneumoniae (n=11)	OMA	0.03	0.12	0.015	0.5
	TIG	0.06	0.25	0.03	0.25
	DOX	0.12	4	≤0.03	8
	TSX	2	8	≤0.03	16
	AZI	0.12	>32	0.03	>32
	LZD	0.5	2	0.5	16
S. pyogenes (n=12)	OMA	0.06	0.12	0.03	0.12
	TIG	0.06	0.12	0.03	0.12
	DOX	0.12	0.25	0.06	4
	TSX	0.12	0.25	≤0.03	4
	AZI	0.06	0.06	≤0.015	0.06
	LZD	1	1	≤0.06	1
Enterococcus (n=14)	OMA	0.12	0.25	0.06	0.5
	TIG	0.12	0.12	0.06	0.25
	DOX	8	16	0.06	16
	TSX	32	64	≤0.03	64
	AZI	>32	>32	2	>32
	LZD	1	2	1	2

Table 8-11 Continued

Species	Antibacterial agent	MBC (μg/mL)			
		MBC_{50}	MBC_{90}	MIN	MAX
E. coli (n=13)	OMA	>16	>16	8	>16
	TIG	>16	>16	0.5	>16
	DOX	64	>64	64	>64
	TSX	>64	>64	0.06	>64
M. catarrhalis (n=10)	OMA	2	8	0.5	8
	TIG	1	4	0.25	8
	DOX	1	16	0.5	16
	TSX	0.5	2	0.12	64
	AZI	0.03	0.06	≤0.015	0.06
H. influenzae (n=11)	OMA	4	16	2	16
	TIG	2	16	0.25	>16
	DOX	32	64	0.5	>64
	TSX	8	32	≤0.03	64
	AZI	8	32	0.5	32
S. aureus (n=14)	OMA	16	>16	1	>16
	TIG	2	>16	0.5	>16
	DOX	16	32	0.5	>64
	TSX	0.06	8	0.06	>64
	AZI	>32	>32	1	>32
	LZD	64	128	4	128
S. pneumoniae (n=11)	OMA	0.06	0.25	0.03	4
	TIG	0.12	0.5	0.03	1
	DOX	0.25	16	0.06	16
	TSX	2	16	0.12	16
	AZI	2	>32	0.03	>32
	LZD	2	8	0.5	128
S. pyogenes (n=12)	OMA	0.25	2	0.03	2
	TIG	0.12	1	0.06	2
	DOX	2	8	0.12	8
	TSX	0.12	1	≤0.03	8
	AZI	0.25	1	0.06	>32
	LZD	4	16	0.5	16
Enterococcus (n=14)	OMA	>16	>16	8	>16
	TIG	>16	>16	16	>16
	DOX	>64	>64	16	>64
	TSX	>64	>64	0.06	>64
	AZI	>32	>32	>32	>32
	LZD	128	>128	64	>128

Time-kill Studies

Data on the killing kinetics of omadacycline and comparators against *S. aureus* (n =2), *E. coli* (n = 2), *M. catarrhalis* (n = 2), *H. influenzae* (n =2) and *S. pneumoniae* (n =2), *S. pyogenes* (n = 2) isolates were included. The time kill studies confirmed the bacteriostatic activity of omadacycline observed in MBC studies for *S. aureus, E. coli, M. catarrhalis*, and *H. influenzae*. Omadacycline was bacteriostatic against *S. pyogenes* unlike results observed in MBC studies. Omadacycline was bactericidal against the two *S. pneumoniae* isolates; however, 3 log killing was rapid for one isolate (3.7 hours) than for the other (21.5 hours). The time kill activity data for omadacycline were comparable to doxycycline and tigecycline.

8.1.4 Activity in vivo (Animal Studies)

The *in vivo* activity studies were conducted using murine models of infection (sepsis, pneumonia, UTI, burn wound, intraabdominal, and thigh). Due to poor oral availability in rodents, only parenteral dosing was employed in the animal models. The animal studies are summarized in the Appendix 15.4 (Table 15.4.4). The *in vivo* evaluation of biothreat agents is not discussed here as it is not part of the indication sought by the applicant.

***S. pneumoniae* acute systemic infection**

Omadacycline was protective for mice receiving acute lethal, systemic infections from three strains including a tetracycline-resistant strain (ATCC strain 700905) with MICs of ≤0.25. The omadacycline PD_{50} values were equal or lower than comparators.

***S. pneumoniae* pulmonary infection in immunocompetent mice**

The ED_{50} of omadacycline in a murine model of *S. pneumoniae* pulmonary infection was lower than that of minocycline or vancomycin.

***S. pneumoniae* pulmonary infection in neutropenic mice**

The PD_{50} for the determined effective dose of omadacycline in a neutropenic mouse model of respiratory infection, was higher than vancomycin for both tetracycline-susceptible and tetracycline resistant strains of *S. pneumoniae.*

Thigh infection in neutropenic mice

A neutropenic thigh model was used to demonstrate *in vivo* efficacy. Omadacycline was more effective than comparators in infections using both tetracycline-resistant *S. pneumoniae* strains (strain 700905) and methicillin-resistant *S. aureus* strains (MRSA5).

***S. aureus* acute systemic infection**

In a mouse septicemia model, the omadacycline PD_{50} was equal or less than comparators (vancomycin, minocycline, or tigecycline).

***S. aureus* gel foam model of foreign body infection in mice (abscess model)**

In a gel-foam implantation experiment, omadacycline was more effective than comparators (minocycline, vancomycin, or linezolid) in the foreign body infection determination.

***H. influenzae* pulmonary infection in mice**

Omadacycline proved to be more effective than doxycycline and less effective than ciprofloxacin in the *H. influenzae* murine pulmonary infection model

***B. fragilis* granuloma pouch infection in mice**

Efficacy against *B. fragilis* was tested in a murine pouch infection model. Omadacycline was more effective than metronidazole.

Polymicrobial intra-abdominal sepsis in mice
Survival of mice treated for intra-abdominal induced sepsis was greater in those treated with omadacycline than those treated with imipenem or linezolid.

Clinical Microbiology Reviewer's Comment: Omadacycline was comparable and/or more efficacious than other tetracycline class drugs (doxycycline, minocycline, tigecycline) or ciprofloxacin in immunocompetent animals against isolates associated with pulmonary disease (S. pneumoniae, H. influenzae). In immunocompromised mice with pulmonary infection due to tetracycline susceptible and tetracycline resistant S. pneumoniae, omadacycline was less efficacious than vancomycin. In the neutropenic thigh infection model, omadacycline was more efficacious than comparators against S. pneumoniae and methicillin resistant S. aureus but had comparable efficacy compared to vancomycin for mice infected with methicillin susceptible S. aureus. Omadacycline was more effective than metronidazole in the B. fragilis granuloma pouch model.

8.1.5 Drug Resistance

Resistance to omadacycline occurs due to mutations in the target ribosomal binding site (16S rRNA or 30S ribosomal protein S10), ribosomal protection proteins and/or efflux pumps (Heidrich 2016, Poster C1-1413, Jenner 2013)[35, 37] . Omadacycline appears not to be affected by the presence of the ribosome protection protein TET(M) in *S. aureus, E. faecalis,* and *S. pneumoniae* and the TET (K), TET (L) efflux pumps in *S. aureus* and in *E. faecalis,* respectively. In Enterobacteriaceae, elevated omadacycline MIC values were associated with the expression of TET(A) and TET(B) efflux pumps. Another mechanism of resistance to tetracycline class of drugs includes enzymatic degradation of drug. No data related to this mechanism- of resistance were included in the NDA submission.

Spontaneous mutation frequency:
Studies to determine the spontaneous mutation frequency in *S. aureus* were conducted using tetracycline-susceptible and tetracycline resistant isolates expressing t*etK* and *tetM* and single-step and serial passage selections in the presence of omadacycline. No omadacycline resistant isolates were obtained after single step exposure to 4x, 8x, and 16x MIC. Similarly, no resistant isolate was obtained after serial passage of tetracycline-susceptible and -resistant *S. aureus* isolates in sub-MIC omadacycline concentrations after 10 passages (Poster F-752).

The spontaneous mutation frequency was also examined by plating *P. aeruginosa* strain K1525 (efflux pump mexXY-deletion mutant) on Luria-Bertani (LB) agar plates containing

[37] Jenner L, Starosta AL, Terry DS, Mikolajka A, Filonava L, Yusupov M, Blanchard SC, Wilson DN, Yusupova G. Structural basis for potent inhibitory activity of the antibiotic tigecycline during protein synthesis. Proc Natl Acad Sci U S A. 2013 Mar 5;110(10):3812-6

32 mcg/mL of omadacycline. Mutants were observed at a frequency of 2.7x 10^{-8} and the omadacycline MIC was 64 to 128-fold higher in the mutant isolates relative to the parent strain (Table 8-12).

Table 8-12 Characterization of the parent *P. aeruginosa* strain and five isolates from single-step spontaneous mutation selection at 32x MIC omadacycline.

Strain	*nfxB* mutation	Amino Acid Change	Omadacycline MIC (µg/mL)
K1525	None	None	1
NB52022-AVR0001	ΔA_1-C_{71}	ΔMet1-Arg23 and frameshift	128
NB52022-AVR0003	$G_{539}T$	Gly180 -> Val	64
NB52022-AVR0004	$G_{125}A$	Arg42 -> His	128
NB52022-AVR0005	$C_{113}A$	Ala38 -> Asp	128
NB52022-AVR0006	$T_{119}A$	Leu40 -> Gln	128

MIC = minimum inhibitory concentration.
Source: Poster F-752

Serial Passage:
In the serial passage study, four strains of *S. aureus* (1 tetracycline-susceptible strain, 3 tetracycline resistant strain carrying *tetM* or *tetK* gene) were exposed to sub-MIC omadacycline concentration (one dilution below MIC) and passaged for 10 days. No isolates with increased omadacycline MIC values were obtained (Table 8-13; Poster F-752).

Table 8-13 Serial passage of 4 *S. aureus* strains in the presence of sub-MIC omadacycline.

Strain	Tetracycline resistance determinant	MIC (µg/mL)		Omadacycline MIC increase after 10 days of passage
		Omadacycline (initial)	Minocycline (initial)	
S. aureus ATCC 29213	none	0.5	0.25	none
S. aureus MRSA5	*tet*(M)	0.5	4	none
S. aureus PBS468	*tet*(K)	0.5	0.25	none
S. aureus RN4250	*tet*(K)	0.5	0.5	none

ATCC = American Type Culture Collection, MIC = minimum inhibitory concentration, MRSA = methicillin resistant *Staphylococcus aureus*.
Source: Poster F-752

Clinical Microbiology Reviewer's Comment: Resistance to omadacycline was not observed in S. aureus either following a single exposure to drug at 4x, 8x, and 16x MICs or after serial passage at sub-MIC concentrations for 10 days. Spontaneous mutation in P. aeruginosa was shown to be due to nonspecific efflux pumps, and mutants were observed at a frequency of 2.7x 10^{-8}. Efflux was also identified as the primary mechanism of acquired resistance in K. pneumoniae, as suggested by the overexpression of known tigecycline resistance genes such as ramA and acrAB.

Cross-resistance

Clinical isolates from the 2016 SENTRY surveillance program were examined for cross-resistance between omadacycline and tigecycline. This analysis included the following organisms: *S. aureus* (1438 MRSA and 2777 MSSA), *S. pneumoniae* (1317 isolates), *E. coli* and *K. pneumoniae* (5312 isolates) and *H. influenzae* (803 isolates). The scattergrams suggested a weak correlation between omadacycline and tigecycline for *E. coli* and *K. pneumoniae* (R^2= 0.5865) (Figure 8-3).

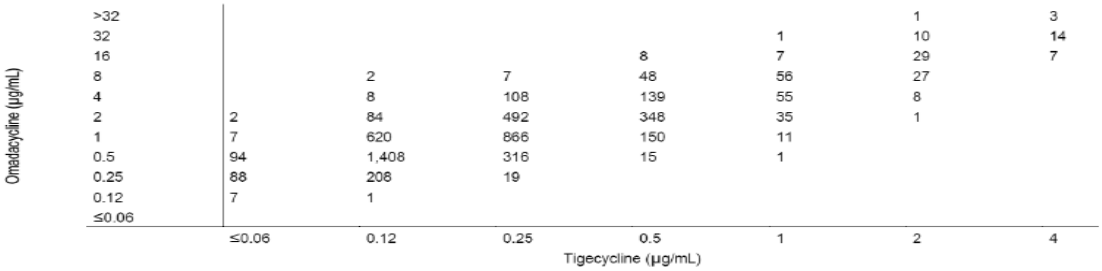


Figure 8-3 Scattergram of Omadacycline vs. Tigecycline for *Escherichia coli* and *Klebsiella pneumoniae* Isolates (n=5,311; R^2 = 0.5865). Source: 17-PAR-01.

8.1.6 Antimicrobial interaction studies

Data from checkerboard studies, designed to investigate the interactions between omadacycline and other antimicrobials, were included (Study 05-07-2015-Paratek 6v2). In general, omadacycline does not appear to interact with most antimicrobials tested. A potential for antagonism between omadacycline and imipenem and between omadacycline and ceftriaxone was observed. The results of this investigation are summarized in Table 8-14. However, the few instances of antagonism observed by the checkerboard could not be confirmed in time kills studies (Study 08-08-2017-Paratek 14).

Table 8-14 Summary of fractional inhibitory concentration index for omadacycline.

Antibiotic	FICI Range			
	E. coli (N=6)	*S. aureus* (N=6)	*Enterococcus* spp. (N=6)	*S. pneumoniae* (N=6)
Ampicillin	1.00-1.37	0.68-1.10	0.65-1.13	0.82-1.01
Ceftazidime	0.74-1.12	0.94-1.23	0.83-1.88	0.87-1.05
Ceftriaxone	1.02-1.87	0.85-1.60	0.35-42.96	0.82-1.13
Imipenem	0.62-1.91	1.11-7.35	0.80-1.38	0.80-1.30
Piperacillin/tazobactam	0.62-2.37	0.63-3.23	0.99-1.79	0.81-1.30
Gentamicin	0.53-2.04	0.54-1.19	0.74-1.38	0.80-2.40
Vancomycin	1.00-1.37	0.99-1.23	0.79-1.38	0.67-1.55
Daptomycin	1.19-1.37	1.19-2.00	0.99-2.96	1.11-2.30
Linezolid	1.23-1.87	1.04-1.23	0.71-1.38	0.89-1.13

FICI: fractional inhibitory concentration index; The mean FICI for the combination was interpreted as follows: ≤ 0.5 = synergy, >0.5-4 = additive/indifferent, and >4 = antagonism
Reference: 05-07-2015-Paratek 6v2

8.2 Clinical Microbiology

8.2.1 Assay Descriptions and Methodologies

ABSSSI studies (PTK0796-ABSI-1108 and PTK0796-ABSI-16301):

For the ABSSSI studies, material (biopsy, debrided tissue, tissue scraping, needle aspirate, pus, deep swab of purulent material) was collected from the site of infection and submitted to the local microbiology laboratory for Gram stain and culture (aerobic and anaerobic). Additionally, blood samples were collected within the 24 hours prior to the first dose of study drug. If bacteria were isolated from baseline blood cultures, repeat blood cultures were performed until negative cultures were obtained. Identification and susceptibility testing were performed at the central laboratory.

The following bacteria were considered as pathogens:

- *Staphylococcus aureus* - isolates were reviewed by oxacillin susceptibility results (methicillin resistant - MRSA and methicillin-susceptible *Staphylococcus aureus*[MSSA])
- Group A, B, C, and G β-hemolytic streptococci (i.e., *Streptococcus agalactiae, Streptococcus dysgalactiae*, *Streptococcus pyogenes*, etc.)
- *Streptococcus anginosus* group (eg, *Streptococcus anginosus*, *Streptococcus intermedius*, *Streptococcus constellatus*)
- *Enterococcus faecalis* - isolates were reviewed by vancomycin susceptibility results (vancomycin resistant *Enterococcus faecalis* and vancomycin susceptible *Enterococcus faecalis*)
- *Enterococcus faecium* - isolates were reviewed by vancomycin susceptibility results (vancomycin resistant *Enterococcus faecium* and vancomycin susceptible *Enterococcus faecium*)
- *Staphylococcus lugdunensis*
- Polymicrobial infection consisting of any combination of *Staphylococcus aureus,* Group A, B, C and G β–hemolytic streptococci and *Streptococcus*

anginosus group. A case by case review was done for other organisms that are not listed.

CABP Study (PTK0796-CABP-1200):
Microbiological assessments (Gram stain, culture, susceptibility testing) were performed using expectorated or induced sputum or bronchoalveolar lavage [BAL] fluid, pleural fluid) at screening. The sputum specimens were found to be adequate if there were < 10 squamous epithelial cells/low power field (lpf) and > 25 polymorphonuclear cells/lpf. All blood samples were cultured under anaerobic or aerobic conditions. If a baseline blood culture was positive, it was repeated until a negative blood culture was obtained, At the end of therapy (EOT) and/or post therapy evaluation (PTE; 5-10 days after last dose) visits, microbiological assessments were performed only for subjects who were clinical failures. All isolates identified by the local laboratory were submitted to the Central Laboratory for verification of genus and species and for standardized MIC testing with omadacycline, moxifloxacin and a panel of currently approved antibiotics.

Urine was also collected at the screening visit to test for the presence of *Legionella pneumophila* and *Streptococcus pneumoniae* antigens. Testing was performed at the local laboratory using kits supplied by the sponsor. Blood samples were also collected at the screening and PTE visits to conduct serology for *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* by the central laboratory.

The diagnostic specimen and criteria used for CABP pathogen are listed below:
- *Streptococcus pneumoniae*
  - Positive BAL, bronchoscopy, pleural fluid, sputum or blood culture; or
  - Positive UAT
- *Haemophilus influenzae*
  - Positive BAL, bronchoscopy, pleural fluid, sputum or blood culture
- *Staphylococcus aureus*
  - Positive BAL, bronchoscopy, pleural fluid, sputum or blood culture
- *Moraxella catarrhalis*
  - Positive BAL, bronchoscopy, pleural fluid, sputum or blood culture; or
- *Legionella pneumophila*
  - Positive BAL, bronchoscopy, pleural fluid, sputum or blood culture; or
  - Positive acute (baseline) or positive convalescent (PTE) immunoglobulin M (IgM) (Euroimmun IgM enzyme-linked immunosorbent assay [ELISA] optical density [OD] ratio of ≥ 1.1)
  - Negative acute (baseline) and positive or indeterminate convalescent (PTE) immunoglobulin G (IgG) (Euroimmun IgG ELISA OD ratio of ≥ 1.1)
  - A positive UAT
- *Mycoplasma pneumoniae*
  - Positive acute (baseline) or positive convalescent (PTE) IgM (Euroimmun IgM ELISA OD ratio of ≥ 1.1)
  - Negative acute (Baseline) and positive or indeterminate convalescent (PTE) IgG

(Euroimmun IgG ELISA OD ratio of ≥ 1.1)

- *Chlamydophila pneumoniae*
  - Positive acute (Baseline) or positive convalescent (PTE) IgM (SeroCP™ IgM cut-off index of > 1.5)
  - Negative acute (Baseline) and positive or indeterminate convalescent (PTE) IgG (SeroCP™ IgG cut-off index of > 1.1)

Clinical Microbiology Reviewer's Comment: The applicant provided package inserts for a Legionella pneumophila IgM or IgG enzyme linked immunosorbent assay (ELISA) Kit manufactured by EUROIMMUN US (Morris Plains, New Jersey [NJ]), a Mycoplasma pneumoniae IgM or IgG ELISA Kit manufactured by GenBio (San Diego, California [CA]), and a Chlamydophila pneumoniae IgM or IgG ELISA Kit manufactured by Creative Diagnostics (Shirley, NY). These serological tests are exempt from premarket notification. For Chlamydophila pneumoniae, the study report states that SeroCP™ IgM and IgG kit was used. However, the applicant provided package insert for the Creative Diagnostic Chlamydophila pneumoniae IgM or IgG ELISA kit. The applicant was asked to clarify which kits were used for M. pneumoniae and C. pneumoniae detection and the cut-off used for diagnosis as the tests stated in the study report and in the microbiology summary was different for these two pathogens. The Creative Diagnostic Chlamydophila pneumoniae IgM or IgG ELISA kits are for research purpose only and cross-reactivity with other respiratory bacterial pathogens is not known. Similarly, for the Mycoplasma pneumoniae IgM or IgG ELISA Kit manufactured by GenBio, no information on cross-reactivity with other respiratory bacterial pathogens is available. Acute and convalescent paired sera should be used to aid in diagnosis along with clinical findings and other laboratory methods. Molecular methods are the preferred method in the absence of culture. Serology test results alone are not recommended for treatment decisions of M. pneumoniae and C. pneumoniae.
In an amendment (eCTD sequence no 0013 dated 5-4-2018), the applicant clarified that the Mycoplasma pneumoniae IgM or IgG ELISA Kit manufactured by GenBio and the Creative Diagnostic Chlamydophila pneumoniae IgM or IgG ELISA kit were used for serology and results interpreted as per package insert.

8.2.2. Clinical Microbiology Analyses of Efficacy (micro-ITT population)

ABSSSI: Two Phase 3 studies PTK0796-ABSI-1108 and PTK0796-ABSI-16301 were conducted to evaluate the efficacy of omadacycline in the treatment of ABSSSI. Only microbiological assessments are discussed here. The analysis population were as follows:

Microbiological modified intent-to-treat (Micro-mITT) population consists of all subjects in the mITT population who had at least 1 Gram positive causative bacterial pathogen identified from a blood culture or from a culture of a the primary ABSSSI site at baseline.

Microbiologically evaluable populations at EOT and PTE (ME-EOT and ME-PTE) consists of all subjects in both the micro-mITT and the clinically evaluable populations at EOT

and PTE, respectively. The microbiological response at the EOT and PTE visits in the ME-EOT and ME-PTE populations were determined to support the clinical findings.

The baseline pathogens from the ABSSSI site or blood culture for the micro-mITT population in the clinical studies PTK0796-ABSI-1108 and PTK0796-ABSI-16301 are summarized in Table 8-15. Majority of the patients had methicillin-sensitive *S. aureus* or methicillin resistant *S. aureus* or *Streptococcus* species at baseline. Across the two studies, 17 patients had vancomycin susceptible *E. faecalis* at baseline.

Table 8-15 Baseline Pathogenic Organisms from the ABSSSI Site or Blood Culture in studies PTK0796-ABSI-1108 and PTK0796-ABSI-16301 (micro-mITT Population)

	Study ABSI-1108		Study ABSI-16301	
Baseline Pathogen	Omadacycline (N = 228) n (%)	Linezolid (N = 227) n (%)	Omadacycline (N = 276) n (%)	Linezolid (N = 287) n (%)
Gram-positive organisms (aerobes)	220 (96.5)	219 (96.5)	270 (97.8)	278 (96.9)
Staphylococcus aureus	156 (68.4)	151 (66.5)	220 (79.7)	233 (81.2)
MSSA	88 (38.6)	102 (44.9)	120 (43.5)	130 (45.3)
MRSA	69 (30.3)	50 (22.0)	104 (37.7)	107 (37.3)
Streptococcus anginosus group	47 (20.6)	37 (16.3)	57 (20.7)	45 (15.7)
Streptococcus constellatus	25 (11.0)	14 (6.2)	9 (3.3)	7 (2.4)
Streptococcus intermedius	12 (5.3)	18 (7.9)	23 (8.3)	24 (8.4)
Streptococcus anginosus	8 (3.5)	7 (3.1)	27 (9.8)	20 (7.0)
Streptococcus pyogenes	11 (4.8)	18 (7.9)	29 (10.5)	16 (5.6)
Enterococcus faecalis (VSE)	10 (4.4)	13 (5.7)	7 (2.5)	10 (3.5)
Staphylococcus lugdunensis	6 (2.6)	3 (1.3)	5 (1.8)	0
Streptococcus mitis	6 (2.6)	4 (1.8)	1 (0.4)	0
Streptococcus Group C	4 (1.8)	1 (0.4)	0	0
Streptococcus viridans group	3 (1.3)	5 (2.2)	3 (1.1)	0
Streptococcus sanguinis	2 (0.9)	6 (2.6)	1 (0.4)	0
Streptococcus Group F	1 (0.4)	4 (1.8)	0	0
Gram-positive organisms (anaerobes)	16 (7.0)	15 (6.6)	17 (6.2)	17 (5.9)
Finegoldia magna	4 (1.8)	5 (2.2)	3 (1.1)	1 (0.3)
Clostridium species	3 (1.3)	2 (0.9)	4 (1.4)	1 (0.3)
Actinomyces odontolyticus	0	0	3 (1.1)	1 (0.3)
Clostridium perfringens	1 (0.4)	5 (2.2)	5 (1.8)	9 (3.1)
Gram-negative organisms (aerobes)	28 (12.3)	23 (10.1)	24 (8.7)	30 (10.5)
Enterobacter cloacae complex	6 (2.6)	4 (1.8)	5 (1.8)	6 (2.1)
Klebsiella pneumoniae	6 (2.6)	5 (2.2)	5 (1.8)	6 (2.1)
Haemophilus parainfluenzae	5 (2.2)	5 (2.2)	1 (0.4)	0
Pseudomonas aeruginosa	3 (1.3)	2 (0.9)	1 (0.4)	2 (0.7)
Enterobacter cloacae	3 (1.3)	1 (0.4)	5 (1.8)	6 (2.1)
Escherichia coli	2 (0.9)	3 (1.3)	4 (1.4)	1 (0.3)
Enterobacter aerogenes	1 (0.4)	3 (1.3)	0	1 (0.3)
Morganella morganii	1 (0.4)	3 (1.3)	1 (0.4)	1 (0.3)
Klebsiella oxytoca	2 (0.9)	1 (0.4)	3 (1.1)	2 (0.7)
Eikenella corrodens	2 (0.9)	2 (0.9)	3 (1.1)	3 (1.0)
Proteus mirabilis	2 (0.9)	1 (0.4)	2 (0.7)	7 (2.4)

Table 8-15 Continued

Baseline Pathogen	Study ABSI-1108 Omadacycline (N = 228) n (%)	Study ABSI-1108 Linezolid (N = 227) n (%)	Study ABSI-16301 Omadacycline (N = 276) n (%)	Study ABSI-16301 Linezolid (N = 287) n (%)
Gram-negative organisms (anaerobes)	17 (7.5)	13 (5.7)	11 (4.0)	12 (4.2)
Prevotella melaninogenica	7 (3.1)	6 (2.6)	2 (0.7)	3 (1.0)
Prevotella intermedia	2 (0.9)	3 (1.3)	2 (0.7)	0
Prevotella denticola	2 (0.9)	1 (0.4)	5 (1.8)	1 (0.3)
Fusobacterium nucleatum	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.0)
Veillonella parvula	0	0	1 (0.4)	3 (1.0)

Percentages were based on the number of subjects in each treatment group.
Subjects with the same pathogen isolated from multiple specimens were counted only once for that pathogen.
Subjects with the same pathogen identified from both the blood and primary ABSSSI cultures were counted only once.
Both MRSA and MSSA were considered distinct pathogens.
When per-subject counts of *Staphylococcus aureus* were presented, subjects with both MRSA and MSSA 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.
Source: Study PTK0796-ABSI-1108, Table 15 and Table 14.1.7.1.1 and Study PTK0796-ABSI-16301, Table 12 and Table 14.1.7.1.1.

The early clinical response and investigator's assessment of overall clinical success at PTE by baseline pathogen are shown in
Table 8-16 and Table 8-17, respectively. Omadacycline was active against *S. aureus* (methicillin susceptible and methicillin resistant), *S. lugdunensis, S. anginosus group (S. anginosus, S. intermedius, S. constellatus)*, *E. faecalis* (vancomycin sensitive), *S. pyogenes, E. cloacae, and K. pneumoniae* in patients with ABSSSI.

Table 8-16 Comparison of Early Clinical Success 48 - 72 h After the First Dose of Study drug by Baseline Pathogen from the ABSSSI Site or Blood Culture in ≥ 6 Subjects in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population).

Baseline Pathogen	ABSI-1108 Omadacycline (N = 228) n/N1 (%)	ABSI-1108 Linezolid (N = 227) n/N1 (%)	ABSI-16301 Omadacycline (N = 276) n/N1 (%)	ABSI-16301 Linezolid (N = 287) n/N1 (%)	Pooled ABSI-1108 and ABSI-16301 Omadacycline (N = 504) n/N1 (%)	Pooled ABSI-1108 and ABSI-16301 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)
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)
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)

N1 = number of subjects in the micro-mITT population in the treatment group with the Baseline pathogen. Percentages were based on N1, the number of subjects with the indicated pathogen.
Subjects with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Subjects 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.
Source: SCP, Section 2.7.2.4, Table 14.2.1.11.1.

Table 8-17 Comparison of Overall Clinical Success at PTE Visit Based on Investigator's Assessment by Baseline Pathogen from the ABSSSI Site or Blood Culture in ≥ 6 Subjects in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population).

	ABSI-1108		ABSI-16301		Pooled ABSI-1108 and ABSI-16301	
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)
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)
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)

N1 = number of subjects in the micro-mITT population in the treatment group with the Baseline pathogen. Percentages were based on N1, the number of subjects with the indicated pathogen.
Subjects with the same pathogen isolated from multiple specimens were counted only once for that pathogen. Subjects 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.
Source: SCP, Section 2.7.2.4, Table 14.2.2.6.1.

Clinical Microbiology Reviewer's Comment: Microbiological response was presumed for most patients. Only 6 subjects in the omadacycline group and 14 in the linezolid group had a response of eradication or persistence. Therefore, only clinical response by baseline pathogen was analyzed. The Gram-negative organisms identified at baseline were present in polymicrobial infections. Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae are mainly observed in complicated skin and skin structure infections. Although good activity was observed at the early time points for polymicrobial infections with Gram negative anaerobes (91.3%) and Enterobacteriaceae (89.5%), the activity was lower at the PTE visit [Gram negative anaerobes (66.7 to 73.9%); Enterobacteriaceae (78.9%)]. The clinical success rate for S. agalactiae in the omadacycline and linezolid arm was 3/4 (75%). The one patient in the omadacycline arm who failed had persistence of pathogen at EOT (MIC = 0.06 mcg/mL). The clinical success rate for S. dysgalactiae was 3/3 (100%) in both omadacycline and linezolid arm.

Bacteremia patients: The microbiological response at EOT by baseline pathogen in subjects with bacteremia is shown in Table 8-18. The majority of subjects had *S. aureus* bacteremia and successful outcome was observed in 6/8 (75%) subjects.

Table 8-18 Microbiological response at EOT by pathogen in ABSSSI subjects with bacteremia.

Baseline Pathogen	PTK0796ABSI-1108		PTK0796ABSI-16301	
	Omadacycline (N= 11)	Linezolid (N=9)	Omadacycline (N = 2)	Linezolid (N =8)
Staphylococcus aureus	6/7	6/6	0/1	3/3
MSSA	3/4	4/4	0/1	2/2
MRSA	3/3	2/2	0/0	0/0
Streptococcus pyogenes	2/2	1/1	0/0	0/0
Streptococcus anginosus	1/1	0/0	0/0	0/0
Streptococcus dysgalactiae	1/1	0/0	0/0	0/0
Streptococcus sanguinis	0/0	0/0	1/1	0/0
Enterococcus faecalis (VSE)	0/0	1/1	0/0	0/0
Streptococcus viridans group	0/0	1/1	0/0	0/0
Streptococcus intermedius	0/0	0/0	0/0	1/1
Granulicatella adiacens	0/0	0/0	0/0	1/1
Moraxella lacunata	0/0	0/0	0/0	1/1
Rothia dentocariosa	0/0	0/0	0/0	1/1

Source: Clinical Microbiology Reviewer Analysis.

Clinical Microbiology Review's comment: The omadacycline MICs for S. aureus in the two subjects in the omadacycline arm with persistence was 0.25 mcg/mL.

The omadacycline MIC ranges, MIC_{50} values, and MIC_{90} values for baseline pathogens in the micro-mITT group are shown in Table 8-19. The omadacycline MIC_{90} for *S. aureus* was 0.5 mcg/mL and similar to that observed in surveillance studies. The omadacycline MIC_{90} for the *Streptococcus anginosus* group was 0.03 mcg/mL and lower than that observed in surveillance studies. Against vancomycin susceptible *E. faecalis*, the omadacycline MIC_{90} was 0.25 mcg/mL and similar to that observed in surveillance studies.

Table 8-19 Omadacycline MIC Summary Statistics for Baseline Pathogens from the ABSSSI Site or Blood Culture micro-mITT Population pooled studies.

Baseline Pathogen	Omadacycline (N=504)			Linezolid (N=514)		
	N1	Range (µg/mL)	MIC_{50}/MIC_{90} (µg/mL)	N1	Range (µg/mL)	MIC_{50}/MIC_{90} (µg/mL)
Gram-positive organisms (aerobes)						
Staphylococcus aureus	365	0.12 - 1	0.25/0.5	375	≤0.25 - 4	2/2
MRSA	168	0.12 - 1	0.25/0.25	151	1 - 4	2/2
MSSA	202	0.12 - 1	0.25/0.5	229	≤0.25 - 4	2/2
Streptococcus anginosus group	96	≤0.008 - 0.25	0.008/0.03	75	≤0.12 - 2	0.5/1
Streptococcus anginosus	32	≤0.008 - 0.12	0.015/0.06	25	0.5 - 2	1/2
Streptococcus intermedius	30	≤0.008 - 0.25	0.008/0.008	37	≤0.12 - 1	0.25/0.5
Streptococcus constellatus	32	≤0.008 - 0.03	0.008/0.03	20	≤0.12 - 1	0.5/1
Streptococcus pyogenes	39	≤0.008 - 0.25	0.06/0.12	33	0.5 - 1	1/1
Enterococcus faecalis	17	0.06 - 0.5	0.12/0.25	25	0.5 - 2	1/2
VSE	17	0.06 - 0.5	0.12/0.25	23	0.5 - 2	1/2
Staphylococcus lugdunensis	11	0.06 - 0.25	0.12/0.12	3	0.5	N/A
Streptococcus mitis	6	≤0.008 - 0.06	N/A	4	0.5 - 1	N/A
Streptococcus oralis	5	0.03 - 0.12	N/A	2	1	N/A
Streptococcus sanguinis	3	≤0.008 - 0.06	N/A	6	0.5 - 1	N/A
Gram-positive organisms (anaerobes)						
Finegoldia magna	7	0.06 - 1	N/A	6	1 - 2	N/A
Clostridium perfringens	6	0.06 - 4	N/A	12	2	2/2
Gram-negative organisms (aerobes)						
Enterobacter cloacae	14	2 - 8	4/8	11	>8	8/8
Klebsiella pneumoniae	10	1 - 4	2/4	11	>8	8/8
Escherichia coli	5	0.5 - 4	N/A	4	>8	N/A
Haemophilus parainfluenzae	5	1 - 4	N/A	0	N/A	N/A
Klebsiella oxytoca	5	1 - 2	N/A	3	>8	N/A
Morganella morganii	2	8 - 16	N/A	4	>8	N/A
Proteus mirabilis	4	4 - >16	N/A	7	>8	N/A
Gram-negative organisms (anaerobes)						
Prevotella denticola	7	0.03 - 0.25	N/A	1	2	N/A
Prevotella melaninogenica	5	0.03 - 0.25	N/A	6	1-2	N/A

Note: MRSA and MSSA are considered distinct pathogens. For subjects with the same baseline pathogen in multiple specimens, the specimen with the highest MIC to the study drug received is used. Minimum inhibitory concentration range is provided for pathogens isolated at least 5 times in at least one of the pooled treatment groups. Minimum inhibitory concentration against 50% of the isolates and MIC_{90} is provided for pathogens isolated at least 10 times in at least one of the pooled treatment groups.

ABSSSI = acute bacterial skin and skin structure infections, MIC = minimum inhibitory concentration, MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration against 90% of the isolates, micro-mITT = microbiological modified intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*, N = Number of subjects in each study, population and treatment group, N1 = Number of subjects with baseline pathogens and susceptibility data available, N/A = not applicable, VSE = vancomycin-susceptible enterococci.

Source: ISM\ Table 14.1.7.7.1

The clinical success at PTE by MIC of the baseline pathogen in pooled ABSSSI studies (micro-mITT population is shown in Table 8-20.

Table 8-20 Clinical success at PTE visit by baseline pathogen and MIC in pooled ABSSSI studies.

Baseline Pathogen	Omadacycline (N = 504)	
	MIC (mcg/mL)	Clinical success n/n2 (%)
S. aureus (methicillin resistant) N1 = 168		
	0.12	23/27 (85.2)
	0.25	105/126 (83.3)
	0.5	14/14 (100.0)
	1.0	1/1 (100.0)
S. aureus (methicillin sensitive) N1 = 202		
	0.12	11/15 (73.3)
	0.25	112/138 (81.2)
	0.5	42/48 (87.5)
	1.0	1/1 (100.0)
S. anginosus group N1 = 96		
	≤0.008	51/63 (81.0)
	0.015	10/13 (76.9)
	0.03	10/13 (76.9)
	0.06	4/5 (80.0)
	0.12	1/1 (100.0)
	0.25	1/1 (100.0)
S. anginosus, N1 = 32		
	≤0.008	11/12 (91.7)
	0.015	5/7 (71.4)
	0.03	8/8 (100.0)
	0.06	3/4 (75.0)
	0.12	1/1 (100.0)
S. intermedius, N1 = 30		
	≤0.008	21/27 (77.8)
	0.015	1/1 (100.0)
	0.06	1/1 (100.0)
	0.25	1/1 (100.0)
S. constellatus, N1 = 32		
	≤0.008	17/23 (73.9)
	0.015	3/4 (75.0)
	0.03	2/5 (40.0)
S. pyogenes, N1 = 39		
	≤0.008	1/2 (50.0)
	0.015	1/1 (100.0)
	0.06	17/22 (77.3)
	0.12	7/13 (53.8)
	0.25	1/1 (100.0)
S. lugdunensis, N1 = 11		
	0.06	3/3 (100.0)
	0.12	6/7 (85.7)
	0.25	1/1 (100.0)

Table 8-20 Continued

Baseline Pathogen	Omadacycline (N = 504)	
	MIC (mcg/mL)	Clinical success n/n2 (%)
Vancomycin susceptible *E. faecalis*, N1= 17		
	0.06	1/1 (100.0)
	0.12	12/12 (100.0)
	0.25	6/7 (85.7)
	0.5	1/1 (100.0)
Enterobacter cloacae, N1 = 14		
	2	1/3 (33.3)
	4	8/9 (88.9)
	8	2/2 (100.0)
Klebsiella pneumoniae, N1 = 10		
	1	2/2 (100.0)
	2	1/3 (33.3)
	4	4/5 (80.0)
Escherichia coli, N1 = 5		
	0.5	1/1 (100.0)
	1	1/1 (100.0)
	2	2/2 (100.0)
	4	1/1 (100.0)
K. oxytoca, N1 = 5		
	1	0/1 (0.0)
	2	4/4 (100.0)
Finegoldia magna, N1 = 7		
	0.06	1/1 (100.0)
	0.12	3/3 (100.0)
	0.25	2/2 (100.0)
	1.0	1/1 (100.0)
Clostridium perfringens, N1 = 6		
	0.06	1/1 (100.0)
	0.5	1/1 (100.0)
	1.0	2/2 (100.0)
	4.0	1/2 (50.0)
Prevotella denticola, N1 = 5		
	1	0/1 (0.0)
	2	4/4 (100.0)
Prevotella melaninogenica, N1 = 5		
	0.03	0/1 (0.0)
	0.06	2/3 (66.7)
	0.25	1/1 (100.0)

MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*, N1 = the number of subjects with the specific baseline pathogen, n = the number of subjects with a clinical success in the specific baseline pathogen and MIC, n2 = the number of subjects with the specific baseline pathogen and MIC, PTE = Post Therapy Evaluation
Source: ISM\Table 14.2.2.8.1

Clinical Microbiology Reviewer's Comment: Omadacycline was active against S. aureus (methicillin susceptible and methicillin resistant), S. lugdunensis, S. anginosus group (S. anginosus, S. intermedius, S. constellatus), S. pyogenes, E. faecalis (vancomycin sensitive), E. cloacae, and K. pneumoniae in patients with ABSSSI. S. mitis is considered as normal flora.

PTK0796-CABP-1200: The microbiological response at the end of therapy (EOT) and post therapy evaluation (PTE) visits in the microbiological intent-to-treat (microITT), and microbiologically evaluable (ME) populations were analyzed to support the clinical findings. The microITT population consisted of all subjects in the ITT population who had at least one causative bacterial pathogen identified from a culture of a respiratory specimen (for example, BAL fluid, pleural fluid, expectorated or induced sputum) or blood, or from a culture-independent method (for example, positive urinary antigen test [UAT] for *S. pneumoniae* or *L. pneumophila*, or positive serology for *L. pneumophila*, *M. pneumoniae*, or *C. pneumoniae*) at baseline. The number of patients in each population group is shown below:

Population	Omadacycline	Moxifloxacin
MicroITT (n = 386)	204	182
ME-EOT (n = 365)	193	172
ME-PTE (n = 357)	188	169

The baseline pathogens from the blood specimens, respiratory specimens, UAT, and/or serology for the microITT population are shown in Table 8-21. These include *Streptococcus pneumoniae* (21.1% omadacycline, 18.7% moxifloxacin), *S. aureus* (5.4% omadacycline, 6.0% moxifloxacin), *Haemophilus influenzae* (15.7% omadacycline; 8.8% moxifloxacin), *Haemophilus parainfluenzae* (8.8% omadacycline, 9.3% moxifloxacin), and *K. pneumoniae* (6.4% omadacycline, 7.1% moxifloxacin). As seen in Table 8-22, the atypical bacteria were identified by using non-culture methods.

Table 8-21 Subjects with CABP pathogens identified at baseline from blood specimens, respiratory specimens, UATs, and/or serology in the microITT Population.

Baseline Pathogen	Omadacycline	Moxifloxacin
	N = 204	N = 182
	n (%)	n (%)
Streptococcus pneumoniae[a]	43 (21.1)	34 (18.7)
PSSP	26 (12.7)	22 (12.1)
Macrolide-resistant	10 (4.9)	5 (2.7)
MDRSP	7 (3.4)	6 (3.3)
Staphylococcus aureus	11 (5.4)	11 (6.0)
MSSA	11 (5.4)	10 (5.5)
Haemophilus influenzae	32 (15.7)	16 (8.8)
Haemophilus parainfluenzae	18 (8.8)	17 (9.3)
Klebsiella pneumoniae	13 (6.4)	13 (7.1)
Escherichia coli	6 (2.9)	7 (3.8)
Moraxella catarrhalis	4 (2.0)	1 (0.5)
Pseudomonas aeruginosa	3 (1.5)	5 (2.7)
Enterobacter cloacae	2 (1.0)	4 (2.2)
Haemophilus parahaemolyticus	2 (1.0)	2 (1.1)
Proteus mirabilis	2 (1.0)	2 (1.1)
Klebsiella oxytoca	1 (0.5)	4 (2.2)
Atypical Pathogens[c]	118 (57.8)	106 (58.2)
Mycoplasma pneumoniae	70 (34.3)	57 (31.3)
Legionella pneumophila[b]	37 (18.1)	37 (20.3)
Chlamydophila pneumoniae	28 (13.7)	28 (15.4)
Atypical Pathogens[d]	73(35.8)	64 (35.2)
Mycoplasma pneumoniae	35 (17.2)	29 (15.9)
Legionella pneumophila[b]	29 (14.2)	28 (15.4)
Chlamydophila pneumoniae	15 (7.4)	14 (7.7)

N = Number of subjects in the microITT population; n = Number of subjects with the specific baseline pathogen. Percentages were calculated based on subjects in the microITT population.
MDRSP = multi-drug resistant *Streptococcus pneumoniae*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; PNSSP = penicillin-nonsusceptible *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; UAT = urinary antigen test.
[a] Overall tabulation of *Streptococcus pneumoniae* included identification from urinary antigen only which would not have susceptibility data.
[b] *Legionella pneumophila* may be detected from serology and/or UAT.
[c] Defined as in the Statistical Analysis Plan which considers an indeterminate convalescent serology result aspositive
[d] For identification by serology, considers only a positive convalescent serology result as positive
Source: CABP\Table 14.1.11.1.1 and CABP\Table 14.2.1.4.1.1

Table 8-22 Subjects with baseline pathogens identified from nonculture methods (microITT Population[a])

Baseline Pathogen	Omadacycline	Moxifloxacin
	N = 204	N = 182
	n (%)	n (%)
***Streptococcus pneumoniae* (culture and/or UAT)**	43 (21.1)	34 (18.7)
Positive via UAT	23 (11.3)	16 (8.8)
Atypical Pathogens	118 (57.8)	106 (58.2)
Mycoplasma pneumoniae (serology positive)	70 (34.3)	57 (31.3)
Legionella pneumophila (culture, serology, and/or UAT)	37 (18.1)	37 (20.3)
Positive via culture	0	0
Positive via serology	35 (17.2)	35 (19.2)
Positive via urinary antigen	5 (2.5)	7 (3.8)
Chlamydophila pneumoniae (serology positive)	28 (13.7)	28 (15.4)

N = Number of subjects in the microITT population.
n = Number of subjects with the specific baseline pathogen.
Percentages were calculated based on subjects in the microITT population.
UAT = urinary antigen test
a Defined as in the SAP which considered an indeterminate convalescent serology result as positive.
Source: Table 14.1.11.3.1.

Clinical Microbiology Review's comment: A third of subjects with atypical bacteria were present as mixed infections. Majority of the polyinfections were with S. pneumoniae (positive blood or sputum culture) and H. influenzae. There were few instances with two atypical bacteria identified by serology in the same specimen.

The baseline omadacycline MIC values for all Gram-positive aerobic pathogens ranged from ≤ 0.008 to 0.25 mcg/mL. For the Gram-negative aerobic pathogens, the omadacycline MIC values ranged from ≤ 0.008 to > 16 mcg/mL (Table 8-23). The omadacycline MICs in the CABP study were similar to those observed in surveillance studies.

Table 8-23 Omadacyline MIC range and MIC_{90} values for baseline pathogen (micro ITT population).

Baseline pathogen	No of isolates	Omadacycline MIC range (mcg/mL)	Omadacycline MIC_{90} (mcg/mL)
Streptococcus pneumoniae	28	0.015-0.12	0.06
PSSP	27	0.015-0.12	0.06
Macrolide-resistant	10	0.03-0.12	0.06
MDRSP	7	0.03-0.12	-
Staphylococcus aureus (methicillin sensitive)	11	0.12-0.25	0.25
Haemophilus influenzae	32	0.5-4	2
Haemophilus parainfluenzae	16	≤ 0.008-4	4
Klebsiella pneumoniae	12	1-16	16
Escherichia coli	6	0.5-4	-
Moraxella catarrhalis	4	0.12-0.25	-
Pseudomonas aeruginosa	3	4-> 16	-
Enterobacter cloacae	2	2-4	-

Haemophilus parahaemolyticus	2	0.5-1	-
Proteus mirabilis	2	16-> 16	-
Klebsiella oxytoca	1	2	-

MDRSP = multidrug resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; MIC = minimum inhibitory concentration; microITT = microbiological intent-to-treat; Source: Table 14.1.14.7

Clinical response by bacterial pathogen was evaluated in the microITT population. Clinical success based on the ECR assessment at 72 to 120 hours by baseline pathogen is shown in Table 8-24. The overall clinical success at PTE (based on the investigator's assessment) by pathogen is shown in Table 8-25. In an amendment (eCTD sequence no. 0014), the applicant provided clinical outcome for subjects with monoinfection due to atypical bacteria.

Table 8-24 Early clinical success by CABP pathogen in microITT population.

Baseline pathogen*	**Omadacycline n/N (%)**	**Moxifloxacin n/N (%)**
Streptococcus pneumoniae	34/43 (79.1)	30/34 (88.2)
PSSP	20/26 (76.9)	21/22 (95.5)
Macrolide-resistant	10/10 (100.0)	5/5 (100.0)
MDRSP	7/7 (100.0)	6/6 (100.0)
Staphylococcus aureus (methicillin sensitive)	10/11 (90.9)	8/10 (80.0)
Haemophilus influenzae	22/32 (68.8)	14/16 (87.5)
Haemophilus parainfluenzae	15/18 (83.3)	14/17 (82.4)
Klebsiella pneumoniae	11/13 (84.6)	11/13 (84.6)
Escherichia coli	4/6 (66.7)	6/7 (85.7)
Moraxella catarrhalis	4/4 (100.0)	1/1 (100.0)
Pseudomonas aeruginosa	2/3 (66.7)	5/5 (100.0)
Enterobacter cloacae	1/2 (50.0)	2/4 (50.0)
Haemophilus parahaemolyticus	2/2 (100.0)	2/2(100.0)
Proteus mirabilis	1/2 (50.0)	2/2 (100.0
Klebsiella oxytoca	0/1 (0.0)	4/4 (100,.0)
Atypical bacteria[a]		
Mycoplasma pneumoniae	54/70 (77.1)	49/57 (86.0)
Legionella pneumophila	31/37 (83.8)	32/37 (86.5)
Serology	29/35 (82.9)	30/35 (85.7)
UAT	5/5 (100.0)	6/7 (85.7)
Chlamydophila pneumoniae	18/28 (64.3)	22/28 (78.6)
Atypical bacteria[b]		
Mycoplasma pneumoniae	25/35 (71.4)	24/29 (85.7)
Legionella pneumophila	31/37 (83.8)	24/28 (85.7)
Serology	23/27 (85.2)	22/26 (84.6)
UAT	5/5 (100.0)	6/7 (85.7)
Chlamydophila pneumoniae	9/15 (60.0)	12/14 (85.8)

n = Number of subjects in the specific category. Percentages are based on the number of subjects with the specified baseline pathogen; N = Number of subjects with the specified baseline pathogen.
MDRSP = multidrug resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; UAT = Urinary antigen test

[a] Defined as in the Statistical Analysis Plan which considers an indeterminate convalescent serology result as positive.
[b] Considered only a positive convalescent serology result as positive
* includes mixed pathogens; Source: Table 14.2.1.4.1.1 and Table 14.2.2.6.1.1.

Table 8-25 Overall Clinical success at PTE visit by CABP pathogen in ME-PTE population.

Baseline pathogen*	Omadacycline n/N (%)	Moxifloxacin n/N (%)
Streptococcus pneumoniae	35/38 (92.1)	30/31 (96.8)
PSSP	22/23 (95.7)	20/20 (100.0)
Macrolide-resistant	10/10 (100.0)	5/5 (100.0)
MDRSP	7/7 (100.0)	6/6 (100.0)
Staphylococcus aureus (methicillin sensitive)	8/10 (80.0)	7/7 (100.0)
Haemophilus influenzae	25/29 (86.2)	16/16 (100.0)
Haemophilus parainfluenzae	13/15 (86.7)	13/14 (92.9)
Klebsiella pneumoniae	9/11 (81.8)	11/13 (84.6)
Escherichia coli	3/4 (75.0)	4/7 (57.1)
Moraxella catarrhalis	3/3 (100.0)	1/1 (100.0)
Pseudomonas aeruginosa	2/3 (66.7)	5/5 (100.0)
Enterobacter cloacae	2/2 (100.0	3/4 (75.0)
Haemophilus parahaemolyticus	2/2 (100.0)	1/1 (100.0)
Proteus mirabilis	1/2 (50.0)	2/2 (100.0)
Klebsiella oxytoca	0/0 (0.0)	4/4 (100,.0)
Atypical bacteria[a]		
Mycoplasma pneumoniae	63/67 (94.0)	49/54 (90.7)
Legionella pneumophila	33/35 (94.3)	35/36 (97.2)
Serology	31/33 (93.9)	33/34 (97.1)
UAT	5/5 (100.0)	7/7 (100.0)
Chlamydophila pneumoniae	25/27 (92.6)	24/27 (88.9)
Atypical bacteria[b]		
Mycoplasma pneumoniae	29/33 (87.9)	24/26 (92.3)
Legionella pneumophila	25/27 (92.6)	27/28 (96.4)
Serology	23/25 (92.0)	25/26 (96.2)
UAT	5/5 (100.0)	7/7 (100.0)
Chlamydophila pneumoniae	14/15 (93.3)	12/13 (92.3)

n = Number of subjects in the specific category. Percentages are based on the number of subjects with the specified baseline pathogen; N = Number of subjects with the specified baseline pathogen.
MDRSP = multidrug resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; UAT = Urinary antigen test
[a] Defined as in the Statistical Analysis Plan which considers an indeterminate convalescent serology result as positive.
[b] Considered only a positive convalescent serology result as positive.
* includes mixed pathogens; Source: Table 14.2.2.6.2.1

Clinical Microbiology Reviewer's comment: Majority of subjects had the microbiological response of presumed eradication. One subject in the omadacycline group had persistence of pathogen [Subject (b) (6) *(Baseline-H. influenzae and Gram-negative bacteria and EOT- H. influenzae). Therefore, analysis was performed using clinical*

success. The efficacy of omadacycline appears to be lower than moxifloxacin at 72-120 hours for H. influenzae, S. pneumoniae, C. pneumoniae and M. pneumoniae. For subjects with mixed infections including atypical bacteria diagnosed based on positive convalescent serology result, the clinical success rates at PTE for L. pneumophila, C. pneumoniae and M. pneumoniae were 90.0% (20/22), 92.3% (12/13), and 86.7% (26/30).

Bacteremia:
The microbiological response at EOT and PTE visit for patients with bacteremia in the microITT population is shown in Table 8-26. Eradication of pathogen was observed in 9/11 subjects with baseline *S. pneumoniae* in the omadacycline arm.

Table 8-26 Overall microbiological response at EOT and PTE visits by baseline pathogen in blood culture in the microITT population.

Baseline pathogen*	**Omadacycline n/N (%)**	**Moxifloxacin n/N (%)**
Streptococcus pneumoniae	9/11 (81.8)	11/11 (100.0)
PSSP	7/9 (77.8)	11/11 (100.0)
Macrolide-resistant	4/4 (100.0)	3/3 (100.0)
MDRSP	1/1 (100.0)	3/3 (100.0)
Staphylococcus aureus (methicillin sensitive)	1/1 (100.0)	0/0
Haemophilus influenzae	1/1 (100.0)	0/0
Klebsiella pneumoniae	0/1 (0.0)	0/0
Escherichia coli	0/0	2/4 (50.0)
Streptococcus mitis	1/1(100.0)	2/2 (100.0)

Source: Listings 16.2.6.1.4, 16.2.6.1.5 and 16.2.6.2.2

Clinical Microbiology Reviewer' comment: The omadacycline MICs of S. pneumoniae from the two subjects who failed clinically were 0.03 mcg/mL and 0.12 mcg/mL.

The relationship between omadacycline MICs for each target baseline pathogen and early clinical response is shown in
Table 8-27. The relationship between omadacycline MICs for each target baseline pathogen and clinical success at EOT and PTE visits is shown in Table 8-28 and

Table 8-29. The highest MIC for *S. pneumoniae* baseline isolate was 0.12 mcg/mL and early clinical response was observed in one subject and maintained at PTE. The highest MIC for *S. aureus (methicillin sensitive)* baseline isolate was 0.25 mcg/mL and early clinical response was observed in two subjects and maintained at EOT and PTE. The highest MIC for *H. influenzae* baseline isolates was 4.0 mcg/mL. The highest MIC for *K. pneumoniae* was 16.0 mcg/mL. Of the two subjects with *K. pneumonia* who failed, one had bacteremia (*K. pneumoniae* - MIC 2.0 mcg/mL).

Table 8-27 Early clinical response by baseline pathogen and MIC (micro ITT population).

Baseline pathogen (N1)	**Omadacycline (N = 204)**	
	Baseline MIC (mcg/mL)	**Clinical success n/N2 (%)**
Streptococcus pneumoniae (28)	0.015	2/2 (100.0)
	0.03	11/14 (78.6)
	0.06	7/10 (70.0)
	0.12	1/2 (50.0)
Staphylococcus aureus methicillin sensitive (11)	0.12	8/9 (88.9)
	0.25	2/2 (100.0)
Haemophilus influenzae (32)	0.5	1/1 (100.0)
	1.0	14/18 (77.8)
	2.0	6/12 (50.0)
	4.0	1/1 (100.0)
Haemophilus parainfluenzae (16)	<=0.008	0/1 (0.0)
	1.0	4/4 (100.0)
	2.0	6/8 (75.0)
	4.0	3/3 (100.0)
Klebsiella pneumoniae (12)	1.0	2/2 (100.0)
	2.0	5/7 (71.4)
	8.0	1/1 (100.0)
	16.0	2/2 (100.0)
Escherichia coli (6)	0.5	1/1 (100.0)
	1.0	3/4 (75.0)
	4.0	0/1 (0.0)

MIC = Minimum Inhibitory Concentration.
N = Number of subjects in the microITT population.
N1 = Number of subjects in the microITT population with the baseline pathogen.
N2 = Number of subjects with the baseline pathogen at the specified MIC.
n = Number of subjects in the specific category. Percentages are based on the number of subjects with the baseline pathogen at the specified MIC

Table 8-28 Clinical success by baseline pathogen and MIC (ME-EOT population).

Baseline pathogen (N1)	**Omadacycline (N = 193)**	
	Baseline MIC (mcg/mL)	**Clinical success n/N2 (%)**
Streptococcus pneumoniae (24)	0.015	2/2 (100.0)

	0.03	12/13 (92.3)
	0.06	8/8 (100.0)
	0.12	1/1 (100.0)
Staphylococcus aureus methicillin sensitive (11)	0.12	7/9 (77.8)
	0.25	2/2 (100.0)
Haemophilus influenzae (30)	0.5	1/1 (100.0)
	1.0	16/18 (88.9)
	2.0	8/10 (80.0)
	4.0	1/1 (100.0)
Haemophilus parainfluenzae (15)	<=0.008	1/1 (100.0)
	1.0	3/4 (75.0)
	2.0	6/7 (85.7)
	4.0	3/3 (100.0)
Klebsiella pneumoniae (10)	1.0	2/2 (100.0)
	2.0	4/5 (80.0)
	8.0	1/1 (100.0)
	16.0	2/2 (100.0)
Escherichia coli (5)	0.5	1/1 (100.0)
	1.0	3/4 (75.0)

MIC = Minimum Inhibitory Concentration.
N = Number of subjects in the ME-EOT population.
N1 = Number of subjects in the ME-EOT population with the baseline pathogen.
N2 = Number of subjects with the baseline pathogen at the specified MIC.
n = Number of subjects in the specific category. Percentages are based on the number of subjects with the baseline pathogen at the specified MIC

Table 8-29 Clinical success by baseline pathogen and MIC (ME-PTE population)

Baseline pathogen (N1)	**Omadacycline (N = 188)**	
	Baseline MIC (mcg/mL)	**Clinical success n/N2 (%)**
Streptococcus pneumoniae (25)	0.015	2/2 (100.0)
	0.03	12/13 (92.3)
	0.06	8/8 (100.0)
	0.12	1/1 (100.0)
Staphylococcus aureus methicillin sensitive (10)	0.12	6/8 (75.0)
	0.25	2/2 (100.0)
Haemophilus influenzae (29)	0.5	1/1 (100.0)
	1.0	16/18 (88.9)
	2.0	7/9 (77.8)
	4.0	1/1 (100.0)
Haemophilus parainfluenzae (14)	<=0.008	1/1 (100.0)
	1.0	2/3 (66.7)
	2.0	6/7 (85.7)
	4.0	3/3 (100.0)
Klebsiella pneumoniae (10)	1.0	2/2 (100.0)
	2.0	4/5 (80.0)
	8.0	1/1 (100.0)
	16.0	2/2 (100.0)

Escherichia coli (4)	0.5	1/1 (100.0)
	1.0	2/3 (66.7)

MIC = Minimum Inhibitory Concentration.
N = Number of subjects in the m ME-PTE population.
N1 = Number of subjects in the ME-PTE population with the baseline pathogen.
N2 = Number of subjects with the baseline pathogen at the specified MIC.
n = Number of subjects in the specific category. Percentages are based on the number of subjects with the baseline pathogen at the specified MIC

Clinical Microbiology Reviewer's Comment: Overall, omadacycline was shown to exhibit activity against S. pneumoniae, S. aureus (methicillin sensitive), H. influenzae, H. parainfluenzae, K. pneumoniae, L. pneumophila, M. pneumoniae and C. pneumoniae in community acquired bacterial pneumonia.

8.2.3. Interpretive Criteria

The Applicant included study reports for Tier 1 and Tier 2 studies for establishing QC ranges ((b) (4) – Report study 2691; Report Study 610, and Report Study 674). The 30 mcg omadacycline disk Lot# 198731 ((b) (4)), and Lot#204477 ((b) (4)) were used for the Tier 2 study with *E. coli ATCC 25922*, *S. aureus ATCC 25923*, *S. pneumoniae 49619* and *H. influenzae ATCC 49247*. Two studies (Report Study 473 and Report Study 594) were conducted to determine the appropriate disk content of omadacycline for performing the disk diffusion susceptibility testing. The Tier 2 study to establish QC ranges was performed as per the Clinical Laboratory Standards Institute (CLSI) M23 guidelines. The susceptibility testing results with omadacycline were one doubling dilution higher in media that has been aged for approximately one month as compared to media prepared and used on the same day as production (Report Study 588). The difference between MIC values with fresh versus aged media was larger with *E. faecalis* and *E. faecium.* Therefore, the CLSI susceptibility test method for omadacycline includes the statement "For broth dilution tests for aerobic organisms, MIC values must be determined in testing medium that is fresh (less than 12 hours old)". Of the isolates tested by both methods, 94% of isolates had MIC values by the agar dilution method that were within 1 dilution of the MIC value obtained by the broth dilution method. The 30 mcg omadacycline disk lot 369643 ((b) (4)) was used to test isolates from the ABSSSI and CABP clinical studies and surveillance isolates collected in 2015 and 2016 using established QC strains and QC ranges. These results were used for scatterplot analysis of correlation of MIC to zone diameters.

The susceptibility test interpretive criteria proposed by the Applicant are shown in Table 8-30. For the FDA analysis, surveillance data, clinical success rates by MIC, and probability of PK-PD target attainment for the target pathogens were considered for establishing breakpoints. Based on the analysis, the FDA proposed breakpoints are shown in Table 8-31.

Table 8-30 Proposed interpretive criteria for omadacycline

Pathogen	Broth Dilution MIC (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
[redacted]						

(b) (4)

Table 8-31. FDA identified breakpoints for Omadacycline

For Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae[a,†]	≤4	8	≥ 16	≥18	16-17	≤15
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.5	1.0	≥ 2.0	≥ 21	19-20	≤18
Staphylococcus lugdunensis	≤ 0.12	0.25	≥0.5	≥ 29	26-28	≤25
Enterococcus faecalis	≤ 0.25	0.5	≥ 1.0	≥18	16-17	≤15
Streptococcus anginosus group[b]	≤ 0.12	0.25	≥ 0.5	≥ 24	18-23	≤17
Streptococcus pyogenes	≤ 0.12	0.25	≥ 0.5	≥19	16-18	≤15

S = Susceptible; I = Intermediate; R = Resistant

† Omadacycline is not active *in vitro* against *Morganella* spp., *Proteus* spp., and *Providencia* spp.

a *Klebsiella pneumoniae* and *Enterobacter cloacae* only

b *Streptococcus anginosus* group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*

For Community Acquired Bacterial Pneumoniae (CABP)

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae [a,†]	≤4	8	≥ 16	≥18	16-17	≤15
Staphylococcus aureus (methicillin-susceptible isolates only)	≤ 0.25	0.5	≥ 1.0	≥ 23	21-22	≤20
Haemophilus species [b]	≤2	4	≥ 8	≥ 20	17-19	≤16
Streptococcus pneumoniae	≤0.12	0.25	≥ 0.5	≥20	17-19	≤16

S = Susceptible; I = Intermediate; R = Resistant

† Omadacycline is not active *in vitro* against *Morganella* spp., *Proteus* spp., and *Providencia* spp.

[a] *Klebsiella pneumoniae* only

[b] *Haemophilus species includes H. influenzae and H. parainfluenzae*

Clinical Microbiology Reviewer's comments:

S. aureus:

1. *For the ABSSSI indication, the susceptible breakpoint of ≤0.5 mcg/mL was based on the MIC_{90} value of 0.5 mcg/mL in surveillance studies and clinical success rates at MIC of ≤ 0.5 for subjects with MSSA (82.1%; 165/201) and for subjects with MRSA (85.0%; 142/167). The PK-PD target attainment analysis using bacterial stasis as the PD parameter in the thigh infection model supports an MIC of 0.12 mcg/mL for S. aureus. However, the clinical data supports the susceptible breakpoint of ≤0.5 mcg/mL.*
2. *For the CABP indication, subjects only had MSSA at baseline and no PK-PD target attainment analysis was performed using S. aureus in a pulmonary infection animal model. The clinical success rate for subjects with MSSA was 77.8% (7/9) at an MIC of 0.12 mcg/mL. The number of subjects with isolates at an MIC of 0.25 mcg/mL is limited (n = 2). However, both subjects had a successful outcome. The MIC_{90} value for MSSA was 0.25 mcg/mL in surveillance studies; setting a breakpoint at 0.12 mcg/mL would cut into the middle of the MIC distribution. Therefore, the susceptible breakpoint of ≤0.25 mcg/mL was set for MSSA.*
3. *The challenges with having two separate breakpoints for S. aureus for ABSSSI and CABP indications were discussed with the Center for Devices and Radiological Health (CDRH). The main challenges were device-related, requiring additional wells to be tested to interpret the susceptibility results. However, as clinical data are not available above an MIC of 0.25 mcg/mL, the susceptible breakpoint was set at an MIC ≤0.25 mcg/mL. The S. aureus breakpoints for CABP can be revisited when data from the planned additional CABP trial become available.*

S. lugdunensis:

1. *In the ABSSSI studies, the omadacycline MIC range for S. lugdunensis isolates (n = 11) was 0.06-0.25 mcg/mL and the MIC_{90} value was 0.12 mcg/mL. The clinical success rate at MIC of ≤ 0.12 for subjects with S. lugdunensis was 90% (9/10). The number of subjects above the susceptible breakpoint of 0.12 mcg/mL is very limited (1 subject).*
2. *No PK-PD target analysis data are available for S. lugdunensis. If the S. aureus PK-PD analysis is used as a surrogate for S. lugdunensis, it can support a breakpoint of 0.12 mcg/mL.*
3. *The available surveillance and clinical data support the susceptible breakpoint of ≤0.12 mcg/mL.*

S. pneumoniae:

1. *The omadacycline MIC range and MIC_{90} for 9980 S. pneumoniae isolates from surveillance studies were 0.03 to 1.0 mcg/mL, and 0.12 mcg/mL, respectively.*
2. *A ≥ 90% probability of PD target (1-log_{10} CFU reduction) attainment in a pulmonary infection model using free drug plasma AUC/MIC for S. pneumoniae is achieved at an MIC value of 0.12 mcg/mL with IV to PO dosing regimen with the loading dose.*
3. *The clinical success rates for subjects with S. pneumoniae was 95.6% (22/23) at an MIC of ≤0.06 mcg/mL, and 1/1 at an MIC of 0.12 mcg/mL. The surveillance data, PK-PD analysis, and clinical data support the susceptible breakpoint of ≤0.12 mcg/mL.*

Streptococcus species other than S. pneumoniae (S. anginosus group and S. pyogenes):

1. *The omadacycline MIC range and MIC_{90} for 465 S. anginosus isolates from surveillance studies were 0.03 to 0.5 mcg/mL, and 0.12 mcg/mL, respectively. The omadacycline MIC range and MIC_{90} for 2561 S. pyogenes isolates from surveillance studies were 0.03 to 0.5 mcg/mL, and 0.12 mcg/mL, respectively.*
2. *The PK-PD of omadacycline for S. pneumoniae in the thigh infection model with stasis endpoint was used as a surrogate for the PK-PD of omadacycline for Streptococcus species. The PK-PD target attainment analysis supports an MIC of 0.12 mcg/mL.*
3. *In the ABSSSI studies, the clinical success rate at MIC of ≤ 0.06 for subjects with S. anginosus group and S. pyogenes was 94/119 (78.9%). There was one subject each with S. anginosus isolate at an MIC of 0.12 and 0.25 mcg/mL with successful clinical outcome. The clinical success rate dropped to 53.8% (7/13) for S. pyogenes at an MIC of 0.12 mcg/mL. However, one subject with S. pyogenes at an MIC of 0.25 mcg/mL had a successful outcome. The overall data supported a susceptible breakpoint of 0.12 mcg/mL for S. anginosus group and S. pyogenes.*
4. *Interpretive criteria for S. mitis were not agreed upon. S. mitis belongs to the viridans group streptococci and are normal inhabitants of oral cavity. In ABSSSI, these organisms are generally considered as contaminants.*
5. *Interpretive criteria could not be established for S. agalactiae as there were insufficient number of clinical isolates. The number of patients with clinical and MIC data was very small (n = 3; MIC range 0.12 -0.5 mcg/mL). Clinical failure was observed in 1 of 2 subjects with S. agalactiae isolate with an MIC of 0.12 mcg/mL.*

E. faecalis:

1. *The omadacycline MIC range and MIC_{90} for 5711 E. faecalis isolates (vancomycin susceptible = 5548; vancomycin resistant = 158) from surveillance studies were 0.03 to 4.0 mcg/mL, and 0.5 mcg/mL, respectively.*
2. *No PK-PD target analysis was conducted for E. faecalis.*
3. *In the ABSSSI studies, the clinical success rate at an MIC of ≤ 0.12 for subjects with vancomycin susceptible E. faecalis was 100% (13/13). Two of three subjects with an isolate with MIC of 0.25 mcg/mL had a successful clinical outcome. There was only one subject with an isolate with MIC of 0.5 mcg/mL who had a successful clinical outcome. Overall, the MIC distribution and clinical data supports the susceptible breakpoint of ≤0.25 mcg/mL.*

Haemophilus species (H. influenzae and H. parainfluenzae):

1. *The omadacycline MIC_{90} for H. influenzae and H. parainfluenzae isolates from surveillance studies was 2.0 mcg/mL.*
2. *The utility of the H. influenzae in vitro model for PK-PD target attainment analysis is not established and was not used for FDA analysis of breakpoints.*
3. *In the CABP study, the clinical success rate for subjects with H. influenzae was 78.9% (15/19) at an MIC of ≤1.0 mcg/mL and 80% (8/10) at an MIC of 2.0 mcg/mL. The clinical success rates for H. parainfluenzae were 85.7% (6/7) at an MIC of 2.0 mcg/mL. Overall, the MIC distribution and clinical data supports the susceptible breakpoint of ≤2.0 mcg/mL.*

Enterobacteriaceae:

1. *The omadacycline MIC range and MIC_{90} for 14,091 E. coli isolates from surveillance studies were 0.12 to >4 mcg/mL, and 2.0 mcg/mL, respectively. The omadacycline MIC_{90} was 2 fold higher for ESBL positive E.coli (n = 2953). For K. pneumoniae (n = 6792), the omadacycline MIC range in surveillance studies was 0.12 to >4.0 mcg/mL, and MIC_{90} was >4.0 mcg/mL. For E. cloacae (n = 2703), the omadacycline MIC range in surveillance studies was 0.5 to >4.0 mcg/mL, and MIC_{90} was >4.0 mcg/mL.*
2. *The PK-PD target attainment analyses for E. coli based on the PD target associated with net bacterial stasis in the thigh infection model demonstrated low percent probabilities of PK-PD target attainment at MIC values observed in surveillance studies.*
3. *The susceptible breakpoint of ≤4.0 mcg/mL was based on limited clinical data. In the ABSSSI studies, the clinical success rate in subjects with E. cloacae at an MIC of 4 was 88.9% (8/9). Additionally, there were two subjects with successful clinical outcome above the MIC of 4.0 mcg/mL. For K. pneumoniae, the clinical success rates at MICs of ≤ 2.0 and 4 were 60% (3/5) and 80% (4/5). In the CABP study, the clinical success rate for subjects with K. pneumoniae was 85.7% (6/7) at an MIC of ≤2.0 mcg/mL. There was one subject each at an MIC of 8 and two subjects at an MIC of 16.0. Both had a successful clinical outcome. Therefore, susceptible breakpoint of ≤4.0 mcg/mL was set for Enterobacteriaceae (E. cloacae and K. pneumoniae only for the ABSSSI indication and K. pneumoniae only for the CABP indication). There were insufficient number of subjects with baseline E. coli to set a breakpoint for this organism.*

The resistant breakpoints are set two-fold higher than the susceptible breakpoint if the MIC distribution includes isolates with MICs higher than the proposed susceptible breakpoint.

The disk zone diameters are provided for the pathogens if the error rates were acceptable using proposed MIC breakpoints.

CDTL Comment:

(b) (4)

Furthermore, there are concerns about the observed mortality imbalance with omadacycline in CABP and a drop-off in efficacy with omadacycline in subgroups of patients with risk factors such as PORT Risk class, age, and in the micro-ITT analysis population. It is also possible that patients with CABP caused by S. aureus may be sicker and have bacteremia and hence establishing a breakpoint in the absence of clinical data is difficult. For these reasons, data in these NDAs only support a S. aureus susceptible breakpoint of 0.25 mcg/mL for CABP, and 0.5 mcg/ml for ABSSSI.

Also, as noted above, this issue was discussed with CDRH and in their assessment, they noted that while additional testing might be needed to support device development, having two separate breakpoints by itself does not pose a problem. Finally, determination of breakpoints is an iterative process and the Applicant will be accumulating additional data in the second CABP trial, as well as other sources of data. The breakpoints can be updated if supported by the additional data.

The decision to have separate breakpoints for S. aureus was based on a thorough evaluation of the available data. While we recognize that it is not ideal to have two separate breakpoints as it could potentially result in confusion/errors in clinical microbiology laboratories, the available data do not support identical breakpoints for both indications. It will be important that microbiology laboratories be appropriately informed about the different susceptibility test interpretive criteria by indication and that they develop and adhere to systems to accurately report the susceptibility information based on the site of infection. The information on susceptibility test interpretive criteria will be presented at the FDA STIC website by indication (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm).

Disk Diffusion:

The correlation of broth microdilution MIC values to disk zone diameters for omadacycline was determined for baseline isolates from all Phase 3 clinical studies and 1109 isolates from the (b) (4) culture collection. The applicant provided disk scatterplots

for methicillin susceptible and methicillin resistant *S. aureus* per the Agency request (amendment eCTD sequence number 0043). In addition, the Applicant provided disk scatter plot for *S. lugdunensis* in relation to coagulase negative staphylococci.

Clinical Microbiology Reviewer's comment:
S. aureus:
The proposed breakpoints result in the following total error rates: very major 0.4%, major 0.08% and minor error rates 1.39% using zone diameters of ≥21 mm (susceptible), 20-19 mm (intermediate), and ≤18 mm (resistant). Discordance rates are within the acceptable rates provided in the CLSI M23 guidance document.

For MSSA, the proposed breakpoints result in the following total error rates: very major 0.1%, major 0.4% and minor error rates 29.7% using zone diameters of ≥23 mm (susceptible), 21-22 mm (intermediate), and ≤20 mm (resistant). Discordance rates are within the acceptable rates provided in the CLSI M23 guidance document.

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9. Review of Safety

9.1 Safety Review Approach

The safety of IV and oral omadacycline for treatment of ABSSSI and CABP was examined primarily in the safety data from 1,073 patients treated in two randomized, adequately controlled phase 3 trials in ABSSSI and a single randomized, adequately controlled phase 3 trial in CABP. The phase 3 pool includes a total of 705 patients who received IV and oral omadacycline regimen at the to be marketed dose and duration and 368 patients who received the oral-only omadacycline regimen for the treatment of ABSSSI at the to be marketed dose and duration.

The safety review will be presented as an integrated analysis of three phase 3 trials in this section. The majority of comparative safety data (i.e., adverse event rates) will be presented either individually for the phase 3 CABP trial, as pooled results from two phase 3 ABSSSI trials, or as a pooled safety results from all phase 3 trials including ABSSSI and CABP based on relevance and appropriateness for each section.

Safety information was also obtained from 22 phase 1 clinical trials and, two phase 2/3 trials in cSSSI. These trials are tabulated in Appendix 16.1.5. Since there are differences in the omadacycline dose, and dosage regimen, study populations and trial designs across these trials, pooling of all these trials together were not considered appropriate for evaluation of safety. All safety analyses will be conducted in the safety population of patients that received the to be marketed dose and duration of therapy. The safety population is defined as patients who were randomized and received at least one dose of the study drug.

Clinical Reviewer's Comment: Since phase 1 trials consisted of a heterogeneous patient population with various doses and durations of omadacycline exposure, these trials are not reviewed individually in detail. However, relevant safety information from those trials are discussed in different sections of this review as appropriate. Similarly, trials in cSSSI utilized different trial designs, dosages and dosing regimen; therefore; only the relevant safety information will be discussed from these trials as appropriate.

9.2 Review of the Safety Database

Overall Exposure

In total, the omadacycline clinical development program includes safety data from 3,315 (1,947 treated with omadacycline) patients who received at least 1 dose of study drug (omadacycline or comparator) in 27 completed studies at any dose or duration of treatment.

In phase 1 studies, 695 patients received omadacycline single doses up to 600 mg IV or oral (multiple doses of 100 mg IV once daily for up to 14 days and 200 IV once daily for up to 7 consecutive days; and oral only doses of 300 to 600 mg once daily for up to 5 consecutive days).

Phase 3 trials, Study ABSI-1108 and Study CABP-1200 utilized IV treatment with the option to switch to oral study drug after at least 3 days of IV treatment (n = 1,415). In Study ABSI-16301, patients received oral only regimen (n = 735). The total duration of treatment was 7 to 14 days in each study.

Across phase 3 trials, the mean total duration of exposure (either IV/oral) was 9 days for omadacycline, 8.5 days for linezolid, and 9.6 days for moxifloxacin. The mean number of days for oral therapy was 6.4 days for omadacycline, 6.8 days for linezolid, and 5.2 days for moxifloxacin.

In Study ABSI 1108, and CABP-1200, the mean number of days on IV therapy was 5.0 days for omadacycline, 4.4 days for linezolid, and 5.7 days for moxifloxacin. The mean number of days on oral treatment was 5.5 days for omadacycline and 5.4 days for linezolid in Study ABSI-1108; and 5.1 days for omadacycline and 5.2 days for moxifloxacin in Study CABP-1200.
In Study ABSI16301, mean total duration of exposure 8.2 days for omadacycline and 8.0 days for linezolid.

Table 9-1 summarizes the overall exposure to omadacycline at any dose and as a part of various regimens.

Table 9-1 Primary Safety Database for the Omadacycline Clinical Development Program

Controlled trials conducted for this indication		
Clinical Trial	New Drug	Active Control
Phase **3 ABSSSI**	OMC (N= 691)	Linezolid (N= 689)
ABSI-1108	N=323	N= 322
ABSI-16301	N=368	N=367
Phase **3 CABP**	OMC (N= 382)	Moxifloxacin (N=388)
CABP-1200	N=382	N=388
Total OMC exposure at proposed dose and duration for indication under review	N=1073	-----
Controlled trials conducted for other **indications**		
Phase **2/3 cSSSI**	OMC	Linezolid
CSSI-0702*	N=111	N=108
CSSI-0804**	N= 68	N=72
Phase **1 studies**	N=695	Active control-Placebo
Total OMC exposure at all doses	N= 1947	----
Source: FDA Clinical Reviewer's Analysis * *Omadacycline dose used in this trial: 100 mg IV Q24h followed by 200 mg PO Q24h* ** *Omadacycline dose used in this trial: 100 mg IV Q24h followed by 300 mg PO Q24h*		

Clinical Reviewers' Comment: The mean duration of IV and oral treatment for IV to oral switch omadacycline trials were similar between treatment groups. Mean total duration of exposure was also similar between treatment groups in all phase 3 trials.

9.3 Patient Disposition

Table 9-2 summarizes disposition of patients in ABSSSI trials and CABP trial.

Table 9-2 Patient Disposition ABSSSI and CABP Trials (safety)

	Pooled ABSSSI Trials		**CABP Trial**	
	OMC N=691	**LNZ N=689**	**OMC**	**MOXI N=388**
Completed Study Treatment	624 (90.3)	603 (87.5)	352 (91.2)	346 (89.2)
Prematurely Discontinued from Study	67 (9.7)	86 (12.5)	34 (8.8)	42 (10.8)
Reason for Premature Discontinuation from Study Tx				
Adverse Event	12 (1.7)	11 (1.6)	17 **(4.4)**	28 **(7.2)**
Lost to Follow-up	23 **(3.3)**	34 **(4.9)**	0	1 (0.3)
Withdrawal by Patient	14 **(2.0)**	14 **(2.0)**	4 (1.0)	3 (0.8)
Physician Decision	10 (1.4)	16 (2.3)	3 (0.8)	9 (2.3)
Death	0	1 (0.1)	4 (1.0)	1 (0.3)
Other	8 (1.2)	10 (1.5)	6 *(1.6)	0
Completed Study	615 (89.0)	604 (87.7)	356 (92.2)	362 (93.3)
Prematurely Discontinued from Study	76 (11.0)	85 (12.3)	30 (7.8)	26 (6.7)
Reason for Premature Discontinuation from Study				
Adverse Event	1 (0.1)	1 (0.1)	7 (1.8)	9 (2.3)
Lost to Follow-up	48 (6.9)	56 (8.1)	0	3 (0.8)
Withdrawal by Patient	20 (2.9)	16 (2.3)	7 (1.8)	8 (2.1)
Physician Decision	1 (0.1)	2 (0.3)	0	1 (0.3)
Death	0	2 (0.3)	6 (1.6)	3 (0.8)
Other	6 (0.9)	8 (1.2)	10 (2.6)	2 (0.5)
Source: Clinical Reviewer's Analysis; *The "other" reasons included: 4 patients were randomized but not dosed; alternative antibacterial was given to 1 patient; 1 patient was enrolled despite meeting exclusion criteria;				

Clinical Reviewer's Comment: When comparing the trials by indications, most common reasons for discontinuations from study treatment or the study were 'lost to follow up' 'and 'withdrawal by patient' in ABSSSI trials, while 'adverse event' was the most common reason to discontinue study treatment in CABP trial. Majority of adverse events that led to discontinuation in CABP trial were worsening of index infection as a trigger to discontinue study treatment and start alternative rescue antibacterial regimen.

9.4 Demographic characteristics of the safety population

Demographic characteristics of patients in the phase 3 ABSSSI trials, and phase 3 CABP trial is summarized in the Table 9-3 below.

Table 9-3 Demographic and Baseline Characteristics for All Patients in the Phase 3 ABSSSI Trials and CABP Trial

	Pooled ABSSSI Trials		CABP Trial	
Characteristics	**OMC (N = 691)**	**LNZ (N = 689)**	**OMC (N = 382)**	**MOXI (N = 388)**
Age (years)	691	689	382	388
Mean	45 (14)	45.5 (14)	61 (15)	62 (15)
Min, max	18, 88	18, 90	19, 97	19, 94
Categorical age (years), n (%)	691	689	382	388
18-65	641 (93)	637 (92.5)	232 (61)	216 (56)
> 65-75	32 (4.6)	26 (4)	76 (20)	89 (23)
> 75	18 (3)	26 (4)	74 (19)	83 (21)
Gender, n (%)				
Female	246 (36)	256 (37)	177 (46)	169 (44)
Male	445 (64)	433 (63)	205 (54)	219 (56)
Race, n (%)	691	689	382	388
White	621 (90)	641 (93)	353 (94)	355 (91.5)
Non-White	70 (10)	48 (7)	29 (8)	33 (8.5)
Ethnicity, n (%)	691	689	382	388
Hispanic or Latino	238 (34)	247 (36)	8 (2)	14 (4)
Not Hispanic or Latino	449 (65)	440 (64)	370 (97)	370 (95)
Not Reported/unknown	4 (0.6)	2 (0.3)	4 (1)	4 (1)
BMI (kg/m2)				
<25	260 (38)	245 (36)	147 (38.5)	145 (37)
25-30	221 (32)	243 (35)	131 (34)	135 (35)
>30	210 (30)	200 (29)	104 (27)	108 (28)
Creatinine clearance, n (%)	688	684	382	388
< 60 mL/min	21 (3)	21 (3)	86 (22.5)	79 (20)
60-89 mL/min	64 (9)	51 (7.5)	93 (24)	102 (26)
> 89 mL/min	603 (88)	612 (89.5)	203 (53)	207 (53)

Source: Clinical Reviewer, ISS, ADSL data set
Phase 3 ABSSSI trials included ABSI-1108 trial (IV to oral switch trial), and ABSI-16301 trial (oral only).
Note: Numbers after decimals are rounded up to nearest integer except 5.

Clinical Reviewer's Comment: Based on the demographic information in the table above, there were no significant differences among the treatment groups in terms of gender, race, age, weight or creatinine clearance. The bulk of the safety database is comprised of white men less than 65 years of age in phase 3 ABSSSI trials, however, over 40% of patients in the CABP trial were >65 years of age, and of those about 20% were above 75 years of age. Notably about 20% of patients had creatinine clearance < 60 mL/min in both treatment arms in the CABP trial as compared to only 3% of patients in the pooled ABSSSI trials.

Majority of sites were in Eastern Europe for Study ABSI 1108 (82%) and CABP 1200 (65%), while Study ABSI16301 (oral only trial) was conducted in United States only. Of note, in Study CABP 1200, there were only 3 patients enrolled in United States. Given the lack of any clear exposure-safety concerns in preclinical and phase 1 trials, the safety profile is not expected to differ based on demographic variables that may result in higher exposures to omadacycline, otherwise for given indications. Safety analyses in subgroups based on demographic factors are presented in 9.1.6 of this review.

Table 9-4 below summarizes the most common underlying medical conditions in phase 3 CABP and ABSSSI trials.

Table 9-4 Summary of Selected Common Medical Conditions by History – Phase 3 Trials (Safety population)

Study Medical Conditions	OMC	Comparator
Study ABSI-1108	**N=323**	**N=322**
Drug abuse	174 (54)	169 (53)
Prior history of ABSSSI	151 (48)	154 (49)
Tobacco user	131 (41)	127 (39)
Hepatitis C	94 (29)	90 (28)
Hypertension	66 (20)	81 (25)
Anxiety	63 (20)	69 (21)
Diabetes mellitus	24 (7)	35 (11)
Study ABSI-16301	**N = 368**	**N = 367**
Drug abuse	268 (73)	258 (70)
Prior history of ABSSSI	200 (56)	198 (55)
Tobacco user	147 (40)	146 (40)
Hepatitis C	116 (32)	129 (35)
Anxiety	76 (21)	78 (21)
Diabetes mellitus	14 (4)	31 (9)
Study CABP-1200	**N = 386**	**N = 388**
Hypertension	191 (49)	195 (50)
COPD / Asthma	83 (22)	76 (20)
Diabetes mellitus	63 (16)	71 (18)
Cardiac failure*	50 (13)	46 (12)
Atrial fibrillation	39 (10)	35 (9)
Coronary artery disease	35 (9)	33 (8)
Myocardial ischemia	24 (6)	27 (7)

Comparator included linezolid (Studies ABSI-1108 and ABSI-16301) or moxifloxacin (Study CABP-1200).
*Includes PT "cardiac failure"; and "chronic cardiac failure"; COPD: chronic obstructive pulmonary disease
Source: Clinical Reviewer; ADMH data set

Clinical Reviewer's Comment: The baseline incidence of underlying medical conditions was similarly balanced between the treatment groups and should not impact study results. The range of underlying comorbidities in the safety population represents that encountered in clinical practice in U.S. population for each indication.
In ABSSSI trials, common comorbid conditions included drug abuse, tobacco user, hepatitis C infection, anxiety, depression, and other wound and skin infections. Notably, slightly higher proportion of patients in ABSI1108 trial had diabetes mellitus (7% and11% in OMC and LNZ group, respectively) as compared to oral only Study ABSI 16301 (4% and 9% in OMC and LNZ group, respectively) which might suggest lesser disease severity in ABSI 16301trial as compared to ABSI1108.
In the CABP trial, common comorbid conditions included hypertension, diabetes mellitus, chronic lung disease (COPD/Asthma), cardiac failure, and atrial fibrillation. About 20% of patients had underlying lung disease (COPD/asthma) and 16% patients had cardiac failure, and 13% patients had diabetes mellitus in CABP trial. In general, patients in need of hospitalization for CABP tend to be older with greater morbidities as compared to patients with ABSSSI (in ABSI1108 trial). Overall, the baseline medical history was similar across treatment arms and should not impact the study results. Demographics based on other baseline diseases characteristics relevant to each indication is presented in individual studies section.

9.5 Adequacy of the safety database as assessed by Clinical Reviewer

The safety database for omadacycline appears to be adequate to assess safety of this drug for the proposed indications (ABSSSI and CABP), dosage regimen, and duration of treatment. A total of 1947 patient received any dose of omadacycline with 1073 received proposed dose and duration of omadacycline (IV and oral combined). Most of the baseline demographics, clinical characteristics, underlying comorbidities, and baseline disease status appeared comparable among the two treatment groups. The Applicant's safety analysis plan was acceptable with an appropriate focus on the anticipated safety issues. The definitions of AEs and method of obtaining descriptive statistics was standard and acceptable. The estimated elimination mean half-life (%CV) for omadacycline is 16 (21.7) h. Therefore, the time period of TEAEs defined as beginning of first dose of study drug to the end of the study visits (approximately Day 30) for phase 3 trials was appropriate and would be anticipated to cover the period of anticipated side-effects.

9.6 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality - Clinical Reviewer's Assessment

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format described in the ICH M2 EWG Electronic Common Technical Document Specification of 2008. The submission was straightforward to navigate with information accessible in the various modules, summaries, and clinical trial reports. Information contained in the submission was relatively complete. The applicant responded appropriately to requests for

additional information. A number of issues were encountered during the review. The naming of the variables (especially PORT Risk classification) was not consistent across datasets, a few of the field names (e.g. regions) were also not consistent across trials (different region coding was used by the Applicant for ABSSSI trials and the CABP trial). A review of a 5% random sample of case report forms (CRFs) for each of the three phase 3 trials was performed. Minor inconsistencies between information contained in the CRFs and the datasets were noted, none of which altered the primary efficacy or safety analysis populations.

In collaboration with OSI, the Site Selection Tool was utilized to choose the following sites for inspection and audit – Site # 254 (Study ABSI1108), Site # 608, 606, and 636 (Study ABSI 16301), in US; Site #140 (Study ABSI1108) in Romania; Site # 307 (Study CABP1200) in Bulgaria and Site # 313 (Study CABP 1200) in Hungary. OSI audit revealed GCP deficiencies at Site #606. A Form FDA 483 was issued by OSI at Site 606 in Study PTK-0796-ABSI-16301 (Soledad Lee; Buena Park, CA), in confirmation of the GCP deficiencies which were also identified by the Applicant previously for this study and reported in the NDA. For all remaining sites, no significant deficiencies were observed; study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and case report forms (CRFs). Except for Site 606, the data from all inspected sites appeared reliable as reported in the NDA per OSI review. The removal of site 606 with potential data integrity issues should not have a great impact on the safety results in the study, as there were no adverse events reported from the 14 patients who were enrolled at site 606.

Categorization of Adverse Events

There were no identified issues with respect to recording, coding, and categorizing AEs. The Applicant appropriately used MedDRA (V. 17.1) coding system for AEs and grading scale to assess severity. Applicant categorized SAEs in accordance with standard, regulatory definitions. All AEs and SAEs were recorded and reported from signing of the ICF to the final follow-up assessment, which was to be conducted 30 to 37 days after the start of the first infusion of study drug.

Certain safety topics of interest are presented as 'key adverse events of special interest', which were identified based on the mechanism of action of omadacycline and biological plausibility which included, hepatic events, GI events, HR elevations, and those that are potential or established tetracycline class related safety topics.

Routine Clinical Tests

The schedule of routine clinical testing was acceptable overall based on the expected safety issues with omadacycline. The Applicant's safety assessment included monitoring of TEAEs and SAEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature), physical examination findings, 12-lead ECG parameters, and changes in clinical chemistry, hematology, coagulation, and urinalysis laboratory values. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials. Urine or serum

pregnancy test was performed at the Screening visit, EOT and PTE visit.

9.7 Safety Results

The Table 9-5 displays the high-level safety overview of phase 3 trials.

Table 9-5 Safety Overview: Omadacycline Phase 3 ABSSSI and CABP trials (Study ABSI-1108, ABSI-16301 and CABP-1200)

	Omadacycline N = 1073 n (%)	Linezolid N= 689 n (%)	Moxifloxacin N = 388 n (%)
Patients with any TEAE	510 (47.5)	284 (41.2)	188 (48.5)
Drug-related TEAE	236 (22.0)	111 (16.1)	69 (17.8)
Serious TEAE	39 (3.6)	13 (1.9)	26 (6.7)
Drug-related serious TEAE	2 (0.2)	1 (0.1)	2 (0.5)
Deaths*	9 (0.8)	3 (0.4)	4 (1.0)
TEAE leading to premature discontinuation of study	33 (3.1)	10 (1.5)	27 (7.0)
Serious TEAEs leading to premature discontinuation of study treatment	16 (1.5)	5 (0.7)	11 (2.8)
Source: FDA Clinical Reviewer *All deaths occurred during study drug administration or in the period of observation following completion of study drug treatment (generally 30 days following randomization but deaths up to 71 days are reported here).			

Clinical Reviewer's Comment: The high-level safety overview suggests that the rates of TEAEs were similar between treatment groups across phase 3 trials. Two (0.2%) patients in the omadacycline arm, who had TEAEs that led to interruption of the study drug infusion, which included 1 patient with events of infusion site extravasation and infusion site irritation, and 1 patient with events of infusion site pain and nausea. Both events occurred in Study ABSI-1108 and are not listed in the above table.
All deaths were deemed unrelated to study drug by the Applicant and Investigator. Detailed analysis of death and other safety analyses are discussed below.

Deaths

There were 17 deaths reported in the omadacycline clinical development program, which included one death in Study CSSI-0804 (cSSSI), in the omadacycline arm on study day 35 due to metastatic lung cancer. In Study ABSI-1108, three deaths occurred (one in the omadacycline

and two in the linezolid arm); and in Study ABSI-16301, 1 death occurred in the linezolid group 94 days after the end of treatment.

In Study CABP-1200, 12 deaths occurred, eight (8) in the omadacycline group, and four (4) in the moxifloxacin group, which included one (1) patient who died on day 71 due to metastatic pancreatic cancer in the moxifloxacin treatment group.

Clinical Reviewer's Comment: Study reports, applicant's narratives, and case report forms describing patient deaths were reviewed. Events were examined to ascertain any evidence that relates death to drug exposure or to lack of drug efficacy. The reviewer's assessment of deaths, reflecting both the applicant's and the reviewer's analyses are presented below.

9.7.1 Mortality in ABSSSI and cSSSI trials

Table 9-6 summarizes mortality in ABSSSI trials (including the phase 2/3 cSSSI trial).

Table 9-6 Mortality in ABSSSI trials (including the Phase 2/3 cSSSI trial)

Patient ID	Age/ Gender	Cause of Death	Last Day of Study Drug	Day of Death
Omadacycline				
Study CSSI-0804	51/M	Lung Cancer (metastatic)	Day 10	Day 35[£]
Study ABSI-1108	60/M	Overdose (illicit drugs)	Day 1	Day 2
Linezolid				
Study ABSI1108	88/M	Cardiac failure	Day 7	Day 12
Study ABSI1108	43/M	Cardiac arrest	Day 7	Day 9
Study ABSI 16301	62/F	Death (intoxication)	Day 10	Day ~100[Σ]

Source: Summary of Clinical Safety
[£]The Final Follow-up was conducted in the trial, 30-37 days after the last dose of study drug.
[Σ] Patient # (b) (6) received last dose of linezolid on Day 10, completed the study on Day 32; died 3 months later on an unknown date. Autopsy was conducted which determined the cause of death as "acute heroin, methamphetamine, tramadol, alprazolam, and diphenhydramine intoxication".
** Patient # (b) (6) received only one dose of omadacycline on Day 1; discontinued study treatment due to an AE of vomiting and was lost to follow up after Day 1; It was later discovered that the patient died on Day 2 due to opiate overdose. The investigator was notified of this information by the county coroner, approximately 6 months after it occurred. Autopsy was not performed.

Narratives of individual deaths are discussed in Appendix 14.5.9

9.7.2 Clinical Reviewer's Analysis of 30-day all-cause mortality in Study CABP-1200

Table 9-7 summarizes 30-day mortality in CABP trial.

Table 9-7 Mortality up to Study Day 30 (Study CABP-1200, ITT)

Mortality up to Study Day 30 (Study CABP-1200, ITT)			
	Omadacycline N = 386	Moxifloxacin N = 388	% Difference (95% CI)
Deaths	8 (2.1%)	3 (0.8%)	1.3 (-0.4, 3.3) p = 0.14
Source: Clinical Reviewer's analysis; ADSL, ADEFFIN, ADAE data sets One additional death occurred in the moxifloxacin group at study day 71; the death was attributable to metastatic pancreatic cancer.			

Clinical Reviewer's Comment: Although, there is a numeric imbalance in the mortality rate between omadacycline and comparator arm in Study CABP 1200, this trial was not powered to examine differences in mortality. The purpose of this review was to examine trends in mortality in the omadacycline versus comparator (moxifloxacin) arm using the information available from CSR, Applicant's narratives, and CRFs describing patient deaths to ascertain any evidence that relates death to the drug exposure or to lack of drug efficacy.

Study CABP 1200 utilized IV to oral switch treatment regimen. All patients were required to receive minimum of 3 days of IV therapy. Of 12 deaths in CABP trial, 9 deaths (6 in omadacycline, and 3 in moxifloxacin arm) led to premature discontinuation from study treatment. The timing of the deaths in the trial in relation to study treatment and a possible relatedness to underlying infection/pneumonia was evaluated. The mortality did not appear to be influenced by the IV or oral therapy.

Table 9-8 summarizes treatment-emergent adverse events (TEAEs) associated with deaths by the system organ class (SOC).

Table 9-8 Treatment-emergent adverse events (TEAEs) associated with deaths by the system organ class (SOC)

	Omadacycline (N = 386) n (%)			Moxifloxacin (N = 388) n (%)		
SOC	< 15 days	15 to 30 days	Total	< 15 days	15 to 30 days	Total
Cardiovascular	3 (0.8)	1 (0.26)	4* (1.0)	1 (0.3)	0	1 (0.3)
Nervous system or cerebrovascular	1 (0.3)	0	1 (0.3)	0	0	0
Respiratory, thoracic, and mediastinal AND Infections and infestations	0	2 (0.5)	2** (0.5)	1 (0.3)	0	1 (0.3)
Infections and infestations	1 (0.3)	0	1 (0.3)	0	0	0
Neoplasms	0	0	0	0	1(0.3)	1(0.3)
Source: Clinical Reviewer's Analysis; ADSL, ADAE, ADEFFIN data sets *One death was due to rupture of thoracic aortic aneurysm, however, this patient although was clinical success at ECR visit, was noted to have worsening pneumonia starting at Day 6. ** 1 patient died with acute respiratory failure due to sepsis and multi-organ failure on study day 25; and 1 patient						

	Omadacycline (N = 386) n (%)	Moxifloxacin (N = 388) n (%)
died with acute respiratory distress syndrome (ARDS) due to worsening pneumonia on study day 30; SOC = System Organ Class, TEAE = treatment emergent adverse event		

Clinical Reviewer's Comment: Four (4) of eight (8) deaths in omadacycline arm could be attributed to worsening pneumonia. In moxifloxacin group, one (1) death was attributed directly to worsening of pneumonia, and other two deaths were associated with cardiac failure in one patient and consequence of an underlying metastatic small cell lung cancer in another patient.

Table 9-9 summarizes deaths in relation to variables that predict disease severity in CABP.

Summary of deaths in relation to variables that predicts disease severity in CABP.			
	OMC (N=386)	MOXI (N=388)	Risk Difference[£]
Deaths	***8/386 (2.1%)***	***3/388 (0.8%)***	***1.3***
PORT Risk Class			
PORT Risk Class II	0/55	0/56	*0*
PORT Risk Class III	3*/241 (1.2)	1/232 (0.4)	*0.8*
PORT Risk Class IV	5/89 (5.6)	2/100 (2.0)	*3.6*
Age Group			
<65	0/223 (0)	0/205 (0)	
≥ 65	8/163 (4.9)	3/183 (1.6)	*3.3*
Age (quartiles)			
19-52	0/105 (0)	0/87 (0)	*0*
53-61	0/96 (0)	0/87 (0)	*0*
62-72	4/89 (4.5)	0/108 (0)	*4.5*
73-97	4/96 (4.2)	3/106 (2.8)	*1.4*
Multilobar Infiltrate	1/93 (1.0)	3/113 (2.6)	*-1.6*
Pleural Effusion	3/60 (5.0)	1/65 (1.5)	*3.5*
COPD/Asthma/Chronic bronchitis	6/83 (7.2)	1/76 (1.3)	*5.9*
Diabetes Mellitus-Type 2	4/63 (6.3)	0/71 (0)	*6.3*
Pathogen identified at baseline	4/204 (1.9)	2/182 (1.1)	*1.4*
Bacteremia at baseline	1/15 (6.6)	1/18 (5.5)	*0*
Elevated total WBC count or leukopenia or elevated bands	5/146 (3.4)	1/144 (0.7)	*2.7*

[£] For exploratory analysis only, trial was not powered to examine differences in mortality, risk difference with wider 95% confidence interval due to smaller sample size.

*One patient, originally classified as PORT Risk Class-II was reclassified by FDA reviewer based on obvious baseline risk score of '87' which was misrepresented as '67'.

Note: Denominator in each column includes patient with specific baseline characteristics;

Pathogens were identified from Respiratory Specimens or blood.
BL=Baseline; Elevated total WBC count (> 12,000 cells/mm3) or leukopenia (WBC < 4,000 cells/mm3) or elevated bands (> 15% immature neutrophils)

Clinical Reviewer's Comment: Examination of subgroups based on variables which predicts disease severity and outcome in CABP revealed that 5 of 8 deaths in the omadacycline group occurred in PORT Risk Class-IV patients and remaining 3 deaths in PORT Risk Class-III. All patients who died were greater than 65 years of age in both treatment groups. In the subgroup of patients older than 75 years, there were three deaths each in omadacycline and moxifloxacin group. Of eight patients who died in the omadacycline group, six had chronic lung disease (COPD/asthma/bronchitis) at baseline as compared to 1 of 3 deaths in the moxifloxacin group who had chronic lung disease. Four of 8 deaths in the omadacycline group had diabetes mellitus at baseline. None of the 3 deaths in the moxifloxacin group had baseline diabetes mellitus. Five (5) of 8 deaths in omadacycline had either elevated white blood cell counts or leukopenia, as compared to 1 of 3 deaths in moxifloxacin group. All three deaths in the moxifloxacin group occurred in patients who had multi-lobar infiltrates at baseline compared to 1 of 8 deaths in the omadacycline group. Among patients with baseline pleural effusion, there were three deaths in the omadacycline group and one death in the moxifloxacin group.

Overall, risk difference in mortality was comparatively higher in omadacycline patients with PORT Risk Class-IV, age >65 years, having underlying lung diseases (COPD/Asthma), diabetes mellitus-type 2, presence of pleural effusion on baseline CXR, and WBC count>12,000 or <4,000. The proportions of deaths with an identified baseline pathogen were similar between treatment groups. Among patients with known baseline pathogen, three (3) of the four (4) omadacycline-treated patients who died had H. influenzae identified at baseline, and one had a mixed infection with K. pneumoniae and P. aeruginosa, isolated from respiratory culture. Of 3 deaths with H. influenzae identified at baseline, 1 patient was co-infected S. pneumoniae, which was also associated with bacteremia; and 1 patient had co-infection with Proteus mirabilis, and E. coli, from respiratory cultures. The omadacycline MIC90 for H. influenzae in the three omadacycline-treated patients who died were between 1 and 2 mcg/mL. Among the bacteremic patients who died, (one in each treatment group), the omadacycline-treated patient had S. pneumoniae bacteremia, and the moxifloxacin-treated patient had E. coli bacteremia.

Table 9-10 below provides a very brief narrative and causes of deaths in CABP trial.

Table 9-10 Brief summary of causes of individual deaths in Study CABP 1200

Table x. Brief summary of causes of individual deaths in Study CABP 1200					
Omadacycline					
	PORT Risk	**DTH DAY**	**Source of Culture: CABP Pathogen**	**Cause of Death**	**Brief Summary**
1	III	2	Sputum and Blood: *S. pneumoniae* Sputum: *H. influenzae*	Septic Shock with MOD	*67-yo, COPD, CHF, DM, pneumococcal bacteremia, H. influ [2] in sputum, decompensated rapidly within few hrs requiring mech. Vent. / ICU and progression to MOF and death within 11 hours of randomization.*
2	III	2	Negative	Cardio-respiratory arrest	*76 yo, RLL pneumonia, stable with no clinical deterioration; had an unwitnessed sudden death day 2, suspect PE or acute silent coronary event, or arrhythmia? EKG on screening and prior to event were reported normal.*
3	IV	2	Sputum: *K. pneumoniae, P. aeruginosa*	Cardiogenic shock secondary to acute MI; CABP; and COPD.	*66 yo, COPD, smoking, no h/o CAD, RUL PNA, Sputum culture K. pneumoniae [2] and P. aeruginosa, rapidly deteriorated on day 2 with signs of hypotension and signs of shock with questionable signs of ischemia in EKG (negative troponin), requiring mech. Vent., transfer to ICU. Dx ed with acute MI/ cardiogenic shock. However, shock secondary to sepsis cannot be ruled out.*
4	IV	9	Sputum: *H. influenzae*	Thoracic aortic aneurysm rupture	*72 yo, COPD, known aneurysm, RUL PNA, sputum H. influ [1], ECR success, on D 7, worsening PNA, Rt apical cavitary lesion, abscess; a persistent large TAA. On D 9 died suddenly. Cause of death was attributed to ruptured aneurysm, however it was not confirmed by imaging or autopsy.*
5	IV	13	Negative	Cerebro-vascular accident with respiratory failure	*68 yo, COPD, CHF, HTN, DM: success at ECR, EOT, d/c D7. re-adm. D13 with hemodynamic instability- diagnosed with CVA; **due to lack of imaging studies, and absence of focal neurological abnormality, septic shock cannot be ruled out.*
6	IV	20	Negative	Cardiogenic shock caused by MI	*90 yo, COPD, CHF, MI, DM, success at ECR, EOT and PTE, d/c D 14; 2 D later non-ST MI.*
7	IV	25	Sputum: *H. influenzae, E. coli,* and *P. mirabilis*	Acute respiratory failure (ARF) due to CABP; Multiple organ failure	*74 yo, asthma, Smoking, asthma, HTN, old MI, cystitis, RML, RUL PNA, sputum H. influ [2], E. coli [1], 10-D h/o "flu" with high fever, productive cough dark, grey sputum, dyspnea, rapidly decompensated, by day2 ICU, req. mech. Vent. was considered progression of CABP. A large amount of bloody sputum aspirated. BAL Cx with H. influ [2]and K. pneumoniae [2]. Complicated hospital course, died day 25.*

Table x. Brief summary of causes of individual deaths in Study CABP 1200					
Omadacycline					
	PORT Risk	**DTH DAY**	**Source of Culture: CABP Pathogen**	**Cause of Death**	**Brief Summary**
8	IV	30	Negative	ARDS due to RLL nosocomial pneumonia	*86 yo, arteriosclerosis, success at ECR, EOT (d/c D12); re-hosp. 9 days after EOT with new PNA, BAL Cx: A. baumannii.*
Moxifloxacin					
1	III	9	Negative	Acute Respiratory Failure	*Worsening CABP by day 3*
2	IV	9	Multiple blood cultures: *E. coli*	Cardiac Failure	*After clinical success at ECR- new symptoms and ECG findings suggestive of a recent MI, and elevated troponin day 7.*
3	IV	20	Negative	Small cell lung cancer-metastatic	*After clinical success at ECR- an incidental diagnosis of a right lung tumor on routine imaging.*
4	*III*	*71*	*Sputum: H. parainfluenzae*	*Pancreatic Cancer-metastatic*	*After clinical success at ECR and EOT-eventual diagnosis of metastatic pancreatic cancer with obstructive icterus/jaundice*
Source: Clinical Reviewer's Analysis Numbers is parenthesis "[] are MIC's of particular organism against omadacycline. Abbreviations: yo= year old; influ= Influenza; mech vent= mechanical ventilation; adm= admitted; BAL cx= bronchoalveolar lavage culture; ECR= early clinical response;					

Baseline characteristics of all deaths occurred in Study CABP 1200 is summarized in Appendix 15.3.13; and detailed patient narratives of all deaths are summarized in Appendix 15.3.21.

Clinical Reviewer's Conclusion on Mortality assessment

Although the rate of mortality in the omadacycline group appears to be similar to the 30-day mortality observed in recently conducted CABP trials, imbalance in mortality in a randomized controlled trial where treatment groups were well balanced with regards to key baseline factors, is concerning. No significant differences in adverse events, SAEs or adverse events leading to treatment discontinuations were seen between treatment groups in the CABP trial (discussed later in the review).
In an attempt to better understand the mortality observed in CABP 1200 trial, and to determine if there is a specific population that might be at risk for increased mortality with omadacycline treatment, a number of analyses were conducted looking at the relationship of death to severity of illness, co-morbidities, demographic characteristics, laboratory data and the timing of deaths.

Various subgroup analyses have identified following factors that were associated with the mortality in CABP 1200 trial:

A higher proportion of patients died in omadacycline group belonged to PORT Risk class-IV. Other patient characteristics where risk difference in mortality were slightly higher in omadacycline patients was: age> 65 years, patients with underlying lung diseases (COPD/Asthma), patients with diabetes mellitus, presence of pleural effusion on baseline CXR, and elevated total WBC count (the majority of patients in OMC who died had WBC>12,000).
In terms contribution of pathogen, 4 patients had baseline pathogen identified from respiratory or blood cultures. Of those, one patient had mixed K. pneumoniae and P. aeruginosa isolated from the sputum, and remaining 3 had H. influenzae, however, 2 of the 3 had coinfection with other pathogens (1 patient had coinfection with S. pneumoniae and bacteremia, and 1 patient had mixed E. coli, and P. mirabilis isolated from sputum. Notably this patient was also diagnosed with hemorrhagic cystitis with P. mirabilis isolated from urine). Bacteremia was present in one patient each in omadacycline (S. pneumoniae bacteremia) and moxifloxacin arm (E. coli bacteremia).

Although four of eight deaths in omadacycline were related to cardiovascular disease outcomes, omadacycline does not appear to have a proarrhythmic risk potential to explain the finding. Furthermore, a sensitivity analysis showed that the same proportion of patients in each treatment group were switched to oral antibacterial drug therapy by day 3 or day 4 based on clinical stability that included normal heart rate, and the tachycardia did not persist among omadacycline-treated patients who had a higher pulse rate at baseline as part of the infectious disease process.

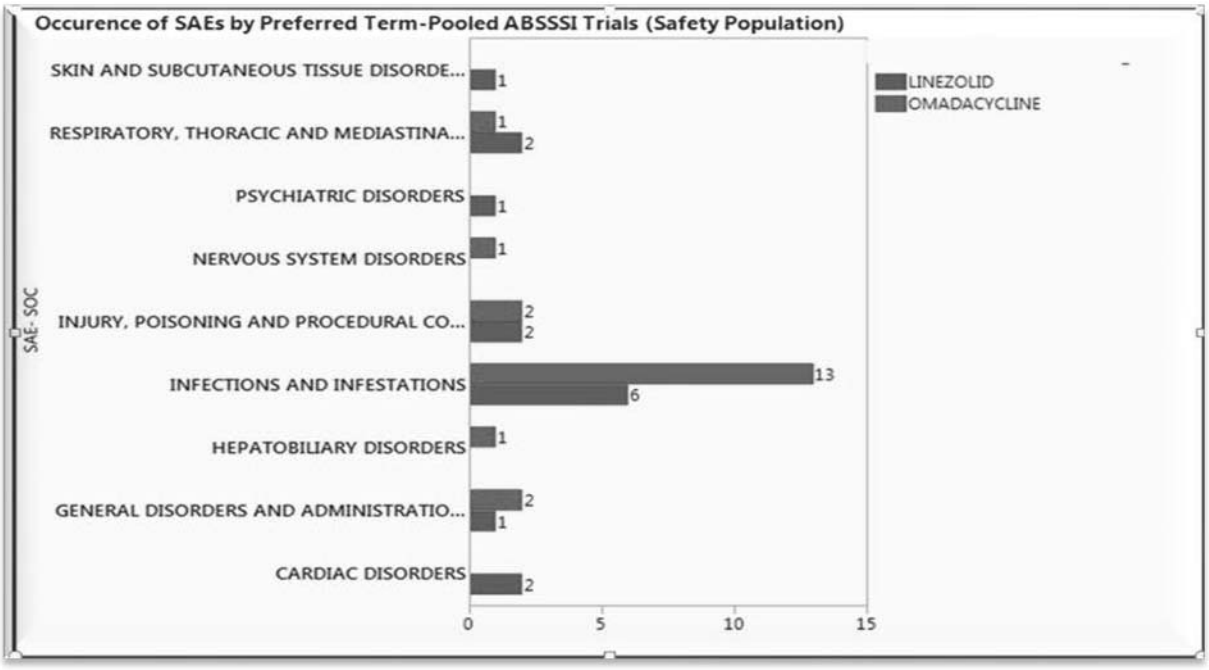
9.7.3 Serious Adverse Events

Table 9-11 provides an overview of SAEs in pooled phase 3 ABSSSI trials and CABP trial.

Table 9-11 Safety Overview- All Phase 3 Trials

	Pooled ABSSSI Trials		CABP Trial	
	OMC N=691	**Linezolid N=689**	**OMC N=386**	**Moxifloxacin N=388**
	n (%)	n (%)	n (%)	n (%)
Completed Study Treatment	624 (90.3)	603 (87.5)	352 (91.2)	346 (89.2)
Prematurely Discontinued from Study	76 (11.0)	85 (12.3)	30 (7.8)	26 (6.7)
Prematurely Discontinued from Study Treatment	67 (9.7)	86 (12.5)	34 (8.8)	42 (10.8)
Adverse Event	12 (1.7)	11 (1.6)	17 (4.4)	28 (7.2)
Lost to Follow-up	23 (3.3)	34 (4.9)	0	1 (0.3)
Withdrawal by Patient	14 (2.0)	14 (2.0)	4 (1.0)	3 (0.8)
Physician Decision	10 (1.4)	16 (2.3)	3 (0.8)	9 (2.3)
Deaths during treatment	0	1 (0.1)	4 (1.0)	1 (0.3)
Other	8 (1.2)	10 (1.5)	6 (1.6)	0
Source: FDA clinical Reviewer's Analysis; ADAE data set; OMC= omadacycline				

Figure 6-1 summarizes SAEs by MedDRA System Organ Class (SOC) in the pooled ABSSSI Trials.
Figure 9-1 SAEs by MedDRA System Organ Class (SOC) in the pooled ABSSSI Trials.



Source: Clinical Reviewer's Analysis

Table 9-12 summarizes SAEs by preferred Term from System Organ Class of "Infections and Infestations".

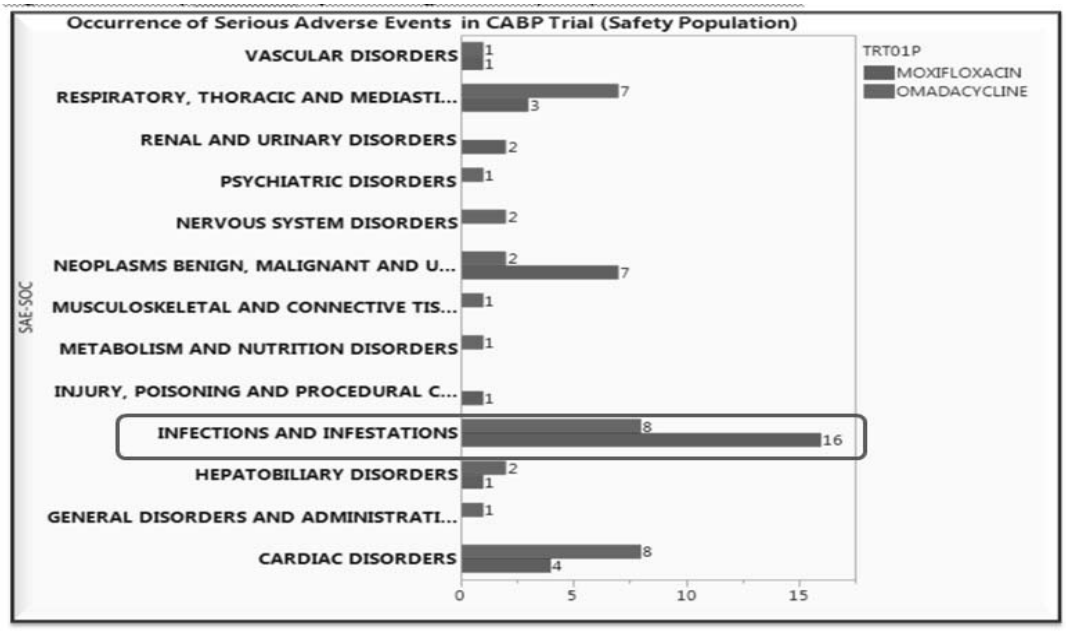
Table 9-12 Summary of SAEs from SOC of "Infections and Infestations"-pooled phase 3 ABSSSI trials

System Organ Class Preferred Term	Omadacycline N=691		Linezolid N=689	
	n	%	n	%
Infections and infestations	**12**	**(1.7)**	**5**	**(0.7)**
Subcutaneous abscess	3	(0.4)	0	0
Wound infection	3	(0.4)	1	(0.1)
Cellulitis	2	(0.3)	2	(0.3)
Bacteremia	1	(0.1)	0	0
Gastroenteritis rotavirus	1	(0.1)	0	0
Hepatitis C	1	(0.1)	0	0
Staphylococcal bacteremia	1	(0.1)	0	0
Sepsis	0	0	3	(0.4)

Source: Clinical Reviewer's Analysis; ISS ADAE data set

In CABP trial, 49 patients (23 (6.0%) omadacycline, 26 (6.7%) moxifloxacin) experienced serious adverse events, including the 12 patients who died. Overall, events from SOC of 'Infections and infestation' were the most frequent type of SAEs followed by 'respiratory thoracic mediastinal disorders' in CABP trial. Figure 9-2 SAEs by MedDRA System Organ Class in the CABP Trial. summarizes SAEs by MedDRA System Organ Class (SOC) in the CABP trial.

Figure 9-2 SAEs by MedDRA System Organ Class in the CABP Trial.



Note: One subject might have SAE from more than one SOC.

Source: Clinical Reviewer's Analysis, ADAE data set

Table 9-13 below summarizes SAEs from System Organ Class of Infections and Infestations in CABP Trial

Table 9-13 Summary of SAEs by Preferred Term from System Organ Class of Infections/Infestations – CABP Trial (safety population)

	Study CABP 1200			
	Omadacycline N=382		Moxifloxacin N=388	
	n	%	n	%
Patients with at Least One SAE	**23**	**(6.0)**	**26**	**(6.7)**
Infections and Infestations	**8**	**(2.1)**	**16**	**(4.1)**
Influenza	3	(0.8)	0	0
Pneumonia	2	(0.5)	6	(1.5)
Cellulitis	1	(0.3)	0	0
Infectious Pleural Effusion	1	(0.3)	1	(0.3)
Septic Shock	1	(0.3)	2	(0.5)
Atypical Mycobacterial Pneumonia	0	0	1	(0.3)
Clostridium Difficile Colitis	0	0	1	(0.3)
Clostridium Difficile Infection	0	0	2	(0.5)
HIV Infection	0	0	1	(0.3)
Infective Exacerbation of Bronchiectasis	0	0	1	(0.3)
Lung Abscess	0	0	1	(0.3)
Pneumonia Viral	0	0	1	(0.3)

Source: Clinical Reviewer's Analysis; ADAE data set

Clinical Reviewer's Comment: Overall, across phase 3 trials, frequencies of serious adverse events by SOC were similar between the omadacycline and comparator groups (39/1073 (3.6%) in omadacycline, 13/689 (1.9%) in linezolid, and 26/388 (6.7%) in moxifloxacin group), except for the SOC of 'Infections and Infestations', which were twice as high in omadacycline arm as compared to linezolid arm in ABSSSI trials (12 (1.7%) omadacycline and 5 (0.7%) linezolid), while converse was seen in CABP trial (8 (2.1%) omadacycline and 16 (4.1%) moxifloxacin arm).

When the specific PT's characterized as SAEs in SOC of 'Infections and Infestations' were examined, it was apparent that majority were related to the progression or worsening of the of the index infection, rather than to an adverse event per se (e.g. wound infection, cellulitis, and subcutaneous abscess in patients with ABSSSI or pneumonia, septic shock, infectious pleural effusion, lung abscess, in patients with CABP, suggesting treatment effect rather than drug toxicity. Majority of these patients were considered as "clinical failures". Serious adverse events from SOC of cardiac disorders were also comparatively higher in omadacycline group (5, 1.3%) as compared to linezolid group (2, 0.5%) in ABSSSI trials.

9.7.4 Dropouts and/or Discontinuations Due to Adverse Effects

Across phase 3 trials, TEAEs that led to discontinuation of study drug was similar between treatment groups. (3.1% of omadacycline patients, 1.5% of linezolid patients, and 7.0% of moxifloxacin patients). Infection and infestation events were the most frequent type of TEAEs that led to discontinuation of study drug (1.3% of omadacycline patients, 0.3% of linezolid patients, 3.6% of moxifloxacin patients).

Although nausea and vomiting were most frequent adverse events noted with omadacycline, discontinuation due to these events were infrequent, occurring in only 4 (0.4%) omadacycline patients (2 patients had vomiting; 1 patient had nausea, vomiting, and hematemesis, and 1 patient had nausea and vomiting).

9.7.5 Significant Adverse Events

This section will discuss TEAEs that were not considered as a 'serious', however, were considered 'significant' based on definition in ICH guideline for industry E3 structure and were graded as "severe". Significant adverse events were similar between the treatment groups. A table of summary of significant adverse events across phase 3 trials is listed in Appendix 15.3.26.

9.7.6 Treatment Emergent Adverse Events and Adverse Reactions

An overview of TEAEs across phase 3 trials is summarized in the Table 9-14.

Table 9-14 Overview of TEAEs in phase 3 trials

	Treatment Groups		
	OMC N = 1073 n (%)	**LNZ N = 689 n (%)**	**MOXI N = 388 n (%)**
Patients with any TEAE	510 **(47.5)**	284 **(41.2)**	188 **(48.5)**
Number of Patients (%) with:			
Drug-Related TEAE	236 **(22.0)**	111 (16.1)	69 (17.8)
TEAE leading to premature discontinuation of study drug	33 **(3.1)**	10 (1.5)	27 **(7.0)**
Source: Clinical Reviewer's analysis			

Clinical Reviewer's Comment: Overall, frequencies of TEAEs were similar between omadacycline and comparator arms across all phase 3 trials (~48%, 42%, and 49% in omadacycline, linezolid and moxifloxacin groups, respectively). TEAEs that were considered by Investigator as 'drug related' occurred at slightly higher frequencies in omadacycline group as compared to the comparators (22 % of omadacycline patients, 16% of linezolid, and 18% of moxifloxacin patients). Majority of those were gastrointestinal events of nausea and vomiting.

Most Frequent TEAEs

Table 9-15 and Table 9-16 Table 9-16 summarizes the most frequent TEAEs that occurred in ≥ 2% of patients in pooled ABSSSI trials and CABP trial, respectively.

Table 9-15 TEAEs Occurring in ≥2% of Patients in Pooled ABSSSI Trials (Safety Population)

Preferred Term	Pooled ABSSSI Trials	
	Omadacycline (N = 691)	Linezolid (N = 689)
	n (%)	n (%)
Nausea	151 (21.9)	60 (8.7)
Vomiting	79 (11.4)	27 (3.9)
Infusion site reactions*	41 (12.7)	27 (8.4)
Alanine aminotransferase increased	28 (4.1)	25 (3.6)
Aspartate aminotransferase increased	25 (3.6)	24 (3.5)
Headache	23 (3.3)	21 (3.0)
Diarrhea	22 (3.2)	20 (2.9)
**Infusion site extravasation, pain, erythema, swelling, and irritation at infusion site		

Table 9-16 TEAEs Occurring in ≥2% of Patients in CABP Trial (Safety Population)

Preferred Term	CABP Trial	
	Omadacycline (N = 382)	Moxifloxacin (N = 388)
	n(%)	n(%)
Alanine aminotransferase increased	14 (3.7)	18 (4.6)
Hypertension	13 (3.4)	11 (2.8)
Gamma-glutamyl transferase increased	10 (2.6)	8 (2.1)
Insomnia	10 (2.6)	8 (2.1)
Vomiting	10 (2.6)	6 (1.5)
Constipation	9 (2.4)	6 (1.5)
Nausea	9 (2.4)	21 (5.4)
Aspartate aminotransferase increased	8 (2.1)	14 (3.6)
Headache	8 (2.1)	5 (1.3)

Clinical Reviewer's Comment: Overall, when comparing across trials, the most frequent TEAEs (that occurred in >2% patients) were similar between the treatment groups. Nausea and vomiting were the most frequently reported TEAEs across phase 3 trials. Both occurred at higher frequencies in omadacycline group as compared to linezolid or moxifloxacin group. TEAEs of infusion site reactions occurred at a higher frequency in ABSI 1108 trial and were rare in CABP trial. Majority of infusion site reactions were either injection site infiltration or extravasation and were recorded as 'infusion site extravasation'. One explanation by the applicant is that infusion site infiltration is typically associated with difficult venous access,

which is common in IV drug users. Study ABSI 1108 consisted of a high proportion of patients with underlying history of IV drug abuse. More than three-quarters of intravenous drug users usually develop scars in the vascular distribution.

Table 9-17 below summarizes the comparison of most frequent TEAEs from SOC of 'Gastrointestinal disorders' across phase 3 trials.

Table 9-17 Number (%) of Patients with the Most Frequent TEAEs (≥ 2% for Any Group) from Gastrointestinal disorders in three phase 3 trials (ABSI-1108, ABSI-16301, and CABP-1200)

Number (%) of Patients with the Most Frequent TEAEs (≥ 2% for Any Group) from Gastrointestinal disorders in three phase 3 trials (ABSI-1108, ABSI-16301, and CABP-1200)						
	Study ABSI-1108		Study ABSI-16301 (ORAL only Study)		Study CABP-1200	
	OMC (N = 323) n (%)	Linezolid (N = 322) n (%)	OMC (N = 368) n (%)	Linezolid (N = 367) n (%)	OMC (N = 382) n (%)	Moxi (N = 388) n (%)
Patients with at	156 (48.3)	147 (45.7)	197 (53.5)	137 (37.3)	157 (41.1)	188 (48.5)
GI disorders	58 (18.0)	51 (15.8)	144 (39.1)	52 (14.2)	39 (10.2)	70 (18.0)
Nausea	40 (12.4)	32 (9.9)	111 (30.2)	28 (7.6)	9 (2.4)	21 (5.4)
Vomiting	17 (5.3)	16 (5.0)	62 (16.8)	11 (3.0)	10 (2.6)	6 (1.5)
Diarrhea	7 (2.2)	10 (3.1)	15 (4.1)	10 (2.7)	4 (1.0)	31 (8.0)
Abdominal pain	---	---	10 (2.7)	4 (1.1)	---	---
Constipation	---	---	---	---	9 (2.4)	6 (1.5)
Source: Clinical Reviewer's Analysis MOXI=moxifloxacin; OMC=omadacycline						

Clinical Reviewer's Comment: TEAEs from Gastrointestinal disorders (especially nausea and vomiting), as mentioned before, occurred at highest rates in omadacycline treatment arm, and majority occurred in oral-only trial (Study ABSI-16301). The onset of most cases of nausea and vomiting events occurred during the oral "loading dose" phase of treatment period (Days 1 and 2) in ABSI16301 trial.

In Study ABSI-1108 and Study CABP-1200, the TEAEs of nausea and vomiting were slightly more common during oral phase as compared to IV administration phase of the trials in omadacycline as well as moxifloxacin groups. However, in linezolid group, TEAEs of nausea and vomiting were slightly more common during IV administration phase. It is noteworthy that although nausea and vomiting occurred at higher frequency in omadacycline as compared to linezolid treatment group, discontinuation of study drug for these events were infrequent in both groups (4 (0.4%) and 1 (0.1%) in omadacycline and linezolid groups).

9.7.7 Adverse Events of Special Interest

Infusion Site Reactions

Table 9-18 below summarizes Infusion associated adverse events that occurred in IV to oral switch trials. Infusion site reactions were mainly observed in ABSSI IV to oral switch trial (Study ABSI 1108).

Table 9-18 Summary of Infusion Site Reaction TEAEs by PT Study ABSI-1108 and Study CABP-1200 (safety population)

	ABSI-1108		CABP-1200	
TEAEs by PT	**OMC (N = 323) n (%)**	**LNZ (N=322) n (%)**	**OMC (N= 382) n (%)**	**MOXI (N=388) n (%)**
Infusion site reactions	**41 (12.7)**	**27 (8.4)**	**3 (0.8)**	**5 (1.3)**
Infusion site	28 (8.7)	19 (5.9)	-	-
Infusion site pain	6 (1.9)	6 (1.9)	1 (0.3)	1 (0.3)
Infusion site erythema	1 (0.3)	0	1 (0.3)	2 (0.5)
Peripheral swelling	4 (1.2)	0	-	-
Infusion site irritation	1 (0.3)	0	-	-
Skin induration	1 (0.3)	0	-	-
Infusion site swelling	0	1 (0.3)	1 (0.3)	0
Infusion site	0	1 (0.3)	0	2 (0.5)
Source: CSR, ADAE data set If a patient had more than 1 TEAE with the same PT, the patient was counted only once for that PT.				

Clinical Reviewer's Comment: All infusion associated adverse events were mild or moderate in intensity. None of the events led to discontinuation of study drug in omadacycline group.

TEAEs from SOC: Hepatobiliary system

In the omadacycline nonclinical studies ≤ 2-fold increases in serum transaminases as compared to control animals were observed. In the phase 1 studies, transient serum ALT elevations were also reported, most notably for IV doses of 300 mg or greater, and were dose limiting at 600 mg IV. Therefore, based on evidence from other tetracycline drugs and from the nonclinical and clinical data in the omadacycline phase-1 studies, hepatic TEAEs (specifically liver enzyme increase) were examined as adverse events of interest.

Table 9-19 below summarizes the hepatic adverse events by category and PT in the phase 3 ABSSSI and CABP trials.

Table 9-19 Hepatic Events reported as TEAEs in phase 3 trials by preferred term

Category PT	OMC (N = 1073) n (%)	LNZ (N=689) n (%)	Moxi (N=388) n (%)

Category PT	OMC (N = 1073) n (%)	LNZ (N=689) n (%)	Moxi (N=388) n (%)
Liver-related events reported as TEAE	**58** (5.4)	**34** (4.9)	**28** (7.2)
ALT increased	42 (3.9)	25 (3.6)	18 (4.6)
AST increased	33 (3.1)	24 (3.5)	14 (3.6)
GGT increased	15 (1.4)	8 (1.2)	8 (2.1)
Blood bilirubin increased	5 (0.5)	1 (0.1)	3 (0.8)
Blood ALP increased	3 (0.3)	1 (0.1)	4 (1.0)
Hypoalbuminemia	2 (0.2)	0	3 (0.8)
Hepatic enzyme increased	1 (0.1)	0	0
Hepatic congestion	0	0	1 (0.3)
Biliary- events reported as TEAE	**7 (0.7)**	**2 (0.3)**	**6 (1.5)**
Blood Total Bilirubin increased	5 (0.5)	1 (0.1)	3 (0.8)
Blood Alkaline phosphatase increased	3 (0.3)	1 (0.1)	4 (1.0)

Source: Clinical Reviewer's analysis; ADAE data set
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase; MOXI=moxifloxacin; OMC=omadacycline

Clinical Reviewer's Comment: All hepatic adverse events including 'ALT increased, and AST increased' were comparable between the omadacycline group and comparators.
In terms of severity, all hepatic AEs of interest were considered mild or moderate in severity, except for 1 patient in CABP trial in omadacycline group, who had a severe TEAE of hypoalbuminemia. One patient in the moxifloxacin group had a serious TEAE of hepatic congestion in CABP trial, which was also graded severe, and 1 linezolid patient in ABSI16301 trial had a severe TEAE of GGT increased.
Treatment-related TEAEs of ALT increased occurred in 3%, and 2% of omadacycline and linezolid patients, respectively in the pooled ABSSSI trials; and 2% each of omadacycline and moxifloxacin patients in the CABP trial.

Hepatic AEs leading to treatment discontinuation

Two patients in the omadacycline group and 2 patients in the moxifloxacin group had liver enzyme elevations, which were mild or moderate, that resulted in discontinuation of the study drug. One additional omadacycline patient (Patient # CABP1200-(b) (6)) had a serious TEAE of hepatic failure on Day 3 following cardiac arrest. The study drug was discontinued, and the event resolved on Day 29.
A brief narrative of 2 patients in omadacycline group (Patient # CABP1200-(b) (6), and CABP 1200-(b) (6)) that led to discontinuation from study drug is discussed below.

Case #1: 1200-(b) (6)
This was a 65-year-old female with a medical history of asthma, cholecystectomy, and hypertension was diagnosed with CABP (PORT Risk class-III). Concomitant medications taken by the patient during the study included ceftazidime, gentamicin, bisoprolol, salbutamol,

montelukast, ramipril, duovent, bromhexine -HCL, ketoprofen, formoterol, metamizole, oseltamivir, dexamethasone, dalteparin, and omeprazole. The patient's received a total of 4 days of IV omadacycline. On day 4, study drug was discontinued due to elevated liver enzymes. The patient's liver chemistry results at study visits are summarized in the table below. The patient completed the study. In the opinion of the investigator, the event was mild in severity and related to the study drug.

Liver chemistry results of Case # 1200- (b) (6)					
Parameter (Reference range)	**BL (Day 1)**	**Day 4**	**Day 5 (EOT)**	**Day 15**	**Day 36**
ALT (10-33 U/L)	26	34	57	99	99
AST (10-36 U/L)	37*	71	105	36	53
ALP (30-115 U/L)	57	63	62	82	77
Bilirubin (0- 18.8)	4.4	3.9	2.5	6.8	8.0
GGT (5-32 U/L)	18	18	25	151	122

Case #2: 1200- (b) (6)

This was a 76-year-old female with a history of osteoarthritis, and mild renal dysfunction was diagnosed with CABP (PORT Risk class III). The patient's sputum culture was positive for *Haemophilus influenzae.* Serology was positive for *Mycoplasma pneumoniae* (IgM baseline-negative/PTE- indeterminate; IgG baseline- negative/PTE-positive). Concomitant medications taken by the patient during the study included ceftriaxone, paracetamol, and diclofenac.
On Study Day 4, the patient's laboratory results showed increased liver enzymes; however, study drug was continued until Day 7 when the patient had EOT visit, and the study drug was discontinued. The patient completed the study. The events were considered resolved by Study Day 12 (Table below) In the opinion of the investigator, the events (increased AST and ALT) were 'moderate' in severity and related to study drug. Based on the limited information provided, this reviewer agrees with the assessment of the investigator.

Liver chemistry results of Case # 1200- (b) (6)					
Parameter (Reference range)	**Day 1**	**Day 4**	**Day 7**	**Day 8 (EOT)**	**Day 12 (PTE)**
ALT (10-33 U/L)	36	143*	176*	174*	12
AST (10-36 U/L)	35	179*	98*	96*	17
ALP (30-115 U/L)	95	209*	273*	276*	43
Bilirubin (0- 18.8) µmol/L)	3.42	3.762	2.736	2.736	5.13
GGT (5-32 U/L)	30	124*	175*	175*	18

Hepatic TEAEs reported as an increase in laboratory values from normal baseline

Among patients with a baseline liver parameter value within the normal range, the proportion with an elevated transaminase level (> 3 × ULN, > 5 × ULN, and > 10 × ULN), an elevated T Bili level (> 1.5 × ULN and > 2 × ULN), and an elevated ALP level (2 × ULN) were analyzed.
Table 9-20 below summarizes these categories using the worst (or highest measurement) post-

baseline during the study for a given patient in across phase 3 trials.

Table 9-20 Hepatic Enzyme elevations in patients with 'Normal Baseline Values' (safety population)

	Treatment Arms		
	Omadacycline	**Linezolid**	**Moxifloxacin**
	N n (%)	**N n (%)**	**N n (%)**
ALT (U/L)			
Normal at Baseline	***772***	***537***	***295***
> 3 × ULN	13 (1.7)	18 (3.4)	11 (3.7)
> 5 × ULN	7 (0.9)	4 (0.7)	1 (0.3)
> 10 × ULN	5** (0.6)	3 (0.6)	0
AST (U/L)			
Normal at Baseline	***858***	***561***	***328***
> 3 × ULN	13 (1.5)	16 (2.9)	5 (1.5)
> 5 × ULN	8 (0.9)	6 (1.1)	1 (0.3)
> 10 × ULN	3 (0.3)	1 (0.2)	0
Total Bilirubin (µmol/L)			
Normal at Baseline	***937***	***593***	***364***
> 1.5 × ULN	7 (0.7)	2 (0.3)	6 (1.6)
> 2 × ULN	5 (0.5)	1 (0.2)	4 (1.1)
ALP (U/L)			
Normal at Baseline	***819***	***523***	***311***
> 2 × ULN	5 (0.6)	1 (0.2)	6 (1.9)
Source: CSR T Bili= Total bilirubin; AST=aspartate amino transferase ALT=alanine amino transferase; BL= baseline			

Clinical Reviewer's Comment: Increases in ALT or AST values to > 5 × and > 10 × ULN in patients with normal values at baseline, were comparable between omadacycline and comparator groups. Elevations in ALT or AST >10x ULN occurred in 5 (0.6%) patients in omadacycline group; 3 (0.6%) patients in linezolid group, and no patient in moxifloxacin group. The risk of hepatic injury associated with omadacycline appears to be similar to the risk of hepatic injury associated with the FDA-approved antibacterial drugs linezolid and moxifloxacin.

Narratives of patients with normal baseline AST/ALT and had post-baseline increase to > 10 × ULN is presented in Appendix 14.5.18.

Clinical Reviewer's Comment: After the Clinical Reviewer's thorough evaluation of hepatic injury in the clinical development program, higher proportions of patients without underlying liver disease had post-baseline liver enzyme elevations as compared to a patient with existing liver disease.

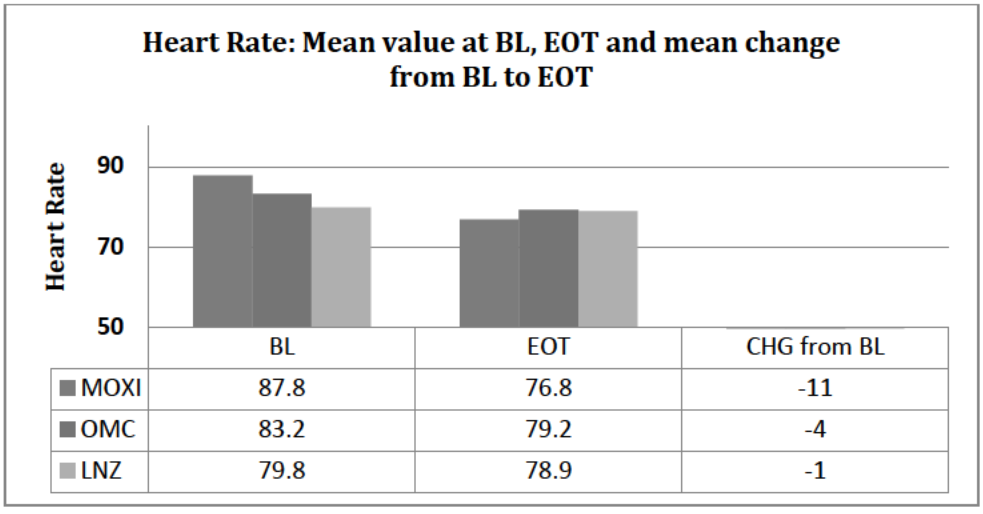
TEAEs from SOC Cardiac Disorders

Heart Rate and Cardiac Events

In nonclinical studies, omadacycline was shown to inhibit binding of 3H-scopolamine to the M2 subtype of the muscarinic acetylcholine receptor. This finding from ex-vivo studies on SA node suggested that omadacycline may affect the HR through an indirect, vagolytic action and that, the HR increase would be more pronounced in patients with high vagal tone. An increase of HR was noted without clear dose-dependency when tested in vivo in cynomolgus monkeys.
In Phase 1 studies in healthy patients, transient, dose-dependent increases in HR were observed following administration of single and multiple IV doses of omadacycline. Study PTK0796-SDES-0501, conducted in healthy adult male patients, who received single IV doses of omadacycline; mean ΔHR was 14 bpm, 2 hours after the start of the 60-minute infusion in 300 mg dose group, 18 bpm and 17 bpm in 400 mg and 600 mg dose groups, respectively.
In the TQTC study (Study PTK0796-TQTC-0803), a single IV omadacycline infusion of 100 mg/30 minutes and 300 mg/60 minutes had an effect on HR with the largest mean ΔHR observed at early time-points (17 bpm at 35 minutes post-dose after the 100 mg dose and 22 bpm at 50 minutes after dosing with 300 mg).

In phase 3 trials of the target population of infected patients, a small HR effect has been observed as compared to the active comparator (moxifloxacin or linezolid). In these phase 3 trials, ECGs were recorded prior to and 30 to 90 minutes after the start of the first and third infusion. Figure 9-3 Mean Heart Rate at BL, EOT and BL to EOT- Phase 3 Trials (Safety Population)
below summarizes the mean Heart Rate of patients at baseline, at end of treatment, and mean change from baseline to end of treatment- Omadacycline Phase-3 Trials.

Figure 9-3 Mean Heart Rate at BL, EOT and BL to EOT- Phase 3 Trials (Safety Population)



	BL	EOT	CHG from BL
MOXI	87.8	76.8	-11
OMC	83.2	79.2	-4
LNZ	79.8	78.9	-1

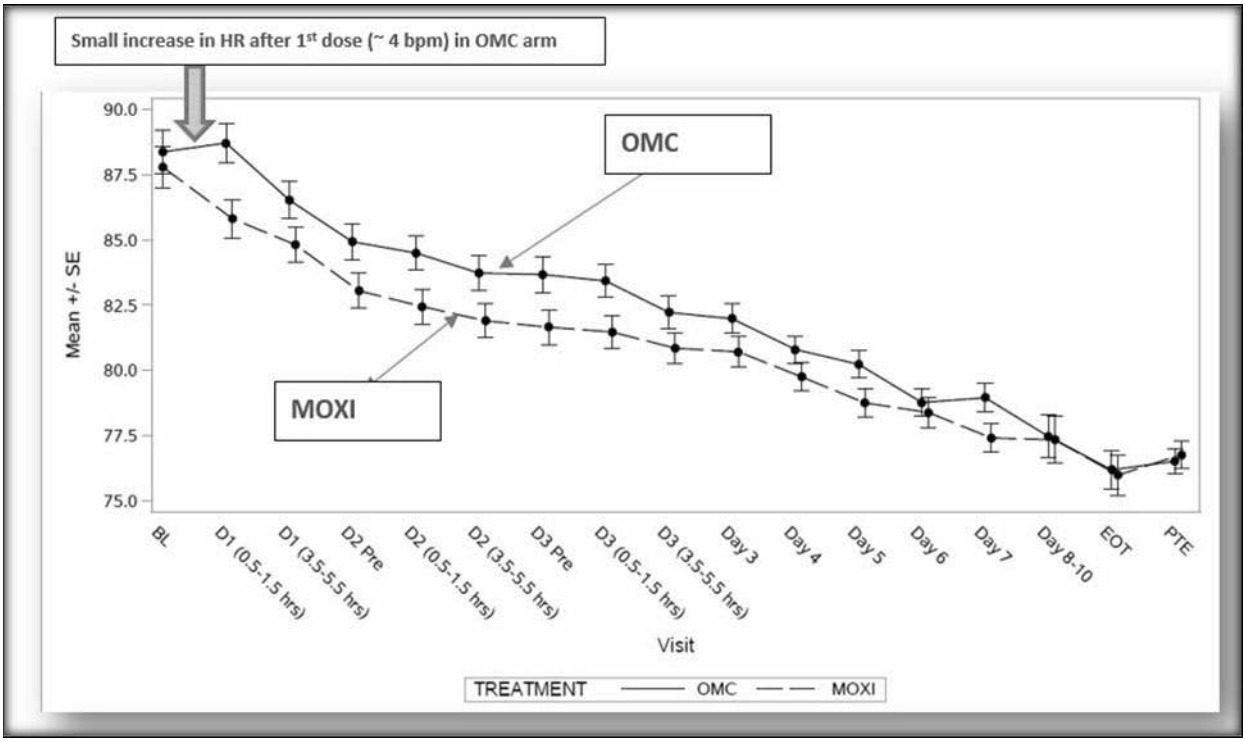
Source: Clinical reviewer's analysis

Clinical Reviewer's Comment: Mean change in heart rate over time across phase 3 omadacycline clinical trials showed that HR tended to decline slightly in all categories at both the EOT and PTE visits from baseline, however, decline was less rapid for omadacycline patients as compared to patients in moxifloxacin treatment.

Figure 9-4 Change in Heart Rate (beats/minute) over time in CABP Trial (Safety population)

below summarizes the mean Heart Rate of patients from first dose of study drug over time in CABP Trial.

Figure 9-4 Change in Heart Rate (beats/minute) over time in CABP Trial (Safety population)



Source: Clinical Reviewer- partly adapted and modified from Figure 6 in CSR.

Clinical Reviewer's Comment: In Study CABP-1200 conducted in patients with acute bacterial pneumonia, with comparatively older population, a total of 5.5% omadacycline subjects and 5.7% moxifloxacin subjects had a HR ≥ 120 bpm at any post-Baseline time point. A small increase of HR (4 bpm) was observed after the first dose of omadacycline. With continued anti-bacterial therapy, no such effect was seen. Heart rate tended to decline in both treatment groups overtime, however, the reduction of mean ΔHR was somewhat smaller in the moxifloxacin group with mean change in 2 bmp and -1 bmp in omadacycline before and after the third dose, respectively as compared to -5 bmp and -7 bpm in moxifloxacin, before and after the third dose, respectively.

Overall, although heart rate increases were observed in healthy subjects treated with omadacycline, this effect was smaller in patients with ABSSSI and CABP and comparable

between treatment arms. Hence imbalance in mortality seen in CABP trial cannot be explained by omadacycline' s vagolytic effect on heart.

Other Cardiac AEs:

Patients with underlying cardiac disease may be more susceptible to a drug-induced increase in HR even though the observed mean HR effect of omadacycline in infected patients was very small. Therefore, an increase of adverse cardiac events that can be associated with an HR elevation, e.g., worsening of angina, acute myocardial infarction, episodes of congestive heart failure, tachycardia, and sudden death were examined.

In Study ABSI-1108, there were 2 patients with an AE of atrial fibrillation, 1 with sinus tachycardia and 1 sinus bradycardia, and 1 patient with ST-segment elevation MI in omadacycline group. In the linezolid group, 1 patient experienced an AE of congestive heart failure and 1 myocardial ischemia, in addition, there were 2 deaths due to serious cardiac AEs in linezolid group, and no deaths in the omadacycline group due to cardiac events in this trial.

In the CABP trial, there were more cardiac AEs in both treatment groups. About 15/386 (4%) in omadacycline group, and 20/388 (5%) patients in moxifloxacin group experienced a cardiac AE, of which 5 (1%) and 2 (0.5%) were 'serious' AEs, and 3 in the omadacycline group and 1 in moxifloxacin group were fatal AEs. The fatal events in the omadacycline group were due to cardiorespiratory arrest, cardiogenic shock secondary to acute myocardial infarction and cardiogenic shock, respectively. In the moxifloxacin group, one death occurred due to a suspected episode of myocardial infarction and heart failure.

Table below summarizes Cardiac AEs of interest by PT across all Phase 3 trials.

Table 9-21 Summary of HR and Cardiac Events of Interest by PT- Pooled Phase 3 Trials (Safety Population)

Table x. Summary of HR and Cardiac Events of Interest by PT- Pooled Phase 3 Trials (Safety Population)			
	Pooled Phase 3 Clinical Trials		
Category PT	**Omadacycline N = 1073 n (%)**	**Linezolid N = 689 n (%)**	**Moxifloxacin N = 388 n (%)**
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 edema	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 ischemia	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
If a patient had more than 1 TEAE with the same category or PT, the patient was counted only once for that category. Percentages were calculated relative to the treatment group N. Source: ISS, ADAE data set			

Clinical Reviewer's Comment: Based on the submitted data, it is difficult to ascertain a direct relationship of omadacycline on the occurrence of cardiac events. The majority of patients who had cardiac events or died due to cardiac AEs had significant underlying co-morbidities including cardiac conditions and diabetes. Inflammation along with other physiological changes triggered by CABP itself could raise the risk of cardiac events in these patients. Cardiac complications (defined as any of the aforementioned events) are the second most common cause of death in CABP patients and known to occur in up to 27% of patients hospitalized with CABP. [38] Cardiac arrest occurs in up to 3% of patients admitted to hospital with CABP.[39]

Tetracycline Class Effects

The applicant has conducted an analysis of AEs commonly related to tetracycline class of drugs, of which omadacycline is a member, including anti-anabolic events as represented by blood urea nitrogen (BUN) increased and azotemia, central nervous system side effects including light-headedness, vertigo or dizziness, hypersensitivity, photosensitivity, pseudotumor cerebri, acute pancreatitis, hepatotoxicity. Notably, pill esophagitis is not uncommonly reported with doxycycline. A summary of tetracycline class related adverse events that occurred across all phase 3 trials is presented in Appendix 14.5.19.

Clinical Reviewer's Comment: All TEAEs associated with tetracycline class were comparable between the treatment groups.

[38] Vicente F Corrales-Medina et al; Lancet 2013; 381: 496–505. February 9, 2013; S0140-6736(12)61266-5
[39] Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)* 2007; **86:** 103–11.

9.7.8 Laboratory Findings

Hematology

Analyses of change over time in hematology and coagulation test results revealed no clinically meaningful change in mean or median values over time for any parameter except for leukocyte and neutrophil counts, which decreased after the baseline visit in both treatment groups, and platelets, which increased after the baseline visit in the omadacycline and moxifloxacin treatment groups. No other clinically meaningful differences between treatment groups were observed at any time point.

Hematology laboratory abnormalities assessed as clinically significant by the investigator were reported as TEAEs. The only laboratory event reported as an AE in ≥ 1% of patients in any treatment group was anemia (1.1% omadacycline, 0.6% linezolid, 0.8% moxifloxacin). None of the TEAEs were considered serious, and none led to study drug discontinuation.
The proportion of patients with at least a 2-grade change (i.e., worsening) from baseline in hematology parameters were similar between the treatment groups. The Table below summarizes the change from baseline to the EOT visit for hematology and coagulation results for the pooled phase 3 trials.

Table 9-22 Leucocytes and Platelets -Absolute and Change from Baseline (Safety population)

	OMC (N = 1073)			Linezolid (N = 689)			Moxifloxacin (N = 388)		
	Value at BL	Value at EOT	Change from BL	Value at BL	Value at EOT	Change from BL	Value at BL	Value at EOT	Change from BL
Leukocytes (× 10^9/L)									
n	1066	985	978	682	615	609	388	357	357
Mean (SD)	9.95	7.58	-2.32	9.73	6.79	-2.77	10.58	9.15	-1.42
SD	(4.587)	(3.064)	(4.144)	(3.831)	(2.148)	(3.539)	(5.175)	(3.647)	(4.831)
Platelets (× 10^9/L)									
n	1023	974	934	662	608	588	352	353	325
Mean	274.08	316.26	42.46	287.70	283.71	-3.20	251.19	343.70	88.73
SD	(95.603)	(111.838	(106.717)	(91.627)	(91.211)	(71.771)	(97.553)	(142.209	(128.371)
Source: ISS Tables 14.3.3.1.4 and 14.3.3.7.4.									

Chemistry

No clinically meaningful changes in BUN values were observed in any treatment group. Lipase values were slightly higher in the omadacycline group compared to the linezolid group but were comparable to the moxifloxacin group. Change from baseline lipase value was +7.52 U/L in the omadacycline group, +2.62 U/L in the linezolid group, and +6.47 U/L in

the moxifloxacin group; in 0.4% omadacycline, 0.9% linezolid, and 0.5% moxifloxacin, patients respectively. Comparable differences were observed for all treatment groups at the PTE visit.

No TEAEs of elevated lipase levels led to discontinuation of study drug or were considered serious. One patient in CABP trial in the omadacycline group had a TEAE of 'chronic pancreatitis' that was deemed to be mild in severity and not related to study drug (no action was taken with study drug, and the event was considered ongoing); no patient had a TEAE of acute pancreatitis. No laboratory-related TEAEs were considered serious.

9.7.9. Vital Signs

Change in heart rate is already discussed in the sub-section 9.1.4, "TEAEs from SOC Cardiac Disorders". The number and percentage of patients who met the clinically notable criterion value and the number and proportion of patients who met both the criterion value and the change from baseline criterion for any time post-Baseline for each vital sign parameter across all phase 3 trials are summarized In Figure 9-5 Clinically Notable Values for HR, Systolic BP, and Diastolic BP at Any Post-Baseline Time Point -Pooled Phase 3 Trials (safety population).

Figure 9-5 Clinically Notable Values for HR, Systolic BP, and Diastolic BP at Any Post-Baseline Time Point -Pooled Phase 3 Trials (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 ≤ 50 bpm	9 (0.8)	20 (2.9)	5 (1.3)
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 ≤ 50 bpm and decrease of ≥ 15 bpm	4 (0.4)	8 (1.2)	5 (1.3)
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 ≤ 90 mmHg	88 (8.2)	30 (4.4)	50 (12.9)
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 ≤ 90 mmHg and decrease of ≥ 20 mmHg	26 (2.4)	7 (1.0)	5 (1.3)
Systolic BP ≥ 180 mmHg and increase of ≥ 20 mmHg	18 (1.7)	13 (1.9)	6 (1.5)
Subjects with diastolic BP value at any post-Baseline visit	1073	689	388
Diastolic BP ≤ 50 mmHg	65 (6.1)	57 (8.3)	23 (5.9)
Diastolic BP ≥ 105 mmHg	39 (3.6)	22 (3.2)	6 (1.5)
Subjects with diastolic BP value at Baseline and any post-Baseline visit	1073	689	388
Diastolic BP ≤ 50 mmHg and decrease of ≥ 15 mmHg	32 (3.0)	32 (4.6)	7 (1.8)
Diastolic BP ≥ 105 mmHg and increase of ≥ 15 mm Hg	30 (2.8)	18 (2.6)	5 (1.3)

Source: SCS Table 29; ISS Table 14.3.4.2.4.

Clinical Reviewer's Comment: The applicant has also analyzed absolute and change from baseline in vital signs, over time across pooled phase 3 trials by the history of hypertension, heart disease, beta-blocker use, and history of tachyarrhythmia. Analyses of change over time in systolic and diastolic BP in patients with or without a history of hypertension, heart disease, beta-blocker use, or tachyarrhythmia revealed no clinically meaningful change in mean or median values over time and no consistent patterns were observed.

The percentage of omadacycline patients with a systolic BP ≤ 90 mmHg, and a decrease of ≥ 20 mmHg was comparable to the linezolid and moxifloxacin groups (2.4% omadacycline, 1.0% linezolid, 1.3% moxifloxacin). Analyses of the mean change over time in HR showed that HR tended to decline slightly in all categories at both the EOT and PTE visits and the decline was less rapid for omadacycline patients as compared to moxifloxacin patients. Details of heart rate changes are discussed in other section of this review (TEAEs from SOC 'Cardiac disorders').

9.7.10. Electrocardiograms (ECGs)/ QT

The applicant has conducted a thorough QT study. The Interdisciplinary Review Team for QT Studies (QT-IRT Team) was consulted to review the data.

The following is an excerpt from the FDA QT Interdisciplinary consult.

"In TQT study, omadacycline caused a dose-/concentration-dependent increase in heart rate which impacted the ability to interpret the ΔΔQTc effects corresponding to the administration of a single therapeutic dose (100 mg IV) as well as a single supra-therapeutic dose (300 mg IV). The largest upper bounds of the 2-sided 90% CI on heart rate for the mean difference between omadacycline (100 mg and 300 mg) and placebo were 18 and 23 bpm, respectively. There was a rapid rise in the heart rate, and the peak heart rate increases coincided with the peak plasma concentrations for the drug. Even though the sponsor had collected pre-dose baseline data for individualized QTc correction (QTcI), the heart rate range in both the pre-dose baseline period and the placebo period did not cover the heart rate range in the treatment period. Furthermore, the sponsor has not accounted for potential QT/RR hysteresis when deriving their QTcI, which could result in a biased estimate of the individual QT/RR relationship. Thus, QTc results from neither the fixed QT correction nor individualized QT correction are interpretable for this study. Therefore, this TQT study is inconclusive regarding the QT prolongation evaluation.

Although the QTc interval could not be characterized in the TQT study due to the confounding increases in heart rate (HR), the safety ECGs collected in Phase 3 clinical trials did not suggest that omadacycline causes large increases in the QTc interval.

Enhanced monitoring of vital signs, in particular, HR around the time of dosing, was instituted by the sponsor in the phase 3 trials. Data from phase 3 CABP trial, Study CABP1200 , which compared omadacycline with moxifloxacin as an active comparator (moxifloxacin is a known QT-prolonging drug and is used as a positive control in typical TQT studies), showed that there were no substantial increases in heart rate after the clinical dosing by IV infusion, and

thus the QTcF measurements in patients could be interpreted without the issue of confounding by heart rate.Even though there was a lack of placebo control in this study, the data showed that the magnitude of QTc effects (ΔQTcF) was less with therapeutic dosing of omadacycline as compared to moxifloxacin. Overall, while no supra-therapeutic dosing was studied in the patient population, no large increases in the QTc interval were observed with the recommended dosing of omadacycline in patients. "

The FDA QT Interdisciplinary team reviewer concluded that within the therapeutic exposure level, omadacycline does not block hERG channels directly and is associated with low pro-arrhythmia risk.

The QT-IRT team also provided suggestions for labeling as follows:
"The evidence from the nonclinical and clinical data indicate a lack of clinically relevant QTc prolongation at the maximum recommended dose of omadacycline."

9.7.11. Analysis of Submission-Specific Safety Issues

Imbalance in mortality in CABP trial was of particular concern in this submission, which is discussed in section 9.1.4.

9.7.12. Safety Analyses by Demographic SubgroupsThe purpose of this section is to provide analyses of safety information for demographic interactions (e.g., age, sex, racial and ethnic subgroups). Various methods and analyses may be used to explore the effect of possible interactions on safety signals/events. For many applications, individual trials are not adequately powered to reach conclusions regarding the safety among the demographic subgroups (sex, race, and age); although pooled analyses, where appropriate, will have greater power, interpretations about the subgroup data should be made with caution. Nonetheless, these analyses, where feasible should be performed, and tables or other graphical representations (e.g., forest plots) should be included. An explanation of the selection of the covariates used in pooled analyses to explore the effect of possible interactions on safety issues/events, including both the approach to the required analyses of the effect of age, sex, and race (21 CFR 314.50(d)(5)(vi)(a)), other analyses (e.g., ethnicity, geographic region) and population used in the analyses should be included.

Gender

In a pooled analysis of 178 women and 435 men participating in clinical studies, there was a small decrease in the clearance of omadacycline in women. However, no notable differences in TEAEs were observed in the omadacycline group between males and females.

Age

No significant differences in pharmacokinetics were observed between healthy elder patients

(n=12, age 65 to 77 years) and younger patients (n=12, age 20 to 43 years) receiving a single oral dose of 50-mg or 200-mg of omadacycline.

Across phase 3 trials, omadacycline patients who reported at least 1 TEAE was comparable between all age groups. The most notable events between omadacycline patients aged 18 to 65, > 65 to 75, and > 75 years of age for any treatment group were nausea, which occurred in the slightly higher percentage of omadacycline patients 18 to 75 years of age versus who were > 75 years of age.

Clinical Reviewer's Comments: Although higher mortality and lower cure rates were observed in patients >65 years of age in CABP trial, review of non-fatal adverse events indicates that increased age does not correlate with a higher rate of adverse events.

Racial or Ethnic Groups

Population pharmacokinetic analysis, which included 12 Asian patients, 105 Black patients, 433 White patients, and 63 patients classified as "other" was performed across studies. No significant influence of race on the pharmacokinetics of omadacycline was found. Across phase 3 trials, omadacycline patients who reported at least 1 TEAE was similar between patients who were non-white than those who were white (61% versus 46%, respectively).

Clinical Reviewer's Comments: There were similar rates of TEAEs other than nausea amongst different racial groups in omadacycline -treated patients and comparator-treated patients. However, it should be noted that minorities represented less than 10% of the total safety population. Thus, firm conclusions regarding a possible interaction of race and safety cannot be determined based on this data.

Body Mass Index

No differences in safety were observed between different BMI categories across phase 3 trials.

History of Diabetes

Other than some differences in the frequency of the TEAEs of nausea and vomiting, only 1 notable difference was observed between patients with or without a history of diabetes in the omadacycline group. TEAEs of diarrhea was reported by a higher percentage of patients with a history of diabetes (11%) than those without diabetes (3%) in the pooled ABSSSI trials.

History of Liver Disease

Hepatic impairment does not impact omadacycline elimination. No apparent trend of omadacycline exposures was observed for both intravenous and oral administration routes in patients with varying degrees of hepatic impairment.

Creatinine Clearance

Other than some differences in the frequency of the TEAEs of nausea and vomiting, few notable differences or consistent trends were observed between patients by the rate of creatinine clearance in the omadacycline group. TEAEs of 'wound infection' was reported by higher percentages of omadacycline patients (9.5%) with the lowest creatinine clearance (< 60 mL/min) than those with higher clearance (1.6% for patients with CrCL 60 to 89 mL/min; and 4.5% for patients with CrCL > 89 mL/min) in the ABSSSI trials.

History of Asthma/COPD

The percentage of patients who had at least 1 TEAE was higher in omadacycline patients with a history of asthma/COPD (57%) compared to patients without a history of asthma/COPD (37%). TEAEs of nausea, vomiting, and constipation occurred in the higher percentage of patients with a history of asthma/COPD compared to patients without a history of asthma/COPD across phase 3 trials.

By Geographical Region

Adverse events were reported more frequently in omadacycline patients enrolled in the US and Rest of World (55% and 54%, respectively) compared to omadacycline patients in Eastern Europe (32%). The most notable events between omadacycline patients by geographic region were nausea and vomiting.

9.7.13. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There are no concerns with human carcinogenicity with omadacycline, given its antibacterial class and short treatment duration. There are no human data available for carcinogenicity or tumor development with omadacycline.

Clinical Reviewers' Comment: Based on the available data from all Phase 3 trials, there is no clinical evidence of carcinogenicity for the omadacycline. In CABP trial, eight (8) patients in omadacycline group and ten (10) patients in moxifloxacin comparator group in overall safety population, experienced an event within the SOC of Neoplasms, Benign, Malignant, and Unspecified. No events from this SOC were reported in ABSSSI trials. Majority of patients (7 of 8) in omadacycline group had lung neoplasms, and 1 patient was reported to have a thyroid neoplasm during the study period. None of the events were considered related to the study drug.

Human Reproduction and Pregnancy

Animal studies indicate that administration of omadacycline during the period of organogenesis resulted in a fetal loss and congenital malformations in pregnant rats and rabbits at 7 times and

3 times the mean AUC exposure, respectively, of the clinical IV dose of 100-mg and the oral dose of 300-mg.

In the omadacycline clinical trials, all women of child-bearing age were required to have a negative serum or urine pregnancy test before enrollment and were required to use contraception for the duration of the study period. No human studies have investigated the potential effects of omadacycline during pregnancy and lactation. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects is 2-4% and of miscarriage in clinically recognized pregnancies is 2 to 4% and 15-20%.

Clinical Reviewers' Comment: One patient in the ABSI16301 trial was discovered to have a positive pregnancy test which was reported on Study Day 2. The patient was immediately discontinued from the study drug and was started on an antibacterial regimen of amoxicillin 500 mg po twice a day to treat the primary ABSSSI. On Study Day 17, the patient reported that she has voluntarily terminated the pregnancy via an elective abortion. There were no TEAEs reported for this patient.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Omadacycline has no known potential for abuse or dependence. No specific information is available on the treatment of overdose with omadacycline. Intravenous administration of omadacycline at a single dose of 600 mg over 60 minutes (equivalent exposure to an oral 1,800 mg dose) in healthy volunteers resulted in no SAEs. In single dose IV toxicity studies conducted with omadacycline in rats, the estimated maximum tolerated dose was 25 mg/kg in males and 25 mg/kg in females. If an overdose occurs, treatment is supportive.

9.7.14. Safety in the Post Market Setting

Safety Concerns Identified Through Post Market Experience

Not applicable.

9.8. Integrated Assessment of Safety

The safety of IV and oral omadacycline for treatment of ABSSSI and CABP was evaluated primarily in the safety data from 1,073 patients treated in two adequate and well-controlled, double-blind Phase 3 clinical trials in ABSSSI and a single adequate and well- controlled, double-blind Phase 3 trial in CABP. The Phase 3 pooled data included a total of 705 patients who received a IV-oral omadacycline regimen, in each targeted indication, as well as 368 patients who received the oral-only omadacycline regimen for the treatment of ABSSSI. Important safety information was also obtained from 22 Phase 1 clinical trials, one Phase 2 and one Phase 3 trial in cSSSI.

The patient population was comparable and balanced between the study treatment groups in all phase 3 trials. The range of underlying comorbidities in the safety population represents that encountered in clinical practice in the U.S. population. There were no significant differences among the treatment groups in terms of gender, race, age, weight or creatinine clearance in the patients. The bulk of the safety database is comprised of white men less than 65 years of age in the phase 3 ABSSSI trials, while, over 40% of patients in the CABP trial were >65 years of age. About 20% of patients had creatinine clearance < 60 mL/min in both treatment arms in the CABP trial as compared to 3% of patients in the pooled ABSSSI trials.

Relative to the comparators, omadacycline has an acceptable safety profile in terms of non-fatal AEs. Adverse events related to study drug and discontinuation of study drug due to any AEs were similar between the treatment groups. The non-fatal severe AEs and common AEs were in general similar in the ABSSSI and CABP trials, with notably increased frequency of vomiting and nausea in the omadacycline treatment group in the ABSSSI trials (especially in ABSI-16301, oral only trial), and infusion site reactions (especially infusion site extravasation) in the omadacycline treatment group in the IV to oral switch study (Study ABSI-1108). All infusion site reactions were mild or moderate in intensity. Interestingly, such infusion site reactions did not occur in the IV to oral switch in the CABP-1200 trial. One possible explanation is that Study ABSI-1108 consisted of a high proportion of patients with an underlying history of IV drug use, and the infusion site reactions might be related to venous access. Most adverse reactions were mild to moderate in severity. The most common adverse reactions that led to study drug discontinuations were from the SOC of 'Infection and infestations' in all three Phase 3 trials, and the majority of those adverse reactions were worsening of index infection under study (either ABSSSI or CABP). These patients were recorded as treatment failures in the efficacy analyses.

Overall, there were no clinically significant adverse event trends in vital signs. In standard radiolabeled ligand binding assays, omadacycline was shown to inhibit binding of H-scopolamine to the M2 subtype of the muscarinic acetylcholine receptor. In the heart, muscarinic M2 receptors serve as mediators of the parasympathetic input that normally is received via the vagus nerve and stimulation of the receptor increases membrane potassium

conductance through the acetylcholine-dependent channel, which slows depolarization and reduces pacemaker activity in the sinoatrial node. An increase in heart rate was observed in healthy volunteers randomized to receive omadacycline in phase 1 studies and in a thorough QT (TQT) study, which was dose-dependent and transient, such increase in heart rate was not seen in phase 3 clinical trials and hence clinical implication of this finding in not known.

There were 17 deaths reported in the omadacycline clinical development program, which included one death in Study CSSI-0804 (cSSSI), in the omadacycline arm on study day 35 due to metastatic lung cancer. Three (3) deaths occurred (one in the omadacycline and two in the linezolid arm) in ABSSSI IV to oral switch trial, and 1 death occurred in the linezolid group 94 days after the end of treatment in ABSSSI oral only trial. Twelve (12) deaths occurred in the CABP trial (8 in the omadacycline group, and 4 in the moxifloxacin group, which included 1 patient who died on day 71 due to metastatic pancreatic cancer in the moxifloxacin treatment group).

In the CABP trial, the 30-day all-cause mortality was 8 (2.1%) in omadacycline group and 3 (0.8%) in the moxifloxacin group. This mortality imbalance in a randomized controlled trial with a well-balanced trial population between two treatment arms is concerning. The treatment groups were similar with regard to key baseline factors, PORT Risk classification, prior antibacterial therapy, other baseline disease characteristics and risk factors for poor prognosis in CABP. No significant differences in non-fatal adverse events, SAEs or adverse events leading to treatment discontinuations were seen between treatment groups in the CABP trial.

An etiology for the imbalance could not be determined from the available data in this submission. No significant differences in non-fatal adverse events, SAEs or adverse events leading to treatment discontinuations were seen between treatment groups in the CABP trial. Risk factors that were observed to be associated with the mortality were, PORT Risk Class-IV, age > 65 years, underlying COPD/asthma, and diabetes mellitus. Overall, other than an imbalance in mortality, omadacycline for the treatment of CABP appears to have a favorable safety profile, and it is plausible that the findings of mortality imbalance, favoring comparator group, could be a chance observation in this single trial. The strength of the association between the risk of mortality with omadacycline treatment is not fully established. However, given the slight reduction observed in efficacy in some key subgroups, a deficit in the efficacy of the tetracycline class of antibacterial drugs with regard to certain serious infections such as hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia it is also possible that this finding reflects a true finding and is related to potentially lower efficacy of omadacycline. Labeling for tigecycline, a tetracycline includes a Boxed Warning regarding the increased risk of mortality seen in a meta-analysis of clinical trials that included a variety of infections.

The Applicant will be required to conduct a post marketing clinical trial to further characterize the risk of mortality. Additionally, to further ensure the safe use of the drug, labeling will include a warning regarding the finding of imbalance in mortality and patients' risk factors that were found to be associated with the mortality in the trial. The second adequate and well-controlled

CABP trial could help in further characterization of the mortality imbalance seen in Study CABP1200.

10. Advisory Committee Meeting and Other External Consultations

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on August 8, 2018.

Please see the transcript for details of the committee discussion.

ABSSSI:

The committee discussed and voted whether the information in the NDAs demonstrated the safety and efficacy of omadacycline for the treatment of acute bacterial skin and skin structure infections. Seventeen (17) members voted "yes" that safety and efficacy had been demonstrated, with one member who voted "no".

These committee members who voted "yes" noted that omadacycline met its non-inferiority margin to linezolid for ABSSSI with two randomized controlled trials. Committee members agreed that it is desirable to have a new intravenous to oral option for this indication and that the potential gastrointestinal side effects are manageable. One member recommended additional studies of pharmacokinetics regarding safety and tolerability in children. Regarding labeling, due to few patients having bacteremia, and lower cure rates in comparison to the comparator observed in patients with bacteremia in intravenous to oral switch ABSSSI trial, committee members suggested that the indication should not include patients with concurrent bacteremia. Some committee members expressed concern about a few elderly patients in the ABSSSI trials and should be noted in labeling. It was also mentioned that the label should include information about the detailed mortality signal from the community acquired bacterial pneumonia (CABP) trial. The one member that voted "no," noted concerns with the ABSSSI trial population being younger than what might be used in clinical practice, and that given the CABP trials showed a potential safety signal in the elderly that this might be seen in clinical practice when treating ABSSSI.

CABP:

The committee discussed and voted whether the information in the NDAs demonstrated the safety and efficacy of omadacycline for the treatment of acute bacterial skin and skin structure infections. Fourteen (14) members voted "yes" and four (4) voted "no".

The committee members who voted "yes" that safety and efficacy had been demonstrated in CABP trial, noted that omadacycline met the regulatory requirements to show non-inferiority to

moxifloxacin for the treatment of CABP. It was questioned whether the 8/3 mortality of omadacycline/moxifloxacin was a statistical variance in the trial by chance alone. Most committee members shared the concern about the potential increased risk, but some also suggested that deaths were to be expected among CABP patients and were reassured that there was no common mechanism among the deaths reported. Committee members noted that mortality rates observed in the omadacycline group were in line with mortality rates observed in other randomized trials conducted in CABP. It was noted that the risk factors for mortality appeared to be in older patients with greater disease severity. Nearly all members suggested a post-marketing evaluation to answer the mortality questions as well as gather more information on specific subgroups including those with bacteremic pneumonia and individuals with higher PORT scores. The committee members recommended postmarketing evaluations to further examine the safety signal of mortality. Those that voted "NO", agreed that efficacy of omadacycline had been established in CABP, but were concerned with the safety signal. One committee member was concerned about the non-adrenergic and vagolytic effect of omadacycline and increased heart rate that was observed in non-clinical and healthy volunteer studies. One member was concerned that three deaths occurred very early in the study. There was also concern about patients that were critically ill, the elderly and those with comorbidities. One committee member was concerned that that the oral formulation of omadacycline as a loading dose would be hard to restrict use in the post-market setting. Another committee member noted concerns regarding omadacycline effectiveness in patients with polymicrobial infection.

11. Pediatrics

The safety and effectiveness of omadacycline in pediatric patients (younger than 18 years of age) has not been studied. The Applicant's request for a partial waiver for the assessment of omadacycline in patients less than 8 years of age will be granted because of the seriousness of adverse reactions observed in tetracycline-class antibacterial drugs in this age group. The Applicant's request for deferral of the assessment in children aged 8 to 17 years for the indications of ABSSSI and CABP will be granted. The planned Pediatric Research Equity Act (PREA) post marketing requirement (PMR) pediatric studies are summarized in section 14. The Pediatric Review Committee (PeRC) agreed with the partial waiver and the Applicant's plan for post marketing evaluation through PREA PMRs, with the evaluation of CABP in children to be initiated after the further evaluation of the mortality safety signal in adults.

12. Labeling Recommendations

12.1. Prescribing Information

Major labeling recommendations or changes are summarized below.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's proposed Labeling**	**FDA proposed Labeling**
Indications and Usage	**1.1 Community-Acquired Bacterial Pneumonia** Community-acquired bacterial pneumonia (CABP) caused by the following: Gram-positive, Gram-negative, and atypical microorganisms: *S. pneumoniae* (penicillin-susceptible and -resistant isolates, macrolide-susceptible and resistant isolates and tetracycline susceptible- and resistant isolates), including cases with concurrent bacteremia, *S. aureus*, *H. influenzae*, *H. parainfluenzae*, *E. coli*, *K. pneumoniae*, *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*. 1.**2 Acute Bacterial Skin and Skin Structure Infections** ABSSSI caused by the following susceptible microorganisms: *S. aureus* (methicillin-susceptible and -resistant isolates), *S. lugdunensis*, *S. pyogenes, S. agalactiae, S. anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus), S. mitis, E. faecalis, E. cloacae, E. coli, K. pneumoniae, Clostridium perfringens, Prevotella denticola, Prevotella melaninogenica, and Finegoldia magna*.	**1.1 Community-Acquired Bacterial Pneumonia** NUZYRA is indicated for the treatment of adult patients with CABP caused by the following susceptible microorganisms: *S. pneumoniae*, *S. aureus* (methicillin-susceptible isolates), *H. influenzae, H. parainfluenzae, K. pneumoniae, L. pneumophila, M. pneumoniae, and C. pneumoniae.* **1.2 Acute Bacterial Skin and Skin Structure Infections** NUZYRA is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by the following susceptible microorganisms: *S. aureus* (methicillin-susceptible and -resistant isolates), *S. lugdunensis*, *S. pyogenes, S. anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *E. faecalis*, *E. cloacae.* and *K. pneumoniae.*
Warnings and Precaution	(b) (4) •The use of NUZYRA during tooth development may cause permanent discoloration of the teeth. (5.2)	**----------WARNINGS AND PRECAUTIONS----------** • Mortality Imbalance in Patients with CABP: In the CABP trial, mortality rate of 2% was observed in NUZYRA-treated patients compared to 1% in moxifloxacin-treated patients. The cause of the mortality imbalance has not been established. Closely monitor clinical response to therapy in CABP patients, particularly in those at higher risk for mortality. (5.1, 6.1) • Tooth Discoloration and Enamel Hypoplasia: The use of NUZYRA during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia. (5.2, 8.1, 8.4) • Inhibition of Bone Growth: The use of NUZYRA during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth. (5.3, 8.1, 8.4). • *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs. (5.5)

Adverse Reactions	**----------ADVERSE REACTIONS-----** **The most common adverse reactions (incidence ≥ 2%) are nausea, and vomiting. (6.1)**	**----------ADVERSE REACTIONS------** The most common adverse reactions (incidence ≥2%) are nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation. (6.1)
Drug Interactions	(b) (4) [redacted]	**----------DRUG INTERACTIONS----------** • Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage while taking NUZYRA. (7.1) • Absorption of tetracyclines, including NUZYRA is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron containing preparations. (2.1, 7.2)
Highlights of Prescribing Information	EPC – (b) (4) [redacted]	**Changed EPC to "tetracycline class antibacterial"**
Sections 8.1, 8.3		**Class labeling wording added** **Clarified or added nonclinical data** **Clarified source and applicability of nonclinical AUC data used for exposure multiples.**
Sections 13.1, 13.2		**Clarified or added nonclinical data** **Clarified source and applicability of nonclinical AUC data used for exposure multiples.** **Addition of drug class information from approved tetracycline class label**
Section 12.2 Pharmacodynamics	**12.2 Pharmacodynamics** Cardiac Electrophysiology (b) (4) [redacted]	**12.2 Pharmacodynamics** **Cardiac Electrophysiology** Based on the nonclinical and clinical data, including electrocardiogram evaluation in the phase 3 clinical trials, one of which had moxifloxacin as a control group, no clinically relevant QTc prolongation was observed at the maximum recommended dose of omadacycline. Cardiac Physiology-Increase in Heart Rate In phase 1 studies conducted in healthy volunteers, transient dose-dependent increases in heart rate have been observed following administration of single and multiple doses of omadacycline. The clinical implication of this finding is unknown *[see Adverse Reactions (6.1)]*. In a standard radiolabeled ligand binding assays, omadacycline was shown to inhibit binding of H-scopolamine to the M2 subtype of the muscarinic acetylcholine receptor. In the heart, muscarinic M2 receptors serve as mediators of the parasympathetic input that normally is received via the vagus nerve and stimulation of the receptor increases membrane potassium conductance through the acetylcholine-dependent channel, which slows depolarization and reduces pacemaker activity in the sinoatrial node.

Section 12.4 Microbiology (Antimicrobial activity was revised based on submitted evidence.)		Antimicrobial Activity Omadacycline has been shown to be active against the following bacteria, both ***in vitro* and in clinical** infections *[see Indications and Usage (1.1, 1.2)]*. Community-Acquired Bacterial Pneumonia (CABP) Gram-Positive bacteria *Streptococcus pneumoniae* *Staphylococcus aureus* (methicillin-susceptible isolates) Gram-Negative bacteria *Haemophilus influenzae* *Haemophilus parainfluenzae* *Klebsiella pneumoniae* Other microorganisms *Chlamydophila pneumoniae* *Legionella pneumophila* *Mycoplasma pneumoniae* Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Gram-Positive bacteria *Enterococcus faecalis* *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates) *Staphylococcus lugdunensis* *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*) *Streptococcus pyogenes* Gram-Negative bacteria *Enterobacter cloacae* *Klebsiella pneumoniae*
Section 14. Clinical Studies		Clinical Studies section was modified from Sponsor's originally proposed language.
Section 17. Patient counselling information	**17 PATIENT COUNSELING INFORMATION** Allergic Reactions Advise patients…… Ask the patient about any previous hypersensitivity reactions to (b) (4) or other tetracycline class antibacterials *[see Warnings and Precautions (5.4)]*. Administration with Food Instruct patients to fast (b) (4) hours before and 2 hours after taking (b) (4) tablets and not to consume dairy products, antacids, or multivitamins for 4 hours after taking (b) (4) tablets *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*. (b) (4) Advise patients that antibacterial drugs	**17 PATIENT COUNSELING INFORMATION** Nausea and Vomiting Advise patients that nausea and vomiting can be an adverse reaction to NUZYRA. Advise patients that a greater proportion of patients who received the oral loading dose of NUZYRA for treatment of ABSSSI experienced nausea and vomiting. Allergic Reactions Advise patients that allergic reactions, including serious allergic reactions, could occur and that serious allergic reactions require immediate treatment. Ask the patient about any previous hypersensitivity reactions to NUZYRA, or other tetracycline class antibacterials *[see Warnings and Precautions (5.4)]*. Administration with Food Instruct patients to fast 4 hours before and 2 hours after taking NUZYRA tablets and not to consume dairy products,

	including (b) (4) should only be used to treat bacterial infections. ….. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by (b) (4) or other antibacterial drugs in the future. Diarrhea Advise patients that diarrhea is a common problem caused by (b) (4) which usually ends when the (b) (4) is discontinued. Sometimes after starting treatment with (b) (4) patients can develop watery or bloody stools (with or without stomach cramps and fever). If this occurs, patients should contact their physician as soon as possible.	antacids, or multivitamins for 4 hours after taking NUZYRA tablets *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*. Tooth Discoloration and Inhibition of Bone Growth Advise patients that NUZYRA, like other tetracycline-class drugs, may cause permanent tooth discoloration…… your healthcare provider right away if you become pregnant during treatment *[see Warnings and Precautions (5.1, 5.2) and Use in Specific Populations (8.1, 8.4)].* Lactation Advise women not to breastfeed during treatment with NUZYRA and for 4 days after the last dose *[see Use in Specific Populations (8.2)]* Diarrhea Advise patients that diarrhea is a common problem caused by antibacterial drugs, including NUZYRA, which usually ends when the antibacterial drugs is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery or bloody stools (with or without stomach cramps and fever). If this occurs, patients should contact their physician as soon as possible. Tetracycline Class Adverse Reactions Inform patients that NUZYRA is similar to tetracycline-class antibacterial drugs and may have similar adverse reactions *[see Warnings and Precautions (5.6)]*. 13. Antibacterial Resistance Advise patients that antibacterial drugs including NUZYRA should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When NUZYRA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by NUZYRA or other antibacterial drugs in the future.

Refer to NUZYRA (omadacycline) prescribing information for details.

12.2. Patient Labeling

Not applicable.

13. Risk Evaluation and Mitigation Strategies (REMS)

Based on the review from Division of Risk Management, a REMS is not recommended.

14. Post marketing Requirements

As discussed previously, the Applicant's request for a deferral of pediatric evaluation in children 8-17 years of age is acceptable. The following are the agreed post marketing requirements and milestone dates:

PMR-1 Conduct a single dose pharmacokinetic and safety study in children ages 8 to 17 years who are receiving antibacterial drug therapy for an infectious disease

Draft Protocol Submission: 05 /2019
Final Protocol Submission: 08 /2019
Study Completion: 12 /2020
Final Report Submission: 05 /2021

PMR-2 Conduct an active-controlled safety study in children 8-17 years who have acute bacterial skin and skin structure infection

Draft Protocol Submission: 11 /2020
Final Protocol Submission: 02 /2021
Study Completion: 12 /2023
Final Report Submission: 05 /2024

PMR-3 Conduct an active-controlled safety study in children 8-17 years who have community-acquired bacterial pneumonia

Draft Protocol Submission: 03/2023
Final Protocol Submission: 06/2023
Study completion: 12/2025
Final Report Submission: 03/2026

The safety signal of the mortality imbalance in the CABP trial will be further evaluated in a prospective, (b) (4) *controlled trial in CABP. The trial should have adequate power to ascertain the significance of the safety signal. In this case, a trial conducted in a manner identical to Study CABP-1200, with approximately 390 patients per treatment group of patients with PORT III/IV baseline disease severity scores, will yield a statistically significant finding if the pre-specified mortality imbalance of 8 deaths in the omadacycline group and 3 deaths in the control group are observed. In this case, the findings of the mortality imbalance will be a true*

finding. An observation of a more balanced mortality between treatment groups in a second trial will provide reassurance that the mortality imbalance observed in Study CABP-1200 was a chance finding, but additional post marketing evaluations to evaluate mortality will be needed in this setting, such as routine pharmacovigilance monitoring. It should also be noted that this trial can be designed to evaluate the oral loading dose in patients with CABP, for example, by evaluation of PK data in a subgroup of patients.

At the PeRC discussion in August 2018, it was recommended that the initiation of pediatric study in CABP should follow the completion and evaluation of all-cause mortality in the 505 (o) safety PMR trial to be conducted in adults with CABP. The following is the 505(o) Safety PMR and milestone dates:

PMR-4 Conduct an active-controlled safety and efficacy trial in adults with community-acquired bacterial pneumonia

Draft Protocol Submission: 01 /2019
Final Protocol Submission: 03 /2019
Study completion: 11/2022
Final Report Submission: 04 /2023

The following 505(o) safety PMR is designed to evaluate the important safety signal of the development of resistance to omadacycline:

PMR-5 Conduct a United States surveillance study for five years from the date of marketing (b) (4) to determine if resistance to omadacycline has developed to those organisms specific to (b) (4) indications in the label

Final protocol submission: December 2018
First study report: May 2020
Second study report: May 2021
Third study report: May 2022
Fourth study report: May 2023
Fifth study report: May 2024
Study completion date: December 2023
Final report submission date: May 2024

The Applicant notes that each of the interim reports for PMR-5 will be cumulative over time. As such, the fifth interim report will be cumulative for all 5 years and will serve as the final report.

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15. Appendices

15.1. Nonclinical Pharmacology/Toxicology Appendices

None

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

15.2.1. Summary of Bioanalytical Method Validation and Performance

Validated LC/MS/MS (liquid chromatography with tandem mass spectroscopy) methods were used for quantification of omadacycline in human plasma, urine, dialysate, bronchial alveolar lavage (BAL) fluid & BAL cellular pellets. The analytical method validation and performance are acceptable.

Dilution integrity was verified within each clinical pharmacology study when sample dilutions were performed. The sample preparation, stability, analysis accuracy, and precision in each clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and are deemed to be acceptable.

15.2.2. Population PK/PD Analysis

Applicant conducted population PK analysis for omadacycline using data from ten Phase 1 studies. The model described omadacycline plasma PK profiles following single and multiple doses of both IV and oral omadacycline. The model was then updated with data from three Phase 1 studies, 1 Phase 1b study, and 3 Phase 3 studies. Among these additional Phase 1 studies, the first study evaluated omadacycline PK in renally impaired patients (Study PTK0796-RENL-15102). The second study evaluated omadacycline pulmonary penetration (Study PTK0796-BAL-15104). The third study assessed high doses of the tablet formulation utilized in Phase 3 studies (Study PTK0796-MDPO-16105). The data from Phase 1b uUTI study (Study PTK0796-UUTI-15103), two Phase 3 ABSSI studies (Studies PTK0796-ABSI-1108 and Study PTK0796-CSSI-0804P), and a Phase 3 CABP study (PTK0796-CABP-1200) were used to update the Population PK model. The Applicant used the Phase 3 ABSSSI study PTK0796-ABSI-16301 for external validation of the population PK model.

Description of data used in population PK analysis by the Applicant

The final analysis dataset used by the Applicant consisted of 11331 plasma PK samples collected from a total of 613 subjects. Most of the plasma concentrations (88.4%), were collected from Phase 1 studies. Of the 613 subjects, 180 (29.4%) were enrolled in Phase 3 studies, 31 (5.0%) were enrolled in the Phase 1b uUTI study, and the remaining subjects were enrolled in Phase 1 studies. Compared to the dataset used to develop the original population PK model, 3772 (33.3%) of the plasma concentrations and 294 (48.0%) subjects were new. In addition to the plasma concentrations, ELF concentrations were also available from Study PTK0796-BAL-15104. A total of 41 BAL samples were collected from 41 subjects. All samples were above the lower limit of quantification and all were included in the final analysis. Summary statistics of baseline subject descriptors for the overall PK analysis population are presented in Table 15-1. The analysis population was 71.0% male and 70.6% Caucasian. The mean (SD) age was 39.3 (14.8)

years and weight was 78.4 (14.6) kg. The population contained overweight and obese subjects, as evidenced by a BMI median of 25.6 kg/m^2 (overweight) and a maximum BMI of 49.3 kg/m^2 (obese). The mean (SD) CLcr value was 99.8 (28.1) mL/min/1.73 m^2 and CLcr ranged from 5.5 to 185 mL/min/1.73 m^2. Of the 613 subjects, 211 (34.4%) had an infection (either a skin infection, CABP infection, or a uUTI).

Table 15-1 Summary statistics of subject demographics, clinical laboratory measures, and disease-related indices for the overall PK analysis population.

Variable		N (%)	Mean (SD)	Median	Minimum	Maximum
Age (yr)		613	39.3 (14.8)	37.0	18	88
Weight (kg)		613	78.4 (14.6)	77.5	36.0	148
Height (cm)		613	173 (9.2)	174	137	201
BSA (m^2)		613	1.92(0.19)	1.92	1.25	2.73
BMI (kg/m^2)		613	26.2 (4.5)	25.6	16.0	49.3
CLcr (mL/min/1.73 m^2)		613	99.8 (28.1)	113	5.5	185
Albumin (mg/dL)		613	4.33 (0.46)	4.40	2.20	5.30
Race	Caucasian	433 (70.6)	—	—	—	—
	Black	105 (17.1)	—	—	—	—
	Asian	12 (2.0)	—	—	—	—
	Other	63 (10.3)	—	—	—	—
Sex	Male	435 (71.0)	—	—	—	—
	Female	178 (29.0)	—	—	—	—
Presence of cirrhosis	No	595 (97.1)	—	—	—	—
	Yes	18 (2.9)	—	—	—	—
Presence of infection	No	402 (65.6)	—	—	—	—
	Yes	211 (34.4)	—	—	—	—
Presence of skin infection	No	483 (78.8)	—	—	—	—
	Yes	130 (21.2)	—	—	—	—
Presence of CABP infection	No	563 (91.8)	—	—	—	—
	Yes	50 (8.2)	—	—	—	—
Presence of uUTI	No	582 (94.9)	—	—	—	—
	Yes	31(5.1)	—	—	—	—

Source: Applicant's population PK report, Table 4, Page 47.

Methods

The population PK analysis was performed in NONMEM 7.3. A linear, three compartment model with zero-order IV input, or first-order oral absorption with transit compartments to account for the apparent delay in oral absorption, best described the time-course of omadacycline in plasma following both IV and PO administration. Data from Study PTK0796-BAL-15104 was used to characterize the time-course of omadacycline in ELF when updating the structural model. Various ELF models were evaluated, which included ELF as a separate biophase compartment, a sub-compartment of peripheral compartment 1 (Vp1), and a sub-compartment of peripheral compartment 2 (Vp2). The ELF model that best described the ELF data was included in the structural model moving forward. Figure 15-1 shows the basic structure of the population PK model.

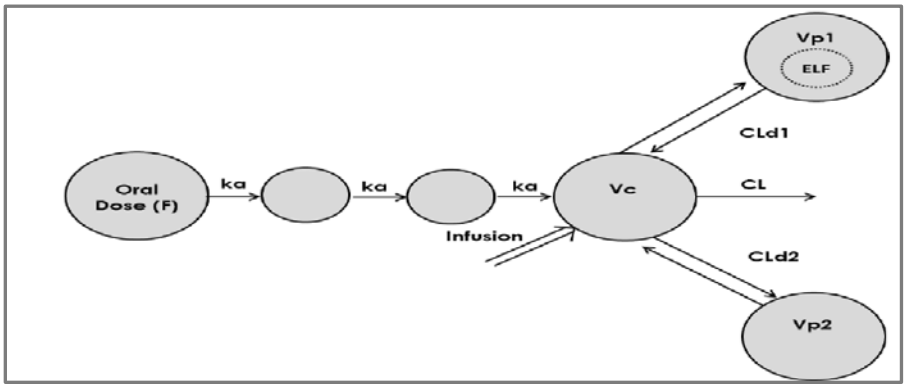


Figure 15-1. Illustration of the base structural population PK model for omadacycline.
Source: Applicant's population PK report, Figure 1, Page 37.

The Applicant conducted a covariate search using stepwise forward selection. These covariates are summarized in Table 15-1. All parameter-covariate relationships for continuous covariates were centered on the median covariate value. Model qualification was through performing prediction-corrected visual predictive check (PC-VPC). In a PC-VPC, the variability coming from binning across independent variables is removed by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin. In addition, the Applicant performed an external validation, using data from Study PTK0796-ABSI-16301.

Results
The final population PK parameter estimates are shown in

Table 15-2. The ability of the final model to describe the population PK of omadacycline as evaluated with PC-VPCis shown in Figure 15-2 to Figure 15-4. The PC-VPCs are acceptable because the observed 90% prediction interval (90% PI) and median from both the model simulated and those observed data are almost identical. The final population PK model was a linear three-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 the tablet or capsule formulations. ELF concentrations were modeled as a sub-compartment of Vp1. These ELF concentrations were estimated in NONMEM as rate of change of concentration of omadacycline, hence concentration of omadacycline at any given time was estimated. In the final model, bioavailability was decreased for all doses of the (b) (4) formulation and for free-base capsules at doses greater than 200 mg. Bioavailability also decreased when administered in the fed condition. This was implemented using the absolute time of food consumption relative to dosing. Bioavailability further decreased when food was administered before oral omadacycline (rather than after) or when the food contained dairy products. Sex was the only significant covariate identified. All ELF parameters were modeled as fixed effects (i.e., no IIV) given that there was only one BAL sample per subject for measuring omadacycline concentration in ELF. The PK parameter estimates for omadacycline during loading dose and maintenance dose are shown in Table below.

Table 15-2 Population PK parameter estimates for the final population PK model.

Parameter	Final estimate	%SEM
CL (L/hr)	10.3	0.682
Proportional change in females	-0.156	12.0
Vc (L)	21.1	2.20
CLd1 (L/hr)	101	2.20
Proportional change in females	0.500	27.6
Vp1 (L)	79.9	0.0842
Proportional change in females	-0.176	16.9
CLd2 (L/hr)	21.3	0.242
Vp2 (L)	129	1.45
Proportional change in females	-0.271	9.45
ka (hr^{-1})	1.74	1.55
F_0	0.00663	4.99
F_{max}	0.252	0.996
Proportional decrease for (b) (4) or freebase capsules > 200 mg	-0.280	21.8
$AMTIME_{50}$ (hr)	0.568	0.0567
Proportional increase for consuming food pre-dose	1.68	8.15
Proportional increase for consuming food w/dairy products pre-dose	3.59	4.48
γ	1.73	0.484
ELF Frac[a]	1.63	5.69
ω^2 for CL	0.0497 (22.3% CV)	7.72
ω^2 for Vc	0.885 (94.1% CV)	10.9
ω^2 for CLd1	0.423 (65.0% CV)	10.8
ω^2 for Vp1	0.0776 (27.9% CV)	10.6
ω^2 for Vp2	0.0759 (27.5% CV)	9.59
ω^2 for F	0.154 (39.2% CV)	5.28
ω^2 for ka	0.0599[b] (24.5% CV)	4.79
IOV for ka	0.0599[b] (24.5% CV)	4.79
IOV for F	0.0495 (22.2% CV)	3.21
Covariance(CL,CLd1)	-0.0415 (r^2 = 0.0819)	23.3
Covariance(CL,Vp2)	0.0258 (r^2 = 0.176)	16.4
$\sigma^2_{CCV, plasma}$	0.0217 (14.7% CV)	0.0399
$\sigma^2_{Additive, plasma}$	0.00145 (0.0381 SD)	0.163
$\sigma^2_{CCV, ELF}$	0.206 (45.4% CV)	24.5
$\sigma^2_{Additive, ELF}$	0.000403 (0.0201 SD)	Fixed

Note: Abbreviations are provided in the Abbreviation Listing.
a. Frac represents a proportionality term allowing for scaling of the amount of omadacycline in the ELF to a true concentration.
b. A single parameter was used to describe both ka IIV and IOV.

Source: Applicant's population PK report, Table 15, Page 82.

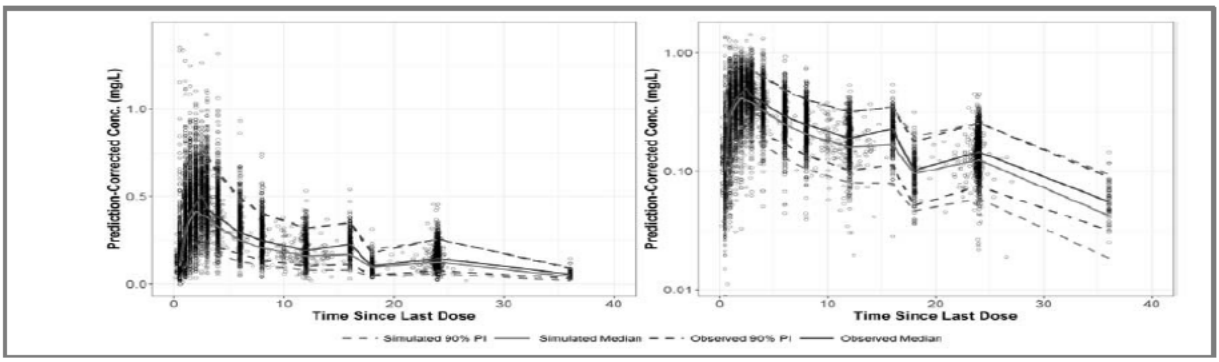


Figure 15-2 Prediction-corrected comparison of observed and simulated omadacycline plasma concentrations.

Source: Applicant's population PK report, Page 89, Figure 19.

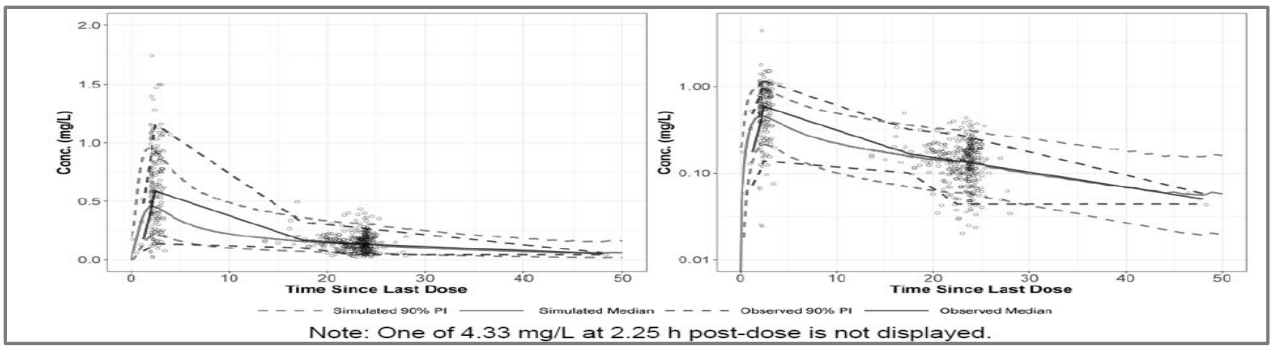


Figure 15-3 Visual predictive check using data following administration of omadacycline 450 mg in Study PTK0796-ABSI-16301 Left panel is under normal scale and right panel is under log-normal scale.

Source: Applicant's population PK report, Figure 21, Page 91.

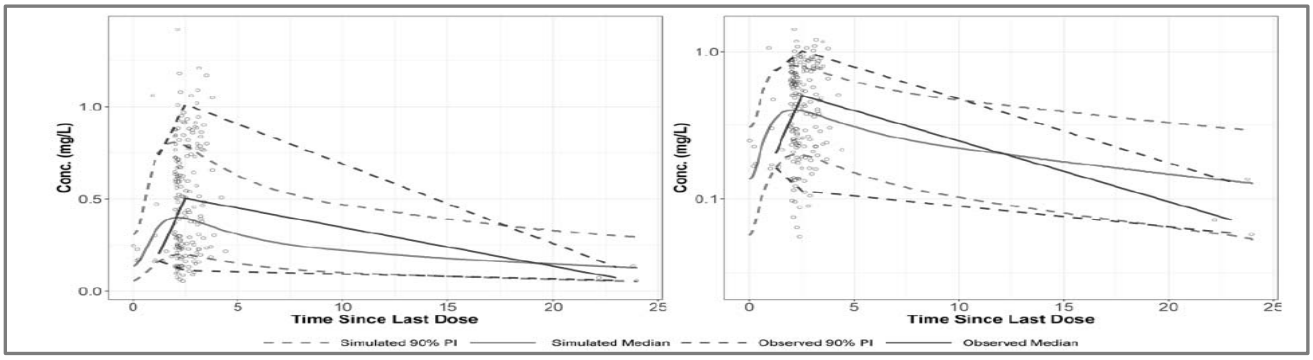


Figure 15-4 Visual predictive check using data following administration of omadacycline 300 mg in Study PTK0796-ABSI-16301. Left panel is under normal scale and right panel is under log-normal scale.

Source: Applicant's population PK report, Figure 21, Page 91.

Table 15-3 Pharmacokinetic parameter estimates of omadacycline stratified by route of administration and dosing period.

Parameter	Intravenous administration with PO switch (N=105)[a]		Oral administration (N=127) [b]	
	Day 1	Day 3	Day 1	Day 3
Geometric mean AUC, mg/L/hr (%CV)	12.2 (26.7)	11.1 (27.7)	9.78 (43.4)	8.81 (37.3)
Geometric mean CL, L/hr %CV)	9.3 (22.3)		11.4 (27.2)	
Geometric mean Vc, L (%CV)	28.3 (55.6)		37.8 (206)	
Geometric mean Vp1, L (%CV)	69.1 (17.0)		74 (17.7)	
Geometric Vp2, L (%CV)	114 (23.3)		122 (22.7)	
Geometric Vss, L (%CV)	211 (24.0)		234 (38.8)	

[a] Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. [b] Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.

Source: FDA analysis.

ELF penetration ratio

The plasma and ELF concentrations for omadacycline are displayed in. The profiles display Day 3 data following administration of omadacycline 100 mg q12h on Day 1 followed by 100 mg IV q24h. ELF concentrations appear to be slightly higher than the plasma concentrations and peak slightly later. The applicant used the final population PK model to determine omadacycline plasma and ELF exposures after 100 mg of omadacycline IV infusion at 0, 12, 24, 48, and 72 hours. Day 3 total-drug plasma exposures ranged from 4.15 to 23.1 mg·h/L with a median of 10.8 mg·h/L. Day 3 total-drug ELF exposures ranged from 6.79 to 37.6 mg·h/L with a median of 17.5 mg·h/L. Using an omadacycline protein binding value of 21%, the total-drug ELF: free-drug plasma penetration ratio was 2.06.

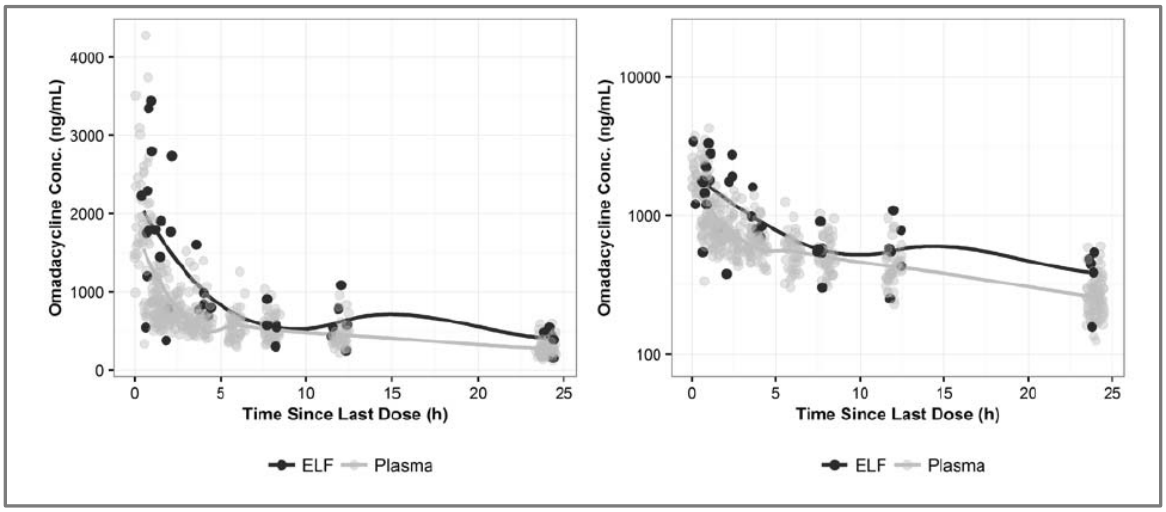


Figure 15-5 Plasma and ELF omadacycline concentration-time data for healthy subjects in Study PTK0796-BAL-15104.

Source: Applicant's population PK report, Figure 3, Page 49.

Effect of renal impairment

Final population PK model did not identify serum creatinine as a significant covariate. Plasma concentration-time profiles following administration of omadacycline 100 mg IV administration in the PTK0796-RENL-15102 study are displayed in Figure 15-6. This study enrolled healthy volunteers and dialysis patients. In the dialysis arm, omadacycline was administered 0 to 2 hours post-dialysis. Profiles are colored according to renal function, where subjects with CLcr values above 90 mL/min are colored grey and subjects on hemodialysis are colored maroon. Profiles are similar for both groups of patients suggesting that renal impairment does not influence omadacycline PK.

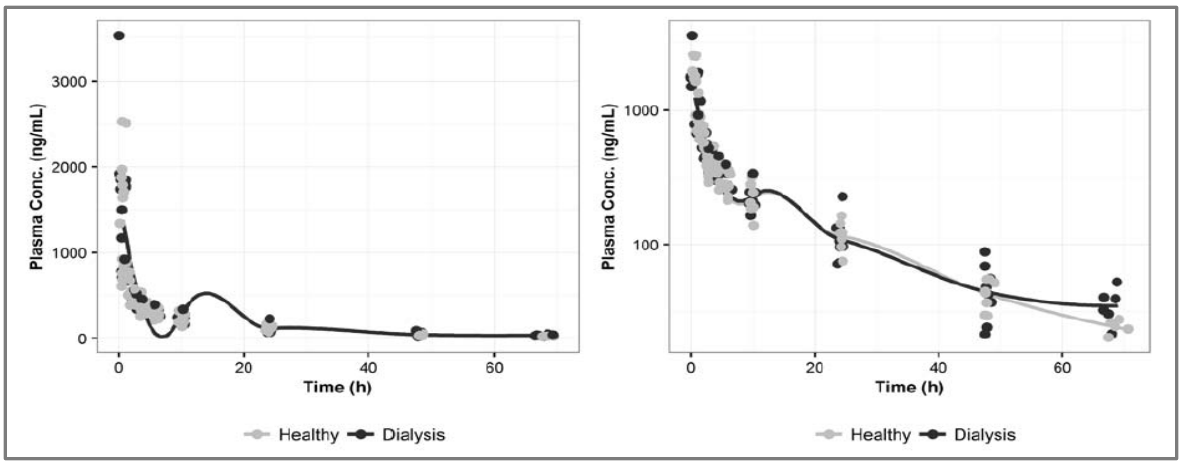


Figure 15-6 Plasma omadacycline concentration-time data for subjects in Study PTK0796-RENL-15102 stratified by renal impairment category.
Source: Applicant's population PK report, Figure 2, Page 48.

Effect of sex
Sex was a statistically significant covariate on multiple parameters. Specifically, the relationships resulted in a 15.6% lower clearance, a 50% higher CLd1, a 17.6% lowerVp1, and a 27.1% lower Vp2 for females relative to males. The applicant conducted simulations of typical male and female subjects using the final model which showed that Cmax was lower by 9%, Cmin higher by 25%, and AUC0-inf was 15.6% higher for females relative to males following IV administration of a single 100 mg omadacycline dose. Similar findings were found for oral administration of the tosylate tablet. Based on the estimates of AUC, no dose adjustment is needed.

Clin-Pharm Reviewer's comment: Applicant's population PK analysis reasonably described the population pharmacokinetics of omadacycline as shown in the visual predictive checks based on the ability of the model's simulated 90% PI and medians to be almost identical to observed 90% PI and medians. The submitted final population PK model is reproducible and FDA reviewer agrees with the identified covariates, which supports applicant's labeling claims. It is worth noting that patient population is not a covariate on PK based on the population PK model. The AUC on Day 3 appears to be lower for PO administration compared to IV administration with PO switch based on proposed dosing regimen by Applicant. The exposure of oral loading dose and IV loading dose was simulated by population PK model in CABP population or generated by non-compartmental analysis in healthy subjects or uUTI patients. Based on the comparison, the exposure of oral loading dose of 450 mg once daily for two days was relatively lower than that of IV loading doses as shown in Figure 15-7.

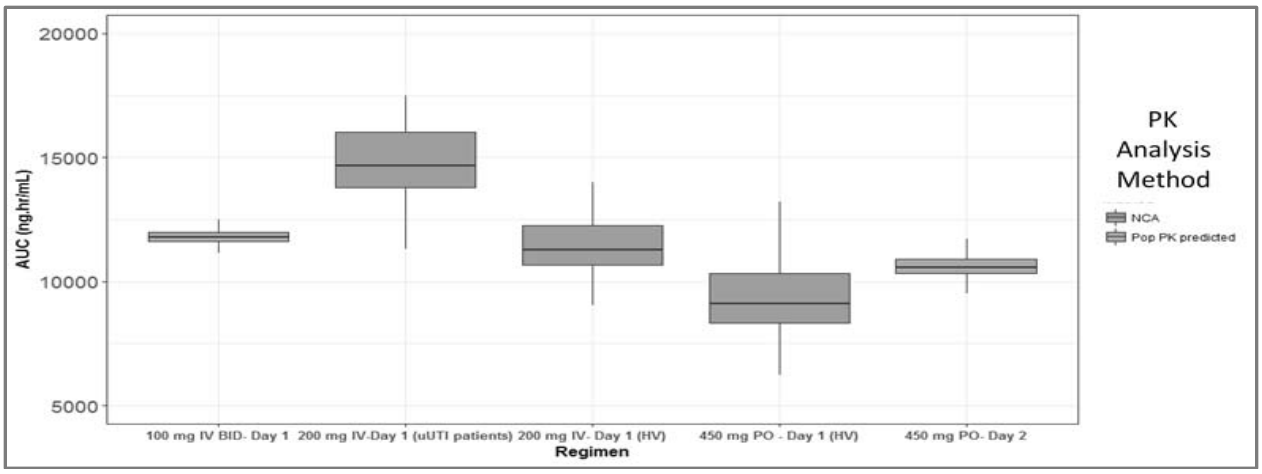


Figure 15-7 Comparison of AUCs following different loading doses for CABP population.
Source: FDA analysis.

15.2.3. Exposure-response analysis

CABP

The Applicant did not conduct exposure-response analysis for CABP due to limited number of evaluable omadacycline-treated patients with CABP that had PK data from Study PTK0796-CABP-1200. Of the 101 and 98 omadacycline-treated patients in the microbiologically evaluable – end of treatment (ME-EOT) and microbiologically evaluable - post-therapy evaluation (ME-PTE) populations of Study PTK0796-CABP-1200 with appropriate source of pathogen and MIC data, only 11 and 10 patients had PK data, respectively. Given the limited number, the Applicant stated that successful clinical and microbiological responses were observed for all patients at EOT and PTE and for all but one patient at Early Clinical Response (ECR). Also, total-drug ELF and free-drug plasma AUC:MIC ratios exceeded nonclinical targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* in the three patients with *S. Pneumoniae* at baseline who had PK data. Among the seven patients with *H. influenzae* or *H. parainfluenzae*, total-drug ELF AUC:MIC ratios exceeded non-clinical targets associated with a 1-$\log_{10}$ CFU reduction for *H. influenzae* for six of the seven patients.

ABSSSI

The PK-PD analyses for efficacy were based on data from patients with sufficient PK data in the ME populations of each study and the subset of patients with *S. aureus* at baseline (n=182 and 128, respectively). The PK-PD results from the Applicant are summarized in Figure 15-8and were included in PTA analysis:

The probability of clinical success at ECR increased as free-drug plasma AUC:MIC ratio increased. At a free-drug plasma AUC:MIC ratio that approached 0, the percent probability of clinical success at ECR was approximately 80%. At a free-drug plasma AUC:MIC ratio of 14.7, the percent probability was 90%.

PK-PD relationships for clinical response at ECR of greater statistical significance were also evident when free-drug plasma AUC:MIC ratio was evaluated as two- and three group variables.

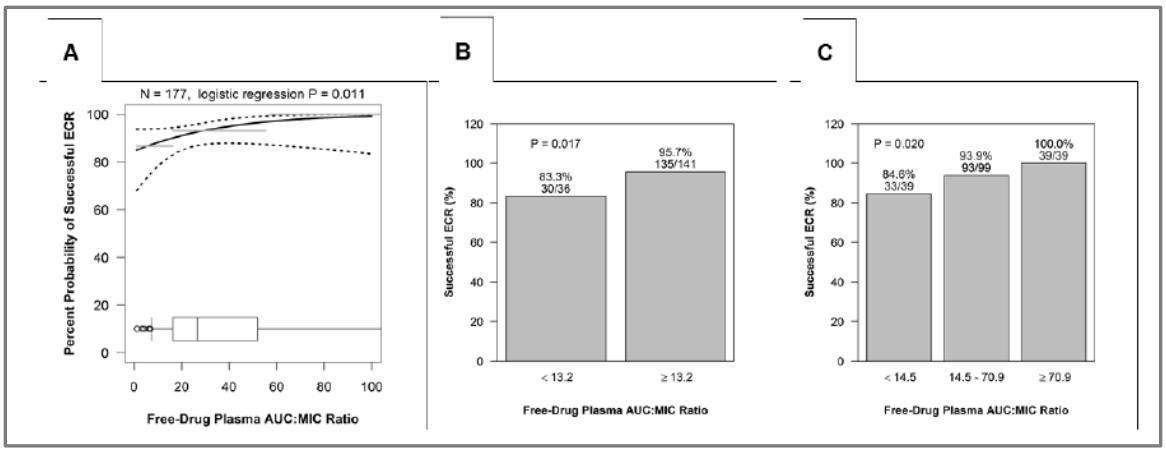


Figure 15-8 Univariable Relationships Between the Percent Probability of a Successful ECR and Free-Drug AUC:MIC Evaluated as a Continuous (A), Two-Group (B), or Three-Group Variable (C) Based on Data from all Patients.

Source: Applicant's summary of Clinical Pharmacology report 3, Figure 31 Page 229.

Clin-Pharm Reviewer's comment: The exposure-response analysis performed by the Applicant is acceptable, the reviewer agrees with conclusions reached by the Applicant.

Pharmacokinetics/Pharmacodynamic Target Attainment Assessment

CABP:

Monte Carlo Simulation to assess probability of target attainment (PTA)

Omadacycline dose fractionation studies performed by the Applicant show that AUC:MIC was correlated to efficacy in an in vitro *H. influenzae* model and a *S. pneumoniae* pneumonia model. The mean AUC/MIC targets associated with 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* using total-drug ELF and free-drug plasma AUCs were 12.3 and 13.6, respectively. For *H. influenza*, the mean in vitro AUC/MIC target associated with 1-$\log_{10}$ CFU reduction from baseline was 8.3. The Applicant conducted the PTA analysis based on AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* and *H. influenza* using ELF derived from the population PK model. The Applicant used AUC:MIC ratio targets which were randomly assigned based on an estimated log normal distribution of AUC:MIC ratio targets. The FDA reviewer conducted an analysis using both free-drug plasma AUC and total-drug ELF AUC of omadacycline derived from population PK model, and corresponding mean AUC/MIC targets.

S. pneumoniae

Table 15-4 show Applicant's PTA results while Table 15-5 and

Table **15-6** summarizes the results by FDA reviewer, for *S. pneumoniae*. The FDA reviewer and the Applicant's results are comparable when total-drug ELF is used. Using free-drug plasma AUC, the FDA reviewer found that the percent probabilities of PK-PD target attainment for *S. pneumoniae* ≥ 90% at a MIC value of 0.12 µg/mL were achieved for both IV to PO and PO dosing regimens. (b) (4)

Table 15-4 Percent Probabilities of PK-PD Target Attainment by MIC and Overall Based on Randomly Assigned Total-Drug ELF AUC:MIC Targets Associated with a 1-log_{10} CFU Reduction from Baseline for *S. pneumoniae* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens[a].

MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC[b]			
	IV to PO dosing regimen			PO dosing regimen
	100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Days 2-3 with a PO switch to 300 mg PO q24h on Days 3 or 5			450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3
	Days 1 to 2[c]	Day of PO switch[d]		Days 1 to 2[c]
		Day 3	Day 5	
0.12	100	100	100	100
0.25	100	99.9	99.8	98.9
0.5	99.3	95.5	94.1	89.5
1	82.9	67.9	63.8	59.5

Shaded cells indicate percent probabilities of PK-PD target attainment ≥90%.

a. A total-drug ELF AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline for *S. pneumoniae* based on a neutropenic murine lung-infection model was randomly assigned based on an estimated log normal distribution of PK-PD targets associated with the same endpoint.

b. Shaded cells indicate PK-PD target attainment values ≥90%.

c. Based on the assessment of average total-drug ELF AUC_{0-24} on Days 1 and 2.

d. Based on the assessment of total-drug ELF AUC_{0-24} for the day of the PO switch.

Source: Applicant's summary of Clinical Pharmacology 3, Table 121, Page 217

Table 15-5 Percent Probabilities of PK-PD Target Attainment by MIC Based on total-drug ELF AUC:MIC Targets Associated with a 1-log_{10} CFU Reduction from Baseline for *S. pneumoniae* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
0.12	100	100	100	100
0.25	100	100	100	99.0
0.5	99.9	97.1	93.4	90.3
1	87.4	74.5	63.0	61.7

a-Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.

Source: FDA analysis

Table 15-6 Percent Probabilities of PK-PD Target Attainment by MIC Based on free-drug plasma AUC:MIC Targets Associated with a 1-log_{10} CFU Reduction from Baseline for *S. pneumoniae* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
0.12	99.4	97.9	96.8	95.0
0.25	93.0	88.7	86.0	84.1
0.5	81.1	79.0	75.9	73.8
1	64.0	60.6	57.5	56.0

a-Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.
Source: FDA analysis

H. influenzae

Table 15-7 shows Applicant's PTA results while Table 15-8 and Table 15-9 summarizes the results by FDA reviewer, for *H. influenzae*. The results are comparable when using ELF targets. When plasma target is used, the FDA reviewer found that the percent probabilities of PK-PD target attainment for *H. influenzae* ≥ 90% at a MIC value of 0.25 µg/mL were achieved for IV to PO and PO dosing regimens. (b) (4)

Table 15-7 Percent Probabilities of PK-PD Target Attainment by MIC and Overall Based on Randomly Assigned Total-Drug ELF AUC:MIC Targets Associated with a 1-$\log_{10}$ CFU Reduction from Baseline for *H. influenzae* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens[a].

MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC[b]			
	IV to PO dosing regimen			PO dosing regimen
	100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Days 2-3 with a switch to 300 mg PO q24h on Days 3 or 5			450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3
	Days 1 to 2[b]	Day of PO switch[c]		Days 1 to 2[d]
		Day 3	Day 5	
0.25	100	100	100	100
0.5	100	99.9	99.8	98.7
1	99.5	93.0	90.2	82.7
2	68.8	45.3	39.6	36.5

Shaded cells indicate percent probabilities of PK-PD target attainment ≥90%.

a - A total-drug ELF AUC:MIC ratio target associated with a 1-log10 CFU reduction from baseline for *H. influenzae* based on an one- compartment *in vitro* infection model was randomly assigned based on an estimated log normal distribution of PK-PD targets associated with the same endpoint. b - Based on the assessment of average total-drug ELF AUC0-24 on Days 1 and 2. c - Based on the assessment of total-drug ELF AUC0-24 for the day of the PO switch. d - Based on the assessment of total-drug ELF AUC0-24 for Days 1 and 2.
Source: Applicant's summary of Clinical Pharmacology 3, Table 122, Page 218

Table 15-8 Percent Probabilities of PK-PD Target Attainment by MIC Based on total-drug ELF AUC:MIC Targets Associated with a 1-$\log_{10}$ CFU Reduction from Baseline for *H. influenzae*

Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
0.25	100	100	100	100
0.5	100	100	98.5	95.7
1	97.6	93.7	84.4	82.7
2	81.6	46.2	36.7	33.0

a-Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.
Source: FDA analysis

Table 15-9 Percent Probabilities of PK-PD Target Attainment by MIC Based on Free-Drug Plasma AUC:MIC Targets Associated with a 1-$\log_{10}$ CFU Reduction from Baseline for *H. influenzae* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
0.25	100	100	97.0	95.0
0.5	96.1	93.0	90.1	88.9
1	70.4	66.3	63.3	61.0
2	7.37	5.43	4.40	2.56

a-Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.
Source: FDA analysis

ABSSSI: Monte Carlo Simulation to assess probability of target attainment (PTA)

Nonclinical targets associated with net stasis were used from the neutropenic mouse thigh infection model. In the neutropenic mouse thigh model, high variability in AUC:MIC targets were noted. *S. aureus* targets ranging from 13.8 to 51.3 (mean 23.7), 17.5 to 53.4 (mean 33.3) for *S. pneumoniae*, and 28.4 to 98.8 (mean 64.1) for *E. coli*. The Applicant used AUC:MIC ratio targets which were randomly assigned based on an estimated log normal distribution of AUC:MIC ratio targets.

S. aureus

The Applicant obtained percent probabilities of PK-PD target attainment were ≥ 90% at the MIC_{90} value of 0.12 µg/mL for IV to PO and PO dosing with the loading dose across days of

assessment as summarized in Table 15-10 and Table 15-11. This result was in a good agreement with the FDA's analysis. However, for breakpoint determination, the Applicant proposed to use clinical PK-PD data. Minimum inhibitory concentration data were available for *S. aureus* from 365/504 (72.4%) omadacycline-treated subjects. Omadacycline MIC values ranged from 0.12 µg/mL to 1 µg/mL in the omadacycline treated subjects with most of the isolates between an MIC of 0.25 to 0.5 µg/mL. Clinical success rates were 83.3% (304/365) for S. aureus with MIC values ≤1 µg/mL, (b) (4)

Table 15-10 Percent Probabilities of PK-PD Target Attainment by MIC Based on Randomly Assigned Free-Drug Plasma AUC:MIC Ratio Targets Associated with Net Bacterial Stasis for S. aureus Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens[a] .

Clinical PK-PD model or non-clinical PK-PD target attainment	MIC (µg/mL)	Percent probabilities of a successful ECR or PK-PD target attainment by MIC			
		IV to PO dosing regimen			PO dosing regimen
		100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Days 2 or 2-3 with a PO switch to 300 mg PO q24h on Days 3 or 4			450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3
		Days 1 to 2[a]	Day of PO switch[b]		Days 1 to 2[a]
			Day 3	Day 5	
PK-PD target attainment	0.06	100	100	100	99.7
	0.12	100	98.9	98.2	94.8
	0.25	91.3	71.7	68.2	60.8
	0.5	35.1	18.5	16.0	15.7

Shaded cells indicate percent probabilities of PK-PD target attainment ≥90%.
a. Based on the assessment of average free-drug plasma AUC_{0-24} on Days 1 and 2.
b. Based on the assessment of free-drug plasma AUC_{0-24} for the day of the PO switch.

Source: Applicant's summary of Clinical Pharmacology 3, Table 123, Page 221

Table 15-11 Percent Probabilities of PK-PD Target Attainment by MIC Based on Free-Drug Plasma AUC:MIC Targets Associated with a Net Bacterial Stasis for *S. aureus* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
0.06	100	100	100	99.4
0.12	99.5	99.0	96.2	97.0
0.25	90.5	76.3	73.7	70.8
0.5	38.7	24.0	21.3	19.1

a-Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.
Source: FDA analysis

Streptococcus species

The assessment of PK-PD target attainment for Streptococcus species based on the nonclinical PK-PD target associated with net bacterial stasis provided support for IV to PO and PO omadacycline dosing regimens with loading doses and a susceptibility breakpoint of 0.06 µg/mL

Table 15-12 Percent Probabilities of PK-PD Target Attainment by MIC Based on Randomly Assigned Free-Drug Plasma AUC:MIC Ratio Targets Associated with Net Bacterial Stasis for *Streptococcus sp.* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens[a].

MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC[b]			
	IV to PO dosing regimen			PO dosing regimen
	100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Days 2 or 2-3 with a PO switch to 300 mg PO q24h on Days 3 or 4			450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3
	Days 1 to 2[b]	Day of PO switch[c]		Days 1 to 2[b]
		Day 3	Day 5	
0.03	100	100	100	100
0.06	100	99.9	99.7	98.3
0.12	99.1	91.6	89.4	82.9
0.25	66.4	44.2	40.5	36.6
Overall	96.3	91.9	90.8	87.5

Shaded cells indicate percent probabilities of PK-PD target attainment ≥90%.

a. A free-drug plasma AUC:MIC ratio target associated with net bacterial stasis for *Streptococcus* species based on data from a murine-thigh infection model was randomly assigned based on an estimated log normal distribution of PK-PD targets associated with the same endpoint.
b. Shaded cells indicate PK-PD target attainment values ≥90%.
c. Based on the assessment of free-drug plasma AUC0-24 for the day of the PO switch.

Source: Applicant's summary of Clinical Pharmacology 3, Table 124, Page 223

Table 15-13 Percent Probabilities of PK-PD Target Attainment by MIC Based on Free-Drug Plasma AUC: MIC Targets Associated with a Net Bacterial Stasis for *Streptococcus sp.* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
0.03	100	100	100	100
0.06	100	100	99.9	98.0
0.12	99.9	94.0	92.3	89.9
0.25	70.4	51.1	49.7	46.8

a-Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.

Source: FDA analysis

Enterobacteriaceae

The results of the PK-PD target attainment analyses for *E. coli* showed low percent probabilities of PK-PD target attainment at MIC values encompassing the range of observed in vitro surveillance data for *E. coli*. This result was not consistent with clinical data; the clinical success rates for the Enterobacteriaceae were high in both the ABSSSI and CABP studies. At a MIC value of 0.06 µg/mL, percent probabilities of PK-PD target attainment ranged from 87 to 99% across assessment days for the IV to PO and PO dosing regimens (Table 15-14 and Table 15-15). (b) (4) MIC data were available for *E. coli* from 5/504 (1.0%) omadacycline-treated subjects. Omadacycline MIC values for *E. coli* ranged from 0.5 µg/mL to 4 µg/mL in the omadacycline treated subjects. Clinical success rates were 100% (5/5) for *E. coli* with MIC values ≤4 µg/mL.

Table 15-14 Percent Probabilities of PK-PD Target Attainment by MIC Based on Randomly Assigned Free-Drug Plasma AUC:MIC Ratio Targets Associated with Net Bacterial Stasis for *E.Coli* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens[a]

MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC[b]			
	IV to PO dosing regimen			PO dosing regimen
	100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Days 2 or 2-3 with a PO switch to 300 mg PO q24h on Days 3 or 4			450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3
	Days 1 to 2[b]	Day of PO switch[c]		Days 1 to 2[b]
		Day 3	Day 5	
≤0.015	100	100	100	100
0.03	100	99.6	99.4	97.5
0.06	97.3	89.2	87.0	82.1
0.12	70.0	52.7	50.0	45.7

Shaded cells indicate percent probabilities of PK-PD target attainment ≥90%.

a. A free-drug plasma AUC:MIC ratio target associated with net bacterial stasis for *E. coli* based on data from a murine-thigh infection model was randomly assigned based on an estimated log normal distribution of PK-PD targets associated with the same endpoint.

b. Shaded cells indicate PK-PD target attainment values ≥90%.

Source: Applicant's summary of Clinical Pharmacology 3, Table 125, Page 225

Table 15-15 Percent Probabilities of PK-PD Target Attainment by MIC Based on Free-Drug Plasma AUC:MIC Targets Associated with a Net Bacterial Stasis for *E. Coli* Among Simulated Patients after Administration of IV to PO or PO Omadacycline Dosing Regimens.

MIC (µg/mL)	Percent probability of PK-PD target attainment by MIC			
	Intravenous administration with PO switch		Oral administration	
	Day 1[a]	Day 3[a]	Day 1[b]	Day 3[b]
≤0.015	100	100	100	100
0.03	100	100	99.7	97.0
0.06	99.2	93.3	89.0	86.8

Loading dose given as 100 mg infused over 30 min twice daily on day 1, or 200 mg infused over 60 min once a day on day 1, followed by 300 mg q24h from day 2. b - Loading dose given as 450 mg given orally once a day 1 and day 2 followed by 300 mg q24h from day 3.
Source: FDA analysis

Clin-Pharm Reviewer's conclusions: (b) (4) *. The FDA Reviewer provided PTA analysis using both total-drug ELF AUCs and free-drug plasma AUCs. According to the Reviewer's analysis, PTA supports breakpoints of 0.5 and 1 µg/mL for S. pneumoniae and H. influenza using ELF AUC, respectively, while the breakpoints were 0.12 and 0.5 µg/mL using free-drug plasma AUC. For ABSSSI, similar breakpoint of 0.12 and 0.12 µg/mL were obtained by the FDA reviewer and Applicant for S. aureus and Streptococcus species, based on nonclinical data. For E. coli, our PTA analysis supports a breakpoint of 0.03 µg/mL.* (b) (4) *Furthermore, the Applicant used AUC: MIC ratio targets which were randomly assigned based on an estimated log normal distribution of AUC: MIC ratio targets. Even though the Applicant's approach was different from the FDA reviewer where mean AUC/MIC targets were used, it is acceptable and comparable results were obtained from the Applicant and the Reviewer.*

15.2.4. Review of Individual Study Reports

The following clinical pharmacology related individual studies of PTK0796 (omadacycline) were reviewed.

Study # PTK 0796-SDES-0501

Study Title: A Placebo-Controlled, Randomized, Double-Blind, Phase I Study in Healthy Male Subjects to Investigate the Safety, Tolerability and Pharmacokinetics of Ascending Single and Multiple Intravenous Doses of PTK 0796

STUDY OBJECTIVES:
The primary objective of this study was to determine the safety and tolerability of a range of single doses of PTK 0796 in healthy young male volunteers. The secondary objective of the study was to determine the pharmacokinetic profiles of single doses of PTK 0796 in healthy, young male subjects.

STUDY DESIGN:
Test Product, Dose, Mode of Administration: PTK 0796 HCL for Injection, 25 to 600 mg by i.v. infusion over 30 or 60 minutes. This is not to-be-marketed formulation.
Duration of Treatment: Single dose
Within each dose level, subjects were randomized on a 3: 1 basis to receive either PTK 0796 or placebo. Overall, a total of 55 subjects were dosed 41 who received a single dose of PTK 0796 and 14 who received placebo. Among the 41 subjects who received PTK 0796, a total of 6, 6, 5,

and 6 subjects received single doses of 25, 50, 100 and 200 mg at 0.5 mg/mL, respectively, and 5, 5, 6, and 2 subjects received single doses of 200, 300, 400, and 600 mg at 1.0 mg/mL, respectively.

200 mg dose was given in two cohorts to confirm that increasing the concentration of the infusion from 0.5 to 1.0 mg/ml was not associated with adverse effects.

PK Sample Collection: Blood samples obtained pre-dose, and 17 PK samples over 72 hours post-dose.

Bioanalytical Method Description:

Plasma samples of omadacycline were analyzed by a validated LC/MS/MS method. Analytical method using sodium heparin as the anticoagulant was used for Study # PTK 0796-SDES-0501. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to summary of bioanalytical method validation section for details of validation methods.

RESULTS:

Summary of pharmacokinetics:

A summary of pharmacokinetic parameters obtained following single i.v. doses of PTK 0796 ranging from 25 to 600 mg is provided in Table 1. Figure 1 and Figure 2 present results of linear regression analysis of dose proportionality for mean AUCinf and Cmax. respectively.

Table 1. Summary of mean (SD) pharmacokinetic parameters (PTK0796-SDES-0501)

Omadacycline Group (mg)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{last} (ng·h/mL)	AUC_{0-24h} (ng·h/mL)	AUC_{∞} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V (L)
Dosed over 30 minutes:								
25 (N=6)	280 (58.7)	0.5 (0.25-0.55)	868 (209.7)	915 (183.4)	1260 (296.0)	11.7 (3.40)	20.9 (5.31)	333 (38.7)
50 (N=6)	789 (347.5)	0.3 (0.25-0.55)	2564 (581.6)	2384 (575.8)	3484 (1422.5)	20.5 (20.45)	15.8 (4.49)	380 (191.3)
100 (N=5)	1130 (346.0)	0.3 (0.25-0.55)	5435 (905.2)	4319 (847.9)	5958 (812.5)	14.1 (2.82)	17.1 (2.45)	353 (114.0)
200 A (N=6)	2008 (798.2)	0.4 (0.25-0.55)	10344 (2420.7)	7504 (1766.5)	11068 (2534.2)	18.7 (4.06)	18.8 (4.00)	506 (152.8)
200 B (N=5)	2602 (364.1)	0.3 (0.25-0.55)	11701 (2065.6)	9073 (1269.9)	13336 (2031.7)	19.0 (4.47)	15.3 (2.26)	412 (84.0)
Dosed over 60 minutes:								
300 (N=5)	2459 (681.2)	0.5 (0.50-1.05)	17443 (3358.1)	12835 (2718.5	18421 (3377.6)	19.3 (3.48)	16.7 (3.13)	467 (118.9)
400 (N=6)	3206 (711.3)	1.1 (0.50-1.05)	21468 (3456.1)	14709 (2160.5)	24118 (3814.8)	26.0 (4.50)	17.0 (2.91)	640 (163.7)
600 (N=2)	4511 (113.6)	0.8 (0.50-1.05)	34269 (2424.1)	24919 (914.0)	36023 (2404.9)	17.1 (0.11)	16.7 (1.11)	411 (30.1)

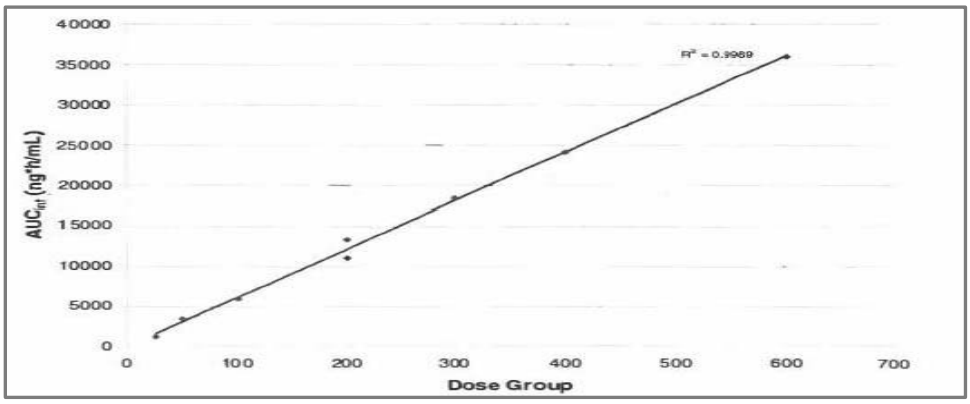
The 25-, 50-, 100- and 200A-mg cohorts received 0.5 mg/mL over 30 minutes; 200B-mg received 1 mg/mL over 30 minutes and the 300-, 400-, and 600-mg cohorts received 1.0 mg/mL over 60 minutes

AUC_{0-24h} = area under the concentration versus time curve from time zero to 24 hours, AUC_{∞} = area under the concentration versus time curve from time zero to infinity, AUClast = area under the concentration versus time curve from time zero to the last measured concentration, CL = systemic clearance, C_{max} = maximum plasma concentration, SD = standard deviation, $t_{1/2}$ = terminal half-life, t_{max} = the time the maximum plasma concentration was observed, V = volume of distribution.

[a]Median and range reported for t_{max}

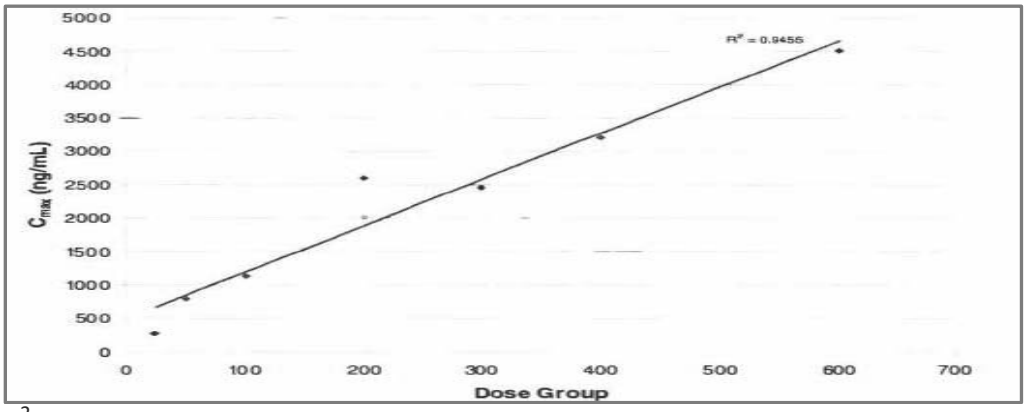
Source: Table 11-1, CSR PTK 0796-SDES-0501 page 48

Figure 1. Linear regression for dose proportionality for mean AUC_{0-inf} following a single dose of PTK 0796 - All Dose Groups



R^2=0.9969
Source: Figure 11-3, CSR PTK 0796-SDES-0501 page 50

Figure 2. Linear regression for dose proportionality for mean Cmax following a single dose of PTK 0796 All Dose Groups



R^2=0.9455
Source: Figure 11-4, CSR PTK 0796-SDES-0501 page 50

Safety Analysis:
Five subjects in 3 highest dose groups (300 to 600 mg) had one or more elevated ALT values. In 4 of the 5 subjects, maximal ALT values ranged from 74 to 83 IU/ml (-2x upper limit of normal [ULN]), occurring on Days 2 to 5 (24 to 96 hours post-infusion), then followed by a steady decline to the normal range.

Study # PTK0796-MDES-0601

PTK0796-MDES-0601 was a multiple ascending iv dose PK study of omadacycline. Originally, the study consisted of five treatment cohorts, the first two cohorts with 10 subjects each and the next three cohorts with 14 subjects each (Table 2).
The primary objective was to evaluate the safety and tolerability of a range of multiple IV doses of PTK 0796 in healthy adult male subjects.

Table 2. Treatment groups and dose levels

Cohort	Regimen	Number of Subjects (PTK 0796: Placebo)	Dosing Schedule
1	100 mg q24h x 7d	7:3	Day 1: a single dose Day 2: no dosing; only PK Days 3 to 9 (7d) or 3 to 16 (14d), inclusive: daily dosing
2	200 mg q24h x 7d	7:3	
3	100 mg q24h x 14d	7:7	
4	200 mg q24h x 7d	10:4	Days 1 to 7, inclusive: daily dosing
5	200 mg q24h x 7d	10:4	

All doses were given as 1 mg/ml solutions in saline administered over 30 minutes. The control treatment was placebo consisting of the same volume of saline alone administered at the same rate.
For cohorts 1, 2 and 3, tri-potassium ethylene diamine tetra-acetic acid (EDTA) was used as the anticoagulant in the sample tubes. It was determined by the Applicant that this may have led to underestimating plasma drug concentrations. For cohorts 4 (200 mg q24h x7d) and 5 (200 mg q24h x7d), a different analytical method using sodium heparin as the anticoagulant that was used. Therefore, PK parameters were determined for these two cohorts.
The rationale for same doing regimen 200 mg q24h x7d was to obtain additional data regarding the frequency of increases in ALT.

PK Sample Collection:
On Day 1 of the infusion, PK blood samples were drawn at pre-dose and 15 samples over 36 hours collected following the start of infusion. On day 3 to 7 PK blood sample were drawn just prior to dosing. Blood samples were additionally obtained at 24, 36, 48 and 72 hours following the start of the last infusion.

Summary of pharmacokinetics:
PK data from cohorts 4 and 5 are presented in Table 3.
Table 3. Summary for PK Parameters (Study PTK0796-MDES-0601)

Parameter (units)	Dose of Omadacycline	Study Day	N	Mean	SD
C_{max} (ng/mL)	200-mg q24h X 7d Cohort 4	Day 1	10	2958.00	491.00
		Last day of infusion	10	3551.00	801.35
	200-mg q24h X7 Cohort 5	Day 1	10	2783.00	728.93
		Last day of infusion	10	3358.00	436.70
$AUC_{0-\tau}$ (ng·hr/mL)	200-mg q24h X7 Cohort 4	Day 1	10	12205.00	1657.76
		Last day of infusion	10	18003.00	2891.23
	200-mg q24h X7 Cohort 5	Day 1	10	11176.10	1980.30
		Last day of infusion	10	17382.00	2983.04
$t_{1/2}$ (h)	200-mg q24h X7 Cohort 4	Day 1	10	14.23	2.52
		Last day of infusion	10	25.20	3.61
	200-mg q24h X7 Cohort 5	Day 1	10	15.62	3.93
		Last day of infusion	10	23.74	2.65
CL (mL/h)	200-mg q24h X7 Cohort 4	Last day of infusion	10	11337.10	1588.33
	200-mg q24h X7 Cohort 5	Last day of infusion	10	11796.50	1917.88
Vss (mL)	200-mg q24h X7 Cohort 4	Last day of infusion	10	285390.0	50064.12
	200-mg q24h X7 Cohort 5	Last day of infusion	10	282300.0	36123.31
R_{AC}(AUC)	200-mg q24h X7 Cohort 4	Last day of infusion	10	1.48	0.15
	200-mg q24h X7 Cohort 5	Last day of infusion	10	1.56	0.08

$AUC_{0-\tau}$ = area under the concentration versus time curve over a dosing interval, CL = systemic clearance, C_{max} = maximum plasma concentration, PK = pharmacokinetics, q24h = every 24 hours, R_{AC}(AUC)=accumulation ratio (Day 7/Day 1), SD = standard deviation, $t_{1/2}$ = terminal half-life, Vss = volume of distribution at steady-state.

Source: Table 11-2, CSR PTK 0796-MDES-0601, page 49

Clin-Pharm Reviewer's assessment and conclusions:
Omadacycline exposure increased in a dose proportional manner over the dose range of 25 to 600 mg following single iv dose.
Female subjects were not included in the both SAD and multiple dose iv studies.
After daily dosing of 200-mg iv omadacycline for 7 days, CL and Vss were not similar to that after single dose administration. CL and Vss values were slightly lower in multiple dose administration study. However, mean half-life estimates increased following 7 days of iv dosing as compared to that after single iv dose administration on Day 1.
Accumulation ratio following daily dosing of 200-mg iv omadacycline for 7 days was 1.5. Thus, plasma accumulation of omadacycline is deemed to be moderate by the reviewer, and this extent of accumulation is expected based on reported half-life ($t_{1/2}$) of 14-25 hours.

Safety analysis:
Mild, transient increases in ALT and AST were observed among 9 of the 41 PTK 0796-treated subjects in study PTK 0796-MDES-0601, which resolved either prior to the end of treatment or during follow-up.

Study # PTK0796-MDPO-16105

Study Title: A Phase 1, Randomized, Double-Blind, 3-Period, Crossover Study to Evaluate Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses of Omadacycline or Placebo in Healthy Adult Subjects
Study site: (b) (4)

STUDY OBJECTIVES:
The primary objective of the study was to assess and compare the pharmacokinetics of 300-, 450-, and 600 mg doses of oral omadacycline administered daily over 5 days.

STUDY DESIGN: The study consisted of a screening period (Day –21 through Day –2), 3 baseline periods (Day –1 of each period), 3 treatment periods (Day 1 through Day 5 of each period), and a study completion visit (within 6 to 10 days after the last dose of study drug in Period 3). There was a washout of at least 5 days between the last dose in 1 period and the first dose in the next period. On Day 1 through Day 5 of each period, subjects received treatments after a fast of 6 hours. A total of 33 subjects were enrolled in this study and received at least 1 dose of omadacycline (26 subjects) or placebo (7 subjects).
Test Product, Dose, Mode of Administration:
• Oral omadacycline 300 mg (2 × 150-mg tablets)
• Oral omadacycline 450 mg (3 × 150-mg tablets)
• Oral omadacycline 600 mg (4 × 150-mg tablets)
This study was conducted with Crystalline Tosylate Salt (b) (4) tablets, which is the to-be marketed formulation.

Duration of Treatment: Once daily doses of omadacycline were administered on Day 1 through Day 5 of Period 1, Period 2, and Period 3, with a washout of at least 5 days between the last dose in 1 period and the first dose in the next period.

PK Sample Collection: Blood samples for PK assessments of omadacycline were collected from all subjects at the following time points: 0 (pre-dose) and 12 PK samples were collected over 24 hours after dosing on Day 1 and Day 5 in each period. The 24-hour blood sample for Day 1 was collected before dosing on Day 2 for each period.
Urine samples for PK assessments of omadacycline were collected and pooled from a subset of subjects at the following intervals: pre-dose, 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after the Day 5 dose in Period 2 and after the Day 1 and Day 5 doses in Period 3. The 12- to 24-hour urine sample for Day 1 was collected before dosing on Day 2.

Bioanalytical Method Description:

Plasma and urine samples of omadacycline were analyzed by a validated LC/MS/MS method. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.2.1 for details of validation methods.

RESULTS:

Summary of pharmacokinetics (Tables 1 & 2):

Omadacycline AUC and Cmax increased in a less than proportional manner as omadacycline dose increased from 300 to 600 mg on both Day 1 and Day 5. The mean $t_{1/2}$ was similar across the 3 dose levels, ranging from 13.03 to 13.66 hours on Day 1 and from 15.49 to 16.83 hours on Day 5.

Table 1. Mean (CV) Plasma Pharmacokinetic Parameters of Omadacycline by Treatment – Day 1

Parameter	Treatment A (n=25)	Treatment B (n=24)	Treatment C (n=24)
AUC_{0-24} (ng•h/mL)	6644.8 (25.3)	8976.5 (26.6)	10020.5 (25.7)
AUC_{last} (ng•h/mL)	6634.2 (25.3)	8962.5 (26.6)	10004.5 (25.7)
C_{max} (ng/mL)	648.8 (24.0)	874.2 (26.6)	954.5 (23.2)
T_{max} (h)[a]	2.50 (1.50, 3.00)	2.50 (1.50, 3.00)	2.51 (1.00, 3.00)
$T_{1/2}$ (h)	13.66 (12.5)[b]	13.45 (12.9)[c]	13.03 (11.8)[c]
λ_z (/h)	0.0515 (11.9)[b]	0.0524 (12.6)[c]	0.0539 (11.6)[c]

Abbreviation: CV, coefficient of variation
Treatment A: 300 mg omadacycline (2 × 150-mg tablets)
Treatment B: 450 mg omadacycline (3 × 150-mg tablets)
Treatment C: 600 mg omadacycline (4 × 150-mg tablets)
[a] For T_{max}, the median (minimum, maximum) values are presented.
[b] n = 24 ($T_{1/2}$ and λ_z were not estimable for 1 subject).
[c] n = 23 ($T_{1/2}$ and λ_z were not estimable for 1 subject).

Source: Table 11-2. Clinical Study Report PTK0796-MDPO-16105, page 66

Table 2 Mean (CV) Plasma Pharmacokinetic Parameters of Omadacycline by Treatment - Day 5

Parameter	Treatment A (n=23)	Treatment B (n=24)	Treatment C (n=23)
AUC_{0-24} (ng•h/mL)	9267.2 (26.8)	13366.7 (26.0)	16420.3 (27.1)
AUC_{last} (ng•h/mL)	9270.2 (26.8)	13368.3 (25.9)	16424.6 (27.1)
C_{max} (ng/mL)	808.8 (25.9)	1077.3 (25.0)	1305.5 (26.6)
T_{max} (h)[a]	2.50 (1.00, 3.00)	2.50 (1.50, 4.00)	2.50 (2.00, 4.00)
$T_{1/2}$ (h)	15.49 (10.7)[b]	16.83 (8.1)[c]	16.75 (6.8)[b]
λ_z (/h)	0.0453 (12.5)[b]	0.0415 (8.7)[c]	0.0416 (6.6)[b]

Abbreviation: CV, coefficient of variation

Note: Subject (b) (6) (300 mg omadacycline) and Subject (b) (6) (600 mg omadacycline) were excluded from the Day 5 summary due to vomiting before reaching the pharmacokinetic steady state on Day 5.

Treatment A: 300 mg omadacycline (2 × 150-mg tablets)

Treatment B: 450 mg omadacycline (3 × 150-mg tablets)

Treatment C: 600 mg omadacycline (4 × 150-mg tablets)

[a] For T_{max}, the median (minimum, maximum) values are presented.

[b] n = 21 ($T_{1/2}$ and λ_z were not estimable for 2 subjects).

[c] n = 23 ($T_{1/2}$ and λ_z were not estimable for 1 subject).

Source: Table 11-3. Clinical Study Report PTK0796-MDPO-16105, page 67

Statistical Analysis of Plasma Pharmacokinetic Parameters of Omadacycline

The statistical analysis of dose-normalized omadacycline PK parameters for Day 1 and Day 5 are presented in Tables below, respectively.

Table 3 Statistical Analysis of Dose-Normalized Omadacycline Pharmacokinetic Parameters - Day 1

Parameter	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means (%)	90% CI of Ratio (%)
AUC_{0-24}/Dose	A	25	21.32			
(ng•h/mL/mg)	B	24	18.64	B/A	87.44	(77.41, 98.77)
	C	24	16.18	C/B	86.79	(76.71, 98.20)
				C/A	75.89	(67.20, 85.71)
AUC_{last}/Dose	A	25	21.28			
(ng•h/mL/mg)	B	24	18.61	B/A	87.45	(77.42, 98.78)
	C	24	16.15	C/B	86.78	(76.70, 98.19)
				C/A	75.89	(67.19, 85.71)
C_{max}/Dose	A	25	2.09			
(ng/mL/mg)	B	24	1.81	B/A	86.71	(76.17, 98.71)
	C	24	1.54	C/B	85.26	(74.76, 97.23)
				C/A	73.92	(64.95, 84.14)

Abbreviations: CI, confidence interval; LS, least squares

Notes: An analysis of variance model was fitted to the log-transformed dose-normalized AUCs and C_{max} data, with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect.

Treatment A: 300 mg omadacycline (2 × 150-mg tablets)

Treatment B: 450 mg omadacycline (3 × 150-mg tablets)

Treatment C: 600 mg omadacycline (4 × 150-mg tablets)

Source: Table 14.2.4. Clinical Study Report PTK0796-MDPO-16105, page 68

Table 4 Statistical Analysis of Dose-Normalized Omadacycline Pharmacokinetic Parameters - Day 5

Parameter	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means (%)	90% CI of Ratio (%)
AUC_{0-24}/Dose	A	23	30.09			
(ng•h/mL/mg)	B	24	28.83	B/A	95.82	(90.39, 101.59)
	C	23	26.46	C/B	91.78	(86.58, 97.30)
				C/A	87.95	(82.96, 93.25)
AUC_{last}/Dose	A	23	30.10			
(ng•h/mL/mg)	B	24	28.84	B/A	95.80	(90.37, 101.57)
	C	23	26.47	C/B	91.80	(86.59, 97.32)
				C/A	87.94	(82.95, 93.24)
C_{max}/Dose	A	23	2.62			
(ng/mL/mg)	B	24	2.32	B/A	88.58	(83.19, 94.32)
	C	23	2.11	C/B	90.72	(85.20, 96.60)
				C/A	80.36	(75.47, 85.58)

Abbreviations: CI, confidence interval; LS, least squares

Notes: An analysis of variance model was fitted to the log-transformed dose-normalized AUCs and C_{max} data, with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect. Subject (b) (6) (300 mg omadacycline) and Subject (b) (6) (600 mg omadacycline) were excluded from the Day 5 statistical analysis due to vomiting before reaching the pharmacokinetic steady state on Day 5.

Treatment A: 300 mg omadacycline (2 × 150-mg tablets)

Treatment B: 450 mg omadacycline (3 × 150-mg tablets)

Treatment C: 600 mg omadacycline (4 × 150-mg tablets)

Source: Table 14.2.5. Clinical Study Report PTK0796-MDPO-16105, page 69

Dose Proportionality Assessment and Statistical Analysis of Accumulation of Omadacycline

The dose proportionality assessment of omadacycline for Day 1 and Day 5 are presented in Following two tables below, respectively.

Table. 5 Dose Proportionality Assessment of Omadacycline-Day 1

Parameter	N	Estimated Intercept (a)	Estimated Slope (b)	Standard Error of Slope	90% CI of Slope Lower-Upper
AUC_{0-24} (ng•h/mL)	73	5.307	0.607	0.147	0.362-0.852
AUC_{last} (ng•h/mL)	73	5.305	0.607	0.147	0.362-0.852
C_{max} (ng/mL)	73	3.175	0.574	0.147	0.328-0.819

Abbreviation: CI, confidence interval

Notes: The power model, ln(parameter) = a + b*ln(dose) + error, was used on individual log-transformed parameter values to estimate the slope and corresponding 90% CI. Random effects of intercept and slope were included.

Source: Table 14.2.6. Clinical Study Report PTK0796-MDPO-16105, page 70

Table.6 Dose Proportionality Assessment of Omadacycline-Day 5

Parameter	N	Estimated Intercept (a)	Estimated Slope (b)	Standard Error of Slope	90% CI of Slope Lower-Upper
AUC_{0-24} (ng•h/mL)	70	4.406	0.824	0.130	0.607-1.041
AUC_{last} (ng•h/mL)	70	4.407	0.824	0.130	0.607-1.041
C_{max} (ng/mL)	70	2.740	0.687	0.129	0.472-0.902

Abbreviation: CI, confidence interval

Notes: The power model, ln(parameter) = a + b*ln(dose) + error, was used on individual log-transformed parameter values to estimate the slope and corresponding 90% CI. Random effects of intercept and slope were included. Subject (b) (6) (300 mg omadacycline) and Subject (b) (6) 600 mg omadacycline) were excluded from the Day 5 statistical analysis due to vomiting before reaching the pharmacokinetic steady state on Day 5.

Source: Table 14.2.7. Clinical Study Report PTK0796-MDPO-16105, page 70

Dose proportionality over the dosing range of 300 to 600 mg for omadacycline was not confirmed for systemic exposures for either Day 1 or Day 5, as the 90% CIs of the slope defined by the power model were not contained within the dose proportionality bounds (0.678 to 1.322, i.e., [1 + ln(0.8)/ln(dose_ratio), 1 + ln(1.25)/ln(dose_ratio)]). Both AUCs and Cmax exhibited less than dose-proportional increases over the dosing range from 300 to 600 mg.

The statistical analysis of accumulation of omadacycline is summarized in Table 7.

Table 7. Statistical Analysis of Accumulation of Omadacycline

Parameter	Dose	Day	N	Geometric LS Means	Day Comparison	Ratio of Geometric LS Means (%)	90% CI of Ratio (%)
AUC_{0-24} (ng•h/mL)	300 mg	1	25	6378.3	Day 5/Day 1	139.6	(126.6, 153.9)
		5	23	8903.2			
	450 mg	1	24	8404.3	Day 5/Day 1	153.3	(137.0, 171.6)
		5	24	12887.1			
	600 mg	1	24	9676.7	Day 5/Day 1	162.3	(150.8, 174.6)
		5	23	15702.7			
C_{max} (ng/mL)	300 mg	1	25	625.1	Day 5/Day 1	123.7	(111.8, 136.7)
		5	23	773.0			
	450 mg	1	24	815.3	Day 5/Day 1	127.8	(112.8, 144.8)
		5	24	1042.0			
	600 mg	1	24	926.3	Day 5/Day 1	135.2	(126.3, 144.7)
		5	23	1252.3			

Abbreviations: CI, confidence interval; LS, least squares

Notes: A linear mixed-effect model with day as a fixed effect and subject as a random effect was fitted to the natural log-transformed pharmacokinetic parameters. Subject (b) (6) (300 mg omadacycline) and Subject (b) (6) (600 mg omadacycline) were excluded from the statistical analysis due to vomiting before reaching the pharmacokinetic steady state on Day 5.

Source: Table 14.2.8. Clinical Study Report PTK0796-MDPO-16105, page 71

The accumulation ratios for AUC_{0-24} ranged from 1.40 to 1.62, and the accumulation ratios for Cmax ranged from 1.24 to 1.35.

Urine Pharmacokinetic Parameters (Table 8 & 9)

Collection of urine was added as part of protocol amendment 1. However, due to the timing of the implementation of the amendment, few subjects had urine collected and thus the urine PK assessment is limited.

Table 8. Mean (CV) Urine Pharmacokinetic Parameters of Omadacycline by Treatment - Day 1

Parameter	Treatment A (n = 2)	Treatment B (n = 3)	Treatment C (n = 1)
Ae_{0-24} (mg)	20.37 (8.3)	25.06 (16.8)	31.96
Fe_{0-24} (%)	6.79 (8.3)	5.57 (16.8)	5.33
CLr (L/h)	3.01 (11.4)	2.80 (9.6)	4.17

Treatment A: 300-mg omadacycline (2 × 150-mg tablets)
Treatment B: 450-mg omadacycline (3 × 150-mg tablets)
Treatment C: 600-mg omadacycline (4 × 150-mg tablets)

Ae_{0-24} Cumulative amount of unchanged drug excreted in urine from 0-24 hours.
Fe_{0-24} Fraction of the dose excreted unchanged in urine from 0 to 24 hours.
CLr Renal clearance
Source: Table 14.2.10. Clinical Study Report PTK0796-MDPO-16105, page 72

Table 9. Mean (CV) Urine Pharmacokinetic Parameters of Omadacycline by Treatment - Day 5

Parameter	Treatment A (n = 3)	Treatment B (n = 5)	Treatment C (n = 4)
Ae_{0-24} (mg)	26.14 (14.6)	30.81 (33.0)	51.82 (14.8)
Fe_{0-24} (%)	8.71 (14.6)	6.85 ((33.0)	8.64 (14.8)
CLr (L/h)	3.28 (27.2)	2.38 (34.9)	3.05 (19.9)

Treatment A: 300-mg omadacycline (2 × 150-mg tablets).
Treatment B: 450-mg omadacycline (3 × 150-mg tablets).
Treatment C: 600-mg omadacycline (4 × 150-mg tablets).

Source: Table 14.2.10. Clinical Study Report PTK0796-MDPO-16105, page 72
Ae_{0-24} Cumulative amount of unchanged drug excreted in urine from 0-24 hours.
Fe_{0-24} Fraction of the dose excreted unchanged in urine from 0 to 24 hours.
CLr Renal clearance

Clin-Pharm Reviewer's assessment and conclusions:

Omadacycline exposure increased in a less that proportional manner with the increase in once-daily oral dose from 300 mg to 600 mg. Statistical analyses showed that both AUC and Cmax exhibited less than dose-proportional increases over this dose range.

The accumulation ratios for AUC_{0-24} ranged from 1.40 to 1.62, and the accumulation ratios for Cmax ranged from 1.24 to 1.35. Thus, plasma accumulation of omadacycline is deemed to be moderate by the reviewer, and this extent of accumulation is to be expected based on the reported half-life ($t_{1/2}$) of approximately 13 to 16 hours.

The mean $t_{1/2}$ was similar across the 3 dose levels, ranging from approximately 13.0 to 13.7 hours on Day 1 and from 15.5 to 16.8 hours on Day 5.

At steady state, the mean fraction of the total oral omadacycline dose excreted unchanged in urine ranged from 6.9 to 8.7% and the CLr at steady-state, ranged from 2.38 to 3.28 L/h, although there was limited number of subjects that provided urinary excretion data.

Study # CPTK796A2101

Study title: **An open-label study to assess the absorption, distribution, metabolism, and elimination of [^{14}C]-labeled omadacycline (PTK796) in healthy male subjects following a single oral dose of 300 mg PTK796**

Study center: (b) (4)

STUDY OBJECTIVES:

Primary objective

The primary objective of the study was to determine PTK796 pharmacokinetics and total radioactivity and its metabolites in plasma following a single 300 mg dose.

Secondary objective

The secondary objectives of the study were to identify and quantify the metabolites of PTK796 in plasma, urine and feces, to elucidate key biotransformation pathways and clearance mechanisms of PTK796 and to assess the safety and tolerability of PTK796, and its metabolites, in healthy male subjects following a single oral dose of C-14 labeled 300 mg PTK796.

STUDY DESIGN:

This was an open-label, single-dose, absorption, distribution, metabolism and excretion (ADME) study conducted in 6 healthy male subjects.

The study consisted of a screening period (Day -21 to -2), a baseline visit (Day -1), an eight-day period which included 168 hours (h) of in-house observation (Days 1 to 7). The study completion evaluation was done on the day of discharge (Day 8). Subjects were required to fast overnight prior to the dose and until 4 hours after dose administration.

Test Product, Dose, Mode of Administration: The radiolabeled study drug was provided as individually packaged doses of 2 x 150 mg oral capsules with planned specific activity of 4.33 kBq/mg (total dose 1.30 MBq, 35 µCi; actual was 1.35 MBq or 36.6 µCi) [^{14}C]PTK796 (omadacycline tosylate (b) (4)) in (b) (4) capsules. Each subject received an oral dose of 300 mg [^{14}C]PTK796 on day 1.

Duration of Treatment: The minimum stay of the subjects in this study was 8 days.

PK Sample Collection:

After administration of the ^{14}C-PTK796 dose, plasma samples were collected for total radioactivity, PK analysis and metabolite profiling/identification at the following time points: 0 (pre-dose), 17 PK samples were collected over 144 hours post dose, additional sample was collected in event of discontinuation from the study. During the entire in-patient observation period, all urine was collected (Day 1 through morning of Day 8). The urine collected from each subject was pooled by time period post-dose (0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h). One pre-dose fecal sample was collected from each subject during the Screening Visit (Day -2 or -1). After the ^{14}C-PTK796 dose administration, all feces were collected completely, and the collection identified with the appropriate 24 hour sample numbering including all toilet paper used, during the entire phase (Day 1 through morning of Day 8).

Bioanalytical Assay: Total radioactivity levels were determined by using ^{14}C radioactivity concentrations in blood, plasma, urine, and feces measured by liquid scintillation counting. Analytes were analyzed by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS). Performance of the bioanalytical method was acceptable.
Please refer to section 15.2.1 for details of validation methods.

RESULTS:

Total radioactivity data in plasma (Tables 1):

Following a single oral dose of radiolabeled [^{14}C] PTK796, the mean total radioactivity peak concentration in blood was 608±73.6 ngEq/mL and was reached between 1.5 and 4 h. In plasma, the mean total radioactivity peak concentration was 612±81.5 ngEq/mL and was reached between 1 and 3 h. The mean AUC_{last} of total radioactivity in plasma was 3096.1±1547.7 ngEq•h/mL while the mean AUC_{last} of total radioactivity in blood was 1867.2±1322.2 ngEq•h/mL.

Table 1. Summary of PK parameters for total radioactivity in plasma

Subject ID	Tmax* (h)	Cmax (ngEq/mL)	AUC0-8** (ngEq·h/mL)	AUClast*** (ngEq·h/mL)	AUCinf (ngEq·h/mL)	T1/2 (h)
(b) (6)	2	634	3454.0	3454.0	NC	NC
	3	712	4075.0	4075.0	NC	NC
	2.5	647	3508.3	5048.3	NC	NC
	2.5	482	2306.3	1416.3	NC	NC
	1	645	3509.0	3509.0	NC	NC
	3	553	2002.3	1074.3	NC	NC
Mean	----[a]	612	3142.5	3096.1	NC	NC
SD	----[a]	81.5	804.3	1547.7	NC	NC

----[a] = not included

NC = not calculated due to insufficient quality data points for estimation of elimination rate constant

*Tmax median was 2 h (range 1 - 3 h)

** Parameter not part of the original analysis plan; post-hoc analysis and calculation for comparison with PTK796 plasma exposure.

*** Plasma concentrations were BLQ after 4hrs for subjects (b) (6). Therefore, AUClast is AUC0-4hrs, which is less than the estimated AUC0-8hrs.

Pharmacokinetic parameters of PTK796 in plasma:

The key pharmacokinetic parameters of PTK 796 in plasma are summarized in Table 2.

Table 2. Plasma concentrations of PTK796 (ng/mL) in human plasma and PK parameters of PTK796 in plasma following an oral dose of 300 mg [^{14}C]PTK796

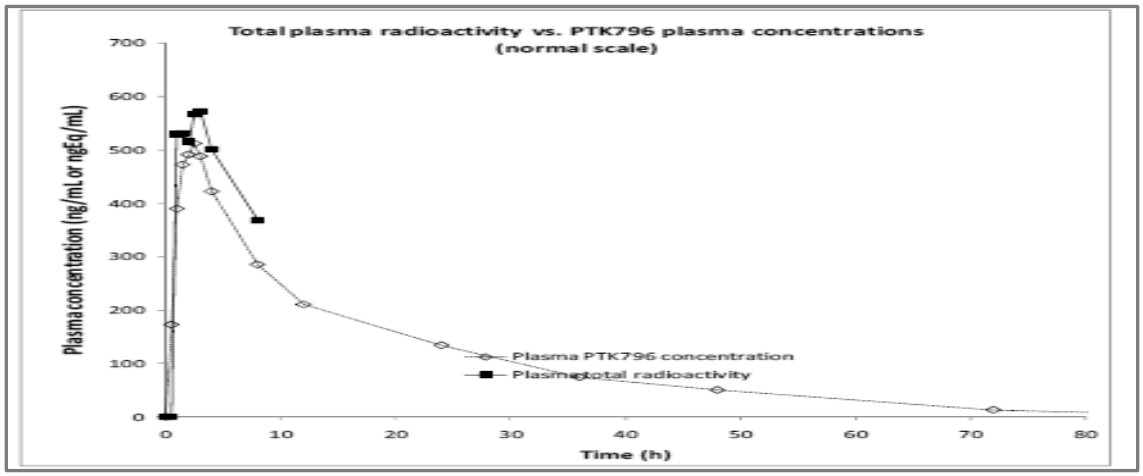
Cmax (ng/mL)	566	660	553	472	645	479	563 ± 79.5
Tmax(h)	2	2.5	4	1.5	1	2.5	2.5
AUClast (ng•h/mL)	6690	11263	10728	7892	7842	7022	8573 ± 1941
AUCinf (ng•h/mL)	7604	12122	11366	8459	8766	8194	9418 ± 1857
T1/2 (h)	16.7	19.6	17.5	18.7	15.5	17.6	17.6 ± 1.45
CL/F (L/hr)	39.5	24.7	26.4	35.5	34.2	36.6	32.8 ± 5.90
Vz/F (L)	948.8	698.9	668.0	957.2	763.3	930.6	827.8 ± 132.9
N.S. = no sample available N/AV = not available							

Source: PT-Table 14.2-2.3 CSR Study No. CPTK796A2101 page 96.

The plasma radioactivity values up to 8 h are available and PTK796 in plasma were detected up to 72 h.

Figure 1 below shows that both the total plasma radioactivity and PTK796 concentration values were similar up to 8 hours.

Figure 1. Total plasma radioactivity vs. PTK796 plasma-time concentrations

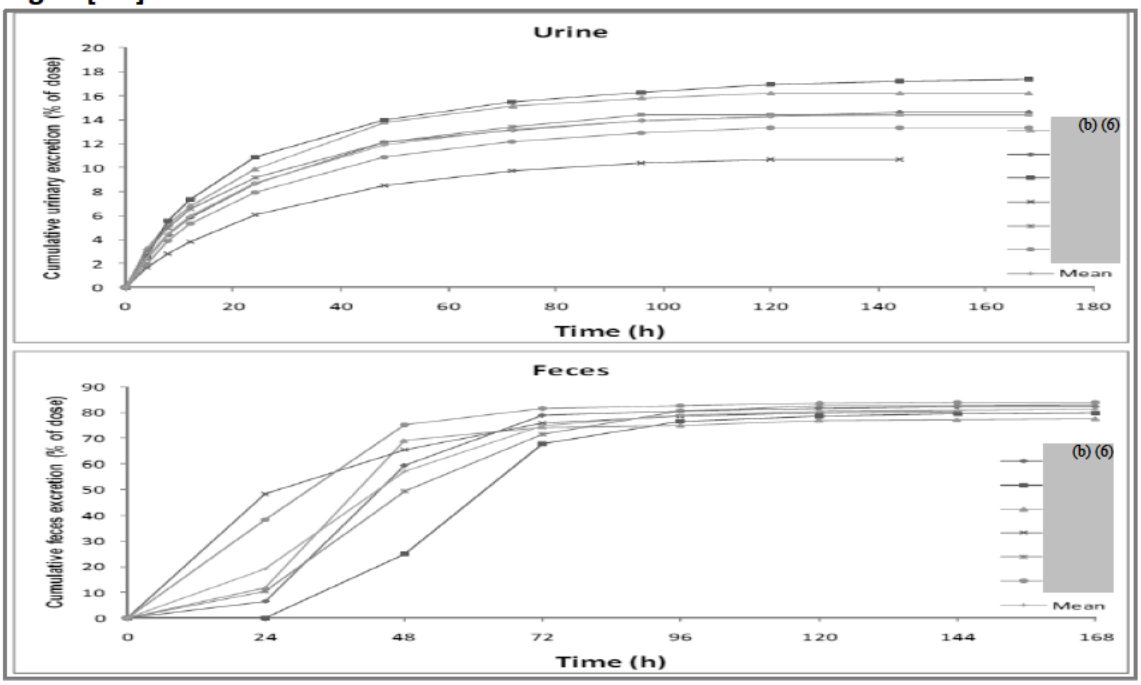


Source: Figure 11-7 CSR Study No. CPTK796A2101, Page 56

In addition, a post-hoc calculation of the $AUC_{0\text{-}8h}$ for total plasma radioactivity and $AUC_{0\text{-}8h}$ for PTK796 plasma showed that both estimates were comparable (3142.5 ngEq•h/mL and 3019.3 ng•h/mL, respectively), suggesting little or no metabolites were present in the plasma.

The cumulative excretion of radioactivity in urine and feces is shown in Figure 2. These plots indicate that excretion by both routes was complete at the time last sample collection. Excretion of radioactivity in urine and feces following oral administration of 300 mg [^{14}C]PTK796 is given in Table 4.

Figure 2. Cumulative urinary and fecal excretion of radioactivity after a single oral dose of 300 mg of [^{14}C] PTK796



Source: PT-Figure 14.2-2.49; PT-Table 14.2-2.4 and PT-Table 14.2-2.5 CSR Study No. CPTK796A2101 Page 70

Table 4. Excretion of total radioactivity (% of dose) in human subjects following an oral dose of 300 mg [^{14}C] PTK796

	Subject					(b) (6)	Mean ± SD
Urine	16.2	14.6	17.4	10.7	14.4	13.3	14.4 ± 2.33
Feces	82.1	80.0	77.5	80.1	82.8	84.0	81.1 ± 2.34
Total	98.3	94.6	94.9	90.8	97.2	97.3	95.5 ± 2.73

Source: Table 14.2-2.6 CSR Study No. CPTK796A2101 Page 99

Clin-Pharm Reviewer's Conclusions:

The PTK796 radiolabeled form used in this study yielded similar plasma pharmacokinetic parameters as that observed from other PK studies.

The mass balance achieved in this study of 6 healthy male subjects was 95.5% of the administered radioactive dose of PTK976 in the urine and feces over a period of 7 days.

In plasma, urine, and feces no metabolites were detected.

Comparison of concentrations of total plasma radioactivity and PTK796 plasma concentrations over time showed very similar profiles suggesting the lack of any circulating metabolites in plasma.

The majority of PTK796 radioactivity was recovered in the feces at 81.1%, while urinary recovery was much lower at 14.4%. This indicates that PTK976 is mainly eliminated by non-renal mechanisms.

Study # PTK0796-BAL-15104

Study Title: An Open-Label, Parallel Group, Multiple IV Dose Study to Assess Intra-Pulmonary Steady-State Concentrations of Omadacycline and Tigecycline in Healthy Adult Subjects

Study Center: (b) (4)

STUDY OBJECTIVES:
The primary objective of this study was to determine concentrations of omadacycline in epithelial lining fluid (ELF) and alveolar cells (AC) and define the time course of pulmonary distribution with concurrent plasma pharmacokinetic (PK) sampling of omadacycline in healthy adult subjects.
The secondary objective of this study was to evaluate the PK of omadacycline in pulmonary and plasma compartments in healthy adult subjects.

The exploratory objective of this study was to determine the PK of omadacycline in pulmonary and plasma compartments compared to tigecycline PK in pulmonary and plasma compartments in healthy adult subjects.

STUDY DESIGN:
Test Product, Dose, Mode of Administration: Omadacycline 100 mg was administered iv by 30 minute infusions every 12 hours (q12h) on Day 1 and then once every 24 hours (q24h) on Days 2 to 4, for a total of 5 doses.

Reference Therapy, Dose and Mode of Administration: Tigecycline was administered iv by 30 minute infusions q12h. Subjects received a single dose of 100 mg tigecycline, followed by a 50-mg dose of tigecycline 12 hours later on Day 1. Subjects then received 50 mg tigecycline q12h on Days 2 and 3, and a single 50-mg dose on Day 4, for a total of 7 doses.

Duration of Treatment: The total duration of omadacycline treatment was 4 days.

PK Sample Collection:

PK blood collection
Blood samples were collected for plasma PK assessments at 0, 0.5 (end of infusion), and 9 PK samples over 24 (omadacycline-treated subjects only) hours post-dose for all subjects on Day 4.

Bronchoscopy, BAL (bronchoalveolar lavage), and AC collection
Omadacycline subjects had collections at 0.5, 1, 2, 4, 8, 12, or 24 hours after the Day 4 dose.

Tigecycline subjects had collection at 2, 4, 6, or 12 hours after the Day 4 dose.
A blood sample to determine urea concentration was obtained at the time of the BAL second instillation.

Bioanalytical Assay: Plasma, BAL & BAL cellular pellets, urea in human plasma and BAL samples of omadacycline were analyzed by a validated LC/MS/MS method. Validation and performance of the bioanalytical method was acceptable.
Please refer to section 15.2.1 for details of validation methods.

RESULTS:

Summary of pharmacokinetics:

Plasma PK parameters after iv administration of 100 mg of omadacycline and 50 mg of tigecycline are summarized in Table 1.

Table 1. Summary of Plasma PK Parameters by Treatment Following IV Doses of 100 mg Omadacycline or 50 mg Tigecycline on Day 4

Parameter Statistic	Omadacycline	Tigecycline
AUC_{0-12} (h*µg/mL)		
n	-	17
Mean (SD)	-	2.20 (0.416)
CV%	-	18.85
Geometric Mean	-	2.17
Median	-	2.21
Min, max	-	1.3, 3.0
AUC_{0-24} (h*µg/mL)		
n	41	-
Mean (SD)	12.14 (3.224)	-
CV%	26.55	-
Geometric mean	11.75	-
Median	11.50	-
Min, max	7.2, 19.5	-
C_{max} (µg/mL)		
n	41	17
Mean (SD)	2.12 (0.680)	0.98 (0.210)
CV%	32.16	21.42
Geometric mean	2.02	0.96
Median	1.94	1.01
Min, Max	1.0, 4.3	0.6, 1.4
T_{max} (h)		
n	41	17
Median	0.50	0.50
Min, max	0.0, 1.0	0.5, 0.5
$T_{1/2}$ (h)		
n	41	17
Mean (SD)	16.01 (3.475)	11.44 (2.578)
CV%	21.70	22.54

Table 1 continued

Parameter Statistic	Omadacycline	Tigecycline
Median	15.35	11.42
Min, max	8.9, 23.6	8.0, 18.3
λ_z (1/h)		
n	41	17
Mean (SD)	0.05 (0.010)	0.06 (0.013)
CV%	22.46	20.34
Median	0.05	0.06
Min, Max	0.0, 0.1	0.0, 0.1
V_{ss} (L)		
n	41	17
Mean (SD)	189.84 (52.654)	314.72 (66.747)
CV%	27.74	21.21
Geometric mean	182.50	308.09
Median	188.79	303.58
Min, max	84.2, 306.5	189.3, 475.2
CL_{ss} (L/h)		
n	41	17
Mean (SD)	8.79 (2.212)	23.11 (4.051)
CV%	25.17	17.53
Geometric mean	8.51	22.78
Median	8.69	22.60
Min, max	5.1, 13.8	16.6, 31.9

λ_z = terminal phase rate constant, AUC_{0-12} = area under the (concentration/time) curve from time 0 to 12 hours after dosing, AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours after dosing, CL_{ss} = clearance at steady state, C_{max} = maximum (peak) observed plasma concentration, CV% = percent coefficient of variation, iv = intravenous, max = maximum, min = minimum, PK = pharmacokinetic, SD = standard deviation, $T_{1/2}$ = terminal elimination half-life, T_{max} = time to reach maximum observed plasma concentration, V_{ss} = volume of distribution at steady state.

Source: Table 14.2.1.2. Clinical Study Report: PTK0796-BAL-15104, page 59

• The Vss was high, and consistent with extensive tissue distribution for both drugs.

Pulmonary PK Data:

The AUC_{ELF}, AUC_{AC}, and AUC_{plasma}, as well as the ratios of AUC_{ELF} to AUC_{plasma} and AUC_{AC} to AUC_{plasma} were determined from pooled pulmonary concentration data and were summarized by treatment group in Table 2.

Table 2. Summary of the AUC_{AC}, AUC_{ELF}, and AUC_{Plasma}, Ratio of AUC_{AC}/AUC_{plasma}, and Ratio of AUC_{ELF}/AUC_{plasma} by Treatment

	Omadacycline		Tigecycline	
Descriptive Statistics	AUC Mean	AUC Median	AUC Mean	AUC Median
AUC_{AC} (h·µg/mL)	302.46	292.31	38.50	34.54
AUC_{ELF} (h·µg/mL)	17.23	16.74	3.16	3.04
AUC_{Plasma} (h·µg/mL)	11.73	11.80	1.85	1.83
AUC_{AC}/AUC_{plasma}	25.79	24.77	20.77	18.87
AUC_{ELF}/AUC_{plasma}	1.47	1.42	1.71	1.66

AUC_{AC} = area under the (concentration/time) curve in alveolar cells, AUC_{ELF} = area under the (concentration/time) curve in epithelial lining fluid, AUC_{Plasma} = area under the (concentration/time) curve in plasma.

Source: Table 14.2.2.17. Clinical Study Report: PTK0796-BAL-15104, page 61

• The mean AUC for ELF and AC of omadacycline were approximately 5-times and 8-times higher, respectively, than that for tigecycline.

• The mean AUC estimates for ELF for omadacycline and tigecycline were approximately 50 and 70% higher, respectively, than the AUC in plasma, with omadacycline showing higher exposure in ELF than tigecycline.
A summary of the BAL and plasma sample urea concentrations is provided in Table 3.

Table 3. Summary of BAL and Plasma Sample Urea Concentrations (ng/mL) by Treatment

Descriptive Statistics	Omadacycline	Tigecycline
BAL		
n	41	17
Mean (SD)	4.33 (2.718)	4.25 (2.581)
CV%	62.77	60.66
Median	3.43	3.56
Min, Max	1.4, 14.8	1.9, 12.5
Plasma		
n	41	17
Mean (SD)	296.45 (74.335)	381.69 (120.197)
CV%	25.07	31.49
Median	277.93	314.42
Min, Max	183.3, 576.5	231.8, 645.0

BAL = bronchoalveolar lavage, CV% = percent coefficient of variation, max = maximum, min = minimum, PK = pharmacokinetic, SD = standard deviation.

Clin-Pharm Reviewer's assessment and conclusions:
Omadacycline appears to penetrate into the lungs of healthy subjects, as evidenced by the mean intrapulmonary penetration ratios in epithelial lining fluid (ELF) and alveolar cells (AC) of 1.47 and 25.8, respectively.

Study # CPTK796A2103

Study Title: A randomized, open label, five period, complete cross over study to evaluate the effects of food content and timing on the relative bioavailability of a single oral dose of PTK796 in healthy subjects
Study center: (b) (4)

STUDY DESIGN:
Test Product, Dose, Mode of Administration: Orally administered PTK796 film coated tablets were supplied to the investigator at dose strength of 150 mg which are the to-be marketed tablet formulation of omadacycline.
Duration of Treatment: The total duration of this study for each subject was planned to be approximately 9 weeks, which included 5 single dose study periods each separated by approximately one week.
This was an open-label, randomized, five-period, complete cross-over study in healthy subjects with five treatment conditions:
• A: Fasted (control)

• B: Light, non-fat meal 1 hour (h) after dose administration
• C: Light, non-fat meal 2 h after dose administration
• D: Standard, low-fat meal 2 h after dose administration
• E: High fat meal (per Food and Drug administration [FDA] guidance) 2 h after dose administration

All morning meals that were provided 1 or 2 h after dose administration. Per protocol, dairy and/or calcium rich components were excluded. Table 1 below shows components of different types of meals in this study.

Table 1. Components of different types of meals in this study

Components of Light Non-fat Meal

Content	Calories
Protein	30%
Carbohydrate	≥65%
Fat	≤5%
Total breakfast calories:	300-350

Components of Standard Low-fat Meal

Content	Calories
Protein	30%
Carbohydrate	50%
Fat	20%
Total breakfast calories:	800-1000

Components of FDA High-fat Meal

Content	Calories
Protein	20%
Carbohydrate	30%
Fat	50%
Total breakfast calories:	800-1000

PK Sample Collection: For each treatment, pre-dose and 12 blood samples over 48 h post-dose were collected.

Bioanalytical Method Description:

The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.4.1 for details of validation methods.

RESULTS (Table 2 & 3):

Summary of pharmacokinetics:

The pharmacokinetic parameters after administration of 300 mg PTK796 under fasting and different fed conditions are presented in Table 2. The geometric mean ratio for each pharmacokinetic parameter (Fed/Fasted) and 90% confidence interval for each ratio are

presented in Table 3. Six subjects vomited on 10 occasions within 4 h of dose administration; PK data from those occasions were excluded from the PK analysis.

Table 2. Summary statistics of PK parameters by treatment

Treatment	Statistic	AUC0-24 (ng*h/mL)	AUClast (ng*h/mL)	AUC0-inf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)
A	n	33	33	33	33	33	33
(fasting, reference)	Mean (SD)	5519 (1323.2)	7617 (1792.4)	8785 (2048.6)	484.7 (124.15)	2.42 (0.77)	16.93 (2.22)
	% CV mean	23.98	23.53	23.32	25.62	31.84	13.14
	Geo-mean (CV%)	5369 (24.41)	7412 (24.43)	8549 (24.48)	470.6 (24.73)	2.31 (32.16)	16.79 (12.74)
	Median (range)	5605 (2730–9800)	7758 (3730–13000)	8818 (4320–14200)	485.0 (304–863)	2.5 (1.5–4.0)	17.20 (13.2–24.5)
B	n	32	32	32	32	32	32
(light non-fat meal 1 hr post-dose)	Mean (SD)	4153 (713.52)	5654 (934.98)	6469 (1060.2)	444.2 (124.49)	1.72 (0.38)	16.76 (1.62)
	% CV mean	17.18	16.54	16.39	28.03	22.01	9.66
	Geo-mean (CV%)	4094 (17.41)	5580 (16.59)	6388 (16.27)	429.9 (25.67)	1.68 (21.12)	16.69 (9.47)
	Median (range)	4173 (2760–5900)	5694 (3860–7930)	6432 (4610–9220)	413.5 (248–877)	1.5 (1.0–2.5)	16.30 (14.1–21.1)
C	n	34	34	34	34	34	34
(light non-fat meal 2 hrs post-dose)	Mean (SD)	5043 (956.17)	6881 (1288.8)	7960 (1606.2)	531.1 (134.74)	2.21 (0.54)	16.79 (1.72)
	% CV mean	18.96	18.73	20.18	25.37	24.40	10.27
	Geo-mean (CV%)	4952 (19.76)	6760 (19.66)	7799 (20.91)	514.7 (26.00)	2.13 (29.68)	16.70 (10.66)
	Median (range)	5039 (3160–7460)	6992 (4360–9870)	7962 (4960–11400)	525.5 (282–879)	2.5 (1.0–3.0)	16.60 (12.0–20.7)
D	n	36	36	36	36	36	36
(standard low-fat meal 2 hrs post-dose)	Mean (SD)	5060 (1053.4)	6843 (1369.6)	7809 (1501.5)	560.3 (123.52)	2.28 (0.47)	16.63 (1.76)
	% CV mean	20.82	20.01	19.23	22.05	20.62	10.60
	Geo-mean (CV%)	4946 (22.54)	6701 (21.58)	7659 (20.78)	545.8 (24.48)	2.22 (26.51)	16.54 (10.96)
	Median (range)	4973 (2510–7420)	6637 (3500–9850)	7589 (4030–11000)	561.5 (231–848)	2.5 (1.0–3.0)	16.85 (12.7–19.9)
E	n	37	37	37	37	37	37
(High fat meal 2 hrs post-dose)	Mean (SD)	4902 (904.6)	6649 (1251.4)	7656 (1494.5)	515.9 (94.828)	2.16 (0.57)	17.00 (2.21)
	% CV mean	18.45	18.82	19.52	18.38	26.17	12.98
	Geo-mean (CV%)	4823 (18.40)	6536 (18.89)	7516 (19.71)	507.7 (18.35)	2.07 (31.85)	16.86 (13.14)
	Median (range)	4666 (3220–7220)	6319 (4360–9690)	7364 (4950–10600)	485.0 (310–735)	2.5 (1.0–3.0)	16.77 (12.2–21.9)

Source: PT-Table 14.2-1.3 and PT-Table 14.2-1.4, CSR study number CPTK796A2103, page 55

Under fasted conditions and when all types of meals were given at 2 h post-dose, the T_{max} (median) was 2.5 h after PTK796 administration, while an earlier T_{max} (median) of 1.5 h was observed when a light meal was given at 1 h post-dose.
Meal size and fat content did not have a significant impact on PTK796 absorption and systemic exposure at 2-hour post dose; however, the timing of the meals effected systemic exposure (Table 2).

Table 3. Geometric mean ratio (Fed/Fasted) and 90% confidence intervals for PK parameters

Treatment groups comparison	AUC0-24 ratio (90% CI)	AUClast ratio (90% CI)	AUCinf ratio (90% CI)	Cmax ratio (90% CI)
B/A (light non-fat meal 1 hr post-dose / fasting)	0.76 (0.72 – 0.81)	0.75 (0.71 – 0.80)	0.75 (0.70 – 0.79)	0.91 (0.84 – 0.98)
C/A (light non-fat meal 2 hrs post-dose/ fasting)	0.91 (0.86 – 0.96)	0.90 (0.85 – 0.95)	0.90 (0.85 – 0.96)	1.08 (1.00 – 1.16)
D/A (standard low-fat meal 2 hrs post-dose/ fasting)	0.90 (0.85 – 0.95)	0.88 (0.84 – 0.93)	0.88 (0.83 – 0.93)	1.13 (1.06 – 1.22)
E/A (high fat meal 2 hrs post-dose/ fasting)	0.89 (0.84 – 0.94)	0.87 (0.82 – 0.92)	0.87 (0.82 – 0.92)	1.08 (1.00 – 1.16)
The number of subjects (n) available for each treatment were A=33, B=32, C=34, D=36 and E=37				

Source: PT-Table 14.2-1.1 CSR study number CPTK796A2103, page 56

Clin-Pharm Reviewer's Conclusions:

Regardless of the types of meal (light non-fat, standard low-fat, or FDA high fat), when the meals were given at 2 hours post-dose, the AUCinf was 10 to 13% lower compared to fasted conditions, and Cmax was not substantially altered. Of note, the lower limits of the 90% CI's for the GMR of AUCinf were either at or just slightly below 0.80 for the light non-fat, standard non-fat, and FDA high-fat meals ingested at 2 hours post-dose. When a light non-fat meal was given at 1-hour post-dose, the AUCinf was 25% lower and Cmax was reduced by 9%, when compared to fasted conditions.

In summary, the extent of absorption (AUCinf) of omadacycline was marginally reduced to a similar extent, while the rate of absorption (Cmax) was not substantially altered by low-fat, standard fat, and the FDA high-fat meals when ingested 2 hours post-dose. The extent of absorption was deemed by the reviewer to be significantly reduced when the light non-fat meal was ingested at 1-hour post dose; it would be expected that ingestion of either the standard low-fat or the FDA high-fat meal at 1 hour post dose would result in an even greater reduction of the extent of absorption, and possibly the rate of absorption, of omadacycline.

Therefore, food / meals should not be ingested until at least 2 hours post-dose administration of omadacycline to minimize the food effect on bioavailability with the to-be-marketed tablet formulation.

Study # CPTK796A2104

Study Title: **A randomized, open-label, four periods, cross-over study to evaluate the single dose pharmacokinetics, safety, and tolerability of multiple formulations of omadacycline (formally PTK796) in healthy subjects**

Study center: (b) (4)

STUDY OBJECTIVES:
Primary objective: To evaluate the bioavailability of the 300 mg oral PTK796 (b) (4) tablet compared with 100 mg intravenous infusion.
Secondary objectives: To compare the pharmacokinetics of two oral formulations (slow dissolving tablet, and oral solution) with the PTK796 (b) (4) tablet.
Microbiology Reviewer's Comment: This review will focus only on the PK results for the (b) (4) *300 mg tablet and IV formulations.*

STUDY DESIGN:
Test Product, Dose, Mode of Administration:
Treatment 1: PTK796 IV 100 mg IV infusion.
Treatment 2: PTK796 oral 300 mg (b) (4) tablet.
Treatment 3: PTK796 oral 300 mg slower dissolution tablet.
Treatment 4: PTK796 oral 300 mg oral solution.

Duration of Treatment: The study consists of a 21-day screening period, 4 baseline periods, and 4 treatment periods (single dose of each formulation) followed by a study completion evaluation approximately 1 week (± 1 day) after the last drug administration. Each of the four treatment periods was followed by 7-day washout.

	Period 1	Period 2	Period 3	Period 4
Sequence 01	T1	T4	T2	T3
Sequence 02	T2	T1	T3	T4
Sequence 03	T3	T2	T4	T1
Sequence 04	T4	T3	T1	T2

PK Sample Collection: Blood samples (2 mL) for analysis were collected in heparin-containing tubes:
• IV treatment arm: pre-dose, 12 samples over a period of 48 h post-dose.
• Oral treatment arms: pre-dose, 12 samples over a period of 48 h post-dose

Bioanalytical Method Description:
Plasma samples of omadacycline were analyzed by a validated LC/MS/MS method. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.4.1 for details of validation methods.

RESULTS:

Summary of pharmacokinetics:

The pharmacokinetic parameters of PTK796 following administration of the PTK796 IV 100 mg IV infusion, PTK796 oral 300 mg (b) (4) tablet, are in Table 1.

Table 1-Summary statistics of PK parameters per treatment

Treatment	Statistic	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	CL or CL/F* (L/h)
100 mg IV infusion	n	21	21	21	21	21	21
	Mean (SD)	8770 (1370)	9960 (1540)	1790 (660)	0.469 (0.0930)	16.8 (1.55)	10.3 (1.78)
	CV% mean	15.6	15.5	36.8	19.8	9.3	17.3
	Geo-mean	8660	9840	1700	0.457	16.7	10.2
	CV% geo-mean	16.5	16.3	34.9	25.8	9.7	16.3
	Median	8610	9670	1780	0.500	16.7	10.3
	[Min; Max]	[5650;11100]	[6550;12500]	[968;3860]	[0.250;0.567]	[12.8;18.7]	[8.00;15.3]
300 mg (b) (4) tablet	n	21	21	21	21	21	21
	Mean (SD)	8840 (1980)	10300 (2490)	541 (107)	2.83 (0.730)	16.8 (1.70)	30.7 (6.45)
	CV% mean	22.4	24.3	19.8	25.8	10.1	21.0
	Geo-mean	8650	10000	531	2.74	16.7	30.0
	CV% geo-mean	21.6	23.0	19.0	27.2	10.4	23.0
	Median	7890	9050	520	3.00	16.5	33.1
	[Min; Max]	[6150;12300]	[7340;15300]	[398;806]	[1.50;4.00]	[12.6;20.7]	[19.6;40.9]

* CL for IV infusion; CL/F for oral tablet

Source: PT-Table 14.2-1.3, CSR Study No. CPTK796A2104, page 53

Table 2. Geometric mean ratio and 90% CI for PK parameters

Parameter (Unit)	--Geo-mean ratio (90% CI)-- T2/T1 (300 mg (b) (4) tablet / IV 100 mg infusion)
AUClast (h*ng/mL)	0.98(0.89,1.07)
AUCinf (h*ng/mL)	1.00(0.93,1.07)
Cmax (ng/mL)	0.31(0.27,0.35)

Treatment 1: PTK796 IV 100 mg IV infusion.

Treatment 2: PTK796 oral 300 mg (b) (4) tablet.

Source: PT-Table 14.2-1.1, PT-Table 14.2-1.2 CSR Study no. CPTK796A2104, page 51

A 300 mg dose of PTK796 (b) (4) tablets provided similar exposure relative to the 100 mg IV infusion dose, as indicated by the geometric mean ratio (90% confidence interval) of 1.00 (0.93 – 1.07) and 0.98 (0.89 – 1.07) for AUCinf and AUClast, respectively (Table 2). The absolute bioavailability of the PTK796 (b) (4) tablet was estimated to be 34.5%.

Compared to the (b) (4) tablet, the oral solution yielded 19% higher omadacycline exposure.

Clin-Pharm Reviewer's assessment and issues:

The Reviewer agrees with the Applicant's assessment that the omadacycline oral 300 mg (b) (4) tablet (b) (4) meets bioequivalence criteria relative to omadacycline 100 mg IV infusion, as the 90% confidence intervals of the ratio of geometric means for AUC_{last} and AUC_{inf} were within BE limits of 0.80 – 1.25.

Conclusion: *PTK796 300 mg oral tablet given as to-be-marketed (b) (4) formulation provided equivalent total exposure to the 100 mg IV infusion.*

Study # PTK0796-FDEF-15101

Study Title: A Phase 1, Randomized, Open-Label, 4-Period, Complete Crossover Study to Evaluate the Relative Bioavailability of a Single Oral Dose of Omadacycline in Healthy Subjects Following the Consumption of Food (standard high-fat nondairy and standard high-fat dairy meal)
Study site: (b) (4)

STUDY OBJECTIVES:
The primary objective of this study was to evaluate the relative bioavailability of a single oral dose of omadacycline at various times after the consumption of food in healthy adult subjects.

STUDY DESIGN:
The study consisted of a screening period (Days –21 through –2), 4 baseline periods (Day –1 of each period), 4 treatment periods (Days 1 through 2 of each period), and a study completion visit (within 6 to 10 days of the last dose of omadacycline). There was washout of at least 5 days between doses in each period.
On Day 1 of each period, subjects received a single oral dose of 300 mg omadacycline at various times after the consumption of food. During the 4 treatment periods, subjects fasted overnight (no food or drink except for water for at least 6 hours) and then were served:
A. no meal before the dose (control), a standard high-fat (nondairy) meal was served 3 hours after dosing
B. a standard high-fat (nondairy) meal completed at 4 hours before dosing
C. a standard high-fat (nondairy) meal completed at 2 hours before dosing
D. a standard high-fat meal including dairy completed at 2 hours before dosing

The high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal as per Food and Drug Administration guidance, and provides approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

The standard high-fat meal (nondairy) consisted of 2 eggs fried in 2 teaspoons of olive oil, 2 turkey sausage patties, 2 hash browns fried in 2 teaspoons of olive oil, and 8 fluid ounces of apple juice.
Out of total 855 calories, fat derived 59.0% of calories, carbohydrate derived 27.0% of calories, and protein derived 14.0% of calories).

The standard high-fat meal including dairy consisted of 2 eggs fried in 2 teaspoons of butter, 2 strips of bacon, 2 slices of white toast with 2 teaspoons of butter, 2 hash browns cooked in 2 teaspoons of butter, and 8 fluid ounces of whole milk. Out of total 985 calories, fat derived 59.9% of calories, carbohydrate derived 27.8% of calories, and protein derived 12.3% of calories.

During all 4 treatment periods, subjects had no food or drink except water for at least 3 hours after dosing and no dairy products, antacids, or multivitamins for 4 hours after dosing.

Test Product, Dose, Mode of Administration: Omadacycline 300 mg, as 2 × 150-mg to-be-marketed tablets, administered orally
Duration of Treatment: Single doses of omadacycline were administered on Day 1 of Periods 1, 2, 3, and 4, with a washout of at least 5 days between doses in each period.
PK Sample Collection: Blood samples for PK assessments of omadacycline were collected from all subjects at the following time points: before dosing (pre-dose) and 12 PK samples over 24 hours after dosing in each period.

Bioanalytical Method Description:
Plasma samples of omadacycline were analyzed by a validated LC/MS/MS method. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.2.1 for details of validation methods.

RESULTS:
Summary of pharmacokinetics:
Plasma Pharmacokinetic Parameters of Omadacycline are summarized by treatment in Table 1.
Table 1. Mean (CV) Plasma Pharmacokinetic Parameters of Omadacycline

	300 mg Omadacycline[a]			
Parameter (unit)	Treatment A (n=31)	Treatment B (n=31)	Treatment C (n=31)	Treatment D (n=31)
$AUC_{0\text{-}inf}$ (ng•h/mL)[b]	10158.60 (27.0)[c]	8793.25 (29.2)	5998.57 (25.4)	4028.85 (44.1)
$AUC_{0\text{-}t}$ (ng•h/mL)	7206.33 (28.1)	6083.89 (26.3)	4165.43 (23.4)	2784.04 (44.4)
$AUC_{0\text{-}24}$ (ng•h/mL)	7205.19 (28.1)	6083.70 (26.3)	4164.91 (23.4)	2788.23 (44.3)
C_{max} (ng/mL)	640.84 (25.3)	554.03 (25.0)	388.03 (22.4)	271.10 (42.6)
T_{max} (h)[d]	2.50 (1.50, 4.05)	2.92(1.00, 6.00)	2.92(1.00, 6.00)	2.92 (1.00, 6.00)
$T_{1/2}$ (h)	13.81 (10.3)[c]	13.61 (12.7)	13.61 (12.2)	13.50 (14.7)

Abbreviations: CV, coefficient of variation.
Note: Subjects (b) (6) withdrew prematurely after Period 2, hence n=31 for all treatments (Subject (b) (6) did not receive Treatments A and D, and Subject (b) (6) did not receive Treatments B and C).
[a] Treatment A: no meal before the dose (control), a standard high-fat (nondairy) meal was served 3 hours after dosing
Treatment B: a standard high-fat (nondairy) meal completed at 4 hours before dosing
Treatment C: a standard high-fat (nondairy) meal completed at 2 hours before dosing
Treatment D: a standard high-fat meal including dairy completed at 2 hours before dosing
[b] $AUC_{0\text{-}inf}$ estimates are unreliable and must be viewed with caution; $\%AUC_{extrap}$ was >20% in all instances.
[c] n = 30; a terminal mono-exponential phase could not be unambiguously identified for Subject (b) (6)
[d] For T_{max}, the median (minimum, maximum) values are presented.
Source: Table 14.2.1.2. CSR PTK0796-FDEF-15101, page 61.

The mean estimates of Cmax and AUC of omadacycline were higher when omadacycline 300 mg was administered with no meal before dosing and then a standard high fat nondairy meal ingested 3 hours post-dose (Treatment A) when compared to ingestion of a standard high-fat meal, either nondairy or including dairy, at various times before dosing (Treatments B, C, and D). The mean Cmax and AUC estimates were progressively lower across Treatments B, C, and D, and in particular with ingestion of either standard high fat nondairy or standard high fat dairy meals at 2 hours before omadacycline dosing. Ingestion of a standard high fat nondairy meal at 4 hours before dosing showed the smallest decline in mean Cmax and AUC. By contrast, there were no appreciable differences in Tmax and $t_{1/2}$ between all 4 treatments.

Statistical Analysis of Effect of Food

The statistical analysis of the effect of food on omadacycline PK parameters is presented in Table 2.

Table 2. Statistical Analysis of the Effect of Food on Plasma Pharmacokinetic Parameters of Omadacycline

Parameter (Unit)	Treatment[a]	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means (%)	90% CI of Ratio (%)
AUC_{0-24} (ng•h/mL)	A	31	7384.288			
	B	31	6154.528	B/A	83.346	(74.927, 92.712)
	C	31	4258.530	C/A	57.670	(51.847, 64.147)
	D	31	2757.002	D/A	37.336	(33.594, 41.495)
AUC_{0-t} (ng•h/mL)	A	31	7388.221			
	B	31	6156.815	B/A	83.333	(74.917, 92.694)
	C	31	4260.503	C/A	57.666	(51.845, 64.140)
	D	31	2753.518	D/A	37.269	(33.535, 41.419)
AUC_{0-inf} (ng•h/mL)[b]	A	30[c]	10624.104			
	B	31	8995.928	B/A	84.675	(75.814, 94.571)
	C	31	6209.693	C/A	58.449	(52.336, 65.276)
	D	31	4028.715	D/A	37.921	(33.984, 42.313)
C_{max} (ng/mL)	A	31	656.879			
	B	31	555.192	B/A	84.520	(75.880, 94.143)
	C	31	394.746	C/A	60.094	(53.954, 66.933)
	D	31	267.038	D/A	40.653	(36.529, 45.241)

Abbreviations: CI, confidence interval; LS, least squares.

Notes: A linear mixed-effect model with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect was fitted to the natural log-transformed PK parameters.
Subjects (b) (6) withdrew prematurely after Period 2, hence n=31 for all treatments (Subject (b) (6) did not receive Treatments A and D, and Subject (b) (6) did not receive Treatments B and C).

[a] Treatment A: no meal before the dose (control), a standard high-fat (nondairy) meal was served 3 hours after dosing
Treatment B: a standard high-fat (nondairy) meal completed at 4 hours before dosing
Treatment C: a standard high-fat (nondairy) meal completed at 2 hours before dosing
Treatment D: a standard high-fat meal including dairy completed at 2 hours before dosing

[b] AUC_{0-inf} estimates are unreliable and must be viewed with caution; $\%AUC_{extrap}$ was >20% in all instances.

[c] N = 30; a terminal mono-exponential phase could not be unambiguously identified for Subject (b) (6)

Source: Table 14.2.1.3. CSR PTK0796-FDEF-15101, page 63

Clin-Pharm Reviewer's assessment and conclusions:

The rate (Cmax) and extent of absorption (AUC) of omadacycline were not substantially altered when a high-fat nondairy meal was ingested 4 hours pre-dose.

The rate and extent of absorption was deemed by the reviewer to be significantly reduced when a high-fat nondairy or dairy containing meal is ingested 2 hours pre-dose.

The results indicated that the effect of food was significant when given 2 hours pre-dose and more pronounced when dairy is included with a high-fat meal.

Therefore, food / meals with or without dairy should not be ingested any sooner than 4 hours pre-dose of omadacycline administration to minimize the food effect on bioavailability with the to-be-marketed tablet formulation.

Study #CPTK796A2201

Study Title: An open-label, fixed sequence study to evaluate the pharmacokinetics and safety of single IV and oral doses of omadacycline (formally PTK796) in subjects with mild, moderate, and severe hepatic impairment compared to healthy subjects with normal liver function.

Study centers: The study was conducted in 2 centers

1. (b) (4)
2. (b) (4)

(b) (4)

STUDY DESIGN:

This was an open-label, fixed-sequence study in subjects with mild, moderate, and severe hepatic impairment categorized according to the Child-Turcotte-Pugh scoring method and healthy subjects. Two separate groups of healthy subjects were enrolled, one of which was matched to the subjects with mild hepatic impairment and the other group was matched to the subjects with moderate hepatic impairment. The groups were matched based on sex, age (± 10 years), weight (± 10 kg) and smoking status. There were no healthy subjects matched to subjects with severe hepatic impairment. The study design is presented in Table 1.

Table 1. Study Design

Subjects	Treatment			Study completion
	Period 1	Washout period	Period 2	EOS
Healthy subjects and subjects with mild hepatic impairment	100 mg IV single dose PTK796	≥ 7 days	300 mg oral single dose of PTK796	7-10 days
Healthy subjects and subjects with moderate hepatic impairment	50 mg IV single dose PTK796	≥ 7 days	150 mg oral single dose of PTK796	7-10 days
Subjects with severe hepatic impairment	50 mg IV single dose PTK796	-	-	7-10 days

EOS = End of study.

Test Product, Dose, Mode of Administration:

The study medication was administered by oral (150 mg tablet) and IV (100 mg lyophilisate vials) routes.

Duration of Treatment:

Mild and moderate hepatic impairment groups were treated with single dose (IV/Oral) of omadacycline in 2 treatment periods and severe hepatic impairment group was treated with a single dose (IV only) of omadacycline in period 1.

PK Sample Collection:

Pre-dose, and 14 samples over a period of 96 hours post dose.

Bioanalytical Method Description:
Plasma samples of omadacycline were analyzed by a validated LC/MS/MS method. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.2.1 for details of validation methods.

RESULTS:
Summary of pharmacokinetics:
PTK796 PK parameters in hepatic impairment and matched healthy subjects following IV or oral administration are presented in Table 2. The geometric mean ratio and 90% confidence intervals of AUC_{last}, AUC_{inf}, and C_{max} for all treatment groups are presented in Table 3.

Table 2. Summary Statistics for Plasma PK Parameters Per Treatment Group for PTK796

Treatment	Statistic	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL or CL/F (L/hr)	Vz or Vz/F* (L)
Mild hepatic impaired subjects								
PTK796 100 mg IV lyophilisate	n	5	5	5	5	5	5	5
	Mean (SD)	9733.6 (1942.85)	9733.6 (1942.85)	2514 (669.5)	0.4 (0.14)	12.8 (1.87)	10.63 (2.24)	191.72 (15.47)
	CV% mean	20.0	20.0	26.6	34.2	14.6	21.1	8.1
	Geo-mean	9573.2	9573.2	2442.55	0.38	12.69	10.45	191.23
	CV% geo-mean	20.83	20.83	27.46	39.38	15.14	20.83	8.04
	Median	9371.05	9371.05	2630	0.5	13.46	10.67	185.87
	(Min; Max)	(7165.25, 11795)	(7165.25, 11795)	(1820, 3420)	(0.25, 0.5)	(10.38, 14.84)	(8.48, 13.96)	(175.04, 208.97)
PTK796 300 mg oral dose	n	4	4	4	4	4	4	4
	Mean (SD)	5839.34 (2764.7)	5839.34 (2764.7)	465.5 (216.55)	2 (0.71)	13.18 (2.96)	72.1 (59.72)	1208.84 (678.3)
	CV% mean	47.3	47.3	46.5	35.4	22.5	82.8	56.1
	Geo-mean	5092.42	5092.42	421.19	1.92	12.92	58.91	1098.16
	CV% geo-mean	76.7	76.7	59	33.7	23.89	76.7	50.57
	Median	6621.18	6621.18	475	1.75	13.46	45.32	913.89
	(Min; Max)	(1858.15, 8256.85)	(1858.15, 8256.85)	(200, 712)	(1.5, 3)	(9.53, 16.29)	(36.33, 161.45)	(787.85, 2219.72)
Moderate hepatic impaired subjects								
PTK796 50 mg IV lyophilisate	n	6	5	6	6	5	5	5
	Mean (SD)	3541.67 (397.06)	3555.78 (442.25)	873.33 (208.2)	0.33 (0.13)	8.35 (1.82)	14.22 (1.61)	168.28 (17.77)
	CV% mean	11.2	12.4	23.8	38.7	21.8	11.3	10.6
	Geo-mean	3524.43	3535.19	852.55	0.31	8.21	14.14	167.51
	CV% geo-mean	10.66	11.9	24.55	36.97	20.36	11.9	10.8
	Median	3471.1	3471.08	882.5	0.25	7.99	14.4	168.82
	(Min; Max)	(3114.05, 4300.05)	(3114.05, 4300.05)	(606, 1190)	(0.25, 0.5)	(6.87, 11.42)	(11.63, 16.06)	(142.27, 191.53)
PTK796 150 mg oral dose	n	6	6	6	6	6	6	6
	Mean (SD)	3213.47 (827.81)	3213.47 (827.81)	313.5 (103.98)	1.92 (0.58)	9.21 (0.5)	50.06 (16.43)	658.58 (190.84)
	CV% mean	25.8	25.8	33.2	30.5	5.4	32.8	29.0
	Geo-mean	3112.09	3112.09	301.34	1.85	9.2	48.2	639.45

Table 2 continued

Treatment	Statistic	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL or CL/F (L/hr)	Vz or Vz/F* (L)
	CV% geo-mean	29.56	29.56	30.49	28.02	5.38	29.56	25.92
	Median	3270.33	3270.33	286.5	1.75	9.08	45.88	585.88
	(Min; Max)	(1833.35, 4391.15)	(1833.35, 4391.15)	(207, 511)	(1.5, 3)	(8.7, 9.99)	(34.16, 81.82)	(492.49, 1027.23)
Severe hepatic impaired subjects								
PTK796 50 mg IV lyophilisate	n	5	5	5	5	5	5	5
	Mean (SD)	4483.62 (530.59)	4483.62 (530.59)	910.4 (157.11)	0.5(0)	11.21 (2.61)	11.27 (1.29)	183.83 (54.64)
	CV% mean	11.8	11.8	17.3	0	23.2	11.4	29.7
	Geo-mean	4459.03	4459.03	899.57	0.5	10.95	11.21	177.17
	CV% geo-mean	11.71	11.71	17.45	0	25.19	11.71	31.4
	Median	4273.95	4273.95	864	0.5	12.7	11.7	185.25
	(Min; Max)	(4000.08, 5150.45)	(4000.08, 5150.45)	(715, 1120)	(0.5, 0.5)	(7.84, 13.73)	(9.71, 12.5)	(126.39, 247.54)
Healthy subjects (matched to mild hepatic impaired subjects)								
PTK796 100 mg IV lyophilisate	n	6	5	6	6	5	5	5
	Mean (SD)	10851.28 (2595.05)	11319.45 (2602.69)	1828.33 (456.75)	0.46 (0.1)	16.25 (0.65)	9.14 (1.65)	213.08 (33.27)
	CV% mean	23.9	23.0	25.0	22.3	4.0	18.1	15.6
	Geo-mean	10631.73	11115.63	1784.18	0.45	16.24	9	210.72
	CV% geo-mean	21.58	20.72	24.24	28.87	3.99	20.72	17.37
	Median	10290.3	10536.4	1795	0.5	16.23	9.49	222.89
	(Min; Max)	(8510.45, 15911.7)	(9524.6, 15911.7)	(1370, 2620)	(0.25, 0.5)	(15.53, 17.27)	(6.28, 10.5)	(156.55, 240.14)
PTK796 300 mg oral dose	n	6	6	6	6	6	6	6
	Mean (SD)	6533.46 (1665.25)	6533.46 (1665.25)	445 (74.99)	2.08 (1.02)	14.37 (1.62)	48.35 (11.73)	988.45 (194.52)
	CV% mean	25.5	25.5	16.9	49.0	11.3	24.3	19.7
	Geo-mean	6364.37	6364.37	439.87	1.91	14.29	47.14	971.98
	CV% geo-mean	25.33	25.33	16.7	47.82	11.39	25.33	20.49
	Median	6458.23	6458.23	429	2	14.34	46.75	1006.02
	(Min; Max)	(4636.4, 9276.15)	(4636.4, 9276.15)	(368, 548)	(1, 4)	(12.31, 16.41)	(32.34, 64.71)	(764.47, 1200.92)
Healthy subjects (matched to moderate hepatic Impaired subjects)								
PTK796 50 mg IV lyophilisate	n	6	6	6	6	6	6	6
	Mean (SD)	4198.68 (720.82)	4198.68 (720.82)	844.33 (147.67)	0.5 (0.27)	11.25 (3.01)	12.21(2.09)	191.81 (31.24)
	CV% mean	17.2	17.2	17.5	54.8	26.7	17.2	16.3
	Geo-mean	4147.19	4147.19	833.58	0.45	10.91	12.06	189.79
	CV% geo-mean	17.36	17.36	17.7	55.94	28.04	17.36	15.89
	Median	4161.48	4161.48	846	0.5	11.15	12.03	186.57
	(Min; Max)	(3370.58, 5162.6)	(3370.58, 5162.6)	(675, 1050)	(0.25, 1)	(7.69, 14.46)	(9.69, 14.83)	(159.18, 243.35)
PTK796 150 mg oral dose	n	6	6	6	6	6	6	6
	Mean (SD)	3161.73 (1032.57)	3161.73 (1032.57)	247.83 (55.08)	1.67 (0.26)	12.38 (2.65)	51.23 (14.57)	881.37 (192.08)
	CV% mean	32.7	32.7	22.2	15.5	21.4	28.4	21.8
	Geo-mean	3037.06	3037.06	242.28	1.65	12.13	49.39	864.3
	CV% geo-mean	31.14	31.14	24.24	14.94	23.01	31.14	21.88
	Median	2981.58	2981.58	259	1.5	12.81	50.91	891.69
	(Min; Max)	(2067.6, 5029.75)	(2067.6, 5029.75)	(167, 306)	(1.5, 2)	(8.45, 15.59)	(29.82, 72.55)	(670.69, 1189.03)

*CL and Vz for IV infusion; CL/F and Vz/F for oral formulation.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = (sqrt (exp (variance for log transformed data)-1))*100.

Source: PT-Table 14.2-1.2 and PT-Table 14.2-1.3. CSR Study No. CPTK796A2201, page 48

Table 3. Geometric Mean Ratio Comparison of and 90% Confidence Intervals for Primary PK Parameters (Hepatic Impaired Subjects/Healthy Subjects)

	Group 1[1]		Group 2[2]		Group 3[3]
Parameter (unit)	100 mg IV PTK796	300 mg oral PTK796	50 mg IV PTK796	150 mg oral PTK796	50 mg IV PTK796
AUClast (hr*ng/mL)	0.90 (0.73, 1.11)	0.79 (0.50, 1.24)	0.85 (0.75, 0.97)	1.02 (0.75, 1.40)	1.08 (0.91, 1.27)
AUCinf (hr*ng/mL)	0.86 (0.69, 1.07)	0.79 (0.50, 1.24)	0.88 (0.78, 0.99)	1.02 (0.75, 1.40)	1.08 (0.91, 1.27)
Cmax (ng/mL)	1.42 (1.10, 1.84)	0.96 (0.64, 1.42)	1.02 (0.84, 1.25)	1.24 (0.94, 1.65)	1.08 (0.89, 1.31)

[1] Group 1: mild hepatic impairment vs. Matched healthy subjects.
[2] Group 2: moderate hepatic impairment vs. Matched healthy subjects.
[3] Group 3: Severe hepatic impairment vs. healthy subjects matched to group 2, receiving 50 mg IV PTK796.

Source: PT-Table 14.2-1.5 and PT-Table 14.2-1.6. CSR Study No. CPTK796A2201, page 49

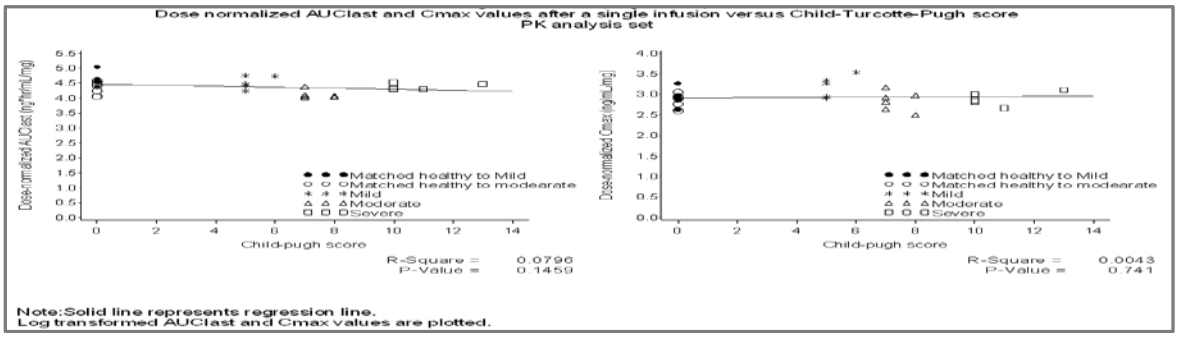
Similar clearance was observed for the different cohorts; geometric means for CL were10.45, 14.14, 11.21, 9.00, and 12.06 L/hour for mild hepatic impairment, moderate hepatic impairment, severe hepatic impairment, healthy subjects matched to mild hepatic impairment, and healthy subjects matched to moderate impairment, respectively.

For oral PTK796, the rate of absorption of PTK796 was similar across the cohorts, with median Tmax of 1.75 hours for the mild and moderate hepatic impaired subjects, and 1.5 to 2.0 hours for the healthy cohorts. Generally, higher inter-subject variability was observed with oral dose treatment arms compared to the IV infusion.

The statistical analysis of the key PK parameters showed that PTK796 exposure (AUC) and C_{max} were comparable between the hepatic impaired subjects with the matching healthy subjects. For the mild hepatic impairment cohort, while a higher C_{max} was observed compared to healthy subjects in the 100 mg IV infusion arm (geometric mean ratio 1.42), this trend was not observed in the moderate or severe hepatic impairment subjects.

The pooled analysis of dose normalized omadacycline AUC or C_{max} across all study groups after IV administration showed no clear relationship between exposure to omadacycline and Child-Turcotte-Pugh score (Figure 1).

Figure 1. Dose-Normalized AUC_{last} and C_{max} of PTK796 vs. Child-Turcotte-Pugh score Following IV Administration, Healthy Subjects Were Assigned a Score of Zero



Source: PT-Figure 14.2-1.2. CSR Study No. CPTK796A2201, page 45

Clin-Pharm Reviewer's assessment:
PTK796 exposures were similar between the subjects with hepatic impairment (regardless of Child-Turcotte-Pugh score) and the matched healthy subjects following IV or oral administration. Likewise, hepatic impairment did not significantly impact PTK796 clearance following either IV or oral administration.
The Reviewer agrees with the Applicant that a dose adjustment does not appear warranted for patients with mild, moderate or severe hepatic impairment.
PK analysis was done for 4 subjects in the mild hepatic impairment 300 mg oral dose group and variability of PK parameters (%CV) was high in the mild hepatic impairment 300 mg oral dose group. However, this trend was not shown in moderate hepatic impairment oral dose group.*

**One subject with mild hepatic impairment (Subject # (b) (6)) received only a single intravenous dose of PTK796 and was subsequently withdrawn from the study due to development of a rash, Subject # (b) (6) did not receive PTK796 orally in Period 2.*
One subject (Subject # (b) (6)) from the mild hepatic impairment group (IV and oral) was excluded from PK analysis as their bioanalytical results was not reportable due to bioanalytical interferences in their samples
Conclusions:
The data from this study suggest no dose adjustment for PTK796 in subjects with hepatic impairment is warranted.

Study # PTK0796-RENL-15102

Study Title: An Open-Label Study to Evaluate the Pharmacokinetics and Safety of a Single IV Dose of Omadacycline in Renal Impairment (RI) Adult Subjects as Compared to Matched Healthy Adult Subjects
Study centers:
(b) (4)

STUDY OBJECTIVES:
Primary Objective:
To compare the pharmacokinetics (PK) of omadacycline in adult subjects with end-stage renal disease (ESRD) on hemodialysis to matched healthy adult subjects
Secondary Objectives:
• To evaluate the safety and tolerability of single iv doses of omadacycline administered to adult subjects with ESRD;
• To determine the proportion of omadacycline removed by hemodialysis;
• To determine the urine concentration of omadacycline after iv administration.

STUDY DESIGN:
Treatment Period 1:

All qualified subjects will be administered a single dose of 100 mg omadacycline for iv infusion on Day 1. The infusion solution will be prepared at the site and administered over approximately 30 minutes. The healthy subjects only received a single iv 100 mg dose of omadacycline. The subjects with ESRD received the first dose of study drug on Day 1 at 0 to 2 hours post dialysis. This dose was given in association with either the Friday or Saturday dialysis session to ensure a 72-hour gap from the start of study drug infusion before the next dialysis session (assuming a 3-day per week intermittent dialysis schedule).

Treatment Period 2:

After a washout period of 10 to 20 days, the subjects with ESRD received a second dose of study drug approximately 60 to 90 minutes prior to dialysis. Healthy subjects will complete the study after Treatment Period 1 and will not continue into Treatment Period 2.

Test Product, Dose, Mode of Administration:

Omadacycline, 100 mg iv infusion given continuously over 30 minutes (at least 30 minutes and not more than 45 minutes)

Duration of Treatment:

For healthy subjects:

• Single dose of omadacycline 100 mg iv.

For ESRD subjects:

• Single dose of omadacycline 100 mg iv;
• Additional dose of omadacycline 100 mg iv, separated by a washout period of 10 to 20 days.

PK Sample Collection:

For healthy subjects and for ESRD subjects completing Period 1 (post-hemodialysis):

• Day 1: Predose, 0.5 (end of infusion), 6 samples over a period of 10 hours post dose;
• Day 2: 24 hours post dose;
• Day 3: 48 hours post dose;
• Day 4: Approximately 68 hours post dose (65 to 70 hours post dose, immediately prior to next dialysis).

For ESRD subjects completing Period 2 (Pre-hemodialysis):

• Day 1: Predose, 0.5 (end of infusion), 6, 10 hours post dose;
• Day 2: 24 hours post dose;
• Day 3: 48 hours post dose;
• Day 4: Approximately 68 hours post dose (65 to 70 hours post dose, immediately prior to dialysis).

Predialyzer (arterial line) and postdialyzer (venous line) blood samples will be obtained at 2, 3, 4, and approximately 5 (end of dialysis) hours during dialysis, after dose administration.

Urine collection for healthy subjects:

• Predose: Sample (-8 to 0 hours);

All urine will be collected from time of dosing up to 72 hours post dose. Urine will be pooled during the intervals above. At the end of each interval, the time and total volume will be recorded.

Dialysate collection for ESRD subjects:
Dialysate samples will be collected during Treatment Period 2. The entire dialysate should be collected, and its total volume recorded. A sample will be retained for drug concentration analysis at the following hourly intervals during treatment:
• Day 1: 0 to 1 hour, 1 to 2 hours, 2 to 3 hours, 3 to 4 hours, 4 hours until the end of dialysis if required based on the duration of dialysis.

Bioanalytical Method Description:
Plasma, urine and dialysate samples of omadacycline were analyzed by a validated LC/MS/MS method. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.2.1 for details of validation methods.

RESULTS:
Summary of pharmacokinetics:
A summary of the Plasma PK parameters following single IV doses of omadacycline are presented in Table 1. The summary of urine PK parameters is presented in Table 2. The summary of dialysate PK parameters is presented in Table 3.

Table 1. Summary of Plasma Pharmacokinetic Parameters following single IV doses of omadacycline

Cohort	$AUC_{0\text{-last}}$ (h*µg/L)	$AUC_{0\text{-inf}}$ (h*µg/L)	C_{max} (µg/L)	t_{max} (h)	$t_{½}$ (h)	CL (L/h)	V_{ss} (L)
Omadacycline 100 mg IV ESRD Subjects on Stable Hemodialysis (Dosing After Dialysis) (N = 8)	9400 (2100)	10300 (2350)	1880 (735)	0.58 (0.58-1.08)	18.6 (5.21)	10.1 (2.24)	214 (56.1)
Omadacycline 100 mg IV ESRD Subjects on Stable Hemodialysis (Dosing Before Dialysis) (N=8)	9250 (1800)	10200 (1990)	2330 (1020)	0.59 (0.58, 0.77)	18.9 (6.34)	10.1 (2.05)	194 (69.2)
Omadacycline 100 mg IV Healthy Controls (N=8)	9080 (1860)	9760 (1770)	1920 (414)	0.58 (0.58, 0.68)	17.1 (2.60)	10.6 (1.99)	204 (47.6)

Source: Table 14.2.2.1, Table 14.2.2.2 Clinical Study Report (CSR): PTK0796-RENL-15102, page 46
Mean (SD) are shown except for t_{max} where median and range (minimum, maximum) are shown.

Table 2. Summary of Urine Pharmacokinetic Parameters following single IV doses of omadacycline

Cohort	Ae (µg)	CL_R (L/h)	Fe_u
Omadacycline 100 mg IV	27000	3.06	0.270
Healthy Controls (N=8)	(3490)	(0.694)	(0.0349)

Ae =cumulative amount of drug excreted in urine, Fe_u =fraction of the dose renally eliminated
Source: Table 14.2.2.3, CSR: PTK0796-RENL-15102, page 47
Mean (SD) are shown

Table 3. Summary of Dialysate Pharmacokinetic Parameters

Cohort	CLhd (L/h)	Fr	AR (µg)	AR/Dose	AUCp (h·µg/L)
Omadacycline 100 mg IV ESRD Subjects on Stable Hemodialysis (Dosing Before Dialysis) (N=8)	9.25 (1.76)	0.478 (1.14)	7890 (1400)	0.0789 (0.0140)	866 (149)

AR=amount recovered in dialysate, CLhd=hemodialysis clearance, Fr=fraction of total elimination occurring by dialysis
Source: Table 14.2.2.4 CSR: PTK0796-RENL-15102, page 47
Mean (SD) are shown

● The mean $t_{1/2}$ following IV administration of 100 mg of omadacycline ranged from 17.1 to 18.9 hours across the cohorts and periods.
● The mean CL ranged from 10.1 to 10.6 L/hr. The percent of the omadacycline dose in the dialysate during dialysis was 7.89% (7.89 mg).

The results of the statistical comparison of PK parameters for ESRD subjects on stable hemodialysis vs matched healthy control subjects are presented in Table 4. The results of the statistical comparison of PK parameters for ESRD subjects on stable hemodialysis for Period 2 (Test) vs Period 1 (Reference) are presented in Table 5.

Table 4. Statistical Comparison of Pharmacokinetic Parameters for ESRD Subjects on Stable Hemodialysis (dosing after dialysis, Period 1) vs Matched Healthy Control Subjects

PK Parameter	Cohort	Geometric Mean	Ratio of Geometric Mean (%)	90% Confidence Interval
$AUC_{0\text{-last}}$ (h*µg/L)	Cohort 1 Period 1 (Test)	9210	103	85.8 - 124.3
	Cohort 2 (Reference)	8910		
$AUC_{0\text{-inf}}$ (h*µg/L)	Cohort 1 Period 1 (Test)	10100	105	87.7 - 125.8
	Cohort 2 (Reference)	9610		
C_{max} (µg/L)	Cohort 1 Period 1 (Test)	1780	94.3	72.4 - 122.7
	Cohort 2 (Reference)	1880		
CL (L/h)	Cohort 1 Period 1 (Test)	9.91	95.2	79.5 - 114.1
	Cohort 2 (Reference)	10.4		

Source: Table 14.2.3.1 CSR: PTK0796-RENL-15102, page 48
Cohort 1 Period 1 (Test): ESRD subjects on stable hemodialysis (dosing after dialysis). Cohort 2 (Reference): Healthy subjects.

Table 5. Statistical Comparison of Pharmacokinetic Parameters for ESRD Subjects (cohort 1) on Stable Hemodialysis for Period 2 (Test- dosing before dialysis) vs Period 1 (Reference- dosing after dialysis)

PK parameter	Cohort	Geometric Mean	Ratio of Geometric Mean (%)	90% Confidence Interval
$AUC_{0\text{-last}}$	Period 2 (Test)	9090	98.8	94.8 - 102.9
(h*µg/L)	Period 1 (Reference)	9210		
$AUC_{0\text{-inf}}$	Period 2 (Test)	10000	99.5	96.1 - 103
(h*µg/L)	Period 1 (Reference)	10100		
C_{max}	Period 2 (Test)	2180	123	98.3 - 153.6
(µg/L)	Period 1 (Reference)	1780		
CL	Period 2 (Test)	9.95	100	97.1 - 104
(L/h)	Period 1 (Reference)	9.91		

Source: Table 14.2.3.2 CSR: PTK0796-RENL-15102, page 49
Cohort 1 Period 1 (reference): Omadacycline 100 mg ESRD subjects on stable hemodialysis (dosing after dialysis);
Cohort 1 Period 2 (Test): Omadacycline 100 mg ESRD subjects on stable hemodialysis (dosing before dialysis).

The effect of RI was evaluated by calculating the relative bioavailability of the 100 mg IV dose administered in ESRD subjects and healthy control subjects. The results are presented in Table 4 and indicate that RI did not have an impact on the overall extent of exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and CL.

The effect of hemodialysis was evaluated by calculating the relative bioavailability of the 100 mg IV dose administered in ESRD subjects before and after hemodialysis. The results are presented in Table 5 indicate that hemodialysis did not have an effect on the overall extent of exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and CL. However, 90% CI for the C_{max} was wide for ESRD subjects on stable hemodialysis vs matched healthy control.

Clin-Pharm Reviewer's assessment:
The results indicate that RI did not have a significant effect on the overall extent of exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) of omadacycline, nor on its CL, Vss, or $t_{1/2}$.
There was a slight increase in mean C_{max} in ESRD patients when dosed before vs. after hemodialysis (approximately 23% increase) which cannot be attributed to hemodialysis itself as the t_{max} occurred prior to the initiation of hemodialysis.
There was also high inter-subject variability in Cmax in ESRD subjects either with dosing before (%CV=43.7%) or after dialysis (%CV= 37.8%).
The Reviewer agrees with the Applicant that dose adjustment of IV omadacycline does not appear warranted for patients with ESRD who are on hemodialysis.
Conclusions:
Based on the results of this study, no dose adjustment is needed for ESRD subjects on hemodialysis when omadacycline is given by the IV route of administration.

Study # PTK0796-DDI-17106

Study Title: **A Phase 1, Open-Label, 3-Period, Single-Sequence Study to Evaluate the Effect of Verapamil Extended Release and a Light Meal on the Pharmacokinetics, Safety, and Tolerability of Omadacycline in Healthy Adult Subjects**

STUDY OBJECTIVES:
The primary objectives of the study were the following:
• To evaluate the effect of a single oral dose of verapamil extended release (ER) on the pharmacokinetics of omadacycline in healthy adult subjects
• To evaluate the effect of a light meal on the pharmacokinetics of omadacycline in healthy adult subjects
STUDY DESIGN:
Test Product, Dose, Mode of Administration:
Omadacycline 300 mg (2 × 150-mg tablets) administered orally
Verapamil ER 240 mg (1 × 240-mg capsule) administered orally
Duration of Treatment: Single doses of omadacycline were administered on Day 1 of Periods 1, 2, and 3, and a single dose of verapamil ER was administered on Day 1 of Period 2 only. There was a washout of at least 4 days between the last dose in one period and the first dose in the next period.

PK Sample Collection:
Blood samples for PK analysis of omadacycline were collected from all subjects at the following time points: before dosing (pre-dose) and 12 PK samples over 24 hours after dosing with omadacycline (all periods).
All 12 subjects enrolled in this study were male. On Day 1 of each period, after an overnight fast (no food or drink except for water for at least 6 hours), subjects received the following study treatments:
• Period 1: single oral dose of 300 mg omadacycline (2 × 150-mg tablets)
• Period 2: single oral dose of 240 mg verapamil ER (1 × 240-mg capsule) followed by a single oral dose of 300 mg omadacycline (2 × 150-mg tablets) 2 hours later
• Period 3: single oral dose of 300 mg omadacycline (2 × 150-mg tablets) with a light meal (orange juice and toast, excluding dairy products)
For all periods, subjects had no food or drink except water for at least 2 hours after dosing and no dairy products, antacids, or multivitamins for 4 hours after dosing with omadacycline.
For Period 2, subjects remained fasted between the time of verapamil dosing and omadacycline dosing. For Period 3, omadacycline was administered in the morning approximately 90 minutes after starting a light meal (orange juice and toast, excluding dairy products).

Bioanalytical Method Description:
Plasma samples of omadacycline were analyzed by a validated LC/MS/MS method. The sample preparation, stability, analysis accuracy, and precision in this clinical pharmacology study were

reviewed by the Clinical Pharmacology reviewer and met the acceptance criteria. Please refer to section 15.2.1 for details of validation methods.

RESULTS:

Plasma PK parameters of omadacycline are summarized by treatment in Table 1.

Table 1. Summary of Plasma Pharmacokinetic Parameters of Omadacycline by Treatment

Parameter (unit)	Omadacycline Alone (n=12)	Omadacycline With Verapamil (n=10)	Omadacycline With Light Meal (n=10)
AUC_{0-24} (ng•h/mL)[a]	6189.20 (26.8)	7269.36 (14.0)	4255.75 (27.4)
AUC_{0-t} (ng•h/mL)[a]	6189.20 (26.8)	7271.67 (14.0)	4256.54 (27.4)
AUC_{0-inf} (ng•h/mL)[a]	8691.00 (28.7)	10775.23 (17.8)	6513.92 (28.2)
C_{max} (ng/mL)[a]	534.31(23.7)	595.70 (12.6)	370.22 (26.8)
T_{max} (h)[b]	2.75 (1.50-4.00)	2.75 (1.50-4.00)	2.75 (2.00-4.00)
$T_{1/2}$ (h)[c]	12.73 (12.1)	14.00 (10.3)	14.61(9.3)
λ_z (1/h)[c]	0.06 (11.2)	0.05 (10.7)	0.05 (9.5)

Abbreviation: CV, coefficient of variation.
Note: AUC_{0-inf} estimates are not precise as $\%AUC_{extrap}$ was greater than 20% in all instances.
[a] Geometric mean (arithmetic CV) values are presented.
[b] Median (minimum - maximum) values are presented.
[c] Arithmetic mean (arithmetic CV) values are presented.

Source: Table 14.2.3. CSR Study No. PTK0796-DDI-17106, page

The Sponsor notes that AUC(0-inf) estimates are not precise since the %AUC(extrap) was greater than 20% in all instances. Thus, the Reviewer will use AUC(0-t) estimates for interpretation of extent of omadacycline absorption results.

Table 2 Statistical Analysis of Plasma Pharmacokinetic Parameters for Omadacycline

Parameter (unit)	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means (%)	90% CI of Ratio (%)
AUC_{0-24} (ng•h/mL)	Period 1	12	6189.201	–	–	–
	Period 2	10	7335.446	Period 2/Period 1	118.520	(103.393, 135.861)
	Period 3	7	4642.213	Period 3/Period 1	75.005	(64.152, 87.694)
AUC_{0-t} (ng•h/mL)	Period 1	12	6189.201	–	–	–
	Period 2	10	7337.800	Period 2/Period 1	118.558	(103.420, 135.912)
	Period 3	7	4643.583	Period 3/Period 1	75.027	(64.167, 87.726)
AUC_{0-inf} (ng•h/mL)	Period 1	12	8691.000	–	–	–
	Period 2	10	10827.965	Period 2/Period 1	124.588	(108.457, 143.118)
	Period 3	7	7020.771	Period 3/Period 1	80.782	(68.919, 94.688)
C_{max} (ng/mL)	Period 1	12	534.314	–	–	–
	Period 2	10	606.752	Period 2/Period 1	113.557	(101.249, 127.361)
	Period 3	7	424.118	Period 3/Period 1	79.376	(69.609, 90.513)

Abbreviation: LS, least squares.
Note: A linear mixed-effect model with treatment as a fixed effect and subject as a random effect was fitted to the natural log transformed pharmacokinetic parameters.
AUC_{0-inf} estimates are not precise as $\%AUC_{extrap}$ was greater than 20% in all instances.
Period 1: omadacycline alone.
Period 2: omadacycline with verapamil.
Period 3: omadacycline with light meal.

Source: Table 14.2.5.2. CSR Study Number PTK0796-DDI-17106, Page 64

Clin-Pharm Reviewer's assessment and conclusions:

Following a single oral dose of verapamil (P-gp inhibitor), the rate (Cmax) and extent (AUC_{0-t}) of omadacycline absorption were increased by approximately 14% and 18%, respectively, as compared to that when omadacycline was administered alone. The increase in exposure of omadacycline is not deemed to be clinically significant by the reviewer and does not warrant a dose adjustment of omadacycline when co-administered with a P-glycoprotein inhibitor.

The rate (Cmax) and extent of absorption (AUC_{0-t}) of omadacycline were reduced by approximately 20 to 25% when a light nondairy meal was ingested 1.5 hours pre-dose. Similar to the other food effect study, the results from this study also indicates that patients need to be fasted prior to taking omadacycline.

***In vitro* Study Reviews**

<table>
<tr><th colspan="2">Evaluation of PTK796 as a Substrate of Human P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 2 (MRP2)</th></tr>
<tr><td>Study #</td><td>DMPK R1000026</td></tr>
<tr><td>Link</td><td>\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4222-absorp\1000026\1000026-pre-clinical-study-report.pdf</td></tr>
<tr><td>Objectives</td><td>Determine if PTK796 is a substrate of Pgp, BCRP and MRP2</td></tr>
<tr><th colspan="2">METHODS</th></tr>
<tr><td>System</td><td>Caco-2 cells</td></tr>
<tr><td>Was an appropriate system used?</td><td>☑ Yes ☐ No</td></tr>
<tr><td>Control concentrations</td><td>High Permeability Marker: [^{3}H]propranolol, 4.5 µM
High Permeability Marker: [^{14}C]mannitol, 3.9 µM
<table>
<tr><th>Transporter</th><th>Inhibitor (concentration)</th></tr>
<tr><td>P-gp</td><td>LY335979 (1µM)
GF120918 (4µM)</td></tr>
<tr><td>BCRP</td><td>Ko143 (1µM)</td></tr>
<tr><td>MRP2</td><td>MK571 (10 µM)</td></tr>
</table></td></tr>
<tr><td>Are controls and control concentrations appropriate?</td><td>☑ Yes ☐ No
All controls are listed on FDA drug interaction website.</td></tr>
<tr><td>Test (substrate or inhibitor) drug concentrations</td><td>[^{14}C]PTK796 (2.0 µM, 12 µM)</td></tr>
<tr><td>Were test drug concentrations appropriate?</td><td>☑ Yes ☐ No</td></tr>
<tr><th colspan="2">RESULTS AND CONCLUSIONS</th></tr>
<tr><td colspan="2">
<table>
<tr><th>Transporter</th><th>Substrate</th><th>Conclusions</th></tr>
<tr><td>Pgp</td><td>Yes</td><td>P-gp inhibitor reduced the efflux ratio close to one. Inhibitor studies suggested that [^{14}C]PTK796 efflux in Caco-2 monolayers was primarily due to P-gp. In vivo DDI study with</td></tr>
</table>
</td></tr>
</table>

		verapamil was conducted by the Applicant.	
BCRP	No		
MRP2	No		

Assessment of PTK796 as an Inhibitor of human BCRP, P-gp and MRP2	
Study #	DMPK R1000028
Link#	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4223-distrib\1000028\1000028-pre-clinical-study-report.pdf
Objective	In Vitro Study Designed to Assess if PTK796 is an Inhibitor of the Efflux Transporters: BCRP, P-gp and MRP2
Cell System Used	T8 cells, MDA435 T0.3 cells, MDCKII-MRP2 cells
Investigational Drug (concentration range)	0.1 µM -50 µM
Probe Substrate (concentration)	BCRP substrate: Bodipy FL prazosin (BDP) [0.05 µM] P-gp substrate: Rhodamine 123 (Rho123) [0.1 µM] MRP2substrate: [^{14}C]Valsartan (VAL489) [10 µM]
Control Inhibitor (concentration)	FTC (10 µM) CsA (10 µM) Indomethacin (100 µM)
Are controls and control concentrations appropriate?	☑ Yes ☐ No All controls are listed on FDA drug interaction website.

Results and Conclusions: PTK796 was not found to be an *in vitro* inhibitor of BCRP, P-gp and MRP2 at concentration up to 50 µM.

Transporter	Probe Substrate	IC_{50} Values (µM)	
		Investigational Drug	**Control Inhibitor**
BCRP	BDP	No Inhibition	0.584 ± 0.084 µM
P-gp	Rho123	No Inhibition	1.5 ± 0.24 µM
MRP2	[^{14}C]VAL489	No Inhibition	IC_{50} Not determined

Interactions of PTK796 with the Human Renal Uptake Transporters organic anion transporters (OAT)1, OAT3 and organic cation transporter2 (OCT2)	
Study #	1000274, 1000027, 1000518
Link	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4223-distrib\1000027\1000027-pre-clinical-study-report.pdf \\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4223-distrib\1000274\1000274-pre-clinical-study-report.pdf

<table>
<tr><td></td><td>\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4223-distrib\1000518\1000518-pre-clinical-study-report.pdf</td></tr>
<tr><td>Objectives</td><td>Determine if PTK796 is an inhibitor of (OAT1, OAT3 and OCT2)
Determine if PTK796 is a substrate of (OAT1, OAT3 and OCT2)</td></tr>
<tr><td colspan="2">METHODS</td></tr>
<tr><td>System</td><td>OAT1 (hOAT1), OAT3 (hOAT3), hOCT2 stably expressed in human embryonic kidney (HEK) cells</td></tr>
<tr><td>Were appropriate systems used?</td><td>☑ Yes ☐ No</td></tr>
<tr><td>Control concentrations</td><td>
<table>
<tr><th>Transporter</th><th>Substrate</th><th>Inhibitor</th></tr>
<tr><td>OAT1</td><td>[^{3}H]para-aminohippurate ([^{3}H]PAH) 1.0 µM</td><td>Probenecid (100 µM)</td></tr>
<tr><td>OAT3</td><td>[^{3}H]estrone-3-sulfate ([^{3}H]E_3S) 1.0 µM</td><td>Probenecid (100 µM)</td></tr>
<tr><td>OCT2</td><td>[^{14}C]metformin (16 µM)</td><td>Decynium 22 (20 µM)</td></tr>
</table>
</td></tr>
<tr><td>Are controls and control concentrations appropriate?</td><td>☑ Yes ☐ No
All controls are listed on FDA drug interaction website.</td></tr>
<tr><td>Test (substrate or inhibitor) drug concentrations</td><td>
<table>
<tr><th>Transporter</th><th>Substrate</th><th>Inhibitor</th><th>PTK796 concentrations (µM)</th></tr>
<tr><td>OAT1 and OAT3</td><td>X</td><td></td><td>25 µM</td></tr>
<tr><td>OAT1 and OAT3</td><td></td><td>X</td><td>Multiple, 1-25 µM</td></tr>
<tr><td>OCT2</td><td>X</td><td></td><td>10 µM</td></tr>
<tr><td>OCT2</td><td></td><td>X</td><td>20µM, 100 µM</td></tr>
</table>
</td></tr>
<tr><td>Were test drug concentrations appropriate?</td><td>☑ Yes ☐ No</td></tr>
<tr><td colspan="2">RESULTS AND CONCLUSIONS</td></tr>
<tr><td colspan="2">PTK0796 is not a substrate of hOAT1, hOAT3 and hOCT2 under these in vitro assay conditions. PTK796 weakly inhibited the activity of hOAT1 (30% at 25 µM), It is unlikely that omadacycline acts as an inhibitor of OAT1 or OAT3 in vivo at Cmax (~ 2 - 3 µM).
<table>
<tr><th>Transporter</th><th>Substrate</th><th>Inhibitor</th><th>IC_{50} (µM)</th><th>Conclusions</th></tr>
<tr><td>OAT1</td><td>No</td><td>No</td><td>-</td><td>Very weak OAT1 inhibitor and not</td></tr>
</table>
</td></tr>
</table>

				OAT1 substrate
OAT3	No	No	-	Not OAT3 inhibitor or substrate
OCT2	No	No	-	Not OCT2 inhibitor or substrate

In vitro Interaction Studies of PTK796 with Human Liver Uptake Transporters human organic anion transporting polypeptide (OATP)1B1 and OATP1B3	
Study #	1000321
Link	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4223-distrib\1000321\1000321-pre-clinical-study-report.pdf
Objectives	Determine if PTK796 is an inhibitor or substrate of OATP1B1, OATP1B3
METHODS	
System	HEK293 cells stably expressing OATP1B1, OATP1B3
Was an appropriate system used?	☑ Yes ☐ No
Control concentrations	

Transporter	Substrate	Inhibitor
OATP1B1	[^{3}H]$E_2$17βG (1μM)	Rifamycin SV (25 μM or 100 μM)
OATP1B3	[^{3}H]CCK8 (46 nM)	Rifamycin SV (25 μM or 100 μM)
OATP1B1	[^{3}H]$E_2$17βG (1μM)	PTK796 20 μM, 100 μM
OATP1B3	[^{3}H]CCK8 (46 nM)	PTK796 20 μM, 100 μM
OATP1B1	[^{14}C]PTK796 (39.8 μM)	
OATP1B3	[^{14}C]PTK796 (11.5 μM)	

Are controls and control concentrations appropriate?	☑ Yes ☐ No All controls are listed on FDA drug interaction website.
Test (substrate or inhibitor) drug concentrations	Inhibitor: PTK796 20, 100 μM Substrate: PTK796 39.8 μM, 11.5 μM
Were test drug concentrations appropriate?	Test drug concentration appears to be high to determine uptake of [^{14}C]PTK796 by cells expressing OATP1B1, OATP1B3. The applicant has not provided a rationale for selecting this concentration of PTK796. ☐ Yes ☑ No

RESULTS AND CONCLUSIONS

Transporter	Substrate	Inhibitor	IC_{50} (μM)	Conclusions
OATP1B1 & OATP1B3	Unclear			PTK796 is not an OATP1B1 and OATP1B3 substrate at supra-therapeutic concentrations (5-13 fold higher than clinically relevant concentrations of PTK0796.
OATP1B1		No	-	Minimally reduced [^{3}H]E217βG (1.0 μM), Not OATP1B1 inhibitor
OATP1B3		No	-	Minimally reduced [^{3}H]CCK8 (44 nM) accumulation, Not OATP1B3 inhibitor

Study #	Title
R1000061	**Evaluation of PTK796 as an inducer of drug metabolizing enzymes and transporters in primary human hepatocytes**
Link	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4224-metab\1000061\1000061-pre-clinical-study-report.pdf
Objectives	Determine if PTK796 is an inducer of CYP enzymes

METHODS

System and controls

Study	System	# donors	Incubation time
DMPK R1000061	Primary human hepatocytes	3	48 hours

CYP	**Positive control inducer (concentration)**
CYP1A2 and UGT1A1	β-napthoflavone (BNF) 10 μM
CYP3A/CYP2B/2C and UGT1A1	Phenobarbital (PB) 1000 μM
CYP3A/2B/2C and ABCB1	Rifampicin (RIF), 1 μM -50 μM

Was the study design appropriate?

Study	Was the study design appropriate?
	☑ Yes ☐ No

Were test drug concentrations

PTK796 Cmax was ~ 2-3 μM.

PTK796 concentration	Were test drug

appropriate?		concentrations appropriate?	
	1-100µM	☑ Yes ☐ No	

RESULTS AND CONCLUSIONS

CYP	Fold change mRNA	Fold change in enzyme activity	Conclusion
CYP1A2	No Change (PTK796 1-50 µM)	No Change	Potential for in vivo CYP and UGT1A1 induction by PTK796 is very unlikely. Slight increase in enzyme activity of CYP2C19 at PTK796 concentration of 10 µM, which is ~ 5-fold higher than clinically relevant concentration.
CYP2B6	No Change (PTK796 1-50 µM)	No Change	
CYP1B1	No Change	No Change	
CYP2C19	1.3-1.9 (PTK796 1-50 µM)	1.2-1.7 (PTK796 1-10 µM)	
CYP2C8	No Change (PTK796 1-10 µM)	No Change	
CYP2C9	No Change	No Change	
CYP3A4/5	No Change	No Change	
UGT1A1	No Change	No Change	

Study #	Title
DMPK R1000754	**In vitro assessment of cytochrome P450 enzyme inhibition by PTK796**
	Determination of the Inhibitory Potency of PTK796 Towards Human CYP Isoforms
Link	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4224-metab\1000754\1000754-pre-clinical-study-report.pdf
Objectives	Determine if PTK796 is an inhibitor of CYP enzymes
METHODS	
System	

Study	System
Reversible inhibition	Human liver microsomes
Time-dependent inhibition	Human liver microsomes

Was an appropriate system used?	☑ Yes ☐ No
Probe substrates	

	Reversible inhibition	Time-dependent inhibition
Enzyme	Probe substrate	Probe substrates
CYP1A2	Phenacetin	Phenacetin
CYP2A6	Coumarin	Diclofenac
CYP2B6	Bupropion	
CYP2C8	Amodiaquine	
CYP2C9	Diclofenac	
CYP2C19	*S*-Mephenytoin	
CYP2D6	Bufuralol	Bufuralol
CYP2E1	Chlorzoxazone	
CYP3A4/5	Testosterone	Midazolam

Were controls appropriate?	☑ Yes ☐ No
Test drug concentrations	PTK796: 1-50 µM
Were test drug concentrations appropriate?	☑ Yes ☐ No

RESULTS AND CONCLUSIONS

	Reversible inhibition	Time-dependent CYP inhibition	
CYP	IC_{50} (µM)[a]	K_I value[a] (µM)	k_{inact}[a] (min^{-1})
CYP1A2	> 100	No time-dependent inhibition	No time-dependent inhibition
CYP2A6	> 100	Not Determined	Not Determined
CYP2B6	> 100	Not Determined	Not Determined
CYP2C8	> 100	Not Determined	Not Determined
CYP2C9	> 100	No time-dependent inhibition	No time-dependent inhibition
CYP2C19	> 100	Not Determined	Not Determined
CYP2D6	> 100	No time-dependent inhibition	No time-dependent inhibition
CYP2E1	> 100	Not Determined	Not Determined
CYP3A4/5	> 100	No time-dependent	No time-dependent

		inhibition	inhibition

[a]PTK796 concentration estimated to inhibit probe substrate reaction by 50%.
[b]K_I is the concentration producing a half maximal apparent inactivation rate; K_{inact} is the maximal inactivation
At clinically relevant concentrations, omadacycline does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 *in vitro* in human liver microsomes.
Omadacycline showed no apparent time-dependent *in vitro* inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5 at concentrations up to 50 µM.

Metabolic profile in human liver microsomes, contributions of cytochrome P450s and UDP-glucuronosyltransferase to metabolism	
Study #	R1000343
Link	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4224-metab\1000343\1000343-pre-clinical-study-report.pdf
Objectives	Determine metabolic profile of PTK796 in liver microsomes, hepatocytes, S9, cytosol and FMO enzymes
METHODS	
System	Liver microsomes, S9, cytosol, hepatocytes and FMO enzymes
Was an appropriate system used?	☑ Yes ☐ No
Methods	The metabolism of [^{14}C]PTK796 was examined: • in pooled human liver microsomes in the presence of NADPH and/or UDPGA. • with human liver S9, cytosol and the recombinant human FMO enzymes. • in cryo-preserved human hepatoctyes. The samples were analyzed by HPLC with off-line radioactivity detection
Test (substrate or inhibitor) drug concentrations	PTK796 (substrate) 12 or 48 µM
Were test drug concentrations appropriate?	☑ Yes ☐ No
RESULTS AND CONCLUSIONS	
PTK796 metabolism was not observed following *in vitro* incubations with cryopreserved human hepatocytes, liver sub-cellular fractions, and recombinant FMO enzymes.	
In vitro plasma protein binding of PTK796 of mouse, rat, cynomolgus monkey, and human	
Study #	1000512
Link	\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\422-pk\4223-distrib\1000512\1000512-pre-clinical-study-report.pdf
Objectives	Determine PTK796 plasma protein binding

METHODS

In vitro plasma protein binding: Investigation by the ultrafiltration method (incubation at 37°C for 30 min after spiking).
Detection technique: LSC (control test) and UPLC-MS/MS
Concentration range: 10, 100, 1000, and 10000 ng/mL PTK796

RESULTS

Mean plasma protein binding parameters of PTK796 for mouse, rat, monkey and human values (mean ± SD or range) are calculated over the nominal concentration range of 10-10000 ng/mL

Species	Mean unbound fraction [%]			Range unbound fraction (fu) [%]			Mean bound fraction [%]		
Mouse	84.7	±	5.31	77.9	-	89.5	15.3	±	5.31
Rat	73.9	±	12.1	54.4	-	81.2	26.1	±	12.1
Monkey	78.8	±	7.26	72.2	-	84.3	21.2	±	7.26
Human	78.7	±	9.72	65.6	-	87.8	21.3	±	9.72

CONCLUSIONS

PTK796 was weakly bound to plasma proteins of all tested species with no major species differences. In the concentration range of 10-10000 ng/mL PTK796, no concentration dependency of plasma protein binding was found.

15.3. Clinical /Statistical Appendices

15.3.1. Table of Currently Approved Drugs for the Treatment of ABSSSI

Table 15.6.1. Table of Currently Approved Drugs for the Treatment of ABSSSI

Agent Name/ Drug Class	Approval Date	Approved Skin Indication
Vancomycin (tricyclic glycopeptide)	1958	Treatment of complicated SSSI (cSSSI) susceptible isolates: Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus bovis, Viridans streptococci group, and Enterococcus faecalis
Cefazolin (cephalosporin)	1973	Treatment of skin and skin structure infections due to S. aureus (penicillin-sensitive and penicillin-resistant), group P beta-hemolytic streptococci, and other strains of streptococci.
Aztreonam (monobactam)	1986	Treatment of skin and skin-structure infections, including those associated with postoperative wounds, ulcers and burns caused by: Escherichia coli; Proteus mirabilis; Serratia marcescens; Enterobacter species; Pseudomonas aeruginosa; Klebsiella pneumoniae; and Citrobacter species
Ciprofloxacin (fluoroquinolone)	1987	Treatment of SSSI (SSSI) susceptible isolates: Staphylococcus aureus (MSSA), S. epidermidis (MSSE), Strep. pyogenes, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa
Clindamycin (lincomycin)	1989	Treatment of skin and skin structure infections caused by: Streptococcus pyogenes, Staphylococcus aureus (including methicillin- susceptible and resistant isolates), and anaerobes.
Meropenem (carbapenem)	1996	Treatment of complicated skin and skin structure infections (cSSSI) due to: Staphylococcus aureus (methicillin-susceptible isolates only), Streptococcus pyogenes, Streptococcus agalactiae, viridian group streptococci, Enterococcus faecalis (vancomycin-susceptible isolate only), Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis
Levofloxacin (fluoroquinolone)	1996	Treatment of uSSSI susceptible isolates: S. aureus or Strep. pyogenes; Treatment of cSSSI susceptible Gram positive and Gram negative isolates: S. aureus (MSSA only), Strep. pyogenes, E. faecalis, (b) (4) and Proteus mirabilis
Linezolid (oxazolidinone)	2000	Treatment of uSSSI caused by susceptible isolates: Staphylococcus aureus (MSSA only) or Streptococcus pyogenes. Treatment of cSSSI (including diabetic foot infections) caused by susceptible isolates: S. aureus (MSSA/MRSA), Strep. pyogenes, or Strep. agalactiae
Moxifloxacin (fluoroquinolone)	2001	Treatment of uSSSI susceptible isolates: S. aureus or Strep. pyogenes; Treatment of cSSSI susceptible Gram positive S. aureus (MSSA only), Escherichia coli, Klebsiella pneumoniae, or Enterobacter cloacae
Ertapenem sodium (Carbapenem)	2001	Treatment of cSSSI (including diabetic foot infections) caused by susceptible Gram positive and Gram-negative isolates: S. aureus (MSSA/ (b) (4)), Strep. pyogenes, Strep. agalactiae, E. coli, K. pneumoniae, Proteus mirabilis, Bacteroides fragilis, Peptostreptococcus species, Porphyromonas asaccharolytica or Prevotella bivia
Daptomycin (cyclic lipopeptide)	2003	Treatment of cSSSI susceptible Gram-positive isolates: S. aureus (including MRSA), Strep. pyogenes, Strep. agalactiae, Strep. dysgalactiae, E. faecalis (vanco susc. isolates only)
Tigecycline (glycylcycline)	2005	Treatment of cSSSI caused by susceptible isolates: E. coli, S. aureus (MSSA/ MRSA), Strep. anginosus group, Strep. pyogenes, Strep. agalactiae, E. faecalis (vanco susc.), (b) (4), Enterobacter cloacae, E. coli, Klebsiella

		oxytoca, Klebsiella pneumoniae
Telavancin (lipoglycopeptide)	2009	Treatment of cSSSI caused by Gram positive: S. aureus (MSSA/ MRSA), Strep. pyogenes, Strep. agalactiae, Strep anginosus group, E. faecalis
Ceftaroline fosamil (cephalosporin)	2010	Treatment of ABSSSI caused by susceptible Gram positive and Gram-negative isolates: S. aureus (MSSA/MRSA), Strep. pyogenes, Strep. agalactiae, E. coli, K. pneumoniae, K. oxytoca
Dalbavancin (semisynthetic lipoglycopeptide)	2014	Treatment of ABSSSI caused by susceptible Gram-**positive** isolates: S. aureus (MSSA/MRSA), Strep. pyogenes, Strep. agalactiae, Strep. dysgalactiae, Strep. anginosus group, E. faecalis (vanco susc isolates only)
Tedizolid phosphate (oxazolidinone)	2014	Treatment of ABSSSI caused by susceptible Gram-**positive** isolates: S. aureus (MSSA/MRSA), Strep. pyogenes, Strep. agalactiae, Strep. anginosus group, E. faecalis (b) (4)
Oritavancin (semi-synthetic lipoglycopeptide)	2014	Treatment of ABSSSI caused by susceptible Gram-positive isolates: S. aureus (MSSA/MRSA), Strep. pyogenes, Strep. agalactiae, Strep. dysgalactiae, Strep. anginosus group, E. faecalis (vancomycin susceptible isolates only)
Source: Clinical Reviewer Abbreviations: ABSSSI=acute bacterial skin and skin structure infections; cSSSI= complicated skin and skin structure infections; MRSA= methicillin resistant staphylococcus aureus; MSSA= methicillin susceptible staphylococcus aureus; MSSE= methicillin susceptible staphylococcus epidermidis; susc= susceptible; uSSSI= uncomplicated skin and skin structure infections; vanco=vancomycin		

15.3.2. Treatment for CABP (IDSA/ATS Guidelines)

Outpatient treatment
1. Previously healthy and no use of antimicrobials within the previous 3 months
   - A macrolide (strong recommendation; level I evidence)
   - Doxycyline (weak recommendation; level III evidence)
2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
   - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
   - A β-lactam **plus** a macrolide (strong recommendation; level I evidence)
3. In regions with a high rate (>25%) of infection with high-level (MIC ≥16 μg/mL) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation; level III evidence)

Inpatients, non-ICU treatment
- A respiratory fluoroquinolone (strong recommendation; level I evidence)
- A β-lactam **plus** a macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment
- A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) **or** a respiratory fluoroquinolone (level I evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Special concerns
- If *Pseudomonas* is a consideration
  - An antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)
  - **or**
  - The above β-lactam plus an aminoglycoside and azithromycin
  - **or**
  - The above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above β-lactam)
  - (moderate recommendation; level III evidence)
- If CA-MRSA is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)

NOTE. CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

15.3.3. Synopsis of complicated skin and skin structure infections (cSSSI): phase2 /3 trials

The Applicant has conducted a Phase 2 trial and a Phase 3 trial (which was subsequently terminated) in cSSSI. The Phase 2 trial, Study PTK0796-CSSI-0702, compared the safety and tolerability of omadacycline and linezolid in adults with cSSSI. The Phase 3 trial, Study PTK0796-CSSI-0804, in subjects with cSSSI, was designed in accordance with the 1998 FDA guidance on developing antimicrobial drugs for the treatment of cSSSI. The cSSSI studies were not consistent with the current FDA guidance for ABSSSI. Trials used different efficacy endpoints than the two Phase 3 ABSSSI trials reviewed in this submission. In these two cSSSI trials, subjects were considered clinical successes if they met all the following:
did not meet any criteria for Clinical Failure;
at the Test of Cure evaluation (TOC), the Blinded Evaluator indicated that the infection had sufficiently resolved such that antibiotics were not needed.

Subjects were initially treated with study drug iv and then switched to oral therapy. The duration of iv treatment was expected to be 4 to 7 days; the total duration of treatment (iv and oral) was expected to be up to 14 days. Longer durations had to be approved by the Medical Monitor. The test-of-cure (TOC) visit was to occur 10-17 days following the last dose of study drug (iv or oral). The primary analysis population is mITT population, which included all subjects in the ITT population with at least 1 infecting pathogen isolated at baseline. The primary outcome measure was clinical response at the TOC visit in the mITT and CE populations.

Summary of Efficacy of Study CSSI-0702:

The primary outcome measure was clinical response at the TOC visit in the mITT and CE populations. In the mITT population, which included all subjects in the ITT population with at least 1 infecting pathogen isolated at Baseline, the clinical success rate was higher in the PTK 0796 group (89.3%) compared to the linezolid group (75.6%; 95% CI of the difference: 13.6 [1.3, 26.0]). The difference in clinical response rates in the mITT population was due to increased clinical failures and non-evaluable subjects in the linezolid group. In the CE population, defined as subjects in the ITT population who met pre-specified criteria, the clinical success rates were high (98.0% PTK 0796, 93.2% linezolid) and comparable between treatment groups (95% CI of the difference: 4.8 [-1.7, 11.4]). Given that the lower limit of the 95% CI for the treatment difference (PTK 0796 – linezolid) was greater than -20% in the mITT and CE populations, PTK 0796 was considered non-inferior to linezolid.
The microbiologic success rate was higher in the PTK 0796 group (86.9%) compared to the linezolid group (73.1%; 95% CI of the difference: 13.8 [0.9, 26.7]) in the mITT population. In the Microbiologically Evaluable (ME) population, the microbiologic success rates were slightly higher than the mITT population at 94.8% in the PTK 0796 group and 90.5% in the linezolid group (difference 95% CI: 4.3 [-5.3, 14.0]).
PTK 0796 and linezolid demonstrated similar eradication rates for methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA) and for the pooled sample of non-*Staphylococcus aureus* pathogens.

Among all 4 analysis populations, the clinical and microbiologic response rates for PTK 0796 were comparable to linezolid. There were no analyses results suggesting any subgroup or outcome for which PTK 0796 might be less effective than linezolid for the treatment of cSSSI. Post hoc analyses conducted to address issues raised about the measurement of lesion size and resolution of fever during antibiotic therapy revealed similarly favorable outcomes in PTK 0796-treated subjects.

Summary of Safety of Study CSSI-0702:

The incidence of any reported treatment-emergent AEs (TEAE) was comparable between the 2 treatment groups.
The most frequently reported TEAEs in both treatment groups were in the gastrointestinal (GI) disorders system organ class (SOC). The most frequently reported TEAEs in the GI disorders SOC were nausea (11.7% PTK 0796, 7.4% linezolid), vomiting (4.5% PTK 0796, 3.7% linezolid), and diarrhea (2.7% PTK 0796, 5.6% linezolid). In the PTK 0796 group, headache (5.4%) was the only non-GI TEAE reported in more than 5% of subjects. In the linezolid group, headache (7.4%) and alanine aminotransferase (ALT) increased (6.5%) were the only non-GI TEAEs reported in more than 5% of subjects. Three subjects (1 PTK 0796, 2 linezolid) were reported with serious AEs (SAEs). In the PTK 0796 group, the SAE of confusional state (worsening confusion) was related to a pre-existing condition. In the linezolid group, the SAEs included 1 subject with wound infection (recurrent wound infection) due to a pre-existing condition and 1 subject with soft tissue infection (a worsening infection in the right Achilles area) related to a pre-existing condition and poor wound care compliance secondary to homelessness.
Two subjects in the linezolid group discontinued from the study prematurely due to TEAEs (dyspepsia; pruritus and rash erythematous) that were assessed by the investigators as possibly related to test article. One subject in the PTK 0796 group was discontinued from the study due to an AE (gas gangrene) that was not treatment-emergent and was assessed by the investigator as not related to treatment.
Elevations of liver transaminases occurred at low rates and were slightly more prevalent in the linezolid group. No cases were serious or led to premature discontinuation of test article. No clinically meaningful change in mean or median values for any laboratory parameter occurred through TOC, and there were no clinically meaningful differences between treatment groups. There were also no clinically significant adverse trends in vital signs or ECG changes.

Summary of Efficacy of Study CSSI-0804:

Given the study was administratively terminated well before the enrollment target, it was not possible to conclude, based on statistical goals for sample size, non-inferiority of PTK 0796 compared to linezolid treatment. However, analyses of four important study populations (ITT, MITT, CE and ME) suggest that clinical success associated with treatment of cSSSI subjects with PTK 0796 is comparable to that achieved with linezolid.
Sponsor-defined clinical response was the principal efficacy endpoint of interest, as it was based on a stricter, more conservative set of criteria than those used by investigators in their defining clinical success. Sponsor defined clinical response took into account minimum duration

of treatment required for outcomes evaluation, use of pre-study antibiotics, use of potentially confounding systemic antibiotics during the study, and the timing of concomitant potentially, curative surgical procedures as additional factors for categorization of a subject clinical response. In the ITT population, success in each treatment arm exceeded 85% at the TOC (85.3% for PTK 0796 and 88.9% for linezolid). In the CE population (subjects evaluated for efficacy per protocol) the success rates in each treatment arm at TOC were greater than 95% (96.7% for PTK 0796 and 95.5% for linezolid. In the MITT population (ITT subjects for whom a bacterial pathogen was identified) the success rates at TOC were 87.0% for PTK 0796 and 92.6% for linezolid. In the ME population the success rates in each treatment arm at TOC were greater than 95% (95.9% for PTK 0796 and 96.2% for linezolid).
In the ME population, the clinical success rate for MRSA, the most frequently isolated pathogen, was 96.2% (25/26) in the PTK 0796 arm and 93.5% (29/31) in the linezolid arm. The corresponding microbiologic success rate was the same as the clinical response rate for PTK 0796 (96.2%), but slightly greater (96.8%, 30/31) than the clinical response rate for linezolid, because one clinical failure was a microbiologic success (documented eradication) in the linezolid arm.

Summary of Safety of Study CSSI-0804:

The incidence of reported adverse events (AE) was comparable between the two treatment groups. The most commonly reported AEs (≥10% frequency in either treatment group) were nausea (26.5% PTK 0796, 26.4% linezolid), headache (23.5% PTK 0796, 6.9% linezolid), vomiting (8.8% PTK 0796, 15.3% linezolid), diarrhea (4.4% PTK 0796, 18.1% linezolid), and dizziness (10.3% PTK 0796, 8.3% linezolid). CK elevation was reported in 8.8% of PTK 0796-treated subjects compared to 2.8% for linezolid. AEs associated with ALT increases were reported in four linezolid-treated subjects (5.6%) compared to one PTK 0796 subject (1.5%). Six linezolid subjects (8.3%) reported rash compared to one subject (1.5%) on PTK 0796.
Four subjects experienced SAEs (3 PTK 0796 and 1 linezolid). The three SAEs occurring in PTK 0796-treated subjects were small bowel obstruction, large left pleural effusion and worsening depression. The one SAE occurring in linezolid-treated subjects was worsening right hand cellulitis.
Two PTK 0796 subjects discontinued the study prematurely due to AEs; one due to exacerbation of elevated liver enzymes and one due to a small bowel obstruction diagnosed after randomization. The PTK 0796 AE of exacerbation of liver enzyme levels already elevated at enrollment was considered possibly related to study drug by the investigator. The AE of obstruction of the small bowel was considered unlikely related to study drug by the investigator. No other clinically relevant patterns of changes in either lab results or ECG readings were observed.

15.3.4. Schedule of Assessment (CABP Trial)

Study Phase	Screening[b]	Double-blind Phase										Follow-up Phase	
		IV Treatment Phase				IV or PO Treatment Phase							
Study Day[a]		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
		IV Dose 1	IV Dose 2										
Screening and eligibility procedures													
Signed informed consent[g]	X												
Medical history, current medical conditions, demography	X												
Assessment of CABP symptom severity[h]	X			X	X	X	X	X	X	X	X	X	
CXR or CT scan[i]	X												
PORT Risk Class, ABG (or pulse oximetry)[j]	X												
Blood and urine samples for local lab hematology/chemistry/urine tests/pregnancy[k]	X												
Review of inclusion and exclusion criteria/randomization (if eligible)	X												
Clinical procedures and test article administration													
Test article administration and accountability[l]		X	X	X	X	X	X	X	X	X	X		
Physical examination[m]	X			X	X	X	X	X	X	X	X	X	
Vital signs[n]	X	X[o]	X[o]	X[o]	X	X	X	X	X	X	X	X	
12-lead ECG	X	X[p]		X[p]					X		X		
Blood for central lab tests: hematology/chemistry/pregnancy	X[q]					X			X	X	X[q]	X[q]	
AEs[r]	X	X----------											----------X
Prior and concomitant medications[s]	X	X----------											----------X
Plasma samples (in heparin) for PK analyses[t]		X	X	X	X	X	X	X	X				

Study Phase	Screening[b]	Double-blind Phase										Follow-up Phase	
		IV Treatment Phase				IV or PO Treatment Phase							
Study Day[a]		Day 1		Day 2	Day 3	Day 4	Day 5	Day 6[c]	Day 7	Day 10[c]	EOT[d]	PTE[e]	Final Follow-up[f]
		IV Dose 1	IV Dose 2										
Assessment for po switch or need for continued therapy[u]						X	X	X	X	X			
Investigator's assessment of clinical response											X	X	
Microbiological procedures													
Blood culture[v]	X	As Clinically Indicated											
Respiratory culture and Gram stain[w]	X										X	X	
Urine for local lab *Legionella pneumophila* and *Streptococcus pneumoniae* antigen test	X												
Blood for central lab *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae serology*	X											X	

ABG = arterial blood gas; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; BP = blood pressure; CABP = community-acquired bacterial pneumonia; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; eCRF = electronic case report form; EOT = end of treatment; HR = heart rate; ICF = informed consent form; iv = intravenous; IxRS = Interactive Voice Response System/Interactive Web Response System; PK = pharmacokinetics; po = per oral; PORT = Pneumonia Outcomes Research Team; PTE = post therapy evaluation; RR = respiratory rate; SAE = serious adverse event.

[a] Study Day 1 was the first day of test article administration. Subsequent study days may have been consecutive calendar days.

[b] Following the signing of an ICF, all Screening evaluations, with the exception of the blood culture sample collection and radiographic confirmation of pneumonia, were completed within the 24 hours prior to randomization. The blood culture sample collection and radiographic confirmation of pneumonia were completed within the 24 hours prior to the first dose of test article.

[c] The Day 6 visit was optional for subjects that had been switched to po test article and had been discharged from a hospital setting. A Day 10 visit should have been conducted for subjects with treatment extending beyond 9 days, unless this visit coincided with the EOT visit.

[d] Was conducted on the day of, or within 2 days following the last dose of test article; should also have been conducted for any prematurely withdrawn subject.

[e] Was conducted 5 to 10 days after the subject's last day of therapy.

[f] Was conducted 30 to 37 days after the start of the first infusion of test article. The Final Follow-up assessment may have been conducted via telephone contact or by another interactive technology for subjects who were considered to be clinical successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must have been conducted in person.

[g] Written and signed ICF must have been obtained before any assessment was performed.

[h] The investigator assessed the severity of the subject's CABP symptoms of cough, sputum production, pleuritic chest pain, and dyspnea based upon the Community-Acquired Bacterial Pneumonia Subject Symptom Severity Guidance Framework for Investigator Assessment.

[i] Subjects must have had a confirming CXR or CT scan consistent with acute bacterial pneumonia within the 24 hours prior to the first dose of test article.

[j] Only subjects with a PORT Risk Class of II, III, or IV were eligible for enrollment.

[k] Local laboratory hematology and chemistry evaluations required for assessing subject eligibility, urine dipstick test, a urine pregnancy test (for women only), serum transaminase, or bilirubin levels.

[l] Subjects should have received their first dose of test article within 4 hours after randomization. The total duration of test article therapy (iv plus po) for all subjects was at least 7 days and no more than 14 days. The pharmacist or designee was unblinded to prepare appropriate iv doses of the IxRS identified test article. An unblinded field monitor performed drug accountability of iv medication and reviewed the pharmacist's records. Oral test article may have been dispensed and reconciled by blinded or unblinded personnel. Monitoring of oral medication accountability was performed by the blinded or unblinded field monitor. Subjects discharged with po test article were asked to return all unused test article and packaging at each visit. At the EOT visit, subjects discharged with po test article returned any remaining unused po test article and site staff performed accountability.

[m] A full physical examination was completed at Screening; thereafter only changes from Screening measurements were recorded as AEs on the eCRFs.

[n] Vital signs included body temperature, BP, pulse/HR, and RR.

[o] For the first 3 doses of test article, HR, and BP were recorded at the following times: just prior to the first infusion, within 30 to 90 minutes after the start of the first infusion, and at 3.5 to 5.5 hours after the start of the first infusion.

[p] A 12-lead ECG was performed just prior (within 30 minutes) and 30 to 90 minutes after the start of the first infusion of the first and third doses of test article.

[q] Blood was collected from all female subjects for a serum β-hCG pregnancy test at the central laboratory at the Screening, EOT, and PTE visits.

[r] A subject's AEs and SAEs was recorded and reported from the signing of the ICF to the Final Follow-up assessment.

[s] Treatments that had been administered within the 7 days prior to the date of signing the ICF or during the Screening phase were recorded on the eCRF. All medications and significant nondrug therapies administered after the first dose of test article were recorded on the eCRF.

[t] Up to 4 samples were collected per subject between study Days 1 to 7. The PK sample collection schedule for the individual subject was provided by the sponsor.

[u] At any time after the first 3 days of iv treatment (after 4 iv doses), the subject may have been switched to po medication based upon the determination of clinical stability. The first po dose should have been administered in the morning, 12 to 24 hours after the last iv dose. At the investigator's discretion, all therapy may have been discontinued after the seventh day of treatment, when the infection was considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy was no longer needed).

[v] If bacteria were isolated from baseline blood cultures, repeat blood cultures were collected on the day that the positive blood culture was detected. If subsequent blood cultures were also positive, blood cultures were repeated as necessary until negative blood cultures were obtained.

[w] Culture and Gram stain from an adequate quality sputum specimen or other respiratory specimen. At the EOT and/or PTE visit, respiratory specimen cultures and Gram stains were obtained only for subjects who were clinical failures and required alternative antibacterial treatment for CABP.

Source: CSR

15.3.5. Analysis Population CABP

Table below summarizes analyses population and reason for exclusion from specific analysis population category for Study CABP-1200.

Table Overview of Analysis Populations- Study CABP-1200		
	Treatment Group	
	Omadacycline n (%)	Moxifloxacin n (%)
ITT Population	386	388
Safety population	382 (99)	388 (100)
Number excluded from population	4 (1)	0
Reason for exclusion: *Patients that did not receive study drug*		
micro-ITT population	204 **(53)**	182 **(47)**
Number excluded from population	182 (47)	206 (53)
Reason for exclusion: Patients not having a causative bacterial pathogen at Baseline		
Expanded micro-ITT population	218 (56.5)	198 (51)
Number excluded from population	168 (43.5)	190 (49)
Reason for exclusion: *Patients not having a causative bacterial pathogen at Baseline*		
CE-EOT population	357 (92.5)	357 (92)
Number excluded from population	29 (7.5)	31 (8)
Reason for exclusion:		
Did not meet protocol inclusion criterion (3,4,5,6,7)	7 (1)	6 (1.5)
Met protocol exclusion criterion (2,3,4,11,12)	0	2 (0.5)
Met prior antibacterial exclusion criterion (1)	1 (0.3)	2 (0.5)
Received effective systemic concomitant antibacterial therapy from the first dose of study drug through EOT	1 (0.3)	1 (0.3)
Did not receive active study drug	4 (1)	0
Did not meet minimum study drug duration for evaluable success or failure criteria	8 (2)	5 (1)
Investigator's assessment of clinical response at EOT was indeterminate	10 (3)	11 (3)
EOT visit did not occur on the day of, or within 2 days following the last dose of study drug	3 (0.8)	6 (1.5)
CE-PTE population	340 (88)	345 (89)
Number excluded from population	46 (12)	43 (11)
Reason for exclusion:		
Did not meet protocol inclusion criterion (3,4,5,6,7)	7 (2)	6 (1.5)
Met protocol exclusion criterion-2,3,4,11, and12	0	2 (0.5)
Met prior antibacterial exclusion criterion	1 (0.3)	2 (0.5)
Received effective systemic concomitant antibacterial therapy from the first dose of study drug through PTE	2 (0.5)	3 (0.8)
Did not receive active study drug	4 (1)	0

Table Overview of Analysis Populations- Study CABP-1200		
	Treatment Group	
	Omadacycline n (%)	Moxifloxacin n (%)
Did not meet minimum study drug duration for evaluable success or failure criteria	8 (2)	5 (1)
Investigator's assessment of overall clinical response at PTE was indeterminate	16 (4)	16 (4)
The PTE visit did not occur 5-10 days after the last dose of study drug	12 (3)	12 (3)
ME-EOT population	193 (50)	172 (44)
Number excluded from population	193 (50)	216 (55.7)
Reason for exclusion:		
Not included in micro-ITT population	164 (42.5)	185 (48)
Not included in CE-EOT population	11 (3)	10 (3)
Not included in both CE-EOT and micro-ITT populations	18 (5)	21 (5)
ME-PTE population	188 (49)	169 (44)
Number excluded from population	198 (51)	219 (56)
Reason for exclusion:		
Not included in micro-ITT population	152 (39)	176 (45)
Not included in CE-PTE population	16 (4)	13 (3)
Not included in both CE-PTE and micro-ITT populations	30 (8)	30 (8)
Source: Clinical Reviewer; modified from Applicants Table 9, CSR: PTK0796-CABP-1200		

15.3.6. Receipt of Systemic Corticosteroids (CABP1200-ITT population)

Table Systemic Corticosteroids taken between first infusions of study drug to Final Follow up visit - Study CABP1200 (ITT Population)				
Anatomical Therapeutic Chemical Classification (ATC3) Preferred Name	Omadacycline N=386		Moxifloxacin N=388	
	n (%)		n (%)	
Corticosteroids for Systemic Use, Plain	**70**	**18**	**99**	**26**
Methylprednisolone	28	7	41	11
Methylprednisolone Sodium Succinate	11	3	14	4
Dexamethasone	10	3	18	5
Hydrocortisone	7	2	9	2
Prednisolone	6	1	12	3
Prednisone	6	2	8	2
Dexamethasone Sodium Phosphate	3	0.8	1	0.3
Hydrocortisone Sodium Succinate	3	0.8	3	0.8
Budesonide	1	0.3	0	0
Fludrocortisone Acetate	1	0.3	0	0
Hydrocortisone Hydrogen Succinate	1	0.3	2	0.5
Betamethasone	0	0	1	0.3

Table Systemic Corticosteroids taken between first infusions of study drug to Final Follow up visit - Study CABP1200 (ITT Population)		
Anatomical Therapeutic Chemical Classification (ATC3) Preferred Name	Omadacycline N=386	Moxifloxacin N=388
	n (%)	n (%)
Source: Clinical Reviewer's Analysis		

15.3.7. Patient Disposition and Protocol Violation (ABSSSI Trials)

Patient Disposition -Study ABSI-1108 (ITT Population)

Parameter/Category	Omadacycline (N = 329)	Linezolid (N = 326)	All Patients (N = 655)
Randomized	329 (100.0)	326 (100.0)	655 (100.0)
Completed study Treatment	296 (90.0)	288 (88.3)	584 (89.2)
Prematurely discontinued from study Treatment	33 (10.0)	38 (11.7)	71 (10.8)
Reason for premature discontinuation from study treatment			
AE	6 (1.8)	7 (2.1)	13 (2.0)
Lost to follow-up	5 (1.5)	9 (2.8)	14 (2.1)
Withdrawal by patient	8 (2.4)	6 (1.8)	14 (2.1)
Physician decision	7 (2.1)	9 (2.8)	16 (2.4)
Death*	0	1 (0.3)	1 (0.2)
Other	7 (2.1)	6 (1.8)	13 (2.0)
Completed study**	301 (91.5)	294 (90.2)	595 (90.8)
Prematurely discontinued from study	28 (8.5)	32 (9.8)	60 (9.2)
Reason for premature discontinuation from study			
AE	0	1 (0.3)	1 (0.2)
Lost to follow-up	11 (3.3)	18 (5.5)	29 (4.4)
Withdrawal by patient	9 (2.7)	4 (1.2)	13 (2.0)
Physician decision	1 (0.3)	1 (0.3)	2 (0.3)
Death€	1 (0.3)	2 (0.6)	3 (0.4)
Other	7 (2.1)	6 (1.8)	13 (2.0)

Source: Clinical Reviewer's Analysis
*Patients who were randomized but not treated were counted as "other" for reason for premature discontinuation from study drug and from study.
**Summary of patients that completed the study (i.e., received at least 1 dose of study drug and completed EOT, PTE, and Follow-up).
€ One patient (Patient (b) (6)) in the omadacycline group was originally classified as premature discontinuation from study treatment due to an AE and lost to follow-up at the time of study completion. After database lock, however, the site was notified that the patient had died 1 day (Day 2) after study drug discontinuation.

Patient Disposition -Study ABSI-16301 (ITT Population)

Parameter/ Category	Omadacycline (N =368)	Linezolid (N =367)	All Patients (N =735)
Randomized	368 (100.0)	367 (100.0)	735 (100.0)
Completed study Treatment	**328 (89.1)**	**315 (85.8)**	**643 (87.5)**

Parameter/ Category	Omadacycline (N =368)	Linezolid (N =367)	All Patients (N =735)
Prematurely discontinued from study Treatment	40 (10.9)	52 (14.2)	92 (12.5)
Reason for premature discontinuation from study treatment			
AE	6 (1.6)	4 (1.1)	10 (1.4)
Lost to follow-up	18 (4.9)	25 (6.8)	43 (5.9)
Withdrawal by patient	6 (1.6)	8 (2.2)	14 (1.9)
Physician decision	3 (0.8)	7 (1.9)	10 (1.4)
Death	0	0	0
Other	7 (1.9)	8 (2.2)	15 (2.0)
Completed study	314 (85.3)	310 (84.5)	624 (84.9)
Prematurely discontinued from study	54 (14.7)	57 (15.5)	111 (15.1)
Reason for premature discontinuation from study			
AE	1 (0.3)	0	1 (0.1)
Lost to follow-up	37 (10.1)	38 (10.4)	75 (10.2)
Withdrawal by patient	11 (3.0)	12 (3.3)	23 (3.1)
Physician decision	0	1 (0.3)	1 (0.1)
Death	0	0	0
Other	5 (1.4)	6 (1.6)	11 (1.5)
Source: CSR			

Protocol Violation (Study ABSI 1108 and Study ABSI16301)

In Study ABSI-1108, major protocol deviations were uncommon, occurring in < 5% of all subjects for each category. The most commonly reported deviations included visit scheduling/subject visit completion issues (4.6% ITT subjects) and missing endpoint assessments (3.2% subjects). These major types of protocol deviations led to exclusion of such subjects from the evaluable populations; however, these protocol deviations did not have a major impact on the efficacy assessment.

Table: Major Protocol Deviations (Sponsor Defined)-Study ABSI-1108 (ITT Population)			
Subjects with at least 1 major protocol deviation by category	**Omadacycline (N = 329)**	**Linezolid (N = 326)**	**All Subjects (N = 655)**
Visit scheduling/subject visit completion	10 (3.0)	20 (6.1)	30 (4.6)
Missing endpoint assessments	8 (2.4)	13 (4.0)	21 (3.2)
Study treatment/medication compliance	5 (1.5)	5 (1.5)	10 (1.5)
Exclusion criteria	5 (1.5)	1 (0.3)	6 (0.9)
Study procedures/assessments	4 (1.2)	4 (1.2)	8 (1.2)
Concomitant medication	4 (1.2)	5 (1.5)	9 (1.4)
Study treatment administration/dispense	3 (0.9)	2 (0.6)	5 (0.8)
Inclusion criteria	3 (0.9)	3 (0.9)	6 (0.9)
Informed consent	2 (0.6)	1 (0.3)	3 (0.5)
Investigator safety reporting (regulatory/sponsor)	2 (0.6)	2 (0.6)	4 (0.6)
Accidental unblinding	1 (0.3)	1 (0.3)	2 (0.3)

Table: Major Protocol Deviations (Sponsor Defined)-Study ABSI-1108 (ITT Population)			
Subjects with at least 1 major protocol deviation by category	**Omadacycline (N = 329)**	**Linezolid (N = 326)**	**All Subjects (N = 655)**
Source: Clinical Reviewer's and CSR			

In Study ABSI-16301, major protocol deviations occurred in < 10% of all subjects for each category. The most commonly reported deviations included missing endpoint assessments (7.5% of all subjects), visit scheduling issues (5.6% of all subjects), and study treatment compliance issues (3.9% of all subjects).

Table: Major Protocol Deviations (Sponsor Defined)-Study ABSI-16301 (ITT Population)			
Subjects with at least 1 major protocol deviation by category	**Omadacycline (N = 368)**	**Linezolid (N = 367)**	**All Subjects (N = 735)**
Missing endpoint assessments	26 (7.1)	29 (7.9)	55 (7.5)
Visit scheduling/subject visit completion	23 (6.3)	18 (4.9)	41 (5.6)
Study treatment/medication compliance	14 (3.8)	15 (4.1)	29 (3.9)
Inclusion criteria	13 (3.5)	10 (2.7)	23 (3.1)
Study treatment randomization*	7 (1.9)	0	7 (1.0)
Study procedures/assessments	5 (1.4)	4 (1.1)	9 (1.2)
Concomitant medication	2 (0.5)	1 (0.3)	3 (0.4)
Study treatment administration/dispense	1 (0.3)	0	1 (0.1)
Exclusion criteria	0	1 (0.3)	1 (0.1)
Source: Clinical Reviewer's analysis Stratification errors in the IWRS system during study treatment randomization occurred in 7 omadacycline subjects. Errors included 5 omadacycline subjects randomized to the incorrect infection type stratum and 2 omadacycline subjects randomized to the incorrect prior antibacterial stratum.			

15.3.8. Patient Disposition and Protocol Violations (CABP Trial)

Patient Disposition and Protocol violations (ITT Population)-Study CABP1200

Patient Disposition and Protocol violations (ITT Population)-Study CABP1200			
Category	**OMC**	**MOXI**	**Total**
	N= 386	**N=388**	**N=774**
	n (%)	**n (%)**	**n (%)**
Patient Disposition			
Randomized*	386 (100.0)	388 (100.0)	774 (100.0)
Completed study treatment	352 (91.2)	346 (89.2)	698 (90.2)
Prematurely discontinued from study treatment	34 (8.8)	42 (10.8)	76 (9.8)
Reason for premature discontinuation from 'study Treatment'			
AE	17 (4.4)	28 (7.2)	45 (5.8)
Lost to follow-up	0	1 (0.3)	1 (0.1)
Withdrawal by patient	4 (1.0)	3 (0.8)	7 (0.9)
Physician decision	3 (0.8)	9 (2.3)	12 (1.6)
Death	4 (1.0)	1 (0.3)	5 (0.6)
Other	6 (1.6)	0	6 (0.8)
Completed study**	356 (92.2)	362 (93.3)	718 (92.8)

Patient Disposition and Protocol violations (ITT Population)-Study CABP1200			
Category	**OMC**	**MOXI**	**Total**
	N= 386	**N=388**	**N=774**
	n (%)	**n (%)**	**n (%)**
Prematurely discontinued from study	30 (7.8)	26 (6.7)	56 (7.2)
Reason for premature discontinuation from 'study'			
AE	7 (1.8)	9 (2.3)	16 (2.1)
Lost to follow-up	0	3 (0.8)	3 (0.4)
Withdrawal by patient	7 (1.8)	8 (2.1)	15 (1.9)
Physician decision	0	1 (0.3)	1 (0.1)
Death	6 (1.6)	3 (0.8)	9 (1.2)
Other	10 (2.6)	2 (0.5)	12(1.6)
Protocol Violations			
Patients with at least 1 major protocol deviation	92 (23.8)	83 (21.4)	175 (22.6)
Study treatment randomization	25 (6.5)	24 (6.2)	49 (6.3)
Exclusion criteria	24 (6.2)	21 (5.4)	45 (5.8)
Study procedure/assessment	20 (5.2)	20 (5.2)	40 (5.2)
Inclusion criteria	10 (2.6)	11 (2.8)	21 (2.7)
Missing endpoint assessment	11 (2.8)	8 (2.1)	19 (2.5)
Other ICH/GCP deviation	5 (1.3)	5 (1.3)	10 (1.3)
Study treatment compliance	4 (1.0)	5 (1.3)	9 (1.2)
Study treatment administration/dispense	4 (1.0)	0	4 (0.5)
Concomitant medication	2 (0.5)	3 (0.8)	5 (0.6)
Informed consent	1 (0.3)	1 (0.3)	2 (0.3)
(Serious) AE reporting	1 (0.3)	2 (0.5)	3 (0.4)

Source: CSR
*4 patients were randomized but did not receive study drug.
**Patients who received at least 1 dose of study drug and completed EOT, PTE, and Follow-up;

15.3.9. Baseline Pathogen Characteristics (ABSSSI Trials)

Baseline Pathogenic Organisms from the ABSSSI Site or Blood Culture by Genus and Species in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population)

	ABSI-1108		**ABSI-16301**	
Baseline Pathogen	**Omadacycline (N = 228) n (%)**	**Linezolid (N = 227) n (%)**	**Omadacycline (N = 276) n (%)**	**Linezolid (N = 287) n (%)**
Gram-positive organisms (aerobes)	220 (96.5)	219 (96.5)	270 (97.8)	278 (96.9)
Staphylococcus aureus	156 (68.4)	151 (66.5)	220 (79.7)	233 (81.2)
MSSA	88 (38.6)	102 (44.9)	120 (43.5)	130 (45.3)
MRSA	69 (30.3)	50 (22.0)	104 (37.7)	107 (37.3)
Streptococcus anginosus group	47 (20.6)	37 (16.3)	57 (20.7)	45 (15.7)
Streptococcus constellatus	25 (11.0)	14 (6.2)	9 (3.3)	7 (2.4)
Streptococcus intermedius	12 (5.3)	18 (7.9)	23 (8.3)	24 (8.4)
Streptococcus anginosus	8 (3.5)	7 (3.1)	27 (9.8)	20 (7.0)
Streptococcus pyogenes	11 (4.8)	18 (7.9)	29 (10.5)	16 (5.6)
Enterococcus faecalis (VSE)	10 (4.4)	13 (5.7)	7 (2.5)	10 (3.5)

	ABSI-1108		ABSI-16301	
Baseline Pathogen	**Omadacycline (N = 228) n (%)**	**Linezolid (N = 227) n (%)**	**Omadacycline (N = 276) n (%)**	**Linezolid (N = 287) n (%)**
Staphylococcus lugdunensis	6 (2.6)	3 (1.3)	5 (1.8)	0
Streptococcus mitis	6 (2.6)	4 (1.8)	1 (0.4)	0
Streptococcus Group C	4 (1.8)	1 (0.4)	0	0
Streptococcus viridans group	3 (1.3)	5 (2.2)	3 (1.1)	0
Streptococcus sanguinis	2 (0.9)	6 (2.6)	1 (0.4)	0
Streptococcus Group F	1 (0.4)	4 (1.8)	0	0
Gram-positive organisms (anaerobes)	16 (7.0)	15 (6.6)	17 (6.2)	17 (5.9)
Finegoldia magna	4 (1.8)	5 (2.2)	3 (1.1)	1 (0.3)
Clostridium species	3 (1.3)	2 (0.9)	4 (1.4)	1 (0.3)
Actinomyces odontolyticus	0	0	3 (1.1)	1 (0.3)
Clostridium perfringens	1 (0.4)	5 (2.2)	5 (1.8)	9 (3.1)
Gram-negative organisms (aerobes)	28 (12.3)	23 (10.1)	24 (8.7)	30 (10.5)
Enterobacter cloacae complex	6 (2.6)	4 (1.8)	5 (1.8)	6 (2.1)
Klebsiella pneumoniae	6 (2.6)	5 (2.2)	5 (1.8)	6 (2.1)
Haemophilus parainfluenzae	5 (2.2)	5 (2.2)	1 (0.4)	0
Pseudomonas aeruginosa	3 (1.3)	2 (0.9)	1 (0.4)	2 (0.7)
Enterobacter cloacae	3 (1.3)	1 (0.4)	5 (1.8)	6 (2.1)
Escherichia coli	2 (0.9)	3 (1.3)	4 (1.4)	1 (0.3)
Enterobacter aerogenes	1 (0.4)	3 (1.3)	0	1 (0.3)
Morganella morganii	1 (0.4)	3 (1.3)	1 (0.4)	1 (0.3)
Klebsiella oxytoca	2 (0.9)	1 (0.4)	3 (1.1)	2 (0.7)
Eikenella corrodens	2 (0.9)	2 (0.9)	3 (1.1)	3 (1.0)
Proteus mirabilis	2 (0.9)	1 (0.4)	2 (0.7)	7 (2.4)
Gram-negative organisms (anaerobes)	17 (7.5)	13 (5.7)	11 (4.0)	12 (4.2)
Prevotella melaninogenica	7 (3.1)	6 (2.6)	2 (0.7)	3 (1.0)
Prevotella intermedia	2 (0.9)	3 (1.3)	2 (0.7)	0
Prevotella denticola	2 (0.9)	1 (0.4)	5 (1.8)	1 (0.3)
Source: Clinical Reviewer's Analysis				

15.3.10. Clinical Response by Pathogen at ECR in ABSSSI Trials

Table Comparison in Early Clinical Success (ECR) rates by Baseline Pathogen (from ABSSSI Site or Blood Culture) in ≥ 6 Patients in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population)**

	ABSI-1108		ABSI-16301		Pooled ABSI-1108 and ABSI-16301		
Baseline Pathogen	**OMC (N = 228) n/N1 (%)**	**LNZ (N = 227) n/N1 (%)**	**OMC (N = 276) n/N1 (%)**	**LNZ (N = 287) n/N1 (%)**	**OMC (N = 504) n/N1 (%)**	**LNZ (N = 514) n/N1 (%)**	**Difference (95% CI for Pooled Population)**
Gram-positive organisms (aerobes)							
S. 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)	*3.7 (-1.2, 8.6)*
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)	3.4 (-3.1,10.2)
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)	3.7 (-3.3,10.6)
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 Gr	39/47 (83.0)	27/37 (73.0)	54/57 (94.7)	36/45 (80.0)	93/104 (89.4)	63/82 (76.8)	*12.6 (1.9, 24.0)*
S. 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)	22.2 (10.5.40.9)
S. 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)	15.2 (-1.9,31.7)
S. 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)	9.8 (-13.9,34.9)
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)	*8.9 (-16.2, 30.9)*
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)	10.0 (-16.4,33.2)
β-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)	*-11.9 (-28.3,5.5)*
Group A or S. 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)	*-8.2 (25.3,9.6)*
Peptostreptococcus sp.	9/10 (90.0)	5/6 (83.3)	2/3 (66.7)	2/3 (66.7)	11/13 (84.6)	7/9 (77.8)	
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)	
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)	

Source: Clinical Reviewer's Analysis; CSR

**Baseline organism isolated from the culture is listed here. Some of these organisms are not considered causative pathogen for ABSSSI

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.

*** This table includes 13 patients with MSSA from site #606; 13 out of the 14 patients at site #606 had baseline cultures positive for MSSA

15.3.11. Clinical success at ECR by baseline pathogen in bacteremic patients in ABSSSI trials

Table x Clinical Success at ECR by Baseline Pathogen from the Blood Culture-ABSSSI Trial (micro-								
	ABSI-1108				ABSI-16301			
	Omadacycline N=228		Linezolid N=227		Omadacycline N=276		Linezolid N=287	
	n/N1	(%)	n/N1	(%)	n/N1	(%)	n/	(%)
S. aureus	5/6	(83.3)	5/6	(83.3)	0/1	(0.0)	2/3	(66.7)
MRSA	3/3	(100)	2/2	(100.0)	0	0	1/1	(100)
MSSA	2/3	(66.7)	3/4	(75.0)	0/1	(0.0)	1/2	(50)
S. anginosus group	1/1	(100)	0	0	0	0	1/1	(100)
S. anginosus	1/1	(100)	0	0	0	0	0	0
S. intermedius	0	0	0	0	0	0	1/1	(100)
E. faecalis (VSE)	0	0	1/1	(100)	0	0		0
Beta hemolytic streptococcus	1/3	(33.3)	2/2	(100)	0	0	0/1	(0.0)
Group A or Streptococcus pyogenes	1/2	(50)	2/2	(100)	0	0	0/1	(0.0)
Group G or Streptococcus dysgalactiae	0/1	(0.0)	0	0	0	0		0
Granulicatella adiacens	0	0	0	0	0	0	1/1	(100)
Rothia dentocariosa	0	0	0	0	0	0	1/1	(100)
Streptococcus sanguinis	0	0	0	0	1/1	(100)	0	0
Streptococcus viridans group	0/1	(0.0)	1/1	(100)	0	0	0	0
Moraxella lacunata	0	0	0	0	0	1/1	0	0
Source: Clinical Reviewer's Analysis, CSR								

15.3.12. Overall Clinical Success in patients infected with *Staphylococcus aureus* at PTE by the pathogen's resistance profile in Study ABSI-1108 (micro-mITT Population)

Overall Clinical Success in patients infected with ***Staphylococcus aureus*** at **PTE** by the pathogen's resistance profile in Study ABSI-1108 (micro-mITT Population) is summarized below.

	Omadacycline (N=228)				Linezolid (N=227)			
Baseline Pathogen	N1	Clinical Success n (%)	Clinical Failure n (%)	Indeterminate n (%)	N1	Clinical Success n (%)	Clinical Failure n (%)	Indeterminate n (%)
S. aureus	156	130 (83.3)	9 (5.8)	17 (10.9)	151	126 (83.4)	13 (8.6)	12 (8.0)
Resistant to ≥1 antibiotic class	90	74 (82.2)	3 (3.3)	13 (14.4)	67	57 (85.0)	5 (7.5)	5 (7.5)
Resistant to ≥2 antibiotic classes	75	61 (81.3)	3 (4.0)	11 (14.7)	55	47 (85.4)	5 (9.1)	3 (5.5)
Resistant to ≥3 antibiotic classes	43	31 (72.0)	3 (7.0)	9 (21.0)	39	33 (84.6)	4 (10.3)	2 (5.1)

Source - Table 116 SCP Special Studies
Note: N1 = Number of patients in the micro-mITT population in the treatment group with the baseline pathogen. Percentages are based on N1. Patients with the same pathogen isolated from multiple specimens are counted only once for that pathogen. Patients with the same pathogen identified from both the blood and primary ABSSSI cultures are counted only once.

15.3.13. Comparison of Clinical Response over Time in ABSSSI Trials

Table Comparison of Clinical Response Over Time in Study ABSI-1108 and Study ABSI-16301 (m-ITT Population)						
	ECR		EOT		PTE	
Efficacy Outcome	**Omadacycline n (%)**	**Linezolid n (%)**	**Omadacycline n (%)**	**Linezolid n (%)**	**Omadacycline n (%)**	**Linezolid n (%)**
Study ABSI-1108	**N=316**	**N=311**	**N=316**	**N=311**	**N=316**	**N=311**
Clinical success	268 (84.8)	266	281 (88.9)	272	272 (86.1)	260 (83.6)
Clinical failure or Indeterminate	48 (15.2)	45 (14.5)	35 (11.1)	39 (12.5)	44 (13.9)	51 (16.4)
Clinical failure	23 (7.3)	19 (6.1)	15 (4.7)	19 (6.1)	20 (6.3)	27 (8.7)
Indeterminate	25 (7.9)	26 (8.4)	20 (6.3)	20 (6.4)	24 (7.6)	24 (7.7)
Study ABSI-16301	**N = 360**	**N = 360**	**N = 360**	**N = 360**	**N = 360**	**N = 360**
Clinical success	315 (87.5)	297	322 (89.4)	306	303 (84.2)	291 (80.8)
Clinical failure or Indeterminate	45 (12.5)	63 (17.5)	38 (10.6)	54 (15.0)	57 (15.8)	69 (19.2)
Clinical failure	26 (7.2)	32 (8.9)	11 (3.1)	19 (5.3)	12 (3.3)	21 (5.8)
Indeterminate	19 (5.3)	31 (8.6)	27 (7.5)	35 (9.7)	45 (12.5)	48 (13.3)
Source: FDA Statistical analysis and CSR						

15.3.14. Concordance between ECR success and PTE ABSSSI Trials

Concordance between ECR and PTE in ABSI-1108 trial

Drug	ECR	Clinical success n/N (%)	Clinical failure n/N (%)	Indeterminate n/N (%)	Total(N)
Omadacyline	Clinical success	251/268(93.7)	7/268(2.6)	10/268 (3.7)	268
	Clinical failure	12/23 (52.2))	8/23(35.8)	3/23 (13.0)	23
	Indeterminate	9/25 (36.0)	5/25 (20.0)	11/25 (44.0)	25
Total	**ECR**	**272**	**20**	**24**	**316**
Linezolid	Clinical success	240/266(90.2)	16/266(6.0)	10/266(3.8)	266
	Clinical failure	9/19(47.4)	9/19(47.4)	1/19(5.3))	19
	Indeterminate	11/26 (42.3)	2 /26(7.7)	13/26 (50.0)	26
Total		**259**	**27**	**24**	**311**
Source: FDA Statistical Reviewer's Analysis					

Table below provides concordance between ECR success and PTE success for study ABSI-16301.
Concordance between ECR and PTE in ABSI-16301 trial

Drug	ECR	Clinical success n/N (%)	Clinical failure n/N (%)	Indeterminate n/N (%)	Total(N)
Omadacycline	Clinical success	279/315 (88.6)	4/315(1.3))	32/315 (10.2)	315
	Clinical failure	15/26 (57.7)	7/26 (26.9)	4/26(15.4)	26
	Indeterminate	9/19 (47.4)	1/19 (5.3)	9/19 (47.4)	19
Total	**ECR**	**303**	**12**	**45**	**360**
Linezolid	Clinical success	258/297(86.9)	10/297(3.4)	29/297(9.8)	297
	Clinical failure	23/32 (71.9)	6/32(18.8)	3/32(9.4)	32
	Indeterminate	10/31 (32.3)	5/31(16.1)	16/31 (51.6)	31
Total		**291**	**21**	**48**	**360**
Source: FDA Statistical Reviewer's Analysis					

15.3.15. Reasons for systemic antibacterial drugs taken within 72 hours prior to randomization is summarized below.

Table: Reasons for **Systemic Antibacterial Medications** Taken **Within 72 Hours** Prior to First Infusion of Study drug (ITT Population)		
	OMC (N = 386) n (%)	MOXI (N = 388) n (%)
Any systemic antibacterial medication taken within 72 hours prior to first infusion of study drug	89 (23.1)	90 (23.2)
For current CABP prior to randomization	88 (22.8)	88 (22.7)
For Infection prior to randomization not related to CABP	0	1 (0.3)
Concomitant infection unrelated to CABP*	1 (0.3)	0
Other**	0	1 (0.3)
Source: CSR; Clinical Reviewer's analysis *one patient received intraocular and topical antibacterials for the treatment of conjunctivitis. **one patient received a prophylactic antibacterial to reduce the risk of a urinary tract infection after urodynamic testing.		

15.3.16. Receipt of Systemic Antibacterial Medications Taken Between First Infusion of study drug and the EOT and PTE Visits (CE-EOT and CE-PTE Populations)

Reason for Receipt of Systemic Antibacterial Medications Taken Between First Infusion of study drug and the EOT and PTE Visits (CE-EOT and CE-PTE Populations)		
	OMC N (%)	MOXI N (%)
From 1st dose of study drug to EOT visit	**N = 357**	**N = 357**
Any systemic antibacterial medication taken between first infusion of study drug and EOT	21 (6)	33 (9)
Infection prior to randomization not related to CABP	1 (0.3)	0

Insufficient therapeutic effect of study drug	13 (4)	24 (7)
Concomitant infection unrelated to CABP	4 (1)	7 (2)
Other	3 (0.8)	2 (0.6)
1st dose of study drug to PTE visit	**N = 340**	**N = 345**
Any systemic antibacterial medication taken between first infusion of study drug and PTE	27 (8)	39 (11)
Infection prior to randomization not related to CABP	1 (0.3)	0
Insufficient therapeutic effect of study drug	17 (5)	28 (8)
Concomitant infection unrelated to CABP	5 (2)	9 (3)
Other	4 (1)	3 (0.9)
Source: CSR;		

15.3.17. Concordance between ECR and PTE in CABP trial

Most (95% in Omadacycline group and 92% in Moxifloxacin group)) of the patients with 'clinical success' at ECR maintained their response. The percentages of patients who had clinical success at ECR but were reported as a 'clinical failure or indeterminate' at PTE visits were 4.8% (15/313) in the Omadacyclines group and 8.1% (26/321) in the moxifloxacin group. The percenatges of patients who were determined as 'clinical failures or Indeterminate' at ECR and later deemed 'clinical success' at PTE by the investigators were 10.4% (40/386) Omadacycline group and 9.0% (35/388) in the moxifloxacin group.

Table: Concordance between ECR and PTE in CABP trial

Drug	ECR\	Clinical success n/N (%)	Clinical success n/N (%)	Indeterminate n/N (%)	Total (N)
Omadacycline	Clinical success	298/313 (95.2)	9/313 (2.9)	6/313 (1.9)	313
	Clinical failure	35/49 (71.4)	13/49 (26.5)	1/49(2.0)	49
	Indeterminate	5 /24 (20.8)	10 /24 (41.7)	9/24 (37.5)	24
Total		338	32	16	386
Moxifloxacin	Clinical success	295/321 (91.9)	17/321 (5.3)	9/321 (2.8)	321
	Clinical failure	30 /47(63.8)	15/47 (31.9)	2/47 (4.3)	47
	Indeterminate	5/20 (25.0)	10/20 (50.0)	5 /20(25.0)	20
Total		330	42	16	388
Source: FDA Statistical Reviewer's Analysis					

		PTE		
Treatment Group	ECR	Clinical Success n (%)	Clinical Failure n (%)	Indeterminate n (%)
Omadacycline (N = 386)	Clinical success N1 = 313	298 (77.2)	9 (2.3)	6 (1.6)
	Clinical failure N1 = 49	35 (9.1)	13 (3.4)	1 (0.3)
	Indeterminate N1 = 24	5 (1.3)	10 (2.6)	9 (2.3)
Moxifloxacin (N = 388)	Clinical success N1 = 321	295 (76.0)	17 (4.4)	9 (2.3)
	Clinical failure N1 = 47	30 (7.7)	15 (3.9)	2 (0.5)
	Indeterminate N1 = 20	5 (1.3)	10 (2.6)	5 (1.3)

Source: Applicant's SCE; Study PTK0796-CABP-1200, Table 34.
N1 = proportion of patients in the ITT population with a clinical success.

15.3.18. Comparison in Early Clinical Success (ECR) rates by Baseline Pathogen** (from ABSSSI Site or Blood Culture) in ≥ 6 Patients in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population)

	ABSI-1108		ABSI-16301	
Baseline Pathogen	**OMC (N = 228) n/N1 (%)**	**LNZ (N = 227) n/N1 (%)**	**OMC (N = 276) n/N1 (%)**	**LNZ (N = 287) n/N1 (%)**
S. aureus	138/156 (88.5)	131/151 (86.8)	194/220 (88.2)	194/233 (83.3)
MRSA	62/69 (89.9)	44/50 (88.0)	97/104 (93.3)	95/107 (88.8)
MSSA***	77/88 (87.5)	87/102 (85.3)	101/120 (84.2)	103/130 (79.2)
Staphylococcus lugdunensis	6/6 (100.0)	3/3 (100.0)	4/5 (80.0)	0
Streptococcus anginosus Gr	39/47 (83.0)	27/37 (73.0)	54/57 (94.7)	36/45 (80.0)
S. anginosus	8/8 (100.0)	4/7 (57.1)	27/27 (100.0)	17/20 (85.0)
S. intermedius	11/12 (91.7)	14/18 (77.8)	21/23 (91.3)	18/24 (75.0)
S. constellatus	18/25 (72.0)	7/14 (50.0)	8/9 (88.9)	7/7 (100.0)
Enterococcus faecalis	9/10 (90.0)	12/13 (92.3)	7/8 (87.5)	8/12 (66.7)
VSE	9/10 (90.0)	12/13 (92.3)	6/7 (85.7)	6/10 (60.0)
ß-hemolytic streptococcus	10/16 (62.5)	20/22 (90.9)	26/33 (78.8)	15/19 (78.9)
Group A or S. pyogenes	8/11 (72.7)	17/18 (94.4)	24/29 (82.8)	13/16 (81.3)
Enterobacteriaceae	16/18 (88.9)	14/16 (87.5)	18/20 (90.0)	17/24 (70.8)
Enterobacter cloacae	7/9 (77.8)	4/5 (80.0)	5/5 (100.0)	5/6 (83.3)
Klebsiella pneumoniae	6/6 (100.0)	4/5 (80.0)	4/5 (80.0)	5/6 (83.3)

	ABSI-1108		ABSI-16301	
Baseline Pathogen	**OMC (N = 228) n/N1 (%)**	**LNZ (N = 227) n/N1 (%)**	**OMC (N = 276) n/N1 (%)**	**LNZ (N = 287) n/N1 (%)**

Source: Clinical Reviewer's Analysis;

**Baseline organism isolated from the culture is listed here. Some of these organisms are not considered causative pathogen for ABSSSI
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.
*** This table includes 13 patients with MSSA from site #606; 13 out of the 14 patients at site #606 had baseline cultures positive for MSSA

15.3.19. Overall Clinical Success at PTE by baseline pathogen - CABP1200 micro-(ITT population)

Table 2.5.2.1.IR1
Overall Clinical Response at PTE Visit Based on Investigator Assessment by Baseline Pathogen and Mono/Poly-Microbial Subjects
(Excluding pathogens identified in fewer than 10 OMC subjects)
CABP-1200 - microITT Population

	Omadacycline (N=204)		Moxifloxacin (N=182)	
Baseline Pathogen	N1	Clinical Success n (%)	N1	Clinical Success n (%)
Mono-microbial	135	123 (91.1)	112	100 (89.3)
Gram-Positive Bacteria (aerobes)	30	26 (86.7)	23	21 (91.3)
Streptococcus pneumoniae	22	19 (86.4)	11	10 (90.9)
Staphylococcus aureus	3	2 (66.7)	6	6 (100.0)
Gram-Negative Bacteria (aerobes)	37	34 (91.9)	32	24 (75.0)
Haemophilus influenzae	16	15 (93.8)	4	4 (100.0)
Haemophilus parainfluenzae	7	7 (100.0)	7	4 (57.1)
Klebsiella pneumoniae	3	1 (33.3)	7	5 (71.4)
Atypical Pathogens	68	63 (92.6)	55	54 (98.2)
Mycoplasma pneumoniae	39	36 (92.3)	23	22 (95.7)
Chlamydophila pneumoniae	11	9 (81.8)	12	12 (100.0)
Legionella pneumophila	18	18 (100.0)	20	20 (100.0)
Poly-microbial	69	59 (85.5)	70	59 (84.3)
Gram-Positive Bacteria (aerobes)	31	26 (83.9)	33	28 (84.8)
Streptococcus pneumoniae	21	18 (85.7)	23	21 (91.3)
Staphylococcus aureus	8	6 (75.0)	5	3 (60.0)
Gram-Negative Bacteria (aerobes)	42	33 (78.6)	37	32 (86.5)
Haemophilus influenzae	16	11 (68.8)	12	12 (100.0)
Haemophilus parainfluenzae	11	8 (72.7)	10	9 (90.0)
Klebsiella pneumoniae	10	9 (90.0)	6	6 (100.0)
Atypical Pathogens	50	46 (92.0)	51	43 (84.3)
Mycoplasma pneumoniae	31	30 (96.8)	34	28 (82.4)
Chlamydophila pneumoniae	17	16 (94.1)	16	13 (81.3)
Legionella pneumophila	19	17 (89.5)	17	16 (94.1)

Source: IR response Sponsor

15.3.20. Baseline Characteristics of Deaths in CABP1200 (ITT population)

Baseline characteristics of all deaths occurred in Study CABP 1200.											
	SUBJID	COUN	AGE	SEX	ACT IV	ACT PO	DTH DY	BACT	PORT score /Risk Class	Relevant Medical History	Adverse Event by Preferred Term
Omadacycline											
1	(b) (6)	HUN	67	M	1	--	2	Y	87**/III	HTN, COPD, Emphysema, DM-II, Pleural fibrosis	Septic Shock with MOF
2		HRV	76	M	3	--	2		76 /III	HTN	Cardio-respiratory arrest
3		PHL	66	M	2	--	2		126 /IV	COPD, Pulmonary TB	Cardiogenic shock secondary to acute MI; CABP; and COPD.
4		ZAF	72	M	9	--	9		92 /IV	COPD, DM-II, A-Fib, CHF, Thoracic aortic aneurysm	Thoracic aortic aneurysm rupture; (worsening pneumonia Day 6)
5		ZAF	68	M	8	--	13		88 /III	HTN, COPD, DM-II, CHF	Cerebro-vascular accident with respiratory failure
6		ROU	90	F	11	3	20		130 /IV	HTN, DM-II, Chronic bronchitis, Cardiac valvular disease	Cardiogenic shock caused by non-ST segment elevation MI
7		CZE	74	F	5	--	25		124 /IV	HTN, Asthma, Gastroduodenal Ulcer	Acute respiratory failure (ARF) due to CABP; Multiple organ failure
8		POL	86	F	5	5	30		126 /IV	Hyperthyroidism, Arteriosclerosis	ARDS caused by the RLL nosocomial pneumonia.
Moxifloxacin											
1	(b) (6)	POL	85	F	3	--	9		85/III	HTN, A. Fib, Cerebral arterial disease, gastrectomy,	
2		BGR	83	M	9	--	9	Y	113/IV	None	
3		RUS	82	M	9	5	20		92/IV	HTN, COPD, Parkinson's disease	

Source: Clinical Reviewer's Analysis

*** This patient was originally classified in PORT CLASS-II due to the erroneous notation of actual port score of "67" by the investigator.*
Note: One patient in moxifloxacin arm, died on Study Day 71 (# (b) (6) : RUS/72/F/WHITE/4/4/71/1/Multilobar/Unilat/72/HTN, DM-II, h/o cholecystectomy and hysterectomy).
Abbreviations: COUN=country, SUBJID= patient ID; ACT IV= active IV doses received by patient; Act PO; BACT= bacteremia; A. Fib=atrial fibrillation; HTN=hypertension; MI= myocardial infarction; COPD= chronic obstructive pulmonary disease; DM-II= diabetes mellitus type-II;

Table below summarizes baseline Clinical Characteristics of Deaths in Study CABP1200

Baseline Clinical Characteristics of Patients who died in Study CABP1200 (safety population)												
	SUBJID	WBC	HR >90	RR >30	paO2 <60	O2Sat <90%	UREA >20	SBP <90	Cr-Cl	INFILTRATE	Pl-Effusion	Prior Abx [72 H]
OMADACYCLINE												
1	(b) (6)	WBC bet 4,000-12,000	Y	No	No	Y	Y	No	33.87	Unilobar		No
2		WBC bet 4,000-12,000	Y	No	Y	No	No	No	51.9	Unilobar		Y
3		WBC > 12,000	No	No	Y	Y	Y	No	94.78	Unilobar		Y
4		WBC > 12,000	Y	No	Y	Y	Y	No	74.44	Unilobar	Y (Uni-lateral)	Y
5		WBC bet 4,000-12,000	No	No	Y	Y	N	No	59.5	Unilobar	Y (Uni-lateral)	No
6		WBC > 12,000	Y	No	No	N	Y	No	68.44	Unilobar	Y (Uni-lateral)	No
7		WBC > 12,000	Y	Y	No	Y	Y	No	34.44	Multilobar		No
8		WBC > 12,000	Y	No	No	Y	Y	No	43.53	Unilobar		No
MOXIFLOXACIN												
1	(b) (6)	WBC bet 4,000-12,000	Y	No	No	No	No	No	70.58	Multilobar	Y (Bilateral)	No
2		WBC < 4,000	No	No	No	No	No	No	32.02	Multilobar		No
3		WBC bet 4,000 - 12,000	Y	No	No	Y	Y	No	67.82	Multilobar		No

Source: Clinical Reviewer's Analysis

CrCL= creatinine clearance; Normal renal function [CrCL>80 mL/min]; Mild renal impairment [CrCL>50-80 mL/min; Abx= antibacterial; HR=heart rate; RR= respiratory rate; SBP= systolic blood pressure;
Note: None of the patients who died presented with confusion at baseline.

15.3.21. Narratives of the Mortality Outcomes

Case Summaries of Deaths in CABP Trial (Study CABP-1200)

Omadacycline Treatment Arm

1. **Subject #** (b) (6)

This was a 67-year-old white male with a medical history of COPD, emphysema, pleural fibrosis, pleural effusion, hypertension, congestive heart failure, and diabetes mellitus type 2, who died on study day 2 with septic shock.

The patient was enrolled with right lower lobe pneumonia (PORT Risk Class-III). He did not receive any antibiotic treatment for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included various inhaled therapies, including ipratropium and salbutamol theophylline, beta-blockers, enoxaparin, methylprednisolone, insulin, nifedipine, enalapril, and pantoprazole. The patient's sputum culture was positive for *S. pneumoniae*, and *H. influenzae*, and blood culture positive for *S. pneumoniae*. On examination, the patient's temperature was 37°C, respiratory rate was 24 breaths per minute, pulse was 115 beats per minute, blood pressure was 90/60 mm Hg, and O_2 saturation was 86%. Notable abnormal laboratory findings were PaO_2 62 mm Hg, serum urea > 20 and creatinine clearance 33.9 mL/min. The patient was randomized to omadacycline and received the first dose of IV treatment. Within few hours, his condition deteriorated requiring transfer to intensive care unit and mechanical ventilation. Within 11 hours of randomization, his condition further decompensated with progression to septic shock, multi-organ failure, and death. An autopsy revealed right lung pneumonia, COPD, severe cor-pulmonale, chronic stasis in the systemic circulation, hypertrophy of the left ventricle, and widespread arteriosclerosis. The cause of death was attributed to worsening pneumonia.

2. **Subject #** (b) (6)

This was a 76-year-old white male with a medical history of hypertension, past and current smoking, who died on study day 2 with sudden cardiorespiratory arrest.

The patient was enrolled with right lower lobe pneumonia (PORT Risk Class-III). He received a dose of amoxicillin/clavulanate for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included lisinopril, diazepam, furosemide, methylprednisolone, metoclopramide, pantoprazole, oxygen, ibuprofen, tramadol, and ketoprofen. His sputum culture was negative for CABP pathogens and blood cultures were not performed. On examination, the patient's temperature was 38.3°C, respiratory rate was 22 breaths per minute, pulse was 112 beats per minute, and O_2 saturation was 91%. Notable abnormal laboratory findings were PaO_2 < 60 mm Hg, and creatinine clearance of 52 mL/min. The patient was randomized to omadacycline and received two doses of IV treatment. During

morning hours on study day 2, the patient was reportedly stable with no worsening of cardiorespiratory status and oxygen saturation was reported as 91%. An electrocardiogram (ECG) prior to omadacycline dosing showed sinus rhythm at 98 beats per minute, premature supraventricular complexes, and QTcF of 445 milliseconds (which was unchanged from baseline). Vital signs were reported stable. Around mid-day of study day 2, the patient was found dead in his bed. The cardiorespiratory arrest was not witnessed, and therefore no resuscitation was performed. An autopsy was not performed. Pulmonary embolism was suspected during the hospitalization, but this was not confirmed by an imaging study. The cause of death was attributed to sudden 'cardiorespiratory arrest'.

3. Subject # (b) (6)

This was a 66-year-old Asian male with a medical history of COPD, prior smoking, and prior history of pulmonary tuberculosis more than 10 years ago, who died on study day 2 due to cardiogenic shock secondary to acute non-ST segment elevation myocardial infarction (MI), and septic shock due to pneumonia.

The patient was enrolled with right upper lobe pneumonia (PORT Risk Class-IV). He did not receive antibacterial treatment for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included salbutamol, indacaterol/glycopyrronium (beta-receptor agonist and muscarinic anticholinergic), and ipratropium/albuterol inhalation, insulin, and hydrocortisone. His sputum culture grew *Klebsiella pneumoniae* (omadacycline MIC: 2 mcg/mL) and *Pseudomonas aeruginosa* (omadacycline MIC: > 16 mcg/mL).

On examination, the patient's temperature was 36.8°C, respiratory rate was 37 breaths per minute, pulse was 103 beats per minute, blood pressure was 130/70 mm Hg, and O_2 saturation was 83%. Notable abnormal laboratory findings were: leukocytosis with white blood cell counts 15×10^9/L (reference range: 3.7 to 11×10^9/L), moderate renal insufficiency with creatinine clearance (CrCL) of 43.5 mL/min, and serum urea > 20. The patient was randomized to omadacycline arm and received the first dose on study day 1. Vital signs before and after the dose showed no clinically significant changes.

On study day 2, during IV study treatment, the patient complained of moderate dyspnea. Vital signs at that time included temperature 37.1°C, pulse 109 beats per minute, blood pressure 110/60 mm Hg, and respiratory rate of 28 breaths per minute. Later during the morning hours of study day 2, prior to administration of the third dose of study drug, he suddenly developed severe dyspnea, cyanosis, and cold, clammy perspiration while straining in the restroom and transferred to intensive care unit requiring mechanical ventilation. The study drug was discontinued and he was diagnosed with acute myocardial infarction and cardiogenic shock. An ECG revealed lateral wall ischemia in the precordial limb leads, however, troponin- I was negative; a serial troponin-I was not performed. A repeat chest X-ray showed more prominent consolidation of the pulmonary infiltrates, which was reported as most likely of cardiac origin. The patient's family then decided against further resuscitative measures, and all treatment

methods including study drug administration were stopped. Within few hours on the same day, the patient died. An autopsy was not performed. The cause of death was attributed to cardiogenic shock secondary to acute non-ST segment elevation MI, community acquired pneumonia and chronic obstructive pulmonary disease.

4. Subject # (b) (6)

This was a 72-year-old white male with a medical history of COPD, thoracic aortic aneurysm, atrial fibrillation, congestive heart failure, and diabetes mellitus type 2, who died on study day 9 with 'rupture of enlarged thoracic artery aneurysm.'

The patient was enrolled with right upper lobe pneumonia (PORT Risk Class-IV). He received a dose of oral clarithromycin for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included atenolol, furosemide, digoxin, spironolactone, ipratropium/salbutamol, budesonide, paracetamol, amitriptyline, fludrocortisone, carvedilol, ketorolac, and metformin.

The patient's sputum culture grew *H. influenzae* (omadacycline MIC: 1 mcg/mL), and blood cultures were not collected. On examination, the patient's temperature was 35.8°C, respiratory rate was 24 breaths per minute, pulse was 97 beats per minute, blood pressure was 101/68 mm Hg, and O_2 saturation was 83%. Notable abnormal laboratory findings were leukocytosis with white blood cell counts of 12×10^9/L (reference range: 3.7 to 11×10^9/L) and serum urea > 20.

The patient was randomized to omadacycline and his hospital course was uneventful with protocol efficacy assessment of 'clinical success' at early clinical response timepoint. On study day 7, he was reported to have worsening pneumonia. A chest radiograph performed that day showed right pleural effusion; right apical cavitary pneumonia with possible pulmonary abscess; and increasing opacity in the right upper lobe compatible with worsening of pneumonia and a persistent severe large thoracic aortic aneurysm. No changes were made to study treatment. On study day 9, he developed a sudden acute difficulty in breathing, with severe chest discomfort and pain, which was rapidly followed by loss of consciousness and death within 5 minutes. The subject was diagnosed clinically with ruptured thoracic aorta aneurysm. An autopsy was not performed. The cause of death was attributed to rupture of the thoracic aortic aneurysm.

5. Subject # (b) (6)

This was a 68-year-old white male with a medical history of mild to moderate COPD, hypertension, congestive heart failure, peripheral edema, and diabetes mellitus type 2; who died on study day 13 with a diagnosis of cerebrovascular accident (CVA) with respiratory failure.

The patient was enrolled with right lower lobe pneumonia (PORT Risk Class-III). He received a dose of amoxicillin/clavulanate for the qualifying CABP before entering the study. Concomitant

medications taken by the patient during the study included furosemide, glimepiride, insulin, bisoprolol, digoxin, acetylsalicylic acid, paracetamol, hydrocortisone, and enoxaparin sodium.

The patient's sputum culture was negative for CABP pathogens. Blood samples were not cultured. On examination, the patient's temperature was 36.1°C, respiratory rate was 18 breaths per minute, pulse was 88 beats per minute, blood pressure was 110/60 mm Hg, and O_2 saturation was 77%. Notable abnormal laboratory findings were, PaO_2 of 56 mm Hg, mild leukocytosis with white blood cell counts 12.4 × 10^9/L (reference range: 3.7 to 11 × 10^9/L), and serum urea > 20.

The patient was randomized to omadacycline arm and received his last dose of study drug (end of treatment) on study day 7, and was discharged on the same day. His hospital course was uneventful. On study day 13, 6 days after the last dose of study drug, the patient was brought to the hospital with decreased consciousness, dyspnea, generalized edema, abdominal distension, and peripheral cyanosis. The patient was semi-comatose with Glasgow coma scale (GCS) score of 13/15. He was hypotensive with blood pressure 83/59 mm Hg, the temperature was 36°C, respiratory rate was 36 breaths per minute, pulse 53 beats per minute and oxygen saturation was 93%. Twenty minutes later an ECG was performed which showed supraventricular tachycardia at heart rate of 145 beats per minute, and right ventricular hypertrophy. He was placed on 3 L of oxygen supplement and was treated with hydrocortisone, furosemide, and IV fluids. His condition rapidly deteriorated and his GCS score further worsened to 14/15. Within few hours, despite all resuscitative measures, the patient died due to a clinically suspected CVA and respiratory failure. No specific diagnostic or imaging procedures were performed for confirmation. An autopsy was not performed, and the cause of death was attributed to the cerebrovascular accident and respiratory failure.

6. Subject # (b) (6)

This was a 90-year-old white female with a medical history of chronic bronchitis, hypertension, diabetes mellitus type 2, myocardial ischemia, aortic and mitral valvular disease, and anemia, who died on study day 20 with 'cardiogenic shock caused by non-ST segment elevation myocardial infarction (MI)'.

The patient was enrolled with right lower lobe pneumonia (PORT Risk Class-IV) with right pleural effusion. Concomitant medications taken by the patient during the study included acetylcysteine, glucose, insulin, paracetamol, potassium, and metamizole. The patient's sputum culture was negative for CABP pathogens. Blood samples were not cultured. On examination, the patient's temperature was 38°C, respiratory rate was 23 breaths per minute, pulse was 92 beats per minute, blood pressure was 130/80 mm Hg, and O_2 saturation was 98%. Notable abnormal laboratory findings were: mild leukocytosis with white blood cell counts 12.9 × 10^9/L (reference range: 3.7 to 11 × 10^9/L), CrCL 68 mL/min, and serum urea > 20.

The patient was randomized to omadacycline arm and received study treatment for a total of 13 days (10 days of IV followed by 3 days of oral). The patient was assessed 'clinical success' at

ECR, and EOT visits. She received her last dose of study drug on study day 13 and had her EOT visit on study day 14, and she was discharged home the same day. On study day 15, 2 days after the last dose of oral study drug, the patient experienced repeated episodes of angina and was re-hospitalized. On clinical examination, blood pressure was 170/100 mm Hg, pulse 90 beats per minute, and the ECG showed sinus rhythm with left ventricular hypertrophy and secondary ST-T changes. An echocardiogram was unremarkable except for severe aortic stenosis without any hypokinesia. Laboratory results revealed an elevated troponin-I (1.92 µg/mL and 1.04 µg/mL; reference range: 0 to 0.9 µg/mL), and slightly elevated creatine kinase-muscle/brain (CK- MB 27 IU/L), and hyperglycemia. She was diagnosed with acute non-ST segment elevation MI and was treated with aspirin, dalteparin sodium, nitroglycerine, clopidogrel, perindopril, statin, nebivolol, atorvastatin, isosorbide mononitrate, ranitidine, and iv fluids. On study day 20, during morning hours, she developed recurrent episodes of angina, dyspnea, and orthopnea, diaphoresis, leg edema, and bilateral lung crepitation. She was hypotensive with blood pressure between 60/40 and 85/60 mm Hg, respiratory rate between 29 and 30 breaths per minute, pulse 57 to 120 beats per minute, and oxygen saturation of 89%. The patient was diagnosed with cardiogenic shock. Her condition rapidly deteriorated and despite supportive measures within 3 hours, the patient experienced a cardiac arrest, which failed cardiopulmonary resuscitation. An autopsy was not performed. The cause of death was attributed to cardiogenic shock caused by non-ST segment elevation myocardial infarction.

7. Subject # (b) (6)

This was a 74-year-old white female with medical history of asthma, past and current smoking, hypertension, gastroduodenal ulcer, hematuria, anemia, myocardial infarction, cystitis, alcohol abuse and a strong family history of cardiovascular disease, who died on study day 25 with acute respiratory failure (ARF) due to CABP, and multiple organ failure (MOD).

The patient reportedly had “flu-like illness” with high fever, productive cough with dark, grey sputum, breathlessness, and vertigo prior to hospitalization for CABP. The patient was enrolled with right middle and right lower lobe pneumonia (PORT Risk Class-IV) with no pleural effusion. Concomitant medications taken by the patient during the study included beclomethasone/formoterol fumarate inhaler, insulin human, and valsartan-hydrochlorothiazide. The patient’s sputum culture grew *H. influenzae* (omadacycline MIC: 2 mcg/mL) and *E. coli* (omadacycline MIC: 1 mcg/mL); blood cultures were negative. On examination, the patient’s temperature was 36.8°C, respiratory rate was 37 breaths per minute, pulse was 103 beats per minute, blood pressure was 136/74 mm Hg, and O_2 saturation was 83%. Notable abnormal laboratory findings were leukocytosis with white blood cell counts of 18.1×10^9/L (reference range: 3.7 to 11×10^9/L) and serum urea > 20.

The patient was randomized to omadacycline arm and received 5 doses of IV study treatment. The patient was also diagnosed with hemorrhagic cystitis on enrollment into the study which was treated with bladder washings. On study day 2, the patient was transferred to the intensive care unit requiring mechanical ventilation. A large amount of bloody sputum was aspirated. Sputum from an endotracheal aspirate grew the same pathogens as found upon

admission. Cultures from bronchoalveolar lavage grew *H. influenzae* (omadacycline MIC: 2 mcg/mL), and *K. pneumoniae* (omadacycline MIC: 2 mcg/mL). The study treatment was continued. On study day 4, an endotracheal aspirate grew *H. influenzae* (omadacycline MIC: 2 mcg/mL), *E. coli* (omadacycline MIC: 1 mcg/mL), and *Proteus mirabilis* (omadacycline MIC: 16 mcg/mL). The study drug was then discontinued (on study day 4), and she was started on alternative antibacterial therapy with meropenem and other supportive measures. On study day 5, she experienced hemodynamic instability and was noted to have atrial fibrillation with a rapid ventricular response. Attempted cardioversion failed, and she was reported to have severe multi-organ failure. On study day 7, the patient received a single dose of IV gentamicin. On study day 13, right side thoracentesis was performed for the drainage of pleural effusion and the pleural culture grew *coagulase-negative Staphylococcus*. On study day 16, a chest radiograph showed persistent opacity in the right lower lung field. A specimen from an indwelling urinary catheter grew *P. mirabilis* and *E. faecalis* on Study Day 18. The patient gradually developed neuromyopathy and was placed on minimum catecholamine support with continued mechanical ventilation.

The patient was transferred to another hospital for further evaluation and treatment on study day 21. Upon transfer, an ECG showed atrial fibrillation. She was continued on mechanical ventilation, catecholamine support, and verapamil with other supportive measures. By study days 23 and 24, her condition further deteriorated with sepsis, respiratory insufficiency, cardiac failure, oliguria, and worsening hemorrhagic cystitis. Despite all therapeutic measures, no improvement in clinical condition was observed, therefore a decision was made against any further increase in therapy and a do not resuscitate (DNR) order was placed by the family. The patient's condition gradually worsened with anuria, acidosis, and progression to death on study day 25. An autopsy was not performed. The cause of death was attributed to acute respiratory failure due to CABP, and multiple organ failure.

8. Subject # (b) (6)

This was an 86-year-old white female with a medical history of hyperthyroidism and arteriosclerosis; that died on study day 30 due to acute respiratory distress syndrome (ARDS) caused by nosocomial pneumonia (right lower lobe) and left pleural effusion.

The patient was enrolled in the study with a diagnosis left lower lobe pneumonia (PORT Risk Class-IV) and left pleural effusion. She did not receive any antibacterial treatment for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included bencyclane fumarate, thiamazole, heparin, aluminum acetotartrate, quetiapine, and an electrolyte solution. The patient's sputum culture was negative for CABP pathogens. Blood samples were not cultured. On examination, the patient's temperature was 36.5°C, respiratory rate was 28 breaths per minute, pulse was 88 beats per minute, blood pressure was 140/68 mm Hg, and O_2 saturation was 86%. Notable abnormal laboratory findings were: PaO_2 of 56 mm Hg; mild leukocytosis with white blood cell counts 12.4×10^9/L (reference range: 3.7 to 11×10^9/L); elevated serum urea > 20, and mild renal insufficiency with CrCL 69.5 mL/minf.

The patient was randomized to omadacycline arm and received a total of 9 days (five doses of IV followed by five doses of oral administration) of therapy. Her last dose of study drug was on study day 9 when EOT visit was performed. She was assessed as 'clinical successes' at ECR and EOT visits. The patient also had pleurocentesis twice during hospitalization (reason not documented). The patient was discharged from the hospital on study day 12.

On study day 18, (9 days after the last dose of study drug), the patient was re-hospitalized with right lower lobe pneumonia, and symptoms of worsening productive cough. She was drowsy, unresponsive to sound and pain, and had marginally crossed left eyeball with equal and responsive pupils, with negative Babinski reflex and no meningismus. A computerized tomographic (CT) scan of the chest showed right lower lobe infiltrate, left-sided pleural effusion, and atelectasis of the left lower lobe. A CT scan of the head showed no evidence of an acute central nervous system lesion. The CT angiography was negative for pulmonary embolism and revealed dilated pulmonary trunk. An ECG showed normal sinus rhythm at 105 beats per minute with no signs of recent ischemia. Only reported laboratory results were elevated inflammatory markers and D-dimer levels. The patient was started on an antibacterial treatment with ceftriaxone along with other supportive measures. By study day 20, the patient's condition worsened with evidence of respiratory failure. A left pleurocentesis was performed on an emergency basis, obtaining one liter of clear fluid. The patient's condition continued to deteriorate with worsening ARDS, and by study day 24, she also experienced a new onset of atrial fibrillation and worsening heart failure. The patient was treated with amiodarone and was transferred to intensive care unit and placed on mechanical ventilation due to worsening sepsis, pneumonia and circulatory failure. The bronchoalveolar lavage culture (obtained on study day 21), grew *Acinetobacter baumannii* (gentamicin MIC: 4 mcg/mL, colistin MIC: ≤ 0.5 mcg/mL) and *Candida albicans*. Eventually, by study day 30, despite intensive treatment, the patient died. An autopsy was not performed and the cause of death was attributed to ARDS caused by the right lower lobe pneumonia and left pleural effusion. Other anti-infective treatments for the new pneumonia event included ceftriaxone, fluconazole, ciprofloxacin, colistin, and gentamicin.

Moxifloxacin Treatment Arm

1. **Subject #** (b) (6)

This was an 85-year-old white female with a medical history of hypertension, atrial fibrillation, ischemic stroke, dyslipidemia, iron deficiency anemia, basal cerebral circulatory failure, osteoarthritis, gastrectomy, and hypothyroidism, who died on study day 9 due to respiratory failure caused by worsening pneumonia.

The patient was enrolled with left lower lobe pneumonia (PORT Risk Class-III) with a left pleural effusion. She did not receive any antibacterial treatment for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included bencyclane fumarate, thiamazole, heparin, aluminum acetotartrate, quetiapine, and an

electrolyte solution. The patient's sputum culture was negative for CABP pathogens. Blood samples were not cultured. On examination, the patient's temperature was 36.5°C, respiratory rate was 28 breaths per minute, pulse was 85 beats per minute, blood pressure was 140/68 mm Hg, and O_2 saturation was 86%. Notable abnormal laboratory findings were: PaO_2 of 66.4 mm Hg, hemoglobin 6.8 g/dL, mild renal insufficiency with CrCL 69.5 mL/min, and serum urea > 20.

The patient was randomized to moxifloxacin arm and received only three doses of IV study treatment. By study day 3, her condition worsened gradually, and she experienced severe dyspnea with bronchospasm. A chest radiograph revealed shadowing within the lower and central field of the left lung, suspected inflammatory lesions with the possible small amount of fluid in the left pleura. An ECG showed atrial fibrillation with a ventricular rate of 100 beats per minute and no features of recent ischemia. An echocardiogram was remarkable only for the significant incompetence of the tricuspid valve, with normal ejection fraction. Serial arterial blood gas analyses revealed PaO_2 between 25 mm Hg to 71 mm Hg, hypocapnia, and metabolic acidosis. Her serum inflammatory marker level was elevated (CRP of 175 mg/L (reference range: < 5 mg/L)). She was diagnosed with life-threatening severe CABP, study treatment was discontinued, and she was treated with alternative antibacterial treatment with meropenem, clindamycin, and the other supportive measures, including dobutamine, furosemide, and hydrocortisone. On study day 4, sputum culture grew methicillin-resistant coagulase-negative *Staphylococcus hominis* and *Candida albicans*. The antimicrobial regimen was intensified with the addition of tigecycline, fluconazole, and voriconazole. On study day 5, her condition worsened further and she was transferred to intensive care unit and placed on mechanical ventilation. A culture from bronchoalveolar lavage did not show any growth. On study day 9, the patient experienced cardiac arrest with multiorgan dysfunction and died. An autopsy was not performed. The cause of death was attributed to acute respiratory failure due to CABP, along with multiorgan dysfunction, and cardiac arrest.

2. Subject # (b) (6)

This was an 83-year-old white male with no reported medical history, who died on study day 9 due to cardiac failure.

The patient was enrolled with right middle and lower lobe pneumonia (PORT Risk Class-IV) with no pleural effusion. He did not receive any antibacterial treatment for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included glucose. The patient's sputum culture was negative for CABP pathogens; however, multiple blood cultures grew *Escherichia coli* (MIC: 0.12 mcg/mL). On examination, the patient's temperature was 38.5°C, respiratory rate was 17 breaths per minute, pulse was 80 beats per minute, blood pressure was 120/80 mm Hg, and O_2 saturation was 90%. Notable abnormal laboratory findings were: leucopenia with white blood cell counts of 0.7×10^9/L (reference range: 3.7 to 11×10^9/L), immature neutrophils 45%, and renal insufficiency with CrCL of 32 mL/min. Serum urea was reported within normal range.

The patient was randomized to moxifloxacin arm and received a total of 9 days of IV study treatment. No clinically significant changes were noted on study day 2 and 3. Repeat blood culture continued to grow *E. coli* (MIC: 0.06 mcg/mL). On study day 4, the patient's white blood cell counts increased to the level of 15.9×10^9/L (from baseline leucopenia). On study day 7, ECG showed sinus rhythm with multiple ventricular premature beats, new left axis deviation, new negative T-waves in most leads with a marked extensive precordial repolarization disturbance, and new prolonged QTcF of 489 milliseconds. The central cardiologist (iCardiac) interpreted the ECG as suggestive of recent myocardial infarction. Serum troponin was elevated at 0.54 and 0.42 ng/mL (reference range: 0.00 to 0.06 ng/mL). The patient's vital signs remained stable through study day 9 when he received his last dose of study drug (EOT). On the same day (study day 9), at an unspecified time, the patient reportedly developed "severe possible heart failure." No resuscitative measures were performed, and the patient died. An autopsy was not performed, and the cause of death was attributed to cardiac failure.

3. Subject # (b) (6)

This was an 82-year-old white male with a medical history of mild to moderate COPD, past and current smoking, hypertension, Parkinson's disease, ischemic heart disease and decreased appetite, who died on study day 20 due to metastatic small cell lung cancer.

The patient was enrolled with right upper and right middle lobe pneumonia (PORT Risk Class-IV) with no pleural effusion. He did not receive any antibacterial treatment for the qualifying CABP before entering the study. Concomitant medications taken by the patient during the study included aspirin/magnesium, enalapril, aminophylline, and acetylcysteine. The patient's sputum culture grew *H. influenza*. On examination, the patient's temperature was 37.5°C, respiratory rate was 28 breaths per minute, pulse was 110 beats per minute, blood pressure was 160/80 mm Hg, and O_2 saturation was 80%. The only notably abnormal laboratory finding was serum urea > 20. Baseline white blood cell count and creatinine clearance were within normal range.

The patient was randomized to moxifloxacin arm and received a total of 13 days (9 days IV and 4 days oral) of moxifloxacin treatment. On study day 14, a chest radiograph, which was performed as a part of routine procedure, showed a suspicious tumor in the right upper lobe of the lung while there was an improvement in index infection (CABP). On study day 15, computed tomography of the chest was consistent with signs of tumor in the right upper lobe of the lung. On study day 16, a transbronchial biopsy showed invasive small-cell cancer. On study day 20, during early morning hours (7:00 AM), the patient was found dead on his bed, which was not witnessed, therefore, no resuscitation measures were performed. An autopsy showed disintegrated large-nodule central small-cell lung cancer in the right upper lobe with total damage and metastases to the right juxta-hilar lymph nodes, the left lung, and the liver. The staging of the cancer was reported as stage IV and grade 3. The cause of death as per autopsy report was attributed to advanced metastasis of a malignant tumor in the right upper lobe of the lung and metastatic disease with terminal complications.

4. Subject # (b) (6)

This was a 72-year-old white female with a medical history of hypertension, coronary artery disease, atherosclerotic cardiosclerosis, diabetes mellitus type-2, and chronic erosive gastroduodenitis, cholecystectomy, and hysterectomy, who died on study day 71 due to metastatic pancreatic cancer.

The patient was enrolled with left lower lobe pneumonia (PORT Risk Class-III) with a left pleural effusion. She did not receive any antibacterial treatment for the qualifying CABP before entering the study. Her concomitant medications included bisoprolol, mefenamic acid, spironolactone, rosuvastatin, and omeprazole. The patient's sputum culture grew *Haemophilus parainfluenza*. On examination, the patient's temperature was 38.3°C, respiratory rate was 22 breaths per minute, pulse was 68 beats per minute, blood pressure was 140/80 mm Hg, and O_2 saturation was 95%. Laboratory results were unremarkable, with normal white blood cell counts, urea, and creatinine clearance, among others, except she had mildly elevated transaminases (aspartate transaminase (AST) and alanine transaminase (ALT)), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and bilirubin at baseline.

The patient was randomized to moxifloxacin arm and received the last dose of her study treatment on study day 8. She received a total of 4 doses of IV and 4 doses of oral moxifloxacin treatment. On study day 7, the patient was noted to have icterus on physical examination. The laboratory test results showed markedly abnormal liver function tests with a very high elevation of transaminases and bilirubin (AST 555 U/L, ALT 1109 U/L, GGT 1701 U/L, ALP 518 U/L, and total bilirubin 129.6 µmol/L). Evaluations and procedures performed between study day 7 and study day 12 included ultrasound and computerized tomography of the abdomen, gastroscopy, and invasive drainage of the biliary tract. On study day 9, based on the findings of imaging and procedures, she was diagnosed with pancreatic cancer with obstructive icterus and infiltration of the duodenum. Other findings included hepatomegaly, hepatic steatosis, focal atrophic gastritis, and superficial duodenitis. A pancreatic resection was planned and she was transferred to another hospital on study day 12. On study day 15, she underwent an endoscopic external transhepatic biliary drainage along with other management for pancreatic cancer and was discharged from the hospital on study day 27. On study day 71, the patient was reported dead. An autopsy was not performed, and the cause of death was reported as 'a rare form of pancreatic cancer'.

Case Summaries of Deaths from Phase 2/3 cSSSI and Phase 3 ABSSSI Trials

Omadacycline Treatment Arm

Subject # (b) (6) (Study CSSI-0804- Truncated Phase 3 cSSSI trial)

This was a 51-year-old, white male, with a medical history of head injury, craniotomy, spinal fusion surgery, and insomnia; enrolled in Study cSSI-0804 with a diagnosis of complicated skin infection /cellulitis of the left hand. At baseline, the patient was afebrile and other vital signs were normal. The patient was randomized to omadacycline arm and received omadacycline IV for 4 days followed by oral treatment for a total treatment duration of 10 days. Seven days after the end of treatment (day 17), the patient presented with dyspnea and symptomatic pleural effusion and underwent drainage of the effusion. Subsequent imaging and biopsy of pleural mass confirmed the diagnosis of 'large cell metastatic carcinoma of the lung', which was considered untreatable, and he died under palliative care on day 35.

Subject # (b) (6) (Study ABSI-1108)

This was a 60-year-old male with a medical history of IV drug abuse and chronic hepatitis C, who was, enrolled in Study ABSI-1108 with a diagnosis of a wound infection of the upper right leg. The patient received omadacycline IV on day 1. Subsequently on the same day, the patient had an adverse event of vomiting that was considered moderate in severity and related to study drug, which led to discontinuation of the study drug. The subject left the study site and reportedly never returned for follow up visits. It was discovered later that the patient died on day 2 from an 'opiate overdose.' The site was notified of this information by the county coroner 6 months after it occurred and it was confirmed that the patient had failed to return for his subsequent study visits due to the death. An autopsy was not performed.

Linezolid Treatment Arm

Subject # (b) (6) (Study ABSI-1108)

This was an 88-year-old male with a medical history of chronic cardiac and cerebrovascular insufficiency and atrial fibrillation, who entered the study with a wound infection of the left lower leg. The patient received the study drug (linezolid) IV for a total of 7 days, with the resolution of index infection at EOT visit. Five days after the last dose of test article (day 12), the subject died from 'cardiac failure' due to decompensation of chronic cardiac insufficiency. An autopsy was not performed and the event was considered unrelated to the study treatment.

Subject # (b) (6) (Study ABSI-1108)

This was a 43-year-old male with a medical history of hypertension, smoking, and recent motor vehicle accident, who entered the study with a wound infection of the left knee and was randomized to linezolid arm. The patient also received a bedside incision and drainage as a

standard of care prior to randomization. The patient received the study drug IV for 5 days and oral for 2 days. On the morning of study day 9, the patient was found partially responsive with agonal breathing by his wife. He died later that day due to 'cardiac arrest'. An autopsy was not performed and the event was considered unrelated to the study treatment.

Subject # (b) (6) (Study ABSI-16301)

This was a 62-year-old female with medical history of injection drug abuse (heroin), marijuana abuse, chronic hepatitis C, migraine and non-migraine headaches, myopia, tobacco use, insomnia, hysterectomy, osteoporosis, and osteoarthritis of bilateral hands, hips, shoulders and knees. She was enrolled with a diagnosis of wound infection in the right buttock. The patient was randomized to linezolid and received 10 days of oral linezolid treatment and completed the study. This patient was reported dead 94 days after the last dose of the study drug. Following investigation and autopsy with the local coroner's office by the Sponsor, it was found that the cause of death was 'acute heroin, methamphetamine, tramadol, alprazolam, and diphenhydramine intoxication.' In the opinion of the investigator, the event was unrelated to study drug.

15.3.22. EKG parameters in CABP 1200

			Omadacycline N = 382 Mean (SD)	Moxifloxacin N = 388 Mean (SD)
Heart rate (bpm)	Prior to first infusion		84.6 (16.59)	84.2 (16.59)
	ΔHR	30-90 minutes after first dose infusion	4.3 (10.06)	-1.5 (8.26)
		Dose 3, prior to infusion	-1.8 (13.86)	-5.4 (13.89)
		Dose 3, 30-90 minutes after infusion	-1.1 (13.34)	-6.8 (13.19)
		Day 7	-7.4 (15.95)	-8.6 (16.06)
QTcF (msec)	Prior to first infusion		415.0 (24.30)	416.5 (25.21)
	Δ QTcF	30-90 minutes after first dose infusion	0.8 (16.92)	5.8 (15.82)
		Dose 3, prior to infusion	1.4 (18.55)	4.3 (22.04)
		Dose 3, 30-90 minutes after infusion	1.8 (18.14)	11.1 (17.57)
		Day 7	5.4 (22.89)	12.2 (23.06)
PR (msec)	Prior to first infusion		151.4 (25.51)	155.0 (23.67)
	ΔPR	30-90 minutes after first dose infusion	-1.3 (11.19)	0.9 (11.14)
		Dose 3, prior to infusion	-0.4 (11.70)	0.5 (13.17)
		Dose 3, 30-90 minutes after infusion	-0.4 (13.10)	0.9 (12.33)
		Day 7	2.4 (14.72)	1.8 (15.72)
QRS (msec)	Prior to first infusion		98.6 (19.55)	99.4 (19.27)
	ΔQRS	30-90 minutes after first dose infusion	-0.2 (9.80)	-0.8 (14.49)
		Dose 3, prior to infusion	0.4 (16.73)	-0.3 (14.38)
		Dose 3, 30-90 minutes after infusion	-0.3 (10.94)	0.2 (14.93)
		Day 7	-1.2 (12.38)	-0.3 (19.32)

Δ = Change-from-baseline, bpm = beats per minute, ECG = electrocardiogram, HR = heart rate, msec = millisecond, QTcF = heart rate corrected QT interval using the Fridericia formula, SD = Standard deviation.
Source: Table 14.3.5.1 in CSR Study PTK0796-CABP-1200.

15.3.23. Definition of Clinical Failure in ABSSSI Trials

Clinical Failure in ABSSI trials were defined by the criteria below:

- The size of the primary lesion had not been reduced by greater than or equal to 20% compared to Screening measurements.
- Investigator discontinued study drug and indicated that the infection had responded inadequately such that alternative (rescue) antibacterial therapy was needed.
- The patient received antibacterial therapy that may be effective for the infection under study for a different infection from the one under study up through the assessment of ECR (i.e., lesion size) or if no assessment was done in the 48- to 72-h time window, up through 72 h after the first dose of study drug.
- The patient developed an AE that required discontinuation of study drug prior to the ECR assessment or if no assessment was done in the 48- to 72-h time window, up through 72 h after the first dose of study drug.
- Death prior to ECR assessment or if no assessment of ECR (i.e., lesion size) was done in the 48- to 72-h time window, up to 72 h after first dose of study drug.
-

15.3.24. Analysis Population in ABSSSI Trials

The following populations were defined for the efficacy analyses:

ITT population: consisted of all randomized subjects regardless of whether or not the subject received study drug.
mITT population: consisted of all randomized subjects without a Baseline sole Gram-negative ABSSSI pathogen.
Micro-mITT population: consisted of all subjects in the mITT population who had at least 1 Gram-positive causative bacterial pathogen identified from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site at Baseline using a valid sampling technique.
CE-EOT and CE-PTE populations: subjects must have been in the mITT population to be included in the CE-EOT and the CE-PTE populations, and met the additional criteria described in Appendix.
ME-EOT and ME-PTE populations: consisted of all subjects in both the micro-mITT and the CE-EOT and CE-PTE populations, respectively.

Study visits included a baseline visit, an ECR visit at 48-72 hours after the first dose of study drug, an EOT visit on the same day or within 2 days following the last dose of study drug, and approximately 7 to 14 days after the last dose of study drug (PTE visit), and a follow-up telephone contact was to occur approximately 30 to 37 days after the first dose of study drug.

15.3.25. Table Comparison of Early Clinical Success (ECR) by Baseline Pathogen-ABSSSI Trials

Table Comparison of Early Clinical Success (ECR) by Baseline Pathogen** (from ABSSSI Site or Blood Culture) in ≥ 6 Patients in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population)							
	ABSI-1108		ABSI-16301		Pooled ABSI-1108 and ABSI-16301		
Baseline Pathogen	OMC (N = 228) n/N1 (%)	LNZ (N = 227) n/N1 (%)	OMC (N = 276) n/N1 (%)	LNZ (N = 287) n/N1 (%)	OMC (N = 504) n/N1 (%)	LNZ (N = 514) n/N1 (%)	Difference (95% CI for Pooled Population)
Gram-positive organisms (aerobes)							
S. 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)	*3.7 (-1.2, 8.6)*
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)	3.4 (-3.1,10.2)
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)	3.7 (-3.3,10.6)
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 Gr	39/47 (83.0)	27/37 (73.0)	54/57 (94.7)	36/45 (80.0)	93/104 (89.4)	63/82 (76.8)	*12.6 (1.9, 24.0)*
S. 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)	22.2 (10.5.40.9)
S. 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)	15.2 (-1.9,31.7)
S. 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)	9.8 (-13.9,34.9)
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)	*8.9 (-16.2, 30.9)*
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)	10.0 (-16.4,33.2)
β-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)	*-11.9 (-28.3,5.5)*
Group A or S. 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)	*-8.2 (25.3,9.6)*
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 sp.	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)	

Table Comparison of Early Clinical Success (ECR) by Baseline Pathogen** (from ABSSSI Site or Blood Culture) in ≥ 6 Patients in Study ABSI-1108 and Study ABSI-16301 (micro-mITT Population)							
	ABSI-1108		ABSI-16301		Pooled ABSI-1108 and ABSI-16301		
Baseline Pathogen	**OMC (N = 228) n/N1 (%)**	**LNZ (N = 227) n/N1 (%)**	**OMC (N = 276) n/N1 (%)**	**LNZ (N = 287) n/N1 (%)**	**OMC (N = 504) n/N1 (%)**	**LNZ (N = 514) n/N1 (%)**	**Difference (95% CI for Pooled Population)**
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)	
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)	

Source: Clinical Reviewer; SCP, Table 14.2.1.11.1.

**Baseline organism isolated from the culture is listed here. Some of these organisms are not considered causative pathogen for ABSSSI
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.

15.3.26. Table of summary of significant adverse events across phase 3 trials

This section will discuss TEAEs that were not considered as a 'serious adverse events', however, were considered 'significant' based on definition in ICH guideline for industry E3 Structure, and were graded as "severe".

Table: SEVERE TEAEs which were not considered as SAEs in AC3 pool (safety population)									
AESOC	**TRT**	**USUBJID**	**AEDECOD**	**STDY**	**ENDY**	**TRT DUR**	**RELATED**	**OUTCOME**	**Drug D/C**
Investigations	**OMC**	ABSI16301 (b) (6)	Blood CPK increased	3	7	7	N	RECOVERED	N
	LNZ	ABSI16301- (b) (6)	Amylase /Lipase increased	10		10	N	RECOVERING	N
	LNZ	ABSI1108- (b) (6)	Blood CPK increased	15		8	N	UNKNOWN	N
	LNZ	ABSI16301- (b) (6)	GGT increased	15	31	8	N	RECOVERED	N

Table: SEVERE TEAEs which were not considered as SAEs in AC3 pool (safety population)									
AESOC	**TRT**	**USUBJID**	**AEDECOD**	**STDY**	**ENDY**	**TRT DUR**	**RELATED**	**OUTCOME**	**Drug D/C**
	MOXI	CABP1200-(b) (6)	CRP increased	2	10	5	N	RECOVERED	Y
	MOXI	CABP1200(b) (6)	Pro-calcitonin increased	5	8	5	N	RECOVERED	N
Infections and infestations	**OMC**	ABSI1108-(b) (6)	Wound infection	26	43	9	N	RECOVERED	N
	LNZ	ABSI16301(b) (6)	Wound infection	26		10	N	NOT RECOVERED	N
Metabolism/ nutrition D/O	**OMC**	CABP1200-(b) (6)	Vitamin D deficiency	8		5	N	RECOVERING	N
	OMC	CABP1200(b) (6)	Hypoalbuminaemia	26		10	N	UNKNOWN	N
	LNZ	ABSI1108-(b) (6)	Hypernatraemia	4	7	11	N	RECOVERED	N
Gastrointestinal disorders	**OMC**	CABP1200-(b) (6)	Vomiting	5	5	5	Related	RECOVERED	Y
	LNZ	ABSI1108-(b) (6)	Vomiting	2	2	4	N	RECOVERED	N
General D/O Adm Site	**OMC**	ABSI1108-(b) (6)	Pyrexia	1	3	1	N	RECOVERED	Y
	OMC	ABSI16301(b) (6)	Inflammatory pain	1	7	9	N	RECOVERED	N
Neoplasms	**OMC**	CABP1200-(b) (6)	Lung neoplasm	23		10	N	UNKNOWN	N
	OMC	CABP1200-(b) (6)	Lung neoplasm	11		6	N	UNKNOWN	N
Nervous system D/O	**OMC**	ABSI1108-(b) (6)	Headache	5	5	10	Related	RECOVERED	N
	MOXI	CABP1200(b) (6)	Headache	2	4	7	N	RECOVERED	N
Blood/ lymphatic system D/O	**OMC**	CABP1200-(b) (6)	Anaemia	4	5	2	N	RECOVERED	N

Table: SEVERE TEAEs which were not considered as SAEs in AC3 pool (safety population)

AESOC	TRT	USUBJID	AEDECOD	STDY	ENDY	TRT DUR	RELATED	OUTCOME	Drug D/C
Cardiac D/O	**OMC**	CABP1200-(b) (6)	Stress cardiomyopathy	4		3	Related	NOT RECOVERED	Y
Hepatobiliary D/O	**OMC**	CABP1200-(b) (6)	Hepatocellular injury	4	21	14	Related	RECOVERED	N
Pregnancy, puerperium	**OMC**	ABSI16301-(b) (6)	Pregnancy*	2	17	1	N	RECOVERED	Y
Psychiatric D/O	MOXI	CABP1200-(b) (6)	Delirium tremens	1	20	5	N	RECOVERED	N
Respiratory, thoracic/ D/O	MOXI	CABP1200-(b) (6)	Respiratory failure	2	20	5	N	RECOVERED	N

Source: Clinical Reviewer's analysis

*Pregnancy: Subject PTK0796ABSI116301(b) (6) was a 27-year-old female with no reported medical history, was diagnosed with cellulitis on the right upper leg; symptom onset began 5 days prior to enrollment. She was randomized to omadacycline and received the first dose on the same day of screening. The subject's treatment included 1 day of oral (po) omadacycline. The subject's concomitant medications taken during the study included amoxicillin (which she received after discontinuation of omadacycline for cellulitis). During the patient's screening visit, she was administered a urine and serum pregnancy test. The urine pregnancy test turned out negative, but the serum pregnancy test later showed a positive result. Repeat serum pregnancy tests conducted during her unscheduled safety visit (Day 2), End of Treatment (EOT) visit (Day 2), and Post-Treatment Evaluation (PTE) (Study Day 10) confirmed the positive result of the screening test. On Study Day 2, 1 day after the first and last dose of po study drug, the investigator learned of the positive screening serum pregnancy test and immediately discontinued the patient from study drug. The patient was started on an antibacterial regimen of amoxicillin 500 mg po twice a day to treat the primary acute bacterial skin and skin structure infection. She continued with this treatment until Day 10. On Study Day 17, the pregnancy was voluntarily terminated by the patient via an elective abortion. The patient completed the study (returned for the EOT and PTE visits, and the follow-up phone call). In the opinion of the investigator, the event was non-serious, severe, and not related to the test article.

15.3.27. Outcome in Bacteremic Patients Per pathogen: ABSSSI Trials

Table Clinical Success at ECR Visit by Baseline Pathogen from the ***Blood Culture*** in ABSSSI Trials (micro-mITT population)		
Study ABSI 1108		
	Omadacycline (N=228)	**Linezolid (N=227)**
Staphylococcus aureus	4/6	4/6
MRSA	*3/3*	*2/2*
MSSA	*1/3*	*2/4*
Streptococcus pyogenes	1/2	2/2
Streptococcus anginosus group	1/1	0
Streptococcus anginosus	1/1	0
Enterococcus faecalis (VSE)	0	1/1
Streptococcus dysgalactiae	0/1	0
Streptococcus viridans group	0/1	1/1
Study ABSI-16301		
	Omadacycline (N=276)	**Linezolid (N=287)**
Staphylococcus aureus	1	3
MRSA	*0*	*1/1*
MSSA	*0/1*	*2*
Streptococcus sanguinis	1/1	0
Streptococcus pyogenes	0	0/1
Streptococcus anginosus group	0	1
Streptococcus intermedius	0	1/1
Granulicatella adiacens	0	1/1
Rothia dentocariosa	0	1/1
Moraxella lacunata	0	1/1
Source: Clinical Reviewer's Analysis		

15.3.28. Criteria for transition to PO regimen in CABP Trial

For a subject to be considered clinically stable and meet criteria
for transition to a po regimen, they must have had the following findings:

- Temperature ≤ 37.8°C (100°F).
- HR ≤ 100 bpm.
- RR ≤ 24 breaths/minute.
- Systolic BP ≥ 95 mmHg.
- Oxygen saturation ≥ 90% as measured by pulse oximetry or PaO2 ≥ 60 mmHg by ABG.
- No worsening of CABP symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) compared to Screening.
- Normal mental status ("absence of confusion" or pre-illness baseline for subjects who did not
have normal mental status before the onset of pneumonia).
- Ability to maintain po intake.

A switch to po treatment was not permitted until after the subject had completed at least the first 3 days of iv treatment (after 4 iv doses).

15.3.29. Summary of SAEs by System Organ Class and Preferred Term-pooled phase 3 ABSSSI trials and CABP Trial (safety population)

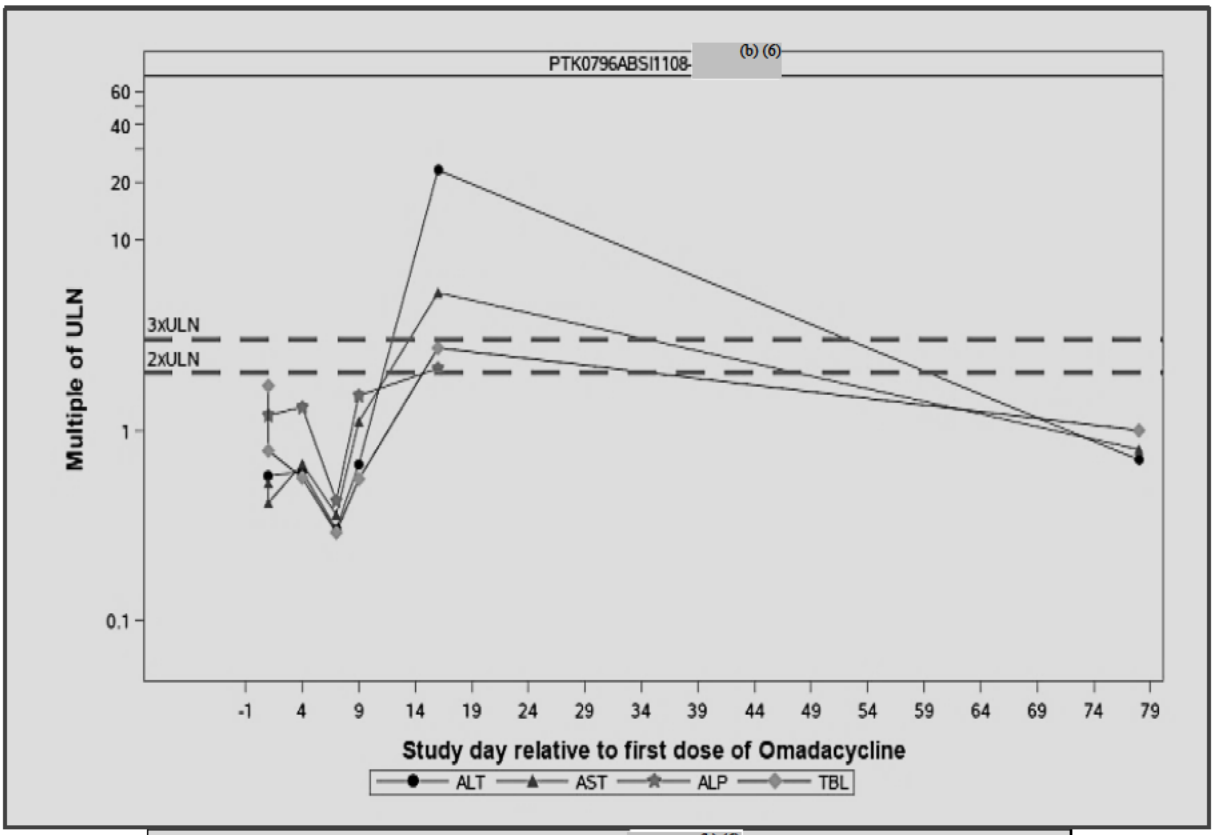
Summary of SAEs by System Organ Class and Preferred Term-pooled phase 3 ABSSSI trials (safety population)				
System Organ Class Preferred Term	**Omadacycline N=691**		**Linezolid N=689**	
	n	%	n	%
Patients with at Least One SAE	16	2.3	13	1.9
Cardiac disorders	**0**	**0**	**2**	**0.3**
Cardiac arrest	0	0	1	0.1
Cardiac failure	0	0	1	0.1
General disorders and administration	**2**	**(0.3)**	**1**	**(0.1)**
Drug withdrawal syndrome	1	(0.1)		0
Non-cardiac chest pain	1	(0.1)		0
Death	0	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)
Bacteremia	1	(0.1)		0
Gastroenteritis rotavirus	1	(0.1)		0
Hepatitis C	1	(0.1)		0
Staphylococcal bacteremia	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	0
Chronic obstructive pulmonary disease	0	0	1	0.1
Pulmonary embolism	0	0	1	0.1
Skin and subcutaneous tissue disorders	**0**	**0**	**1**	**0.1**
Angioedema	0	0	1	0.1
Source: Clinical Reviewer's analysis; ADAE data set				

15.3.30. Narratives of patients with normal baseline AST/ALT and had post-baseline increase to > 10 × ULN

Case #1. (Study ABSI-1108)

This was an 88-year-old female with a medical history of CHF, atrial fibrillation, recent trauma, and surgery, was enrolled in the ABSI1108 trial with a diagnosis of cellulitis of the left lower and upper leg. The baseline ALT and AST and total bilirubin values were within the normal range. However, ALP value at baseline was slightly high (ALP: 138, <2xULN) at baseline. The patient received a total of 9 days of IV study drug treatment. Her EOT visit was on Study Day 9. No abnormalities or worsening of laboratory values were reported during the treatment.

At the PTE visit (Day 16), the patient had an ALT elevation of 767 U/L (>20 X ULN), and an AST value of 190 U/L (>5 X ULN), a total bilirubin value of 51 (>2 X ULN), and an elevated ALP value of 243 U/L (>2 X ULN). No action was taken, and the event was followed until it was considered resolved on Day 37 (Figure and Table below).



Laboratory Results Patient # ABSI 1108-(b) (6)					
	Baseline (Day 1)	Day 4	Day 7	EOT	PTE
ALT (0-44 U/L)	19	20	10	22	767
AST (14-39 U/L)	15	24	13	40	190
Bilirubin (5-20 µmol/L)	3.1	11	5	10	50
ALP (53-129 U/L)	138	152	-	175	243

An additional local laboratory assessment at an unscheduled visit (Day 78) reported ALT values had returned to normal range.

Clinical Reviewer's Comment: No additional information is provided about this patient. It is not known if the patient had taken any hepatotoxic medications after her discharge at EOT. Causality could not be assessed with given information. It is not known if the patient had exposure to hepato-toxins after EOT.

Hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of substantial ALT elevation, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI at a rate roughly 1/10 the rate of Hy's Law cases. Briefly, Hy's Law cases have the following three components[40]:

- *i) The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo*
- *ii) Among trial patients showing such AT elevations, often with ATs much greater than 3xULN, one or more also show the elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)*
- *iii) No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.*

However, in this case, the patient does not qualify for Hy's Law criteria, given the abnormal baseline ALP pointing to other possible obstructive causes.

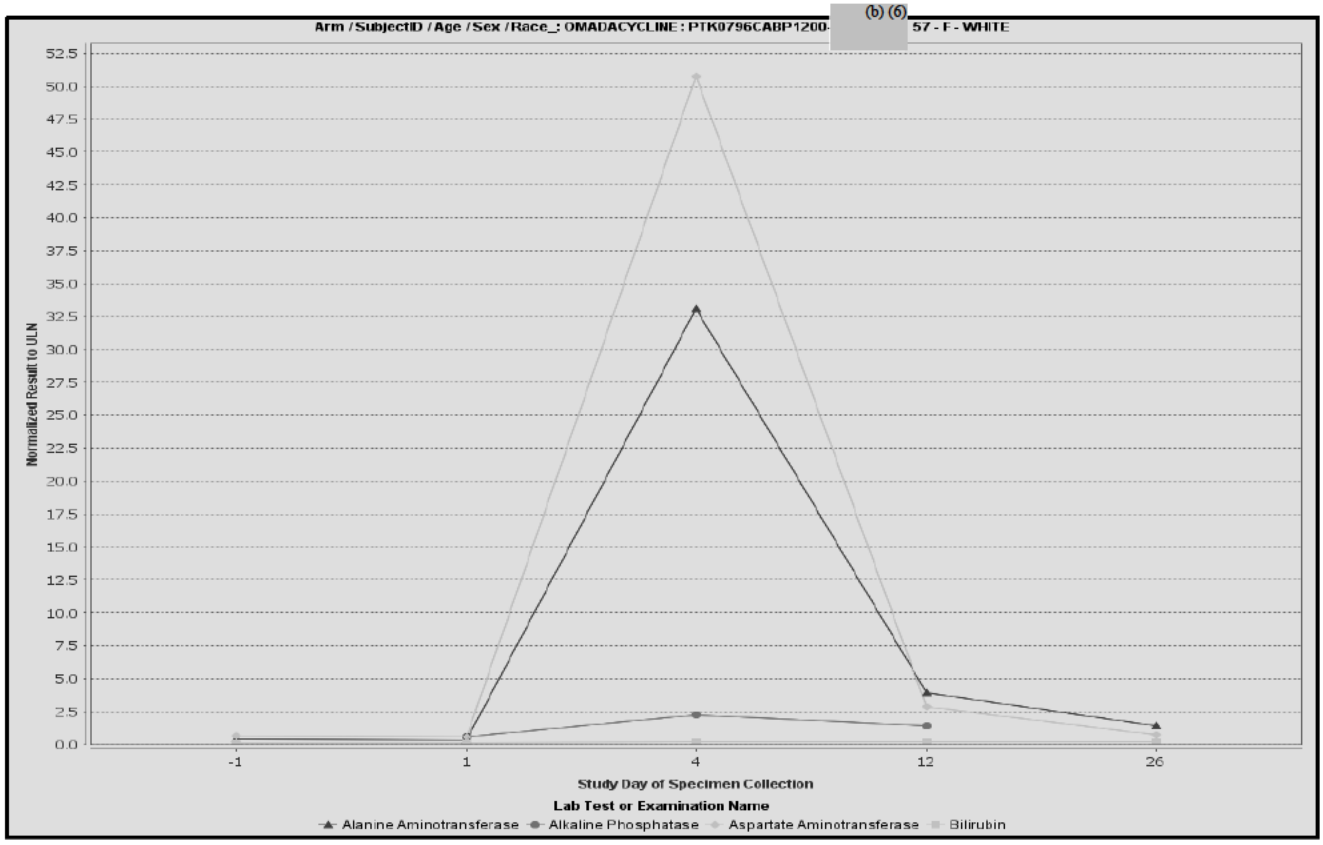
Case #2: (Study CABP1200)

This was a 57-year-old white female with a pertinent medical history of COPD, Insomnia, urinary incontinence, and the headache was enrolled in Study CABP1200 with left lower lobe pneumonia *(*PORT Risk class-II), culture positive for *S. pneumoniae* and was randomized to omadacycline. The patient had a normal baseline liver chemistry results on Day 1. On Study Day 3, the patient was transferred to the intensive care unit due to acute respiratory failure, and supraventricular tachycardia followed by sudden cardiac arrest. The study drug was discontinued due to this event. Subsequent laboratory results showed abnormal chemistry values. On Study Day 4, the patient was diagnosed with severe hepatic failure, and at the same time, she was also diagnosed with severe concurrent infection with influenza AH1N1. The liver chemistry results showed elevated ALT of 1093 U/L (>20 X ULN), AST of 1827 U/L

[40] https://www.fda.gov/downloads/Guidances/UCM174090.pdf

(>40 X ULN), and ALP of 264 U/L (Table and Figure below). The investigator assessed the events of acute respiratory insufficiency, sudden cardiac arrest, supraventricular tachycardia, liver failure, and concurrent infection with influenza AH1N1 as not related to the study drug.

Laboratory Results Patient # CABP1200-(b) (6)				
	Baseline (Day 1)	EOT (Day 4)	PTE (Day 12)	(Day 26) **
ALT (0-44 U/L)	13	1093*	129*	43.24** (0-31 U/L)
AST (14-39 U/L)	22	1827*	104*	22.24 (0-31 U/L)
ALP (53-129 U/L)	69	264*	160*	Not Done
Bilirubin (5-20 µmol/L)	3	4	4	4** (3-17 µmol/L)
GGT (0-54 U/L)	14	98*	215*	Not Done
** local laboratory value and normal range				

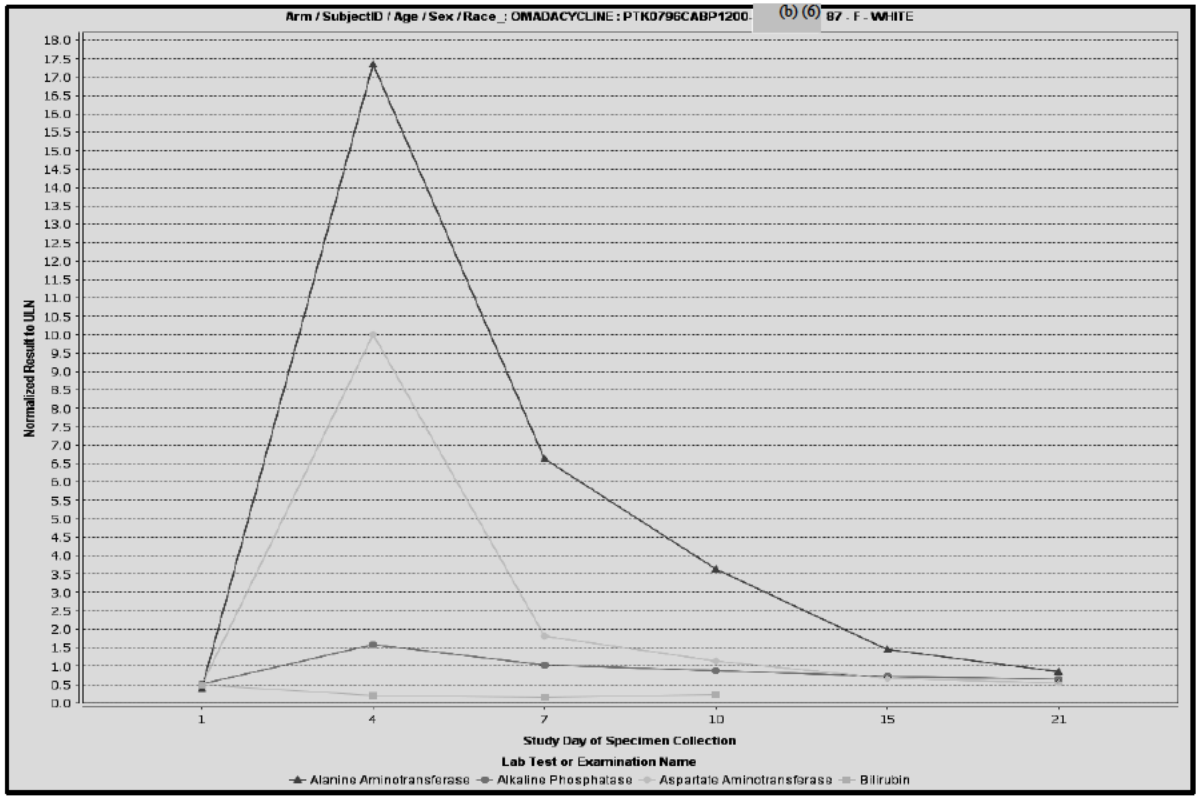


Clinical Reviewer's Comment: This patient's liver enzyme elevation clearly had other contributory factors, including cardiac arrest with resultant hypoperfusion of liver and organ dysfunctions. Furthermore, this patient was also diagnosed with Influenza AH1N1. Elevation of liver transaminase levels has been reported during systemic viral infections. It is known that severe influenza infection can be associated with abnormalities in liver biochemistry that resolve after successful clearance of the virus.

Case#3 (Study CABP 1200)

This was 87-year-old white female with no reported medical history, was diagnosed with CABP of the left lower lobe (PORT Risk class-IV). The patient's sputum culture was positive for *Streptococcus pneumoniae.* The patient had normal liver chemistry at baseline. On Study Day 4, during IV study drug administration, TEAE of 'hepatocellular injury' was reported for this patient. The liver chemistry results showed elevated ALT of 573 U/L (>15 X ULN), AST of 360 U/L (10 X ULN), and ALP of 181 U/L (Table and Figure below). The event was severe; however, no action was taken with the study drug and patient received her last dose of study treatment (10 days of IV and 4 days of oral omadacycline) on Study Day 15. Liver enzymes returned to near normal by EOT visit and completely within normal range by PTE visit.

Laboratory Results Patient # CABP1200-(b) (6)						
	BL-Day 1	Day 4	Day 7	Day 10	EOT-Day 15	PTE-Day 21
ALT (10-33 U/L)	13	573*	219*	120*	48*	28
AST (10-36 U/L)	18	360*	65*	41*	24	19
ALP (30-115 U/L)	59	181*	119*	100	83	74
Bilirubin (0-19 µmol/L)	6.4	4	3	4	< 2.565	< 2.565



Clinical Reviewer's Comment: This case of hepatic enzyme elevations appears to be related to omadacycline based on the timing of occurrence and resolution after the study drug was stopped.

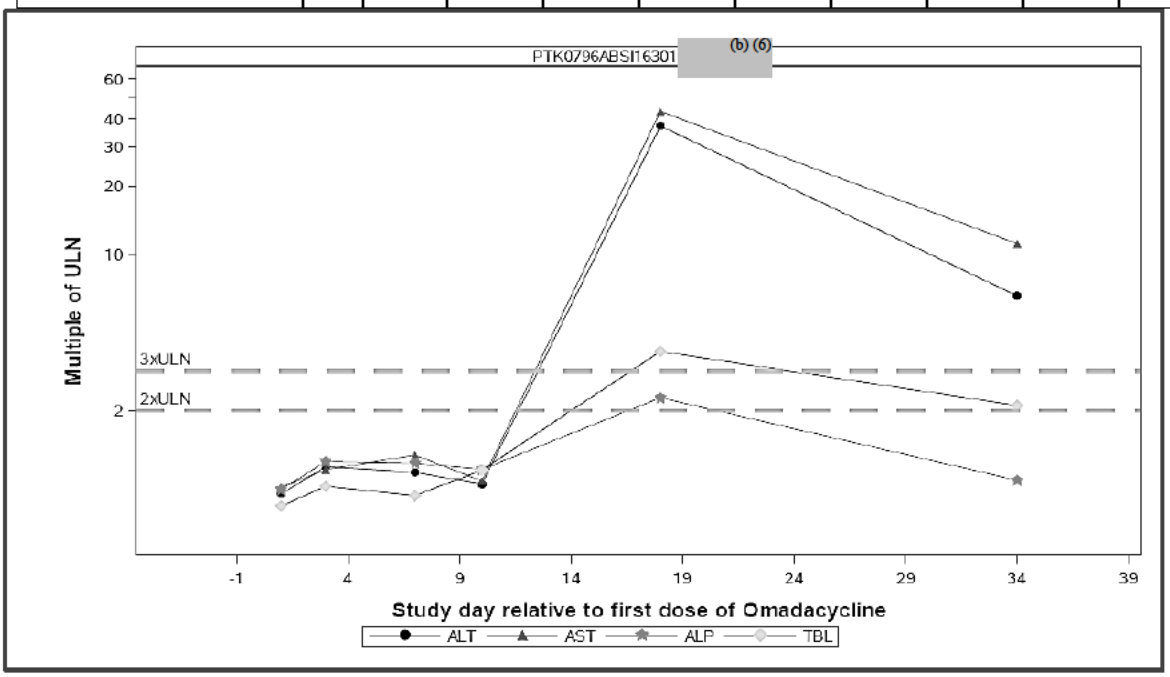
Case#4 (Study ABSI 16301)

This was a 27-year-old female patient with a pertinent medical history of asthma, vascular insufficiency, opiate dependence, and IV drug use, prior history of ABSSSI, chronic pancreatitis, and gallstones, was enrolled with a diagnosis of cellulitis in the right buttock. The baseline liver enzymes were within normal range. The patient was randomized to omadacycline and received 10 days of study treatment.

On Study Day 18 (8 days after the last dose of oral study drug) during PTE visit, the routine laboratory showed, significantly elevated liver enzymes with ALT of 1223 U/L (>30 X ULN), AST of 1462 U/L (> 40 X ULN), ALP was > 2 X ULN, and total bilirubin > 3 X ULN. The investigator also noted that the patient complained of mild nausea and flu-like symptoms. The following day, on Study Day 19, the patient presented to the hospital with complaints of right upper quadrant abdominal pain associated with nausea and vomiting. The laboratory tests performed on that day revealed severe 'transaminitis' with ALT > 40 X ULN, AST > 90 X ULN, and bilirubin > 4 X ULN. On that same day, she had a positive serology test for hepatitis C virus (HCV), and an HCV molecular amplification test detected elevated levels of HCV RNA (5.47 log10 IU/mL).

The patient was thus diagnosed with hepatitis C. Specific testing for hepatitis B virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus was negative. The patient was discharged from the hospital on Study Day 22 after she had an ERCP and other diagnostic tests which showed gallstones and cholecystitis. The patient had completed the study.

Laboratory Results: Patient PTK0796ABSI16301-(b) (6)										
	Scr	Day 3	Day 7	EOT Day 10	PTE Day 18	Day 19	Day 20	Day 21	Day 22	Day 34
ALT (0-33 U/L)	28	37*	35*	31	1223*	2537	2436	2095	1681	337*
AST (14-34 U/L)	31	37*	43*	33	1462*	2579	2403	1598	583	354*
ALP (42-98 U/L)	87	116*	114*	107*	223*	251	222	206	204	126
Bilirubin (5-20 µmol/L)	27	45*	41*	39*	129*	5	4	4	3	36

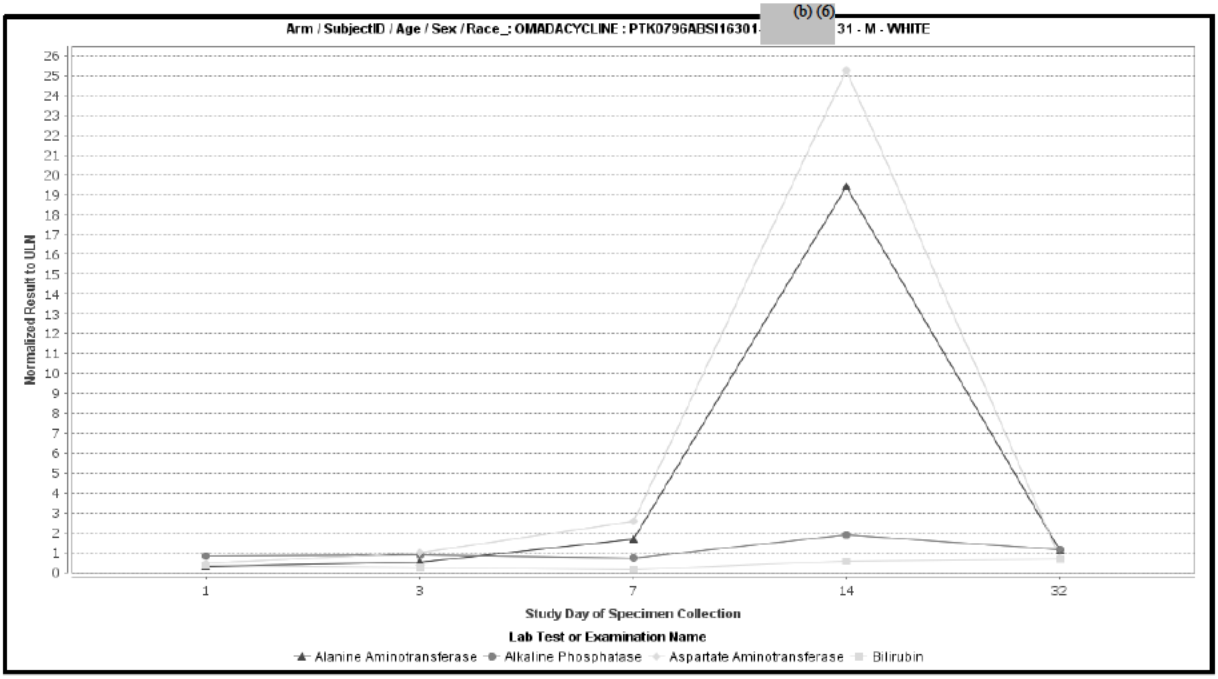


Clinical Reviewer's Comment: This event was unlikely to be related to study drug. Hepatitis C either acute or flare of chronic disease possibly resulted in transaminase elevation.

Case#5 (Study ABSI 16301)

This was a 31-year-old white male, with a pertinent medical history of chronic neck and upper back pain, tobacco abuse, injection drug abuse, and previous ABSSSI on right shoulder was enrolled in ABSI 16301 study, with a diagnosis of wound infection in the right lower arm. The patient was randomized to omadacycline and received the first dose of study drug. His concomitant medications during the study included oxycodone and lidocaine. The patient's liver chemistry results were normal at baseline. The patient received the last dose of the omadacycline on Study Day 7 (EOT visit). The routine laboratory on EOT day showed slightly elevated ALT (< 2x ULN) and AST (> 2x ULN).
On Study Day 14 (PTE visit), 7 days after the last dose routine laboratory showed a significant elevation in liver chemistry values with ALT of > 19 X ULN, AST of > 20 X ULN, GGT of > 3x ULN, and ALP slightly elevated (< 2 X ULN). Serum bilirubin was normal throughout. The investigator subsequently diagnosed the patient with hepatitis A (hepatitis A IgM positive) and hepatitis C (hepatitis C antibody positive).
On Study Day 32, the investigator performed additional serology testing, which revealed the positive hepatitis C antibody result. The liver chemistry results on the same day revealed that ALT and ALP had significantly improved, and AST returned to baseline.

Laboratory Results Patient # ABSI16301- (b) (6)					
	Screening	**Day 3**	**EOT -Day 7**	**PTE -Day 14**	**Day 32**
ALT (0-44 U/L)	13	23	75*	853*	47*
AST (14-39 U/L)	18	39	100*	984*	28
ALP (53-129 U/L)	107	111	97	244*	151*
GGT (0-54 U/L)	9	16	13	183*	35
Bilirubin (5-20 µmol/L)	7	5	3	12	14



Clinical Reviewer's Comment: This patient's liver enzyme elevations were likely related to hepatitis. However, the contribution of omadacycline (or other hepatotoxins that could be taken by the patient) cannot be ruled out completely.

Hepatic TEAEs with an increase in post baseline liver enzyme values – based on history of liver disease

Table x below summarizes increases in liver enzymes based on underlying liver disease history across phase 3 trials.

Table: Liver Chemistry Elevation in Patients With or Without a history of underlying liver disease: Phase 3 Trials (safety population)

	OMC N=1073		LNZ N=689		Moxi N=388	
	With-LD	Wo-LD	With-LD	Wo-LD	With-LD	Wo-LD
ALT(U/L)						
Normal at Baseline	205	826	207	452	9	372
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
>3 x ULN	10 (5)	34 (4)	9 (4)	18 (4)	1 (11)	16 (4)
>5 x ULN	5 (2)	17 (2)	1 (0.5)	4 (1)	0	4 (1)
>10 x ULN	2 (1)	7 (0.8)	0	3 (0.7)	0	1 (0.3)
AST (U/L)						
Normal at Baseline	209	831	208	453	9	370
>3 x ULN	9 (4)	29 (3.5)	9 (4)	18 (4)	0	12 (3)
>5 x ULN	6 (3)	14 (2)	1 (0.5)	6 (1)	0	4 (1)
>10 x ULN	1 (0.5)	5 (0.6)	0	1 (0.2)	0	2 (0.5)
TBL (umol/L)						
Normal at Baseline	210	831	212	454	9	372

Table: Liver Chemistry Elevation in Patients With or Without a history of underlying liver disease: Phase 3 Trials (safety population)						
	OMC N=1073		LNZ N=689		Moxi N=388	
	With-LD	Wo-LD	With-LD	Wo-LD	With-LD	Wo-LD
>1.5 x ULN	1 (0.5)	10 (1)	1 (0.5)	2 (0.4)	0	7 (2)
>2 x ULN	0	6 (0.7)	0	1 (0.2)	0	4 (1.1)
With-LD: With Liver disease; Wo-LD= Without Liver disease						

Clinical Reviewer's Comment: After the Clinical Reviewer's thorough evaluation of hepatic injury in the clinical development program. Higher proportions of patients without underlying liver disease had post-baseline liver enzyme elevations as compared to a patient with existing liver disease. Therefore, the risk of hepatotoxicity associated with omadacycline does not appear to be enhanced in patients with underlying liver disease.

15.3.31. Table of Summary of Adverse Events from Tetracycline Class: Pooled Phase 3 Trials (Safety Population)

Summary of Adverse Events from Tetracycline Class: Pooled Phase 3 Trials (Safety)			
	Pooled Phase 3 Trials		
Category PT	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
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 generalized	0	1 (0.1)	0
Rash generalized	0	1 (0.1)	0
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
Blood urea increased	1 (0.1)	0	0
Blood urea increased	1 (0.1)	0	0
Esophagel disorders	1 (0.1)	0	0
Esophagitis	1 (0.1)	0	0

Pancreatitis	1 (0.1)	0	1 (0.3)
Pancreatitis chronic	1 (0.1)	0	0
Pancreatic pseudocyst	0	0	1 (0.3)
***C. difficile* infection**	0	0	8 (2.1)
C. difficile colitis	0	0	1 (0.3)
C. difficile infection	0	0	6 (1.5)
Pseudomembranous colitis	0	0	1 (0.3)

If a patient had more than 1 TEAE with the same category or PT, the patient was counted only once for that category or PT.
Source: Clinical Reviewer; ISS Table 14.3.1.12.4.

Next section to follow- clinical microbiology Appendices

15.4. Microbiology Appendices

15.4.1. Multiyear global surveillance distribution for Gram-positive isolates.

Species	MIC µg/mL (No. of isolates/Cumulative Percent)										Total	MIC_{50}	MIC_{90}
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8			
Staphylococcus aureus (all)		204	4003	16265	6607	1657	368	153	22	1	29280	0.12	0.25
		0.7	14.4	69.9	92.5	98.1	99.4	99.9	>99.9	100			
Staphylococcus aureus (methicillin-susceptible)		131	2335	9985	3936	900	45	7			17339	0.12	0.25
		0.8	14.2	71.8	94.5	99.7	>99.9	100					
Staphylococcus aureus (methicillin-resistant)	3	70	1668	6280	2671	757	323	146	22	1	11941	0.12	0.5
		0.6	14.6	67.2	89.5	95.9	98.6	99.8	>99.9	100			
Staphylococcus aureus (tetracycline-resistant) per CLSI	1	8	147	986	676	169	76	63	15		2141	0.12	0.5
		0.4	7.3	53.3	84.9	92.8	96.4	99.3	100.0				
Coagulase-negative staphylococci (all)[a]		275	1108	1004	762	1071	582	122	4		4928	0.25	1
		5.6	28.1	48.4	63.9	85.6	97.4	99.9	100				
Coagulase-negative staphylococci (methicillin-susceptible)		158	474	350	165	177	80	11			1415	0.12	0.5
		11.2	44.7	69.4	81.1	93.6	99.2	100					
Coagulase-negative staphylococci (methicillin-resistant)		117	634	654	597	894	502	111	4		3513	0.25	1
		3.3	21.4	40	57	82.4	96.7	99.9	100				
Enterococcus faecalis (all)		387	1593	1827	1286	567	45	4	2		5711	0.12	0.5
		6.8	34.7	66.7	89.2	99.1	99.9	>99.9	100				
Enterococcus faecalis (vancomycin susceptible)		375	1552	1766	1255	552	43	3	2		5548	0.12	0.5
		6.8	34.7	66.6	89.2	99.1	99.9	>99.9	100				
Enterococcus faecalis (vancomycin resistant)	5	6	40	60	30	14	2	1			158	0.12	0.5
	3.2	7	32.3	70.3	89.2	98.1	99.4	100					
Enterococcus faecium (all)		354	1573	860	295	80	27	4	1	1	3195	0.06	0.25
		11.1	60.3	87.2	96.5	99	99.8	99.9	>99.9	100			
Enterococcus faecium (vancomycin susceptible)		188	828	410	137	26	4				1593	0.06	0.25
		11.8	63.8	89.5	98.1	99.7	100						
Enterococcus faecium (vancomycin resistant)		165	734	441	156	54	23	4	1	1	1579	0.06	0.25
		10.4	56.9	84.9	94.7	98.2	99.6	99.9	99.9	100			
Streptococcus pneumoniae (all)		3267	5484	1042	158	28	1				9980	0.06	0.12
		32.7	87.7	98.1	99.7	>99.9	100						
Streptococcus pneumoniae (penicillin susceptible)		2980	4918	908	121	22	1				8950	0.06	0.12
		33.3	88.2	98.4	99.7	>99.9	100						
Streptococcus pneumoniae (penicillin resistant)		24	62	7	4						97	0.06	0.12
		24.7	88.7	95.9	100								

Species	MIC µg/mL (No. of isolates/Cumulative Percent)										Total	MIC_{50}	MIC_{90}
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8			
Streptococcus pneumoniae multidrug resistant (MDRSP)		518	1109	329	61	10	1				2028	0.06	0.12
		25.5	80.2	96.4	99.5	>99.9	100						
Streptococcus pneumoniae (tetracycline-resistant) per CLSI		697	1575	503	84	13	1				2873	0.06	0.12
		24.3	79.1	96.6	99.5	>99.9	100						
Streptococcus agalactiae (all)		225	1060	1161	102	6					2554	0.06	0.12
		8.8	50.3	95.8	99.8	100							
Streptococcus agalactiae (macrolide resistant)		48	380	520	57	4					1009	0.12	0.12
		4.8	42.4	94	99.6	100							
Streptococcus pyogenes (all)		626	1695	212	25	3					2561	0.06	0.06
		24.4	90.6	98.9	99.9	100							
Streptococcus pyogenes (macrolide resistant)		42	210	68	11	1					332	0.06	0.12
		12.7	75.9	96.4	99.7	100							
Streptococcus spp. viridans group (all)[b]		515	563	238	63	8					1387	0.06	0.12
		37.1	77.7	94.9	99.4	100							
Streptococcus spp. viridans group (penicillin susceptible) per CLSI		410	433	161	35	3					1042	0.06	0.12
		39.3	80.9	96.4	99.7	100							
Streptococcus spp. viridans group (penicillin resistant) per CLSI	1	20	30	14	3	1					69	0.06	0.12
	1.4	30.4	73.9	94.2	98.6	100							
Streptococcus anginosus group (all)[c]		216	179	63	6	1					465	0.06	0.12
		46.5	84.9	98.5	99.8	100							

CLSI = Clinical and Laboratory standards institute, MIC = minimum inhibitory concentration, MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates, No. = number.

[a] Organisms include: *Staphylococcus 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)

[b] 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)

[c] Organisms include: *Streptococcus anginosus* (288), *S. anginosus* group (52), *S. constellatus* (89), *S. intermedius* (36)

Reference: 17-PAR-05

15.4.2. Multiyear global surveillance distribution for Gram-negative isolates.

Species	MIC µg/mL (No. of isolates / Cumulative Percent)													
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>	Total	MIC_{50}	MIC_{90}
Enterobacteriaceae (all)	1	26	934	6731	8525	8299	3892				4155	32563	2	>4
		0.1	3	23.6	49.8	75.3	87.2				100			
Enterobacteriaceae (ESBL-phenotype)		6	105	853	1481	1513	852				791	5601	2	>4
		0.1	2	17.2	43.7	70.7	85.9				100			
Escherichia coli (all)		23	881	5952	4535	1914	649				137	14091	1	2
		0.2	6.4	48.7	80.8	94.4	99				100			
Escherichia coli (ESBL-phenotype)		6	96	785	1035	699	268				64	2953	1	4
		0.2	3.5	30	65.1	88.8	97.8				100			
Klebsiella pneumoniae (all)		1	21	211	1736	2968	981				874	6792	2	>4
			0.3	3.4	29	72.7	87.1				100			
Klebsiella pneumoniae (ESBL-phenotype)			8	56	346	737	535				532	2214	2	>4
			0.4	2.9	18.5	51.8	76				100			
Enterobacter cloacae				29	433	1401	562				278	2703	2	>4
				1.1	17.1	68.9	89.7				100			
Haemophilus influenzae	2	8	124	1894	2141	477	30	6	1			4683	1	2
		0.2	2.9	43.3	89	99.2	99.9	>99.9	100					
Moraxella catarrhalis[a]	5	189	205	9								408	0.25	0.25
	1.2	47.5	97.8	100										
Acinetobacter baumannii	25	172	219	249	325	727	702	273	49	11	2	2754	2	8
	0.9	7.2	15.1	24.1	35.9	62.3	87.8	97.7	99.5	99.9	100			
Stenotrophomonas maltophilia			5	34	143	375	282	127	40	14	3	1023	2	8
			0.5	3.8	17.8	54.4	82	94.4	98.3	99.7	100			
Pseudomonas aeruginosa[a]			1	4	5	22	23	90	341	713	787	1986	32	>32
			0.1	0.3	0.5	1.6	2.8	7.3	24.5	60.4	100			

ESBL = extended-spectrum beta-lactamase, MIC = minimum inhibitory concentration, MIC_{50} = minimum inhibitory concentration against 50% of the isolates, MIC_{90} = minimum inhibitory concentration for at least 90% of the isolates.
[a] Data from 2016 surveillance only (North America and Europe) (16-PAR-01).
Reference: 17-PAR-05

15.4.3. Omadacycline MICs against other Gram negative bacteria (surveillance studies)

Species	No of isolates	MIC range (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
H. parainfluenzae	18	0.5 -16.0	1	2
Citrobacter spp	25	0.25 - 4	1	2
C. freundii	51	1-4	2	2
E. aerogenes	61	1-8	2	4
S. marcescens	167	1-16	4	8
K. oxytoca	76	0.5 - 32	1	4
Proteus mirabilis	42	2 - >32	16	32

Source Study (b) (4) Report2691A, 16-PAR-01, Study 594 and Study 473.

15.4.4 . Summary of *in vivo* studies

Organisms	Omadacycline MIC (mcg/mL)	Endpoint	Omadacycline Result	Reference	Comments
Systemic murine model - intraperitoneal (IP) challenge – IV therapy					
S. pneumoniae PBS1339 (6.85×10^2 CFU)	0.125	Survival on day 7	PD_{50} = 3.34 mg/kg	Macone 2014	Tigecycline 4.13 mg/kg
S. pneumoniae 157E (1.02×10^5 CFU)	≤0.06	Survival on day 7	PD_{50} = 1.10 mg/kg	Macone 2014	Doxycycline 1.55 mg/kg
S. pneumoniae 157E (1.02×10^5 CFU)	0.125	Survival on day 7	PD_{50} = 0.09 mg/kg	Poster F-758 and P 927	Doxycycline 1.8 mg/kg
S. pneumoniae 700905* (1.07×10^6 CFU)	≤0.06	Survival on day 7	PD_{50} = 0.45 mg/kg	Macone 2014	Tigecycline 1.72 mg/kg
S. pneumoniae 700905* (1.07×10^6 CFU)	0.25	Survival on day 7	PD_{50} = 0.14 mg/kg	Poster F-758 and P927	Vancomycin 0.14 mg/kg
S. aureus ATCC 29213 (6.40×10^6 CFU)	0.25	Survival on day 7	PD_{50} = 1.74 mg/kg	Macone 2014	Tigecycline 0.73 mg/kg
S. aureus ATCC 29213 (10^7 CFU)	0.5	Survival on day 7	PD_{50} = 0.4mg/kg	Poster F-757	Minocycline 1 mg/kg; Vancomycin 0.4 mg/kg
S. aureus USA 300 (7.13×10^7 CFU)	0.25	Survival on day 7	PD_{50} = 0.90 mg/kg	Macone 2014	Tigecyclien 0.58 mg/kg
S. aureus USA 400 (1.08×10^8 CFU)	0.5	Survival on day 7	PD_{50} = 0.45 mg/kg	Macone 2014	Tigecycline 1.09 mg/kg
S. aureus MRSA5 (1.06×10^8 CFU)	0.25	Survival on day 7	PD_{50} = 0.30 mg/kg	Macone 2014	Tigecycline 1.74 mg/kg
E. coli PBS1478 (6.60×10^7 CFU)	1.0	Survival on day 7	PD_{50} = 2.02 mg/kg	Macone 2014	Tigecycline 1.75 mg/kg; Ciprofloxacin 0.07 mg/kg
E. faecalis 27159 (tet-resistant)	0.5	Survival on day 5	100% survival at 1 mg/kg	Poster P928	Vancomycin = 60% survival at same dose
E. faecium L4001 (VRE) (4.5×10^7 CFU)	0.125	Survival on day 5	100% survival at 15 mg/kg	Poster P928	Linezolid =60% survival at same dose
E. faecalis ATCC 29212 – IV infection (immunocompetent mice)	0.5	Bacterial burden in kidneys	ED_{50} = 4.5 mg/kg	Poster F-757	Linezolid 14.3 mg/kg; Vancomycin 70.3 mg/kg

* Tet(M), azithromycin resistant; PD_{50} was protective dose required for 50% survival; ED_{50} was calculated as the dose that reduced the number of bacteria in the kidneys or thigh tissue by $2\log_{10}$ CFU = colony-forming units, MIC = minimum inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*; iv = intravenous

Organisms	Omadacycline MIC (mcg/mL)	Endpoint	Omadacycline Result	Reference	Comments
Neutropenic thigh model					
S. pneumoniae 157E (10^4 CFU)	0.125	2 log reduction in bacterial burden	ED_{50} = 0.75 mg/kg	Poster F-758	Vancomycin 10.2 mg/kg
S. pneumoniae 700905* (10^5 CFU)	0.25	2 log reduction in bacterial burden	ED_{50} = 0.14 mg/kg	Poster F-758	Vancomycin 10.2 mg/kg
12 *S. pneumoniae* strains	0.03 – 0.06	Bacterial burden in thigh tissue	Mean ED_{50} = 4.00 ±0.88 mg/kg	Craig 24 Feb 2006	No comparator; PK-PD study
S. aureus MRSA5 (10^5CFU)	0.5	2 log reduction in bacterial burden	ED_{50} = 5.9 mg/kg	Poster F-757	Minocycline 35.2 mg/kg; Vancomycin 30.4 mg/kg
S. aureus DSM11823 (MSSA) (2×10^6 CFU)	0.5	Bacterial burden in thigh tissue	~ 1.8 log10 reduction with 25 mg/kg	Poster P929	Vancomycin similar to omadacycline

		at 24 hours			
5 *S. aureus* strains	0.25-0.5	Bacterial burden in thigh tissue	Mean ED_{50} = 1.03 ± 0.42 mg/kg	Craig 24 Feb 2006	No comparator; PK-PD study
3 *E. coli strains* and 1 *K. pneumoniae* strain	0.5-2.0	Bacterial burden in thigh tissue	Mean ED_{50} = 1.33 ± 0.79 mg/kg	Craig 24 Feb 2006	No comparator; PK-PD study
Mouse abscess model - IV therapy					
S. aureus DSM11823 (MSSA) (3.5 x 10^5 CFU)	0.5	Bacterial burden at day 4	4 log_{10} reduction at 10mg/kg	Poster P929	Vancomycin and Linezolid no reduction
Murine sepsis					
S. aureus DSM11823 (MSSA) (1.2 x 10^6 CFU)#	0.5	Survival on day 5	100% survival at 0.3 mg/kg	Poster P930	Vancomycin 10 mg/kg
methicillin- and quinolone-resistant *Staphylococcus aureus* (MQRSA)	0.5	Survival on day 5	100% survival at 3 mg/kg	Poster P930	Vancomycin >10 mg/kg
methicillin-resistant *Staphylococcus epidermidis* (MRSE)	0.5	Survival on day 5	100% survival at 1 mg/kg	Poster P930	Vancomycin 10 mg/kg

* Tet(M), azithromycin resistant; PD_{50} was protective dose required for 50% survival; ED_{50} was calculated as the dose that reduced the number of bacteria in the kidneys or thigh tissue by 2log_{10} CFU = colony-forming units, MIC = minimum inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*; MQRSA = methicillin and quinolone resistant *S. aureus*; MRSE = methicillin-resistant *S. epidermidis*; iv = intravenous; # infection in neutropenic mice required a higher dose (50 mg/kg) for survival compared to 60% survival with same dose of vancomycin.

Organisms	**Omadacycline MIC (mcg/mL)**	**Endpoint**	**Omadacycline Result**	**Reference**	**Comments**
Mouse pulmonary infection model - immunocompromised					
S. pneumoniae GSK1629 (10^6 CFU)	≤0.06	Survival on day 7	PD_{50} = 11.0 mg/kg	Poster F-758	Vancomycin 7.2 mg/kg
S. pneumoniae PBS942 (tet-R; 10^6 CFU)	0.25	Survival on day 7	PD_{50} = 27.1 mg/kg	Poster F-758	Vancomycin 5.4 mg/kg
Mouse pulmonary infection model - immunocompetent					
S. pneumoniae L3TV (serotype 3) (9 x10^6 CFU)	0.06	Reduction in lung burden on day 4 and survival	6 log_{10} reduction at 1mg/kg; 100% survival	Poster P931	Vancomycin similar to omadacycline
S. pneumoniae PBS1339 (10^6 CFU)	≤0.06	Bacterial burden in lungs at 48 hours	ED_{50} = 7.4 mg/kg	Poster P927	Doxycycline 7.2 mg/kg; Ciprofloxacin 28 mg/kg
S. pneumoniae GSK1629 (10^6 CFU)	≤0.06	Bacterial burden in lungs at 48 hours	ED_{50} = 7.4 mg/kg	Poster F-758	Minocycline 35.4 mg/kg
H. influenza PBS981 (10^6 CFU)	1.0	Bacterial burden in lungs at 48 hours	ED_{50} = 4.7 mg/kg	Poster P927	Doxycycline 18.6 mg/kg; Ciprofloxacin 1mg/kg
Mouse Granuloma pouch - IV therapy					
B. fragilis 06688 (6 x 10^6 CFU)	≤ 0.125	Bacterial burden in pouch exudates	6 log_{10} reduction at day	Poster P928	More efficacious than metronidazole same dose
Mouse caecal ligation/polymicrobial peritonitis – IV therapy					
Polymicrobial	NA	Survival at day 10	80% survival at 10 mg/kg BID dose	Poster P928	Imipenem = 70% survival Linezolid = 30% survival
Mouse Pyelonephritis					
E. coli C189P4	0.5	2 log	ED_{50} = 4.3 mg/kg	Poster F-757	Ciprofloxacin <1.0 mg/kg

(1 x 10^7CFU)		reduction in bacterial burden in the kidney			Minocycline 4.5 mg/kg
Infective Endocarditis in Rats					
S. aureus MRSA 32 (5 x 10^5CFU)	0.5	3 log reduction in bacterial burden in heart tissue	ED_{50} = 2.89 mg/kg	Poster B-069	Less efficacious than tigecycline in the ratio of total heart sterilization (2/6 for omadacycline at 5 mg/kg vs. 5/6 for the same dose of tigecycline)

* Tet(M), azithromycin resistant; PD_{50} was protective dose required for 50% survival; ED_{50} was calculated as the dose that reduced the number of bacteria in the lung kidney or heart tissue by 50% or per prespecified log reduction; CFU = colony-forming units, MIC = minimum inhibitory concentration, iv = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*

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16. References

References have been placed as footnotes where needed throughout this review.

17. Financial Disclosure

18. Division Director (OCP)

Concur with the review

19. Division Director (OB)

Concur with the review

20. Division Director (Clinical)

Concur with the review

21. Office Director (OAP)

Concur with the review

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/s/

DEEPAK AGGARWAL
10/02/2018

EDWARD M COX
10/02/2018

Date: 6/6/2018

From: Wendy Wu, Ph.D., Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: James Weaver Ph.D., Consult Lead and David Strauss M.D., Ph.D., Director; DARS/OCP

To: Devi Kozeli, QT-IRT, DCRP, ODE1, OND

Subject: Evaluation of nonclinical study report in NDA209816 ((b) (4) *Study No: DHIZ1004*) that describes the block potency of PTK0796 (omadacycline) on hERG channels as measured with whole-cell voltage clamp method.

Executive Summary

Omadacycline (also designated as PTK 0796) is an antibiotic intended for the treatment of acute bacterial skin and skin structure infections and community acquired bacterial pneumonia. The QT-IRT team has evaluated the TQT study accompanying omadacycline NDA (NDA209816), and the results showed heart rate changes in healthy volunteers that confounded QT_C interpretation. In the Phase 3 clinical study, omadacycline did not alter heart rate or prolong QT_C interval in patients. The QT-IRT team thus asked DARS to evaluate whether hERG channel pharmacology data for omadacycline accompanying this NDA is reliable. Given that hERG channel block-mediated QT_C prolongation raises a regulatory concern for drug-induced proarrhythmia risk, the intent is that a lack of hERG signal within the therapeutic exposure level from *in vitro* hERG channel studies would be used in addition to Phase 3 ECG data to support a negative QT_C drug label.

Omadacycline suppressed hERG current in a concentration-dependent manner. However, at the maximal concentration tested (1000 μg/mL, ~590X therapeutic free concentration), omadacycline suppressed hERG current by ~45% only. By force fitting a Hill equation to the data and constraining maximal % suppression to 100%, DARS reviewer obtained an IC_{50} of 1162 μg/mL for omadacycline against hERG channels. The safety margin of this drug (IC_{50} divided by free C_{max}), which indicates the distance away from proarrhythmia risk, is 685 when calculated using free C_{max} achieved with the therapeutic dose (1.696 μg/mL considering 20% protein-binding) and 484 when calculated using the free C_{max} achieved by the supratherapeutic dose used in TQT study (2.4 μg/mL). These values are higher than the cut-off of 400 set by the FDA CiPA team for drugs without a proarrhythmia risk. DARS reviewer thus concludes that within the therapeutic exposure level, omadacycline does not block hERG channels directly and is associated with low proarrhythmia risk.

This is an urgent consult with a turn-around time of 5-working days from the date of request.

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Background (same as first paragraph above)

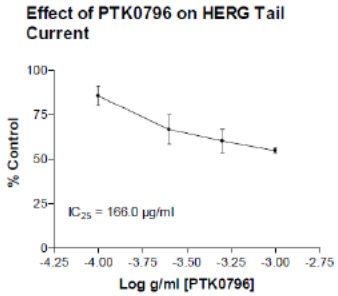
Omadacycline (also designated as PTK 0796) is an antibiotic intended for the treatment of acute bacterial skin and skin structure infections and community acquired bacterial pneumonia. The QT-IRT team has evaluated the TQT study accompanying omadacycline NDA (NDA209816), and the results showed heart rate changes in healthy volunteers that confounded QT_C interpretation. In the Phase 3 clinical study, omadacycline did not alter heart rate or prolong QT_C interval in patients. The QT-IRT team thus asked DARS to evaluate whether hERG channel pharmacology data for omadacycline accompanying this NDA is reliable. Given that hERG channel block-mediated QT_C prolongation raises a regulatory concern for drug-induced proarrhythmia risk, the intent is that a lack of hERG signal within the therapeutic exposure level from *in vitro* hERG channel studies would be used in addition to Phase 3 ECG data to support a negative QT_C drug label.

Evaluation

Effect of PTK0796 on hERG current was examined using electrophysiology technique by (b) (4) for Paratek Pharmaceuticals, Inc. Whole-cell voltage clamp recordings were performed on HEK293 cells stably expressing hERG1a subunit at room temperature. HERG current was evoked with a conventional voltage protocol: from a holding potential of -80 mV, cells were first depolarized to +20 mV for 4.8 s, then down to -50 mV for 5 s, and finally repolarized to -80 mV for 5.2 s. The total voltage protocol duration is 15 s, and presumably this protocol is repeated without a time gap (hence hERG current was recorded every 15 s). The amplitude of hERG current reported in this study was measured as the peak outward current at the -50 mV step.

Four concentrations of PTK0796 were studied: 100, 250, 500, 1000 μg/mL. Each concentration was tested 4 cells, and each cell was exposed to either a single or multiple drug concentrations depending on cell health. HERG current was first recorded in control solution, followed by drug application. Drug exposure time was 10 minutes, at a solution perfusion rate of 1-2 mL/min. HERG current rundown was not examined or monitored in individual cells. Rather, 4 additional cells were recorded in control solution followed by vehicle application to estimate the extent of rundown. The % of rundown ranged from 1-22% for a 10 min recording period (p. 46 of study report; mean ± sem = 91 ± 5%). Drug effects were corrected for mean vehicle rundown. To demonstrate assay specificity, 100 nM of E4031, a potent and selective hERG channel blocker, was tested on 2 cells, and the % block was ~90%. In all, DARS' reviewer deems the research design and method to be solid.

Drug effect. To quantify drug effect on hERG channels, the amplitude of steady state hERG current recorded in drug solution was divided by that recorded in control solution to calculate % residual hERG current. The % residual hERG current was then plotted against drug concentration to illustrate concentration-dependent block (see figure on the right from the study report; p. 22). At the highest concentration tested, PTK0796 achieved only 45% of hERG current suppression. Instead of fitting the data with the Hill equation, the study report used an IC_{25} value to describe drug effect (IC_{25} = concentration that blocks 25% of current). IC_{25} of PTK0796 is 166 μg/mL. DARS' reviewer agrees with the analysis performed in this study.



Data corrected for mean vehicle rundown.

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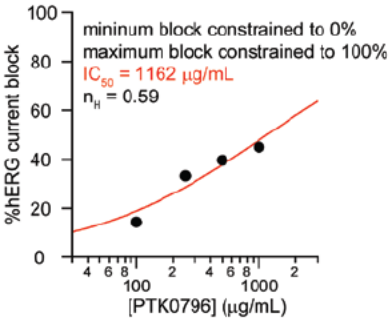
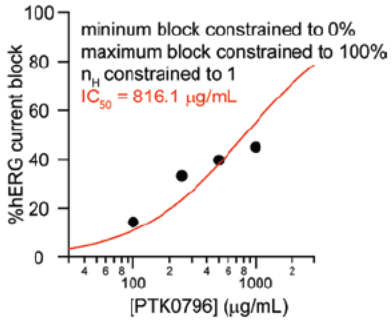
hERG safety margin calculation. HERG safety margin is typically calculated as the ratio of IC_{50} and free C_{max} (IC_{50} = half inhibitory drug concentration). The higher the safety margin, the farther the distance a drug is from carrying a proarrhythmia risk. On June 4, 2018, the FDA CiPA team established a conservative safety margin of 400 to separate drugs with proarrhythmia risk (≤400) from those that do not (>400). To estimate hERG IC_{50} for safety margin calculation, DARS reviewer first plotted % the percent hERG current blocked against drug concentration tested, then force-fit the Hill equation to the data. The two figures on the left show the fitting results. For the figure on the left panel, the maximal % block was constrained at 100%, and minimal % block was constrained at 0. The resulting IC_{50} is 1162 μg/mL, with a Hill coefficient (n_H) of 0.59. For the figure on the right panel, n_H was constrained to 1. This gave an IC_{50} of 816.1 μg/mL. For safety margin calculation, the IC_{50} of 1162 μg/mL was used as it better matched the experimental data that demonstrated <50% block by 1000 μg/mL.





C_{max} information was obtained from Table 5 in section 12.3 of the omadacycline or (b) (4) draft label, which indicates that 100 mg dose (i.v.) produces a steady state C_{max} of 2.120 μg/mL. *In vitro* plasma protein binding of omadacycline is 20%. Thus, free C_{max} at therapeutic exposure level was estimated to be 1.696 μg/mL. This gives hERG safety margin of 685. When safety margin was calculated using the free C_{max} achieved by the supratherapeutic dose used in TQT study (2.4 μg/mL), the value was 484. These values exceed the safety margin cut-off value of 400 recently set by the FDA CiPA team.

Summary and Conclusions

Omadacycline (also designated as PTK 0796) is an antibiotic intended for the treatment of acute bacterial skin and skin structure infections and community acquired bacterial pneumonia. This drug suppressed hERG current when examined using hERG1a-expressing cells and whole-cell voltage clamp method. However, its IC_{50} against hERG channels is 484X when compared with supratherapeutic free exposure level and 685X when compared with free concentration from the proposed dosing regimen. Thus, at the therapeutic exposure level this drug is not expected to block hERG channels and is considered to be of low proarrhythmia risk based on the safety margin calculation.

References and Supporting Documents

(b) (4) Study No: DHIZ1004
\\cdsesub1\evsprod\nda209816\0000\m4\42-stud-rep\421-pharmacol\4213-safety-pharmacol\dhiz1004\dhiz1004-pre-clinical-study-report.pdf

Draft label
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Safety margin calculation by Zhihua Li, Ph.D., FDA CiPA team. Based on 28 CiPA drugs, a safety margin of 400 could safely eliminate all high and intermediate proarrhythmia risk drugs.

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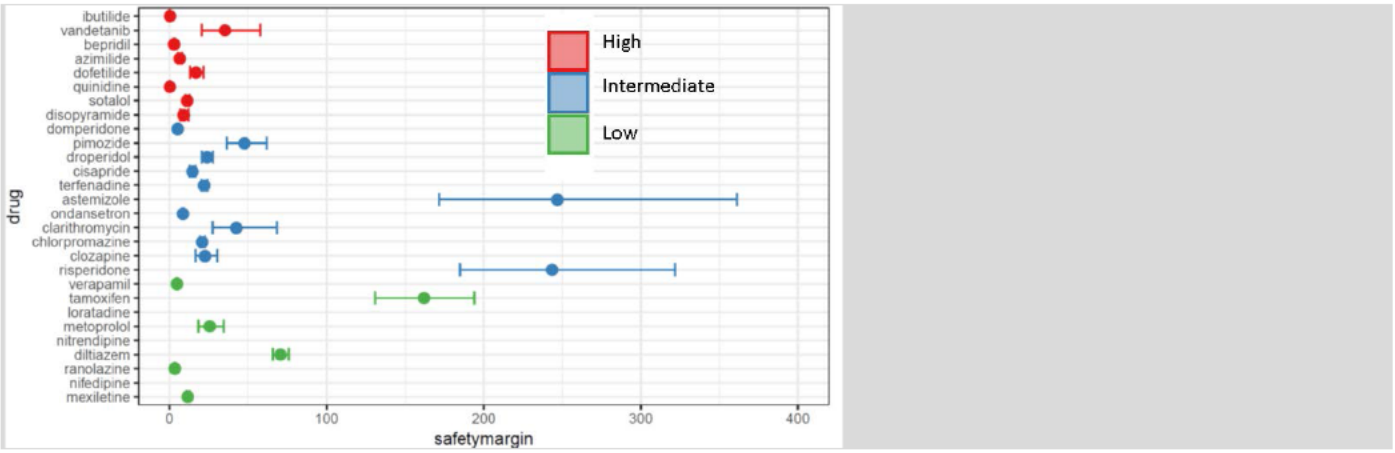

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/s/

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06/14/2018